Parathyroid Gland Disorders

Controversies and Debates

Mahmoud F. Sakr

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To my dear students and colleagues

Preface

In this authored book, we aim at emphasizing established concepts, displaying the ongoing arguments, controversies, challenges, and debates on diagnosis and treatment of different parathyroid gland disorders with a view of clarifying some uncertainties, making suggestions to resolve others, and establishing strategies to reach therapeutic success.

This book, with 107 images and 1673 references, will provide a valuable source of knowledge and reference for all specialists and trainees entrusted with the care of patients suffering from parathyroid gland diseases. It includes 18 chapters, namely, historical review, embryology of the parathyroid gland, surgical anatomy of the parathyroid gland, histology of the parathyroid gland, physiology of the parathyroid gland, calcium: why is it important?, hyperparathyroidism (HPT), osteitis fibrosa cystica, hypothyroidism, metabolic syndromes of parathyroid failure, hungry bone syndrome, post-thyroidectomy hypocalcemia (incidence and risk factors, clinical presentation, prevention), parathyroid transplantation, parathyroid cancer, intraoperative tools in parathyroidectomy, and parathyroidectomy.

It is my collective hope that head and neck surgeons, dentists, maxillofacial surgeons, orthopedic surgeons, endocrinologists, oncologists, pediatricians, and clinicians of other specialties will find this book to be a useful and indispensable resource as they face the most challenging of parathyroid gland disorders to help provide individual patients with the best possible outcome.

Alexandria, Egypt — Mahmoud F. Sakr

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Parathyroid Glands: Historical Review

1

1.1 Introduction

Because of their unique anatomical features, the parathyroid glands (PTGs) were the last of the endocrine glands to be discovered, which greatly hindered proper treatment until the first decades of the twentieth century. Identification of the PTGs, recognition of their important role, and understanding of the diseases that affect them traveled a long journey to the present state of knowledge. Technological developments in the last three decades greatly facilitated the location of the PTGs and the conduction of surgery for hyperparathyroidism (HPT). However, an experienced and dedicated surgeon is still essential to the excellence of treatment [1].

1.2 Parathyroid Gland Discovery and Anatomy

The parathyroid glands (PTGs) were first discovered in 1852 in Indian Rhinoceros at London Zoo by Sir Richard Owen (1804–1892), Professor and Conservator of the Museum at the Royal College of Surgeons of England [2]. In his description of neck anatomy, Owen referred to the PTG as "a small compact yellow glandular body attached to the thyroid at the point where the veins emerged" [2, p. 219]. He suggested they were embryonic portions of the thyroid gland.

The famous German pathologist Rudolph Virchow may have identified one PTG in 1863, when he described a structure in the cervical region, emphasizing that it was not an accessory thyroid gland or lymph node, or any other structure that was familiar to him, though showing no interest in the finding as reported by Dubose et al. (2005) in their review of the history of parathyroid surgery [3].

The PTGs were first discovered in humans in 1880, by Ivar Viktor Sandström (1852–1889), a 25-year-old Swedish medical student, at Uppsala University [4]. Unaware of Owen's description, he described the glands in his monograph "On a New Gland in Man and Fellow Animals" and called them the "glandulae

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parathyroidae" (parathyroid glands) due to their location [5], noting their existence in dogs, cats, rabbits, oxen, and horses [3, 6]. He then initiated dissections in about 50 corpses and confirmed the presence of these glands in humans [7] and described their color, shape, and variations in location. In addition, he held a detailed microscopic analysis of these glands. However, for several years, his description had little attention [8]. Sandström, who received the physician title in 1887, was so disturbed by such lack of recognition of his discovery that he fell into a deep depression, which perhaps may have contributed to his suicide at the age of 37 years.

In 1938, Gilmour published his detailed studies on the gross and histological anatomy of the PTGs, but the unusual location of the glands was first noted in surgical patients by Gaz in 1987 as reported by Skandalakis et al. in 2004 [9].

1.3 Parathyroid Function and Relation to Calcium

The term "tetany" describes a set of neuro-muscular symptoms caused by nervous system hyper-excitability, which can vary from peri-oral paresthesias to cramps and muscle stiffness [10]. Contracture of extremities, with or without peculiar seizures, has been described about 100 years ago when Corvisard introduced the term "tetany" for the first time in 1852. Both Trousseau, in 1862, and Chvostek, in 1876, have defined the clinical signs that characterize "tetany," without, however, defining its origin. The occurrence of tetany after thyroidectomy was first recognized by Anton Wolfer, in 1879, in a patient undergoing total thyroidectomy by Billroth. His explanation for the seizures was that they stemmed from a "brain hyperemia" ensuing in these patients due to thyroidectomy [11]. This explanation led to the development of the "theory of detoxification," which assumed that the tremors and convulsions were caused by toxins not removed from circulation by the thyroid and parathyroid glands [10].

Advances in general anesthesia (1840s) and understanding the importance of antisepsis (1860s) and hemostasis (1870s) allowed the beginning of the first successful operations on the thyroid gland in the following decades. The high mortality rate (over 40%) faced by surgeons of the time began to reduce, mainly by the work of two remarkable surgeons in this area: Theodor Kocher and Theodor Billroth. Patients operated upon by Kocher developed hypothyroidism post-operatively, while those operated upon by Billroth, rarely developed hypothyroidism post-operatively; however, many developed severe tetany with a fatal outcome. William Halsted, after watching operations of the great masters, found that the difference was probably related to the technique. Kocher was extremely meticulous and precise, operating carefully with strict hemostasis. He removed the entire thyroid gland and his patients rarely suffered voice changes or tetany due to preservation of the recurrent laryngeal nerve (RLN) and PTGs. Billroth, in contrast, worked quickly, with less rigorous hemostasis, which probably increased the risk of PTG removal, and the remaining thyroid tissue prevented severe hypothyroidism. For his contributions to thyroid gland physiology, pathology, and surgery, Kocher received the Nobel Prize in 1909.

The French physiologist Eugene Gley first documented the putative function of the PTGs in 1891. During testing in rats, rabbits, and dogs, Gley noted the connection between PTG excision (alone or with thyroidectomy) and the development of muscular tetany. Based on these findings, he recommended extreme caution to surgeons to avoid damaging the PTGs during thyroidectomy and was probably the first to define the essential character of these glands, although not clearly identifying their functions [5].

That same year (1891), Friedrich von Recklinghausen, a famous German pathologist, described a condition characterized by widespread decalcification of the skeleton, associated with the formation of bone cysts, which he called "fibrocystic bone disease," without identifying the source of dysfunction. He described increase in the size of the PTG of that patient, but did not establish a causal relationship between the findings [5]. Max Askanazy [12], in 1903, described a tumor in the PTG in autopsies on patients who had died with the condition described by von Recklinghausen, though also failing to establish the relationship between the two findings. In the early twentieth century, it became clear that PTG removal or ischemia caused tetany. Nevertheless, the main hypothesis was that the glands were responsible for the removal of unknown human body toxins.

The first evidence of the relationship between the PTG and calcium metabolism arose in 1907, when Jakob Erdheim, an Austrian pathologist who studied the PTGs in patients with bone disease, noted that many patients with bone diseases such as osteomalacia and osteitis fibrosa had enlarged PTGs. Unfortunately, he erroneously believed that PTG enlargement was a compensatory response caused by bone disease. In the same year, Erdheim reported the diagnosis of a patient with two simultaneous tumors, one in the PTG and the other in the pituitary, an omen of multiple endocrine neoplasia (MEN) that would be described more than 50 years later.

In 1908, William G. MacCallum, investigating tumors of the PTGs, proposed their role in calcium metabolism [3]. He noted that "tetany occurs in many forms and may be produced by the destruction of the PTGs" [13, p. 119]. MacCallum was the first to describe the improvement of tetany in animals with the instillation of a parathyroid extract. In addition, he pioneered the evidence that post-parathyroidectomy tetany could be corrected with calcium injection. Despite the inconsistency of his results, he was one of the first to suggest that the cause of tetany was related to hypocalcemia [14].

The data provided by MacCallum led William Halsted to initiate the use of calcium and parathyroid extract in his patients with tetany [15]. The determination of serum calcium levels, from 1909, finally allowed more understanding of the association between the PTGs and calcium homeostasis. Only in 1923, Adolf M. Hanson, a student at the University of Minnesota, was able to develop a stable and reproducible parathyroid extract from bovine parathyroid [16]. James Collip, a Canadian biochemist, recognized for collaborating in studies to identify insulin, independently developed studies to improve the parathyroid extract and define the best form of administration for which he obtained the first patent for parathyroid hormone (PTH) extract [17]. In 1925, Collip proved that tetany and symptoms of hypocalcemia could thus be appropriately corrected [17]. Review of knowledge by Boothby, in 1923, concluded that the parathyroid function was related to calcium metabolism [18].

1.4 Evolution of Parathyroid Surgery

Many surgeons who have left their mark on the development of surgery as a science have been intrigued by the PTGs. Interestingly the history of transplants probably began with the PTG. The first transplantation of the parathyroids was performed by Schift and Horsley in 1885 as reported by Niederle et al. [19], and then, in 1892, by Anton von Eiselberg, a Billroth disciple, who performed a large number of auto-transplantations of the PTGs in the peritoneum and the posterior wall of the sheath of the rectus abdominal muscle of cats. He thereby showed that tetany was absent and new vessels had formed in the transplants. Furthermore, tetany occurred after these transplants were removed [20]. Halstead [21] in Baltimore attempted "iso-autotransplantation of the PTGs" in dogs in 1909. He transplanted the tissues of the glands under the abdominal skin or into the parenchyma of the thyroid gland. Halstead and several other researchers called this situation "loan of insufficiency." Later on, in 1936, Shambangh [22] pointed out that the above-mentioned "loan" was not necessary for successful transplantation of these glands. Since then, PTG transplantation, using a range of different techniques, has been a common procedure for the treatment of hypoparathyroidism.

The first *unsuccessful* operation to treat skeletal disease was performed by Oscar Hirsch in Vienna in April 1925. He tried surgically to locate and remove a tumor of the parathyroid, but did not succeed. During the same period, in Vienna the famous pathologist Erdheim [23] expressed his view that, since tumors of the PTGs are compensatory due to bone disease, the operation is contra-indicated.

The first successful removal of the parathyroid may have been carried out in 1928 by medical doctor Isaac Y. Olch, whose intern had noticed elevated calcium levels in an elderly patient with muscle weakness. Prior to this surgery, patients with removed PTGs typically died from muscular tetany [3].

When treating patients with cystic bone lesions in radiological imaging, which evolved with hip fracture and elevated urinary calcium, Felix Mandl initially tried to transplant parathyroid tissue taken from corpses to improve the clinical condition. With failure of this form of treatment, he indicated, on July 30, 1925, a pioneer neck exploration under local anesthesia for excision of a parathyroid tumor, with resolution of symptoms. At 4 months post-operatively, radiological studies showed significant improvement in bone density, and at 6 months, the patient was free of bone pain. However, despite the operation success, symptoms returned 6 years later. The patient was diagnosed with recurrent hyperparathyroidism (HPT) and was again operated upon with resection of two more PTGs, but they were considered normal on histological examination. There was no remission of symptoms and the patient died 3 years later. The autopsy found no signs of parathyroid tissue [24]. Even with the failure in this case, Mandl (1925) was responsible for a number of findings that were useful in the following years; he determined that the disease was not bone primary but originated in the PTGs, demonstrated that tumor resection could be successful in controlling hypercalcemia, showed the possibility of

recurrence, and also suggested the possibility of a family illness [11]. Moreover, Mandl had also the merit of helping Gold and Eiselberg during an operation to remove a parathyroid adenoma in a patient with von Recklinghausen's disease 2 years after his pioneering surgery. After that operation, the term "hyperparathyroidism" (HPT) was first used in the literature [24]. David Barr and Harold Bulger [25] attended a case with similar clinical presentation in 1926, and reported cervical exploration with removal of an adenoma in a 56-year-old patient. With high doses of parathyroid hormone (PTH) and oral calcium post-operatively to treat tetany, symptoms improved and the patient returned to normal life. They were probably the forerunners to define the clinical presentation of HPT with five clinical features; (1) bone thinning, (2) multiple cystic bone tumors, (3) hypotonia and muscle weakness, (4) abnormal calcium excretion in the urine with calcium calculi formation, and (5) high serum calcium levels.

It seems appropriate at this point to mention the US Navy officer, Captain Charles Martell, who is certainly the most famous example of a patient with HPT: his case was described by Fuller Albright in a speech delivered while President of the American Society for Endocrinology. At the Massachusetts General Hospital in Boston, Martell was hospitalized due to severe decalcification of his bone structure. Tests indicated hypercalcemia consistent with HPT. Between 1926 and 1932, he was operated upon six times. Surgeons could not detect the PTGs in the first surgery (1926), and subsequent explorations identified only one gland that was considered normal on histological examination. The patient himself, intrigued by his clinical conditions, conducted an extensive literature review in the library of Harvard University, focusing on locations of ectopic PTGs. After finding an account of mediastinal location of the PTGs in the December 1931 volume of the *Acta Medica Scandinavica Journal*, he realized the possible similarity with his own illness. He then insisted that surgeons carried out another surgical exploration, this time in his mediastinum through a sternotomy. In 1932, Churchill and Cope [26], performing the fifth operation, managed to locate a parathyroid tumor (a large encapsulated adenoma) measuring 3 cm in diameter in the mediastinum. About 90% of the lesion was removed with the remaining tissue being subjected to transplantation, which was not effective. Symptoms of hypocalcemia were serious and 6 weeks after the operation, the patient presented with a ureteral obstruction due to a calculus. Then again, he was operated upon and unfortunately died because of laryngospasm after surgery [26].

1.5 Hyperparathyroidism (HPT)

The notion of HPT and its detrimental effects on the human organism attracted the attention of scientists as early as 1864. It was Engel during that year who originally presented a patient with a parathyroid adenoma and skeletal disease [27]. A similar condition was reported in 1904 by Askanazy (1865–1940) who

was the first to connect "osteitis fibrosa cystica" with tumors of the PTGs [28]. A detailed description of this condition has also been provided in 1891 by von Recklinghausen [29].

The first decades of the twentieth century witnessed the improvement in the diagnosis and treatment of HPT through MacCallum's, Halsted's, Hanson's, and Collip's studies. However, the disease originated from the excessive hormone production was still unknown [1]. Apparently, physicians at the Barnes Hospital in St. Louis were the first to define HPT in an article published in 1929: characteristic bone findings, muscle weakness, kidney stones, and high levels of serum calcium [30]. The initial operation of Mandl and few other successful cases showed that surgery could be a good treatment option for cases of HPT. Nonetheless, little was known about the pathophysiology of this condition. The finding that many patients undergoing resection of adenomas did not have their symptoms improved worried the surgeons of the time. Patients with bone disease often had renal calculi.

Fuller Albright [31], a North American physician from Harvard, after spending a year in Vienna following the work of Erdheim, began to show great interest in calcium metabolism. He undertook studies in patients with kidney stones without bone disease and, for the first time, he could relate the renal condition with parathyroid disease. Albright was the first researcher who managed to understand that the genesis of HPT could stem from different etiologies. In 1934, he was one of the pioneers in the distinction between the different types of HPT [31, 32].

Albright (1900–1969) et al. [31], suggested that primary HPT was due to a single adenoma of one gland or multiple adenomas with primary water-clear cell hyperplasia as well as to parathyroid carcinoma; they also described diffuse cell hyperplasia of all PTGs. Albright and Reifenstein [33], defined primary HPT in their book *The Parathyroid Glands and Metabolic Bone Disease*, which was published in 1948 as: "Primary HPT is a condition in which the PTH is higher than is needed" [34, p. 82]. "Secondary HPT" is "a condition where more PTH is manufactured for some compensatory purposes" [34. p. 82]. Later, the term "tertiary HPT" was adopted for patients who developed parathyroid tumors secondary to renal failure or intestinal malabsorption syndrome with osteomalacia.

Understanding the different etiologies of HPT led to a change in the paradigm of operations for treatment of hypercalcemia. In patients diagnosed with symptomatic primary HPT, surgery is the only treatment that offers the possibility of permanent cure. In asymptomatic patients, there is some controversy about the indication of surgical removal. The accepted criteria to indication surgery are: (1) Calcium serum 1 mg/dL over the limit, (2) urinary calcium excretion >400 mg, (3) 30% reduction in creatinine clearance, (4) osteoporosis (bone densitometry), and (5) age lower than 50 years [35]. Secondary HPT is treated clinically. However, severe pain or bone fractures, significant itching, and calcifications of non-vascular organs in patients who are refractory to appropriate clinical treatment prompt surgery for this condition. Patients with tertiary HPT are usually treated with total parathyroidectomy with preservation of a small fraction of one of the glands.

1.6 Parathyroid Hormone (PTH)

Parathyroid hormone (PTH) was first extracted by Adolph M. Hanson in 1923 and then in 1925 by James B. Collip who subsequently, in 1926, linked HPT to high serum calcium, although the actions of the hormone on the bones, kidneys, and intestines were discovered later in the 1940s. It took about 40 years before the discovery of a more effective method for the measurement of PTH and other peptides by Berson and Yalow [36], causing a revolution in the evaluation of such patients. Improvement in the determination of serum calcium and PTH yielded a great improvement in the understanding of metabolic disorders related to this important ion. The number of patients diagnosed with HPT, even asymptomatic, increased considerably [37], making it possible to uncover the various clinical and metabolic aspects related to diseases of the PTGs. The polypeptide structure of PTH was defined by Ramussen and Craig in 1960 [38]. Studies of PTH levels by Roger Guillemin, Andrew Schally, and Rosalyn Yalow led to the development of immunoassays capable of measuring body substances, and a Nobel Prize in 1977 [3, 4].

This facility for the laboratory diagnosis of HPT led to an exponential increase in operations during the late 1980s. Due to improved diagnosis, patients no longer presented with advanced stages disease, and many were still asymptomatic. However, diagnostic difficulties between adenomas and gland hyperplasia opened the possibility of inadequate or too aggressive surgical procedures [22]. To try to resolve the therapeutic questions in the treatment of primary HPT, Purnell et al. (1971) [39] conducted a great analysis of 143 patients followed for 10 years. The main findings of this well-conducted study were: (1) existence of a great loss to follow-up, both by patients and physician, (2) lack of consensus on specific monitoring tests, (3) absence of predictive factors for disease activation, and (4) recommendation of surgery by an experienced surgeon (minimum of 9–10 operations/year).

1.7 Technological Advances

Discovery of the PTGs and their function was without doubt a major breakthrough for the medical community. Thanks to scientists like R. Owen, V. Sandström, and E. Gley and to surgeons such as W.S. Halstead, Billroth, and many others, huge progress has been made over the centuries, which, combined with technological advances and human ingenuity, has significantly added, and continues to do so, to the total arsenal of medical knowledge regarding the parathyroids.

Success of the early isolated cases encouraged surgeons to recommend parathyroidectomy as a routine procedure to treat hypercalcemia with good initial results [40]. There was also the realization that HPT was not only associated with a solitary parathyroid adenoma, but also with multiple adenomas and with glandular hyperplasia, which could affect all glands. Founded on this knowledge, bilateral cervical exploration became the recommended routine procedure. Parathyroid surgeries were often prolonged, tedious, and unsuccessful operations. Advances in perioperative management, proper positioning of the patient on the operating table,

endotracheal intubation, and the proper use of drains contributed to the growing success of surgery [41]. However, the biggest challenge was still the precise preoperative localization of the PTGs, in order to avoid fruitless or inaccurately indicated explorations that could worsen patients' quality of life. Arteriography was one of the initial methods tried, but failed to demonstrate benefits [42]. Selective blood collection of cervical veins was superior to arteriography, though with difficult conduction and considerable morbidity. Surgical anecdotes of the time, faced with the difficulties of location of the PTGs, originated the quote: "The only localization that a patient needs who has primary hyperparathyroidism is the localization of an experienced surgeon!" [43, p. 1324]. The use of nuclear medicine was another important advance, as well as the neck ultrasonography, allowing the neck exploration to be unilateral in selected cases [44].

A new revolution in the treatment of these patients occurred in 1987, when Samuel Nussbaum described a method for rapid detection of PTH [45]. In the past, the measurement of PTH levels took about 20 h and it was common to inform the patient, still recovering from surgery, of the need for a new cervical exploration [26]. Due to the few minutes half-life of the active PTH, its rapid measurement during operation, and before and after resection of the lesion, rendered a higher degree of certainty of complete resection of abnormal glands. PTH levels falling more than 50% virtually assured excision of all affected glands [45]. The introduction of this new detection method allowed greater procedural safety, more conservative operations, lower hypercalcemia recurrence rate, surgery without the need for hospitalization, and a 40%-reduction in hospital costs [46]. Devices for intra-operative identification through a mapping by marking the PTGs also contribute to achieving a more efficient surgery [47].

The adoption of minimally invasive techniques now allows performing surgeries with very short hospital stay, less pain, lower cost, and minimal scarring, thus improving the cosmetic aspect [48]. Recent recognition of cloning of receptors and discovery of genes responsible for familial syndromes completed our current understanding of their role in health and disease.

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Embryology of the Parathyroid Glands

2

2.1 Embryogenic Origin

The embryonic pharynx consists of a lateral branchial apparatus on each side, and the unpaired ventral floor between them. Each lateral branchial apparatus is formed by six pairs of mesodermal branchial arches, covered externally by ectoderm (branchial clefts), and lined internally by endoderm (pouches).

The embryonic origin of the parathyroid gland (PTG) is from the third and fourth pharyngeal pouches endoderm (Fig. 2.1), but could also have ectoderm and neural crest contributions. This developmental process also generates multiple small parathyroid clusters in addition to the main PTGs [1–4].

During fifth to sixth weeks of gestation, the endoderm of the dorsal surface of the third pouch differentiates into the inferior PTGs, while the ventral surface

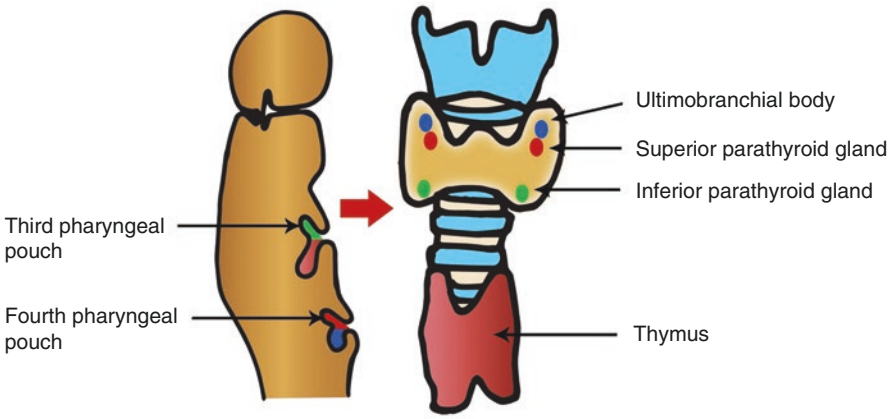

Fig. 2.1 Development of the superior (red color) and the inferior (green color) parathyroid glands from the fourth and third pharyngeal pouches, respectively

M. F. Sakr, *Parathyroid Gland Disorders*,
https://doi.org/10.1007/978-3-031-07418-9_2

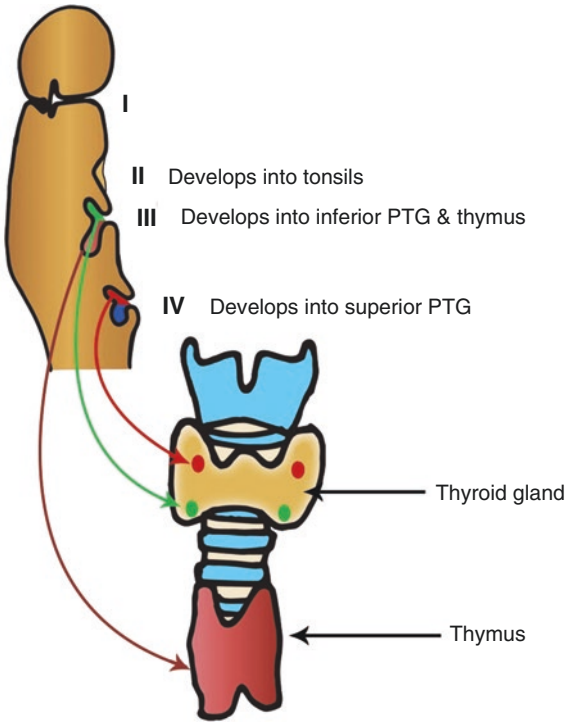

Fig. 2.2 The superior glands migrate inferiorly and medially to end up on the posterior surface of the thyroid. PTG, parathyroid gland

differentiates into the thymus. The endoderm of the dorsal wing of the fourth pouch differentiates into the superior PTGs, while the ventral wing differentiates into the ultimo-branchial body. By the seventh week of gestation, the inferior and superior PTGs migrate inferiorly and medially until they get arrested on the dorsal side of the caudal thyroid. The superior glands end up on the posterior surface of the thyroid (Fig. 2.2). The thymus/parathyroid primordium continues to move in a caudal-ventral-medial direction toward the anterior thoracic cavity. During this time, the parathyroid domain remains attached to the cranial pole of the thymus (Fig. 2.3).

When the thymus passes along the lateral sides of the thyroid, the PTGs detach and remain adjacent to the thyroid, and do not migrate any further caudally. The thymus, in contrast, continues its migration into the anterior mediastinum where it joins its contralateral thymic lobe.

In the adult, the PTGs appear as a pair of inferior and a pair of superior "bumps" on the side of the thyroid (hence the name, "para"). The adult anatomical position is the opposite of the pharyngeal order since the *inferior* PTG originates from the third pharyngeal pouch and the *superior* arises from the fourth. Since the *superior PTGs* descend only slightly during embryologic development, their position in adult life remains quite constant, adjacent to the posterior surface of the middle part of the thyroid lobe, often just anterior to the recurrent laryngeal nerve (RLN) as it enters the larynx. On the other hand, since the *inferior* PTGs travel so far (with the

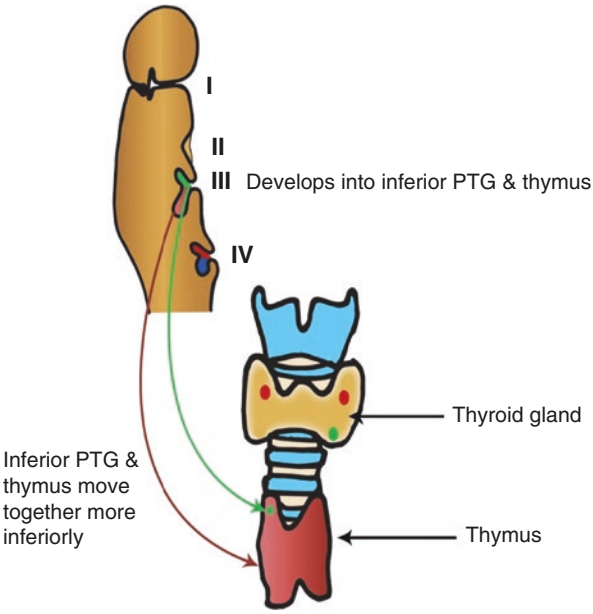

Fig. 2.3 The thymus/parathyroid primordium continues to move in a caudal-ventral-medial direction toward the anterior thoracic cavity. PTG, parathyroid gland

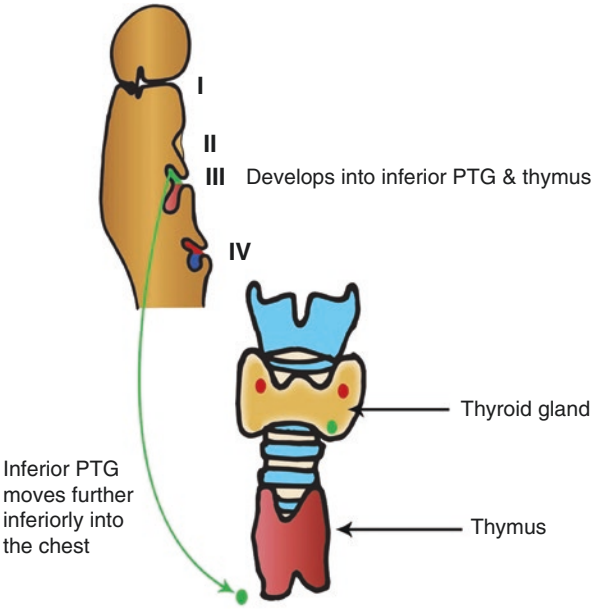

Fig. 2.4 The inferior parathyroid glands migrating further down into the chest (anterior mediastinum). PTG, parathyroid gland

isthmus) in embryologic life, hence they have a wide range of distribution in adults, from just beneath the mandible to the anterior mediastinum (Fig. 2.4). Usually, however, these glands are found on the lateral or posterior surface of the lower part of the thyroid gland [5].

2.1.1 Parathyroid Gland (PTG) Organogenesis

Nearly all of the information available regarding PTG organogenesis has come from studies in *mice*, facilitated by the identification of the early regulator of parathyroid differentiation, *glial cells missing 2*, or *Gcm2* [6]. The expression of *Gcm2* throughout parathyroid organogenesis allowed the tracking of parathyroid-fated cells throughout embryonic development and has been a key to the recent developments in the understanding of parathyroid organogenesis.

Initial PTG organogenesis is closely linked to *thymus* organogenesis—these organs arise from different regions of the same pouches, and during development they undergo a series of morphogenetic events to form separate organs [7]. The initial parathyroid domain forms in the *dorsal*-anterior region of the pharyngeal pouch (pp) and the forming pp-derived organ primordia, the *ventral* domain of which constitutes the developing thymus. These primordia must (in mice and humans) detach from the pharynx via localized apoptosis [7, 8].

The thymus and parathyroid domains separate from each other by less-well-understood mechanisms, likely involving both differential cell adhesion, involvement of surrounding neural crest cells (NCCs), and physical forces derived in part from thymus migration [5, 9]. Current evidence suggests that while the thymus lobes actively migrate, via activity of the NCC-derived capsule [10], the parathyroids do not themselves migrate but are "dragged" along by the migrating thymus lobes until the separation process is complete. This process introduces variability in their final locations, most often near the lateral aspects of the thyroid gland, but can be nearly anywhere in the neck region.

2.1.2 Molecular Regulators of Initial Parathyroid Specification

2.1.2.1 Transcription Factors

Because of their small size, variable location, and indistinct shape, little was known about PTG organogenesis until the identification of the early parathyroid marker *Gcm2*. The *Gcm2* encodes a transcription factor related to the *glial cells missing* gene, originally identified in *Drosophila* as a molecular switch between neural and glial cell fate [11]. Although *Gcm2* does not have this same function in mammals, it plays a critical role in PTG development [12]. However, *Gcm2* expression does not appear to specify parathyroid cell fate or define the parathyroid domain during initial organogenesis. In the absence of *Gcm2*, the parathyroid domain appears to be specified at E10.5. This domain then undergoes rapid and coordinated apoptosis at about E11.5–12 [13]. Thus, other transcription factors and signaling pathways must specify parathyroid fate. While several candidates have been identified, the transcriptional network that specifies cell fate, and directly or indirectly upregulates *Gcm2* expression, has still not been clearly articulated.

A suite of genes including *Hoxa3*, *Pax1*,*9*, *Eya1*, and *Six1* have been proposed to constitute a *Hox-Pax-Eya-Six network* that controls early pouch patterning and organogenesis [4]. While single and double mutants for these genes generally result

in parathyroid agenesis or severe hypoplasia, the exact structure of such a network and whether these genes act individually or in concert to affect parathyroid fate specification are less clear. The first to be identified was *Hoxa3* [14]. Null mutants are *aparathyroid* and *athymic*, and due in part to the classical role of HOX proteins in specifying regional identity, the prevailing model has been that *Hoxa3* specifies third pp identity and patterning [15]. However, recent evidence has demonstrated that in *Hoxa3* mutants, *Gcm2* is expressed in its normal domain, but at very low levels indicating that *Hoxa3* upregulates *Gcm2* but is not required to specify parathyroid fate [16, 17]. Whether this regulation is direct or indirect is unknown; however, evidence from *Hoxa3* +/− *Pax1* −/− mutants suggests that *Hoxa3* may work with the paired box transcription factor PAX1. *Pax1* single mutants have normal initial *Gcm2* expression, but do not maintain it, resulting in significant parathyroid hypoplasia [18]; this phenotype is exacerbated in *Hoxa3* +/− *Pax1* −/− compound mutants.

Eya1 and *Six1* [4] have also been shown to be required for *Gcm2* expression, and mutants result in loss through apoptosis. As loss of *Gcm2* itself is sufficient to cause apoptosis, it is possible that the effects of all of these genes, either individually or as a pathway or network, are mediated by their effect (direct or indirect) on *Gcm2* expression. The two best candidates for transcriptional regulators that specify parathyroid fate are TBX1 and GATA3, both of which are expressed in the parathyroid domain in the third pp and have been implicated in regulating *Gcm2*. *Tbx1* expression is correlated spatially and temporally with *Gcm2*, and its expression in the third pp is unaffected in *Gcm2* null mutant mice [13], indicating that it acts upstream of, or in parallel to, *Gcm2*. However, recent work has shown that ectopic expression of *Tbx1* in the third pp outside the parathyroid domain is not sufficient to induce *Gcm2* expression [19], and *Tbx1* null mutants do not form the caudal pouches at all [20]. Thus, it is unclear whether TBX1 plays any specific role in parathyroid specification or organogenesis and, if so, whether it regulates *Gcm2* expression directly or indirectly. In contrast, GATA3 has been shown to directly bind to the *Gcm2* promoter region and upregulate its expression, and *Gcm2* levels are reduced even in heterozygotes [21]. Whether GATA3 plays a role in organ fate specification is less clear. *Gata3* +/− heterozygotes have fewer *Gcm2-expressing* cells, suggesting that GATA3 could affect cell fate [21]. However, this possibility has not been directly investigated.

The final candidate gene identified so far is *Sox3*. Human mutations in *Sox3* are associated with hypoparathyroidism, and *Sox3* is expressed in the third pharyngeal pouch (pp) and developing parathyroids in mice [22]. However, no direct connection has so far been made between *Sox3* and *Gcm2* expression and other aspects of parathyroid organogenesis, so its specific role is still unknown. Thus, while all of these transcription factors have been shown to affect organogenesis and patterning, the identity of the direct targets for these transcription factors and clear evidence for a role in specifying parathyroid cell fate, as opposed to promoting *Gcm2* expression, are lacking.

2.1.2.2 Signaling Pathways

While transcriptional regulators generally act cell autonomously, signaling pathways can act either within or between tissues to influence cell fate and/or differentiation. Thus, signals that specify parathyroid fate could be expressed either within

the endoderm or in the adjacent NCC mesenchyme, and there is evidence for both. Three signaling pathways, sonic hedgehog (SHH), bone morphogenetic protein 4 (BMP4), and fibroblast growth factor-8/10 (FGF8/10), have been implicated as positive or negative regulators of parathyroid fate in the third pp in mice. All of them are expressed within the endoderm. However, data from *Splotch* mutant mice, which have a deficiency in NCCs, have shown that the size of the parathyroid domain within the pouch is in part determined by signals from the surrounding NCCs [23]. Thus, signals coming from either or both cell types during patterning could influence the location and size of the parathyroid domain within the endoderm.

1. The earliest identified signaling pathway to influence parathyroid fate within the pouch endoderm is *sonic hedgehog* (SHH). The *Shh* null mutant mice fail to establish a prospective parathyroid domain or express *Gcm2*, and thymus fate spreads to encompass the entire pouch [24]. However, there are conflicting data on whether SHH is acting directly within the endoderm or indirectly (either from adjacent endoderm or through an NCC-mediated mechanism) to establish parathyroid fate [24, 25]. Intriguingly, *Tbx1* is known to act downstream of SHH signaling in heart development [26], raising the possibility that SHH acts in part through inducing *Tbx1* in this case as well. However, gain-of-function studies indicate that this pathway is not sufficient to turn on *Gcm2* outside the normal parathyroid domain [19]. These data indicate that either other SHH targets, or additional signals or pathways, may be required to fully induce the parathyroid pathway.
2. The *fibroblast growth factor* (FGF) signaling pathway has also been implicated in suppressing parathyroid fate and/or differentiation. The main *Fgf* gene implicated in third pp patterning and development in mice is *Fgf8*, but as *Fgf8* null mutants fail to form the caudal pouches, loss-of-function approaches are limited. However, members of the sprouty (*Spry*) class of FGF inhibitors are expressed in the third pp in mice, and mutations in these genes cause enhanced and ectopic FGF signaling throughout the pouch at E10.5 and later [7]. In *Spry1,2* double mutants, parathyroid size is reduced, and *Gcm2* expression is delayed, indicating that excessive FGF signaling can suppress parathyroid specification and differentiation. This effect was suppressed by reducing the dosage of *Fgf8*, which is normally expressed in the ventral endoderm and off by E11.5. However, FGF10 is also expressed in the NCC mesenchyme adjacent to the dorsal domain, so some of the effect of FGF signaling on the parathyroid domain may come from FGF10. These results suggest that the effects of FGF signaling on parathyroid organogenesis may occur quite early and both from within the endoderm and from the NCC mesenchyme, to restrict parathyroid fate to the most dorsal domain of the pouch.
3. The last signaling pathway that has been implicated in parathyroid fate specification is the *BMP pathway*, specifically BMP4. The role of BMP4 is less clear, as there is evidence for both a positive and a negative role. Like *Fgf8*, *Bmp4* expression is not expressed in the parathyroid domain but is restricted to the ventral thymus domain. In the SHH null, *Bmp4* expansion throughout the third pp is coincident with loss of the parathyroid domain and expansion of thymus fate.

Furthermore, the expression of the BMP inhibitor Noggin in the NCC mesenchyme surrounding the dorsal parathyroid domain suggests that suppressing BMP signaling is important for parathyroid fate or differentiation. Taken together, these data have been interpreted to indicate an SHH–BMP mutual antagonism in establishing parathyroid and thymus cell fate in the third pp [5]. However, evidence from chick showed that inhibition of BMP signaling (via ectopic Noggin) suppressed *Gcm2* expression, at least at early stages of pouch development, suggesting that BMP signaling is at least transiently a positive regulator of *Gcm2* expression and parathyroid differentiation in this system. The role of BMP signaling in parathyroid fate specification and/or differentiation, and whether there are species-specific differences in this process, requires further investigation.

2.1.3 Differentiation and Survival of Parathyroids: *Gcm2*

Once the parathyroid domain is established, upregulation of *Gcm2* expression is necessary and sufficient for parathyroid differentiation and survival. GCM2 is also known to be important in human PTG development, as both dominant negative [27] and loss-of-function [28] GCM2 alleles are associated with hypoparathyroidism in humans. In the *Gcm2* null mutant mouse, the parathyroid domain is specified, as evidenced by normal expression of the parathyroid-associated genes *Tbx1*, *Ccl21*, and *Casr* (calcium-sensing receptor) in the dorsal domain at E10.5 and failure of the thymus domain to expand into this region [13]. However, these cells fail to upregulate parathyroid hormone (PTH) at E11.5 and undergo coordinated apoptosis soon after, by E12.5. GCM2 also works with the transcription factor "musculo-aponeurotic fibrosarcoma B" (MAFB) to upregulate *Pth* gene expression [29]. *MafB* mutation also affects parathyroid separation from the thymus and may itself be regulated by GCM2.

Thus, upregulation of *Gcm2* is a critical step in early PTG differentiation and survival. *Gcm2* continues to be expressed in parathyroids after the early stages of differentiation, and the loss of parathyroids after downregulation of *Gcm2* expression in *Hoxa3* and *Pax1* mutants suggests that it may still be required for PTG survival at least during fetal development. However, in the absence of conditional deletion of *Gcm2* at later stages, it is not clear if it is required for parathyroid maintenance once they are established.

2.2 Thymus–Parathyroid Connection

2.2.1 Do the Thymus and Parathyroids Have Overlapping Functions?

The primary functions of the thymus and PTGs are quite distinct, with the thymus playing a critical role in producing T-cells and PTGs controlling calcium physiology through the production of parathyroid hormone (PTH). However, the physical connection between the two during early organogenesis has led to reports that these

organs may indeed have overlapping functions. The original report of the *Gcm2* null mutant phenotype received attention because it was the first gene to specifically be required only for PTG organogenesis, and because of the conclusion that the thymus could act as a secondary source of PTH [12]. This conclusion was based on survival of a significant proportion of *Gcm2* null mutants, even in the absence of PTGs, their report of low levels of serum PTH in the absence of PTGs, and on the observation that removing the thyroid and parathyroids together from wild-type mice did not cause death, while removing the thymus as well caused rapid death (presumably due to lack of PTH).

As the PTGs had been thought to be the sole source of physiological PTH, this was considered a significant finding with potential implications for human health [30]. A more recent study reported the ability to generate and isolate parathyroid-like cells from thymic epithelial cells, as an initial effort to produce parathyroid cells for transplant [31]. However, Liu et al. (2010) [2] showed that this conclusion was *not* entirely accurate. Instead, the PTH thought to be produced by the thymus was produced by *authentic parathyroid cells* that remain attached to the thymus during the process of thymus–parathyroid separation in normal organogenesis. These "ectopic" thymus-associated parathyroid cells are the likely source of PTH in the original *Gcm2* null paper and also call into question the identity of the parathyroid cells that were thought to have been generated from thymus cells in the 2011 study, as these could have been parathyroid cells already present in the thymus [31].

While the thymus does not have true parathyroid-like function, the parathyroid domain during initial organogenesis does have a transient thymus-related function. At E11.5, prior to the separation of the two organs, the parathyroid domain expresses *Ccl21*, a chemokine that contributes to initial immigration of lymphoid progenitors to the thymus, which is important in early thymus organogenesis [32, 33]. Therefore, while the thymus does not appear to have any parathyroid function, the parathyroid domain helps recruit lymphoid cells to the thymus, at least during initial organogenesis.

2.3 Stability of Parathyroid Fate

The presence of small clusters of parathyroid cells throughout the neck in both mice and humans, as a consequence of normal development, also has another unusual consequence. In about half of mice and in a substantial percentage of humans, these remnants of the organ separation process can downregulate the parathyroid program and transdifferentiate in a thymus fate, forming small cervical thymi [34, 35].

In addition, Li et al. (2013) [36] have recently shown that about 25% of these cervical thymi have previously differentiated as parathyroid, including prior expression of PTH. These parathyroid-derived cervical thymi (pCT) generate T-cells with a specific functional phenotype that could have implications for the function of the immune system in individuals with pCT [36]. While the mechanisms by which this cell fate switch occurs are unknown, parathyroid fate appears to stabilize at about

the *newborn* stage, after which the frequency of cervical thymi remains constant. This "window of opportunity" for parathyroid cells to downregulate the parathyroid program and transdifferentiate to a thymus fate suggests that there is an underlying instability in parathyroid fate during a specific temporal window during the late fetal stage.

Understanding how cell fate is stabilized is important to therapeutic stem-cell-based interventions in general and to the generation of parathyroid cells for transplant in particular. Parathyroid cells are excellent targets for generation of differentiated cells for transplant from embryonic stem (ES) or induced pluripotent stem (iPS) cells.

2.4 Parathyroid Hormone and Related Protein

2.4.1 Parathyroid Hormone (PTH)

Parathyroid hormone (PTH; also known as parathormone or parathyrin) is a polypeptide (84 amino acids) hormone, which increases the concentration of calcium ions in blood. Its actions oppose the hormone *calcitonin* from the thyroid gland parafollicular cells (C-cells), which decrease calcium. It acts through the PTH receptor in bone, kidney, and gastrointestinal tract (GIT). It stimulates osteoclasts (degrades bone matrix, releasing calcium) and increases calcium GIT tract absorption.

2.4.2 Parathyroid Hormone-Related Protein (PTHrP)

Parathyroid hormone-related protein (PTHrP) was originally identified in the clinical syndrome "humoral hypercalcemia of malignancy." Its developmental role is that of a regulatory protein expressed during the formation of many organs such as mammary gland development (epithelial–mesenchymal interactions) [37] and chondrocyte differentiation [38].

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Surgical Anatomy of the Parathyroid Glands

3

3.1 Overview

The parathyroid glands (PTGs) are four nodular structures, two on each side, typically located on the posterior aspect of the thyroid gland, but separated from the latter by a fibrous capsule. They vary considerably in *shape* and *size* between individuals and within the same individual. Usually, they are ovoid or *bean-shaped* (measuring 2 × 4 × 6 mm), but may be elongated, leaf-like, or multi-lobulated. Their diameter is variable, although it should not be larger than 7 mm, and their individual *weight* ranges from 20 to 45 mg with an average of 30 mg. The inferior PTGs are usually larger than the superior glands [1].

These four glands produce parathyroid hormone (PTH), which helps to maintain calcium homeostasis by acting on the renal tubules and calcium stores in the skeletal system, as well as by acting indirectly on the gastrointestinal tract (GIT) through the activation of vitamin D. Because of their small size, their delicate blood supply, and their usual anatomical position adjacent to the thyroid gland, these glands are at risk of being accidentally removed, traumatized, or devascularized during thyroidectomy leading to post-thyroidectomy hypoparathyroidism and causing hypocalcemia.

3.2 Recognizing Parathyroid Glands and their Number

3.2.1 Recognizing the Parathyroid Glands (PTGs)

The PTGs have a distinct, encapsulated, smooth *surface* that differs from the thyroid gland, which has a more lobular surface, and from lymph nodes (LNs), which are more pitted in appearance.

The PTGs can be recognized by the following: (1) their *color* (light brown to tan), which relates to their fat content, vascularity, and percentage of oxyphil cells

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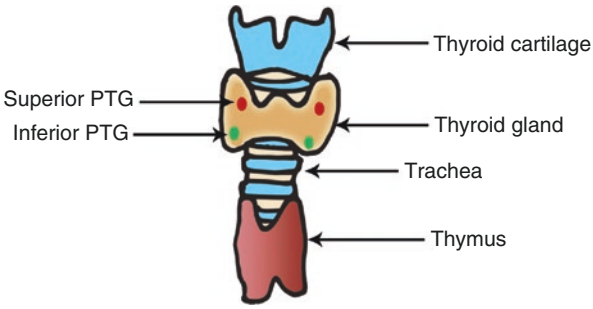

Fig. 3.1 Usual number (four glands, two on each side) and location of the parathyroid glands. PTG, parathyroid gland

within the glands, (2) their distinct *hilar vessel* (small vascular pedicle) that can be seen if the surrounding fat does not obscure the gland's hilum, and (3) the fact that they *bleed freely* when biopsy is performed, as opposed to the yellow fatty tissue, with their darkening color of hematoma formation when they are traumatized.

With experience, the surgeon becomes much more capable of recognizing the PTGs intra-operatively, and of differentiating them from either lymph nodes or adipose tissue. *Frozen-section* examination during surgery can be helpful in their identification [2].

3.2.2 Number of Parathyroid Glands

Most patients have four parathyroids, two on each side (Fig. 3.1), but it is possible to have more or less than four glands.

3.2.2.1 Anomalies of PTG Number

The parathyroid domain shows a relatively high tendency to fragment, leaving small parathyroid clusters either attached to or trailing the thymus into the mediastinum (Fig. 3.2). It is thought that the generation of these microscopic parathyroid clusters is the source of *supernumerary glands* or *accessory parathyroid tissue*. Supernumerary parathyroid glands can occur in up to 15% of population, and as many as 11 glands have been reported. In two-thirds of cases, a fifth gland is inferior to the lower pole of the thyroid gland, while the remaining third of supernumerary glands are typically adjacent to the thyroid between the orthotopic superior and inferior parathyroids.

On some occasions (5%), less than four PTGs can be present; even *complete absence* of PTGs is possible as in case of the genetic abnormalities in some genes encoding for transcription factors required for the parathyroid tissue development (e.g., *Gcm2* gene), or in DiGeorge syndrome.

Another variant may occur due to fusion of both glands during their descent, giving the appearance of "bi-lobed gland" with the final position of "fused glands" usually close to the inferior thyroid artery (ITA [Fig. 3.3]) [3–5].

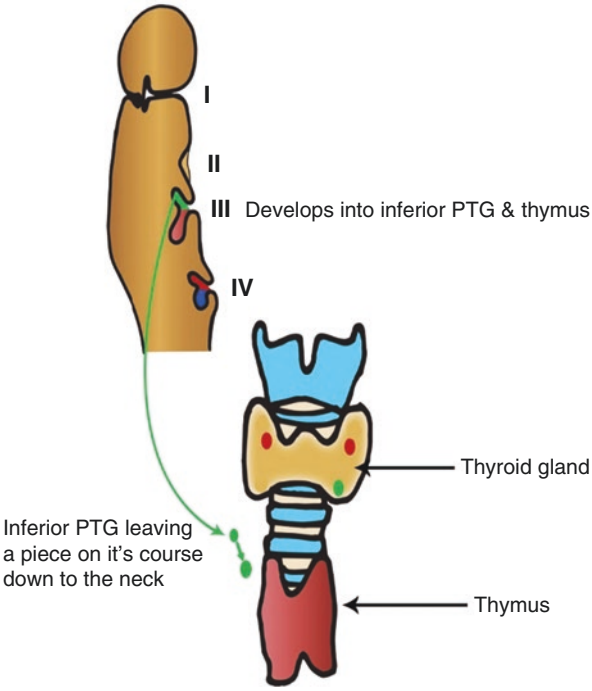

Fig. 3.2 During its descent down into the neck, the inferior parathyroid gland may fragment leaving small parathyroid clusters that are thought to be the origin of supernumerary glands. PTG, parathyroid gland

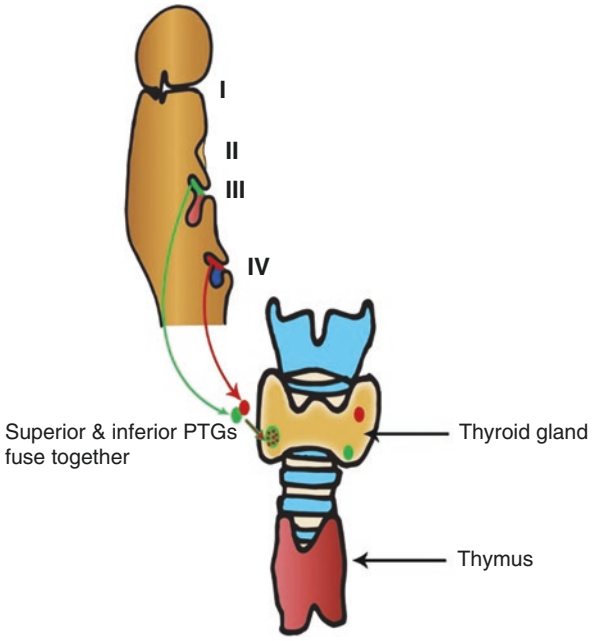

Fig. 3.3 Fusion of the superior and inferior parathyroid glands during their descent, giving the appearance of a bi-lobed gland (its final position is usually close to the inferior thyroid artery). PTG, parathyroid gland

3.3 Location of Parathyroid Glands

As mentioned before, the superior PTGs migrate with the ultimobranchial body, while the inferior glands migrate for a longer distance along with the thymus. It is very important to note that the pathway of descent of the superior and inferior PTGs is variable and therefore the location of PTGs can vary, especially the site of the inferior glands.

3.3.1 Superior Parathyroid Glands

The superior PTGs are derived from the fourth pharyngeal pouch and migrate together with the *ultimobranchial bodies*, which also develop from the same pouch, and, during the fifth week of development, these cells detach from the pharyngeal wall and fuse with the posterior aspect of the main body of the thyroid as it descends into the neck. These cells differentiate into the *parafollicular cells* (C-cells) that secrete *calcitonin* [6]. The superior PTGs migrate a shorter distance than the inferior glands, which results in a relatively more constant location in the neck. Because the superior PTGs travel with the ultimobranchial bodies, they remain in contact with the posterior part of the middle third of the thyroid lobes.

They are most commonly located in the posterolateral aspect of the superior pole (or middle third) of the thyroid gland at the cricothyroid cartilage junction. They are most commonly found 1 cm above the intersection of the inferior thyroid artery (ITA) and the recurrent laryngeal nerve (RLN) in 80% of cases, often just anterior to the RLN as it enters the larynx (Fig. 3.4).

If one considers a coronal plane incorporating the RLN along its trajectory from the mediastinum to the larynx, the superior parathyroid glands are posterior to that plane [7]. Untch et al. (2012) [8] examined the anatomical proximity of parathyroid tumors to the RLN in 136 patients undergoing parathyroidectomy for primary hyperparathyroidism (PHPT) and found that the RLN lies in close at an average of just 0.52 cm from the adenoma. It is closely related to the posterolateral aspect of the superior thyroid pole, often resting on the thyroid capsule. However, it can be in a more caudal position and can sometimes be partially obscured by the RLN, inferior thyroid artery, or tubercle of Zuckerkandl.

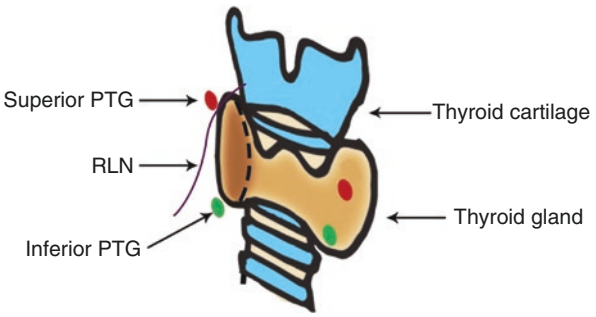

Fig. 3.4 Location of the superior PTG in relation to superior pole of thyroid gland and recurrent laryngeal nerve (RLN) and relation of the inferior PTG to lower pole of the thyroid gland. PTG, parathyroid gland

3.3.2 Inferior Parathyroid Glands

The *inferior* PTGs arise from the *dorsal* part of the *third* pharyngeal pouch, along with the thymus, which arises from the *ventral* part of the *third* pharyngeal pouch. As the inferior PTGs and the thymus migrate together toward the mediastinum, they eventually separate. Because they travel so far in embryologic life, the inferior PTGs have a more variable location than the superior PTGs. In most cases, the inferior PTGs become typically located within 1–2 cm inferior, lateral, or posterior to the inferior pole of the thyroid, often on the posterolateral aspect of the thyroid capsule (Fig. 3.3), while the thymus continues to migrate toward the mediastinum [9]. The inferior PTG is often closely associated with the thickened fat of the thyrothymic ligament and is generally located ventral to the RLN.

The wide range of distribution of the inferior PTGs in adults extends from just beneath the mandible to the anterior mediastinum. They may be found above, or within several centimeters of the lower thyroid pole within the thymic tongue [9].

3.3.3 Variations in Location/Ectopic Glands

Migration patterns during embryogenesis may cause the PTGs to exhibit a variation in location. However, there are particular characteristics of migration observed that can help to identify the superior and inferior PTGs. The position of the PTGs relative to the RLN is very important to differentiate upper from lower glands, as in some cases the cranio-caudal distance may be small [10]. If a coronal plane is made in the path of the RLN in the neck, then the *superior* PTGs will be located *dorsally*, or deeper in the neck, and the *inferior* PTGs will be more *ventral*, or anterior to this plane.

3.3.3.1 Superior PTG Variations

The superior PTG migration path is shorter, and their anatomical location is more constant than the inferior PTGs. Ectopic locations may result from descent failure or laterally directed descent. They may reside further inferior at a considerable distance in the *tracheo-esophageal groove* or *posterior mediastinum.* They may also lie quite deep in the neck toward a *retro-laryngeal*, *retro-pharyngeal*, or *retro-esophageal* location. In about 2–3% of cases, the superior PTG may be found at or above the level of the *upper pole of the thyroid*. Rarely, they can be located within the thyroid gland (*intra-thyroidal*) being completely surrounded by thyroid tissue [11–14]. Such location may result from abnormal migration pattern whereby the superior PTGs can join the ultimobranchial body as it fuses with the median thyroid anlage [15].

In addition to ectopic location from embryological development variability, acquired ectopic localization can occur from pathological gland enlargement. Enlarged glands can migrate by the effect of gravity and movements of the larynx and pharynx during swallowing. This is more common in the superior PTGs than the inferior glands, which are less prone to this acquired migration because of anatomic constraints that theoretically prevent this gravity-induced displacement [15].

3.3.3.2 Inferior PTG Variations

The long descent path of the inferior PTGs with the thymus from the neck into the anterior mediastinum is responsible for their highly variable location, which may be anywhere from the *hyoid bone* down to the *mediastinum*. Approximately, 60% of inferior PTGs are found inferior, lateral, or posterior to the lower pole of the thyroid gland [7]. Failure of an inferior gland to descend with the thymus may result in its location near to the *carotid bifurcation*. Such ectopic location has been observed in 2% of necks in an anatomical study.

The inferior PTGs may be also found in the *anterior/superior mediastinum*, on top or within the thymic remnants. It may also be found in the *thyrothymic tract* [16]. In 0.7–3.6% of cases, an inferior PTG may be *intra-thyroidal* [17].

3.3.3.3 Supernumerary PTG Location

The supernumerary PTGs are usually found at the level of the *lower poles of the thyroid* or in the *thymus*. They can also be found in the *middle mediastinum* at the level of the aorto-pulmonary window, or lateral to the jugulo-carotid axis [18].

3.3.4 Surgical Implications of Variations in Number and Location

The occasional numerical variation of PTGs must be considered by surgeons performing parathyroid explorations. A cervical thymectomy should also be considered when multiple abnormal glands are seen, as supernumerary glands are often found within the thymus. A missed hyper-functioning supernumerary gland may result in persistent primary hyperparathyroidism (PHPT). "Fused glands" may be mistaken for a single bi-lobed gland, which would give a false impression of an unidentified gland during neck exploration. This misinterpretation can be avoided by close inspection of the blood supply to the parathyroid. Each gland will have its own blood supply so even an enlarged single gland has a single vascular pedicle, while a bi-lobed gland has two separate vascular pedicles [4, 5, 15].

The relationship with the RLN is important to consider particularly when a parathyroid adenoma is approached through minimal access, which is the gold standard of management of a single-gland disease nowadays. With limited exposure of surrounding anatomical landmarks, the operating surgeon needs to anticipate if the RLN will be in front of the adenoma (as for superior PTGs), or posterior to the adenoma (as for inferior PTGs). A parathyroid surgeon must be also aware of and familiar with ectopic parathyroid locations; exploration of the superior mediastinum should be considered if inferior glands cannot be identified within the neck. A hemi-thyroidectomy or thoracic surgical approach may be indicated in the surgical management of PHPT if the hyper-functioning parathyroid tissue has been proven to be intra-thyroidal or intra-thoracic, respectively [4, 5, 15].

3.4 Vascular Supply and Innervation

3.4.1 Arterial Supply

Arterial blood to the PTGs is derived via branches of the inferior thyroid artery (ITA) and/or superior thyroid artery (STA). It may also arise via branches from other arteries in their area including the laryngeal, tracheal, and/or esophageal arteries. *The superior PTG* is usually supplied by the ITA or by an anastomotic branch between the ITA and STA. Several studies have indicated that in 20–45% of cases, the superior PTGs receive significant vascularity from the STA, usually in the form of a small parathyroid artery from the posterior branch of the STA, given off at the level of the superior pole of the thyroid gland [19–21].

The inferior PTGs are supplied by the ITA from the thyrocervical trunk. Thus, it is preferable that during thyroidectomy, the secondary and tertiary branches of the ITA (not the main trunk) are ligated under vision in order to preserve not only the RLN, but also the blood supply to the parathyroids. Studies have shown that in approximately 10% of patients, the ITA is absent, most commonly on the left side. In these cases, a branch from the *superior thyroid artery* (STA) supplies the inferior PTG [22]. Inferior PTGs that descend into the anterior mediastinum are usually vascularized by the ITA. If a parathyroid gland is positioned low in the mediastinum, it may be supplied by a *thymic branch* of the *internal thoracic (mammary) artery* or even a direct branch of the *aortic arch* [12].

3.4.2 Venous Drainage

Through parathyroid veins, the inferior, middle, and superior thyroid veins drain the parathyroid glands. The superior and middle thyroid veins drain into the internal jugular vein (IJV), and the inferior thyroid vein drains into the brachiocephalic (innominate) vein [1].

3.4.3 Lymphatic Drainage

Lymphatic drainage of the PTGs is similar to that of the thyroid gland, with lymph vessels draining into the deep cervical and para-tracheal lymph nodes [23].

3.4.4 Innervation

The nerve supply of the PTGs is either direct from the superior or middle cervical sympathetic ganglia, or via a plexus in the fascia on the posterior lobar aspects [24]. The nerve supply controls the blood supply to the gland (vasomotor) rather than hormone secretion (secretomotor). Endocrine secretion of PTH is under hormonal control.

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Histology of the Parathyroid Glands

4

4.1 Gross Appearance

The normal *size* and *weight* of a parathyroid gland (PTG) vary according to anatomical site, gender, and age. It is about 4–6 mm in length, 2–4 mm in width, and 1–2 mm in thickness, with the overall weight of around 20–45 mg. Its *color* also varies from yellow to tan determined by its difference in components of stromal fat, oxyphil cells, and vascularity. Its *shape* also varies from ovoid, bean-shaped, elongated, bi-lobed, or multi-lobed. Gross appearance is not diagnostic; there is significant overlapping appearance with a lymph node or a fragment of thyroid tissue. The gold standard for differentiation between normal and abnormal glands is the gross appearance to an experienced surgeon.

4.2 Microscopic Appearance

Histologically, the parathyroid gland is formed of a small package of parenchyma, dotted with adipocytes (fat cells) as shown in Fig. 4.1, and entwined with a complex vascular network and lined with a capsule (stroma) as shown in Fig. 4.2.

4.2.1 Stroma (Capsule and Trabeculae)

The entire parathyroid gland is encased by a thin fibrous connective tissue capsule (Fig. 4.2). This capsule also separates the PTG from the thyroid gland. Trabeculae (connective tissue) extend inward from the capsule to partially outline irregular lobes and lobules of the parathyroid gland [1].

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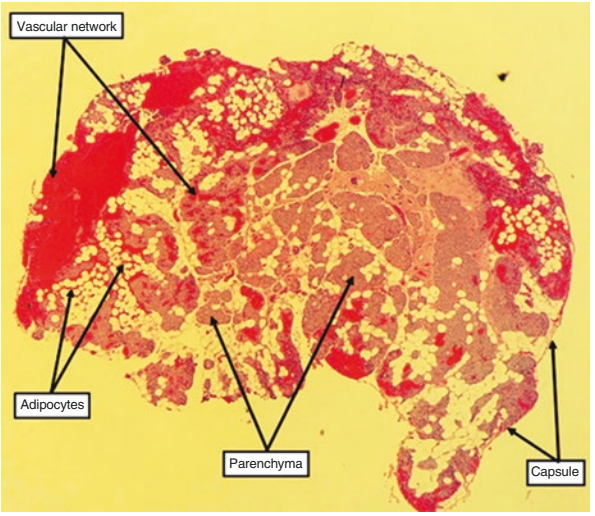

Fig. 4.1 A low-power Hematoxylin and Eosin (H&E) of the parathyroid gland (PTG) showing the vascular network and adipocytes (fat cells)

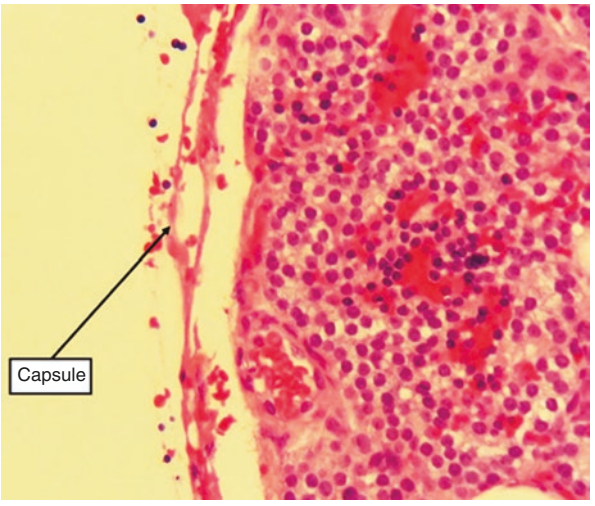

Fig. 4.2 A medium-power H&E showing the thin fibrous capsule of the parathyroid gland (PTG)

4.2.2 Parenchyma

Within the PTGs there are *two main glandular components*: parenchymal cells and fat cells. The proportions of these two types of cells vary with age; in young people, there are only a few sparse fat cells, which increase gradually and about the age of 30 years fat cells constitute 10–25% of the glandular cells. After this age, the proportion of fat cells remains relatively constant as the ratio of parenchyma to fat cells stabilizes at around 50:50 [1].

On a medium power, the parenchymal cells arrange themselves in either a follicular or a cord-like pattern (Fig. 4.3).

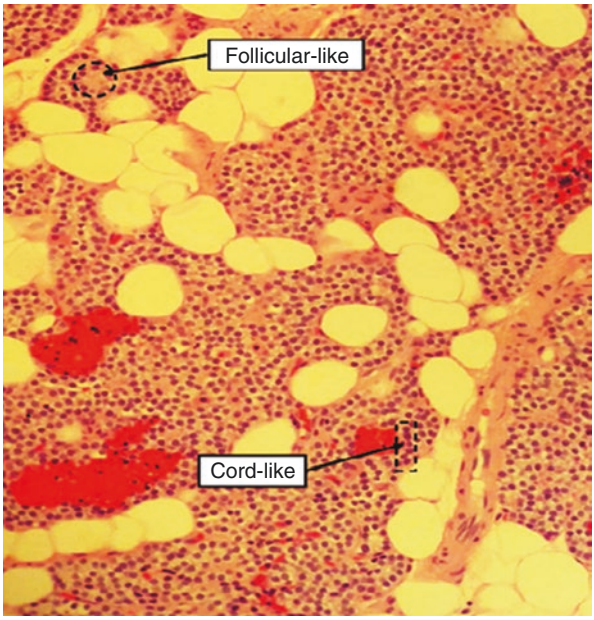

Fig. 4.3 Medium-power H&E of the parathyroid gland showing follicular-like and cord-like parenchymal cell arrangement

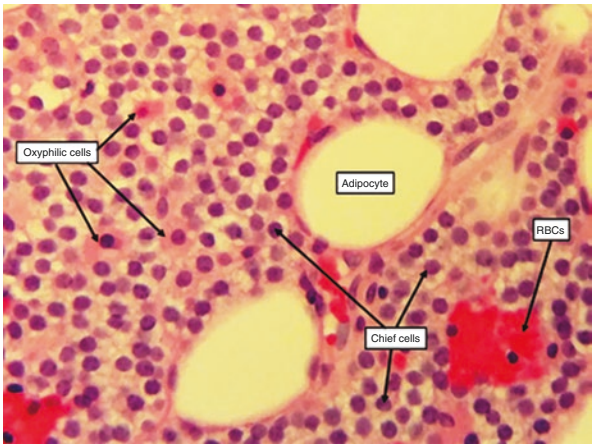

Fig. 4.4 High-power H&E showing distinct cell types (mainly chief and oxyphil cells) seen in the parathyroid gland parenchyma

With a high-power Hematoxylin and Eosin (H&E), the *parenchymal cells* are seen to be made up of two main cell types: the "chief cells" and "oxyphilic cells" (Fig. 4.4).

4.2.2.1 Chief Cells

Chief cells are the most abundant; they are more prevalent than oxyphil cells. They have a small size (5–8 μm in diameter) with dark nuclei and thin rim of lightly stained cytoplasm. Their nuclei are rounded and contain a lot of nuclear chromatin, so appear very dense. Their cytoplasm is rich in lipid droplets, glycogen particles,

free ribosomes, and rough endoplasmic reticulum, in addition to secretory granules. The cytoplasm can either appear clear or slightly eosinophilic (pink) with intracellular lipid.

Chief cells are the *functional* cells of the PTG that produce parathyroid hormone (PTH), which is stored in the cytoplasmic secretory granules. They also have calcium ion-sensing receptors (CaSRs) on their cell membrane that become stimulated in low serum levels of calcium. Receptor activation cascades a message to the cell to control parathyroid function through influence on hormone synthesis, hormone section, and parathyroid cellular proliferation PTH [2].

4.2.2.2 Oxyphil Cells

Oxyphilic cells are fewer in number, but larger in size (8–12 μm in diameter) and much more eosinophilic than the chief cells and, due to the high number of mitochondria within them, have a very grainy-looking cytoplasm. Avidity of the glands in Sestamibi (MIBI) scans is related to the uptake of the isotope by mitochondria of these cells. They are usually only found in adults, appearing at the onset of puberty [3]. Very little is known about the function of these cells, but one theory is that they may be able to produce PTH representing *transitional chief cells* (variant of oxyphilic cell) [4]. With age, however, oxyphil cells often increase in number and begin to form small nodular clusters (Fig. 4.5).

4.2.2.3 Water-Clear Cells

The other parenchymal cells are "water-clear cells" with unknown recognized function, as they are fundamentally inactive [1]. These cells are rarely seen in human PTGs. They are larger in size (8–12 μm in diameter) than chief cells; they have dark nuclei and a watery-clear cytoplasm. Their appearance as "water-clear" is attributed to abundant empty membrane bound vacuoles filling the cytoplasm. It is noteworthy that their presence is usually associated with parathyroid hyperplasia or parathyroid adenoma.

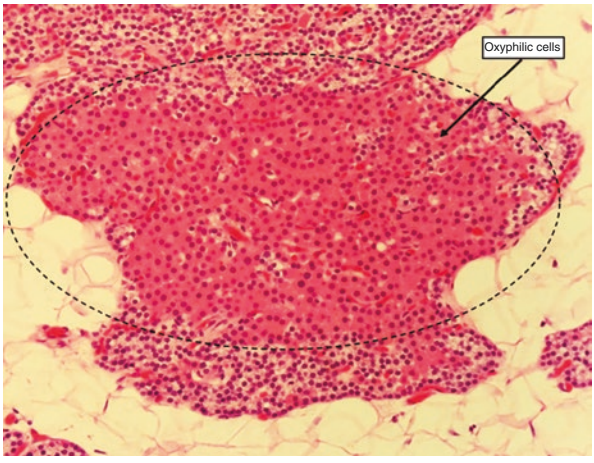

Fig. 4.5 Low-power H&E showing nodular arrangement of oxyphil cells that can occur in the PTG (dotted area)

Table 4.1 Characteristic features of PTG parenchymal cells

Cells	Description
Chief cells	– 6–8 μm, polygonal, central round nuclei; contain granules of PTH
	– Basic cell type; other cell types are due to differences in physiologic activity
	– 80% of chief cells have intra-cellular fat
	– Chief cell is most sensitive to changes in ionized calcium
Oxyphil cells	– Slightly larger than chief cell (8–12 μm); acidophilic cytoplasm due to mitochondria
	– No secretory granules
	– First appear at puberty as single cells, then pairs, then nodules at the age of 40 years
Water-clear cells	– Abundant optically clear cytoplasm and sharply defined cell membranes
	– Chief cells with excessive glycogen

4.2.2.4 Other Cells

Adipose or *fat cells* are also present within the PTG. They increase in number with age. *Vascular* and *nervous cells* are also seen in the parathyroid tissue.

The main characteristics of the parenchymal cells of the PTG are summarized in Table 4.1 below.

4.3 Immunohistochemical (IHC) Features

Normal parathyroid glands stain positive for PTH, neuroendocrine marker such as chromogranin-A and synaptophysin, and keratins; however, none of these markers is entirely specific to parathyroid tissue. Chromogranin-A is a specific neuroendocrine marker that typically stains chief cells more intensely than oxyphil and other cells. Keratin 14 can be used to help in identification of oxyphil adenomas.

Parathyroid tissues and tumors can be differentiated from those of the adjacent thyroid by staining negative for thyroglobulin (Tg) and positive for glial cells missing 2(GCM2), which is a transcription factor associated with embryonic development of parathyroid glands.

Parafibromin and Ki-67 are immunohistochemical markers that can be used to help differentiate between benign and malignant parathyroid tumors. A Ki-67 proliferation index of more than 5% and complete loss of parafibromin expression are strongly associated with parathyroid carcinoma [5].

4.4 Electron Microscopy

The parathyroid gland's composition is primarily chief cells, rich in mitochondria and connected by desmosomes. The plasma membranes of adjacent gland cells show inter-cellular digitations at localized regions. When these cells are "active," many dense, irregularly shaped secretory granules are visible within the cytoplasm

on electron microscopy. A large Golgi complex and numerous free ribosomes are also present in the active cell [6]. When chief cells are "inactive" (resting), the Golgi complex appears smaller, and glycogen accumulations are visible along with lipid bodies within the granular cytoplasm.

Cilia are observed occasionally, either in the inactive chief cells or in the intermediate chief cells (seen in the fetus). They arise in or near the Golgi area and protrude into the inter-cellular space between the adjacent plasma membranes. Between the parenchymal cell strands, there is loose interstitial connective tissue, which contains rich capillaries, unmyelinated nerve fibers, small amount of collagen fibrils, and a few connective tissue cells [7]. The capillary endothelium has relatively thick cytoplasm, as compared to that of the adult PTG as reported by several authors [6, 8, 9]. The endothelium has only a few pores.

Oxyphil cells have a polygonal shape, many mitochondria, and few to no secretory granules within the cytoplasm [6].

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Physiology of the Parathyroid Glands

5

5.1 Basic Biology of Calcium Homeostasis

5.1.1 Plasma Levels of Calcium

Calcium (Ca) and phosphorus (P) are the principal constituents of bone, and together they constitute approximately 65% of its weight. Bone, in turn, contains nearly all of the Ca and P and over half of the magnesium (Mg) in the human body. Although quantitatively minor in amount, each of these ions in the extra-cellular fluid (ECF) and within the cells plays a crucial role in normal physiological processes. In blood, approximately 50% of total calcium is bound to proteins, mainly albumin and globulins. The *ionized calcium* concentration in serum is approximately 5 mg/dL, and it is the fraction that is *biologically active* and tightly controlled by hormonal mechanisms [1].

Extra-cellular calcium is important for the following: (1) excitation–contraction coupling in muscle tissues, (2) synaptic transmission in the nervous system, (3) coagulation, and (4) secretion of other hormones. On the other hand, intra-cellular calcium is an important second messenger regulating the following: (1) cell division, (2) motility, (3) membrane trafficking, and (4) secretion [2].

Normal plasma levels of total Ca vary between laboratories, but the range of total Ca is usually between 8.5 and 10.5 mg/dL [3]. Consequently, ionized Ca levels are measured when required. About 45% of the total Ca exists in the ionized form (biologically active), with a normal level of 4.5–5.0 mg/dL [4]. Ionized Ca levels are inversely affected by the pH of blood; a one-unit rise in pH results in a decrease in the ionized Ca level by 0.36 mmol/L [4].

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5.2 Absorption and Excretion of Calcium and Phosphorus

The usual rates of intake are about 1000 mg/day each for Ca and P, about the amounts in 1 L of milk. Normally, divalent cations such as Ca ions are poorly absorbed from the intestines. However, vitamin D promotes Ca absorption by the intestines, and about 35% (350 mg/day) of the ingested Ca is usually absorbed [5].

Calcium remaining in the intestine is excreted in feces. An additional 250 mg/day of Ca enters the intestines via secreted gastrointestinal juices and sloughed mucosal cells. Thus, about 90% (900 mg/day) of the daily intake of Ca is excreted in the feces (Fig. 5.1) [5].

Nearly, 10% (100 mg/day) of ingested Ca is excreted in the urine. About 40% of the plasma Ca is bound to plasma proteins and is therefore not filtered by the glomerular capillaries. The rest is combined with anions such as P (9%) or ionized (50%) and is filtered through the glomeruli into the renal tubules [5]. Normally, the renal tubules reabsorb 99% of the filtered Ca, and about 100 mg/day is excreted in the urine. Approximately, 90% of the Ca in the glomerular filtrate is reabsorbed in the proximal tubules, loops of Henle, and early distal tubules. Then in the late distal tubules and early collecting ducts, reabsorption of the remaining 10% is very selective, depending on the Ca^{++} concentration in the blood [5].

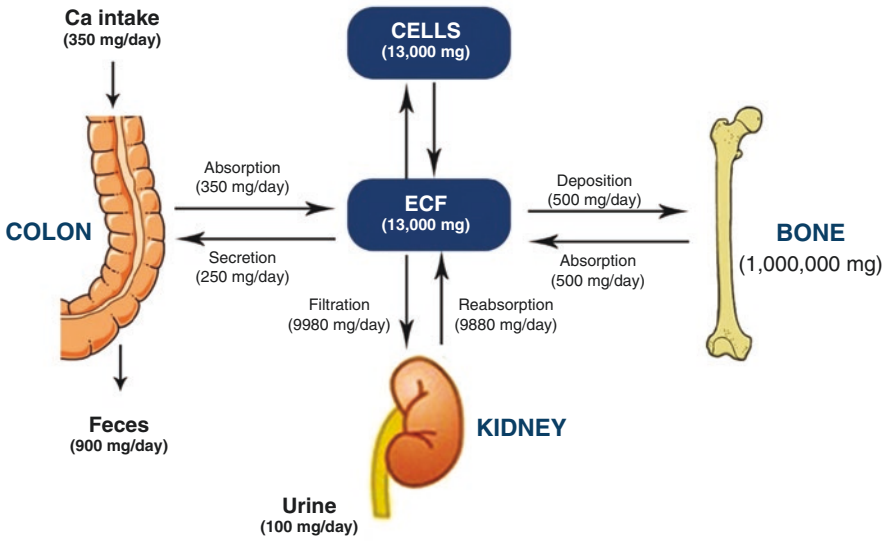

Fig. 5.1 Overview of Ca exchange between different tissue compartments in a person ingesting 1000 mg of Ca/day [5]. Ca, calcium; ECF, extra-cellular fluid

5.3 Key Components of Calcium Homeostasis

Parathyroid glands (PTGs) regulate calcium homeostasis by modulating bone metabolism and absorption of calcium in kidney and intestine. The key components of calcium homoeostasis process include the following:

1. Parathyroid hormone (PTH): Action on bones, gastrointestinal tract (GIT), and kidneys.
2. Vitamin D (active form): 1,25-dihydroxyvitamin-D3 (calcitriol).
3. Calcitonin.

5.3.1 Parathyroid Hormone (PTH)

5.3.1.1 Parathyroid Gland Biology

The PTGs play an essential role in regulating Ca homeostasis via the synthesis and release of PTH, which exerts crucial actions on bones, kidney, and small bowel. When serum calcium levels drop, PTH secretion by the PTG increases. Increased serum calcium level serves as a negative feedback loop signaling the PTGs to reduce PTH release.

Parathyroid *chief cells* have three properties vital to their homeostatic function:

1. They rapidly secrete stored hormone in response to changes in blood calcium.
2. They synthesize, process, and store large amounts of PTH in a regulated manner.
3. They replicate when chronically stimulated.

5.3.1.2 Parathyroid Hormone Biosynthesis

Parathyroid hormone is encoded by a gene in chromosome 11. After translation, PTH is produced by *chief cells* in the form of "*pre-pro-PTH*," which contains 115 amino acids (AAs). In the *endoplasmic reticulum*, 26 AAs are removed, so it is called "*pro-PTH*" (89 AAs). In the *Golgi apparatus*, more AAs are removed by peptidase enzyme, thus forming the *mature PTH* (84 AAs), which is stored in *secretory vesicles* within the cells and is released in blood (after suitable stimulus) when required (Fig. 5.2). When the final entire molecule of PTH (molecular weight 9500, half-life 2–4 min) passes through the liver and kidney, it is cut into N-terminal fragment and C-terminal fragment. The full-length (1–84) molecule and the N-terminal fragment (1–34) possess most of the biological activity [6]. Circulating PTH is metabolized in liver and kidneys and its biological half-life is 5 min.

5.3.1.3 Parathyroid Hormone Function

The main function of PTH is to *keep the blood calcium level stable*: a decrease in blood calcium level, in particular the ionized form, stimulates PTH production and secretion. Parathyroid cells rely on a G-protein-coupled membrane receptor,

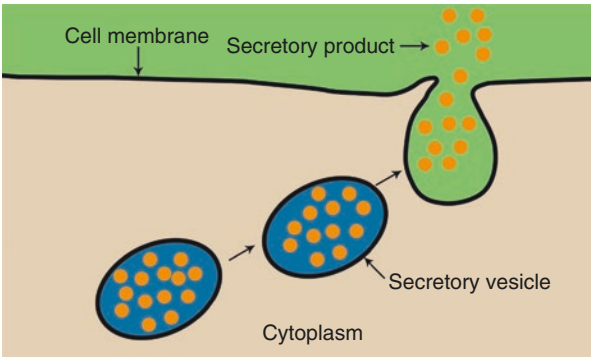

Fig. 5.2 Parathyroid hormone biosynthesis in the chief cell

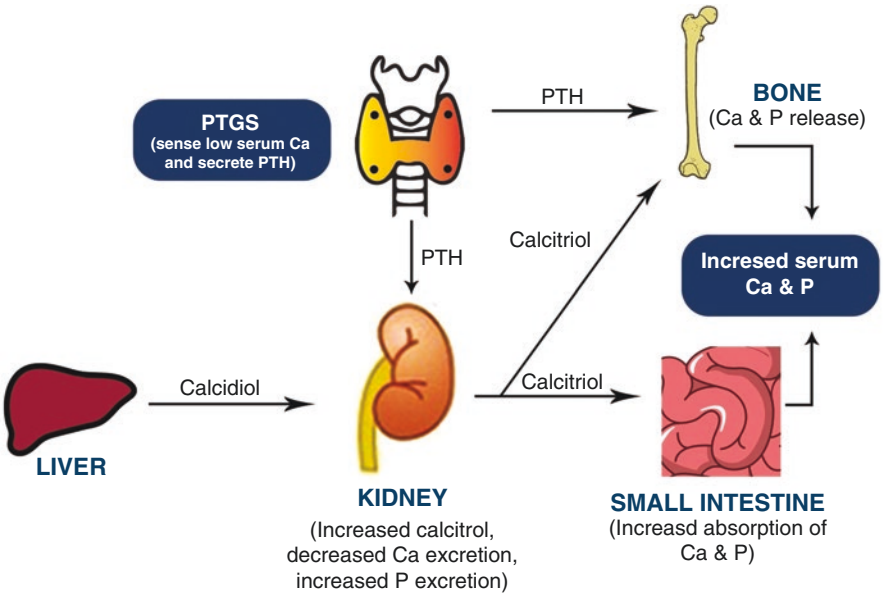

Fig. 5.3 Action of parathyroid hormone (PTH) on target organs: bone, gastrointestinal tract (GIT), and kidneys for homeostasis of calcium (Ca), phosphate (P), and vitamin D. PTGs, parathyroid glands

designated the calcium-sensing receptor (CaSR), to regulate PTH secretion by sensing extra-cellular Ca levels [7]. In the liver, PTH is metabolized (70%) into the active N-terminal component and the relatively inactive C-terminal fraction. The C-terminal component is excreted by the kidneys and accumulates in chronic renal failure [8].

Parathyroid hormone preserves the calcium, phosphate, and vitamin D homeostasis through several main actions on target organs, namely bones, kidneys, and small intestine (Fig. 5.3). The major part of PTH actions on the target organs are mediated by the binding of PTH to a specific PTH type-I receptor and the

stimulation of cyclic adenosine monophosphate (cAMP), a second messenger that, in the case of primary hyperparathyroidism (PHPT), can be found increased at the urinary level. Parathyroid hormone functions, especially so at the intestinal site, are also mediated by active vitamin D (calcitriol), whose formation is stimulated by PTH at the kidney level, again mediated by cAMP. Moreover, vitamin D enhances the skeletal effects of PTH.

Bones

Parathyroid hormone stimulates the release of calcium from bones into blood resulting in bone resorption and increased serum calcium levels. This action is mediated through "osteoclasts," which have the ability to dissolve and degrade hydroxyapatite in the bone matrix. However, such parathyroid hormone effect on osteoclasts is "indirect," since osteoclasts do *not* possess parathyroid hormone receptors. Parathyroid hormone acts on the receptors present on mesenchymal cells of the osteoblast lineage, stimulating their expression of RANKL—Receptor Activator of Nuclear factor Kappa-B Ligand—resulting in increase in their preferential differentiation into osteoclasts, which then function in bone remodeling.

Kidneys

Through its actions on the kidneys, PTH results in increased serum calcium levels. It targets the distal convoluted tubule and collecting duct to stimulate calcium reabsorption. Additionally, it reduces phosphate reabsorption at the proximal convoluted tubule, reducing the availability of phosphate to form insoluble complexes with calcium, resulting in more serum calcium in the ionized form.

Small Intestine

Parathyroid hormone stimulates the synthesis of "1-alpha-hydroxylase" enzyme in the renal proximal convoluted tubule. This enzyme catalyzes the activation of vitamin D by conversion of 25-hydroxy-cholecalciferol to 1,25-dihydroxy-cholecalciferol. Active vitamin D (calcitriol) stimulates calcium absorption in the small intestine through both transcellular (energy dependent) and para-cellular (tight junctions) pathways.

5.3.1.4 Summary of Mechanism of PTH Action

Chief cells in the PTGs secrete PTH, to increase the blood concentration of calcium whenever serum Ca levels fall below normal. First, PTH enhances reabsorption of calcium ions by the kidneys; second, it stimulates osteoclast activity (to increase bone resorption) and inhibits osteoblast activity. Finally, PTH stimulates the synthesis and secretion of calcitriol (active vitamin D) by the kidneys, which enhances calcium (and phosphorus) absorption by the GIT as summarized in Table 5.1 [9].

The recently cloned calcium-sensing receptors (CaSRs) in the parathyroid glands detect changes in Ca levels, which results in a negative feedback loop that decreases PTH production [9]. The PTH acts to limit Ca excretion at the distal convoluted tubule via an active transport mechanism. It also inhibits P reabsorption (at the proximal convoluted tubule) and bicarbonate reabsorption [8].

Table 5.1 Actions of PTH, vitamin D, and calcitonin on target organs

	Bone	Kidney	Intestine
PTH	Stimulates resorption of Ca and P	Stimulates reabsorption of Ca and conversion of 25(OH)-D3 to active vitamin D (calcitriol); inhibits reabsorption of P and bicarbonate	Stimulates Ca and P absorption
Vitamin D	Stimulates Ca transport	Inhibits reabsorption of Ca	Stimulates Ca and P absorption
Calcitonin	Inhibits resorption of Ca and P	Inhibits reabsorption of Ca and P	No direct effects

Ca calcium, *P* phosphorus, *PTH* parathyroid hormone

5.3.2 Vitamin D

Vitamin D3 is formed in the *skin* when a cholesterol precursor is exposed to ultraviolet (UV) light. Activation takes place when the substance undergoes 25-hydroxylation in the *liver* and 1-hydroxylation in the *kidney* [10].

The primary action of 1,25-dihydroxyvitamin-D3 (active vitamin D—calcitriol) is to promote gut absorption of calcium by stimulating formation of Ca-binding protein within the intestinal epithelial cells. Vitamin D also promotes intestinal absorption of *phosphate* ion, although the exact mechanism is still unclear. Negatively charged phosphate ion may passively flow through the intestinal cell because of flux of positively charged calcium ion. In bone, vitamin D may play a synergistic role with parathyroid hormone in stimulating osteoclast proliferation and bone resorption. Compared with parathyroid hormone, vitamin D has a much slower regulatory effect on calcium balance [10].

5.3.3 Calcitonin

Calcitonin, also known as "thyrocalcitonin," is a 32-amino acid linear polypeptide that lowers the levels of serum calcium, counteracting the actions of PTH. It is produced by *para-follicular cells* (also known as C-cells) of the thyroid gland [11].

Mechanism of Action: Receptors for calcitonin are found in bones and the kidneys. Calcitonin inhibits: (1) the activity of osteoclasts in bone, (2) renal reabsorption of calcium (increasing calcium ions in urine), and also (3) absorption of calcium in the intestines. Blood levels of PTH are far more clinically relevant to calcium homeostasis than calcitonin and *no* exogenous replacement for calcitonin is required following thyroidectomy [11].

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Calcium: Why Is It Important?

6

6.1 Introduction

The parathyroid glands (PTGs) are small glands that secrete parathyroid hormone (PTH), which controls serum calcium homeostasis. They develop from the pharyngeal pouches, transient endodermal out-pocketings that also form the thymus and ultimobranchial bodies in vertebrates. The parathyroids vary in number and final location in different vertebrates, including in humans and mice. Usually, four PTGs are present (80%), two on each side (superior and inferior), but three to six glands have also been reported.

Because of their small size, delicate blood supply, and usual anatomical position adjacent to the thyroid gland, these glands are at risk of being accidentally removed, traumatized, or devascularized during thyroidectomy. This results in hypocalcemia because PTH secretion is impaired and cannot mobilize calcium from bone, reabsorb calcium from the distal nephron, and stimulate renal 1α-hydroxylase activity. It usually appears in the first days after surgery and it can be symptomatic or asymptomatic. Risk factors are low level of intra-operative PTH and presence of PTG in the pathological specimen. Patients may present with paresthesia, cramps, tetany, seizures, bronchospasm, laryngospasm, or cardiac rhythm disturbances. *Standard treatment* is calcium supplements and vitamin D analogues.

The PTGs can be recognized intra-operatively by their color (light brown to tan), their small vascular pedicle, and the fact that they bleed freely when biopsy is performed, as opposed to fatty tissue with their darkening color of hematoma formation when they are traumatized. With experience, one becomes much more capable of recognizing the parathyroid glands and of differentiating them from either lymph nodes (LNs) or adipose tissue. Frozen-section examination during surgery can be helpful in their identification [1].

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6.2 Properties of Calcium

Calcium is a chemical element with the symbol "Ca" and atomic number 20 [2]. Some calcium compounds were known to the ancients, though their chemistry was unknown until the seventeenth century. Pure calcium was isolated in 1808 via electrolysis of its oxide by Humphry Davy, who named the element.

Calcium is the most abundant mineral in the human body. About 99% of the calcium in the body is found in bones and teeth, while the other 1% is found in the blood and soft tissue. Calcium concentrations in the blood and extra-cellular fluid (ECF) must be maintained within a narrow concentration range for normal physiological functioning, which is so vital to survival that the body will stimulate bone resorption (demineralization) to maintain normal blood calcium concentrations when calcium intake is inadequate. Thus, adequate intake of calcium is a critical factor in maintaining a healthy skeleton [3].

6.2.1 Solubility

As an example of the wide range of solubility of calcium compounds, *monocalcium* phosphate is very soluble in water, 85% of extra-cellular calcium is as *dicalcium* phosphate with a solubility of 2.0 mM, and the hydroxyapatite of bones in an organic matrix is *tricalcium* phosphate at 100 μM [2].

6.2.2 Binding

Calcium ions may be complexed by *proteins* through (1) binding the carboxyl groups of glutamic acid or aspartic acid residues, (2) interacting with phosphorylated serine, tyrosine, or threonine residues, or (3) being chelated by γ-carboxylated amino acid residues. *Trypsin*, a digestive enzyme, uses the first method; *osteocalcin*, a bone matrix protein, uses the third. Some other bone matrix proteins such as osteopontin and bone sialoprotein use both the first and the second. Direct activation of enzymes by binding calcium is common; some other enzymes are activated by non-covalent association with direct calcium-binding enzymes. Calcium also binds to the phospholipid layer of the cell membrane, anchoring proteins associated with the cell surface.

6.2.3 Calcium Homeostasis

Calcium concentrations in the blood and ECF are tightly controlled in order to preserve normal physiological function. A slight drop in blood calcium concentration (e.g., inadequate calcium intake) is sensed by the parathyroid glands (PTGs), via the cell surface receptors, resulting in increased secretion of parathyroid hormone (PTH). In the kidneys, PTH stimulates the conversion of vitamin D into its active

form (1,25-dihydroxyvitamin D: calcitriol), which rapidly decreases urinary excretion of calcium, but increases urinary excretion of phosphorus. Elevations in PTH also stimulate bone resorption, resulting in the release of bone minerals (calcium and phosphate), which also contributes to restoring serum calcium concentrations. Increased circulating calcitriol also triggers intestinal absorption of both calcium and phosphorus. Similar to PTH, calcitriol stimulates calcium release from bone by activating osteoclasts. When blood calcium rises to normal levels, PTGs stop secreting PTH [4].

A slight increase in blood calcium concentration stimulates the production and secretion of the peptide hormone, *calcitonin*, by the thyroid gland. Calcitonin inhibits PTH secretion, decreases both bone resorption and intestinal calcium absorption, and increases urinary calcium excretion.

Finally, acute changes in blood calcium concentrations do *not* seem to elicit the secretion of the phosphaturic hormone "fibroblast growth factor-23" (FGF-23), which is produced by osteoblasts in response to increases in phosphorus intake [4]. While this complex system allows for rapid control of blood calcium concentrations, it does so at the expense of the skeleton [3].

6.2.4 Bioavailability

Calcium is a common constituent of multivitamin dietary supplements [5], but the composition of calcium complexes in supplements may affect its bioavailability, which varies by solubility of the salt involved: calcium citrate, malate, and lactate are highly bioavailable, while the oxalate is less. Other calcium preparations include calcium carbonate, calcium citrate malate, and calcium gluconate [5]. The intestine absorbs about one-third of calcium eaten as the free ion, and plasma calcium level is then regulated by the kidneys [5].

6.3 Functions of Calcium

Calcium is the fifth most abundant element in the human body [5]. As electrolytes, calcium ions play a vital role in the physiological and biochemical processes of organisms and cells that can be summarized as [5]:

- Signal induction pathways where they act as a second messenger.
- Neurotransmitter release from neurons.
- Contraction of all muscle cell types.
- Cofactors in many enzymes.
- Fertilization: Upon fertilization, the calcium ion concentration of the egg increases greatly, which causes the cortical granule membranes to fuse with the egg plasma membrane, releasing their contents. Later in development, calcium may play a role in cell adhesion. The major cell adhesion molecules are known as cadherins.

Table 6.1 Summary of the physiological functions of calcium

Physiological role of calcium
• Muscle contraction
• Transmission of nerve impulses
• Stimulation of hormone secretion, e.g., insulin
• Blood clotting
• Necessary for activation of some enzymes
• Transport of ions across the cell membrane
• Maintenance of regular heart beat (conducts electricity)
• Fertilization

Extra-cellular calcium ions are important for [6]:

- Maintaining the potential difference across excitable cell membranes.
- Protein synthesis.
- Bone formation.

Most of the calcium is stored in the skeleton complexed with phosphate. Calcium has a wide range of functions that are listed in Table 6.1.

6.3.1 Structure of Bone and Teeth

Calcium is a major structural element in bones and teeth. The mineral component of bone consists mainly of *hydroxyapatite* ($Ca_{10}[PO_4]_6[OH]_2$) crystals, which contain large amounts of calcium, phosphorus, and oxygen. Bone is a dynamic tissue that is remodeled throughout life. *Osteoclasts* begin the process of remodeling by resorbing or dissolving bone. *Osteoblasts* then synthesize new bone to replace the bone that was resorbed. During normal growth, bone formation exceeds bone resorption. Osteoporosis may result when bone resorption chronically exceeds formation [3].

6.3.2 Cell Signaling/Muscle Contraction

Calcium plays an important role in mediating vasoconstriction and vasodilatation, nerve impulse transmission, muscle contraction, and secretion of hormones like insulin [3].

6.3.2.1 Skeletal Muscles

Excitable cells, such as skeletal muscle and nerve cells, contain voltage-dependent calcium channels in their cell membranes that allow for rapid changes in calcium concentrations. When a nerve impulse stimulates a muscle fiber to contract, calcium channels in the cell membrane open to allow calcium ions enter into the muscle cell. Within the cell, these calcium ions bind to activator proteins, which help release a

flood of calcium ions from storage vesicles of the endoplasmic reticulum (ER) inside the cell. The binding of calcium to the protein troponin-c (tropomyocin) allows for the interaction of myosin and actin leading to muscle contraction. The binding of calcium to the protein *calmodulin* activates enzymes that break down muscle glycogen to provide energy for muscle contraction. Upon completion of the action, calcium is pumped outside the cell or into the ER until the next activation [7].

6.3.2.2 Smooth Muscles

In *smooth muscles*, second messenger systems trigger the release of calcium from the ER. Additionally, ligand-gated and voltage-gated calcium channels on the smooth muscle membrane allow for extra-cellular calcium to enter the cell. Calmodulin binds calcium ions and activates myosin light chain kinase to phosphorylase the myosin head, which then binds actin and causes smooth muscle contraction.

6.3.2.3 Cardiac Muscles

Cardiac muscle is governed both by action potentials and extra-cellular calcium influx. The action potential triggers an inward flow of calcium that potentiates additional calcium release from the ER. The contraction of one cardiac muscle cell is communicated to adjacent cells through intercalated disks, thus allowing for the synchronized contraction of cardiac muscle. It is through this mechanism that calcium is used to stabilize the cardiac cell membrane against depolarization in severe hyperkalemia.

6.3.3 Microbiological Functions/Regulation of Protein Function

Ionized calcium also serves many microbiological functions including [8–10]:

- Activating protein kinases.
- Enzyme phosphorylation.
- Mediating cell response to hormones such as epinephrine, glucagon, vasopressin (ADH), secretin, and cholecystokinin.
- Activation of the seven "vitamin K-dependent" clotting factors (through binding) in the coagulation cascade.

6.4 Dietary and Pharmacological Uses of Calcium

A balanced diet includes 1000 mg of calcium daily. The intestine absorbs 200–400 mg of this with the rest excreted in the stool. Any excess calcium absorbed is secreted in urine. Calcium supplementation is common in elderly individuals, where it is prescribed with vitamin D supplements to improve bone mass that is lost with increasing age.

The calcium salts of calcium chloride and calcium gluconate are administered in instances of severe hyperkalemia to stabilize the membrane potential and prevent prolonged cardiac muscle depolarization [11, 12]. Calcium gluconate is also administered in severe cases of post-operative hypocalcemia to prevent and/or treat tetany.

6.4.1 Disease Prevention

6.4.1.1 Osteoporosis

Osteoporosis is a skeletal disorder in which bone mass and strength are compromised, resulting in an increased risk of fracture. Sustaining a hip fracture is one of the most serious consequences of osteoporosis with one person in four dying within 1 year of experiencing an osteoporotic hip fracture [13]. Despite being a common diagnosis in post-menopausal women, osteoporosis also affects 4–6% of men over the age of 50 years [14].

Osteoporosis is a multifactorial disorder, and nutrition is only one factor contributing to its development and progression [15]. Other risk factors include increased age, female gender, estrogen deficiency, smoking, high alcohol intake (three or more drinks/day), metabolic disease such as hyperthyroidism, and the use of certain medications such as corticosteroids and anti-convulsants [16]. Strategies for reducing the risk of osteoporotic fracture include the attainment of maximal peak bone mass (PBM) and reduction of bone loss later in life. A number of lifestyle factors, including diet (especially calcium and protein intake) and physical activity, are amenable to interventions aimed at maximizing peak bone mass and limiting osteoporotic fracture risk [17].

Current National Osteoporosis Foundation guidelines include recommendations of regular muscle-strengthening and weight-bearing exercise to all post-menopausal women and men aged 50 and older [18]. Several calcium trials indicated that the beneficial skeletal effect of increased physical activity was achievable only at calcium intakes above 1000 mg/day in women in late menopause [19].

The progressive loss of bone mineral density (BMD) leading to osteopenia (pre-osteoporosis) and osteoporosis is usually assessed by dual-energy X-ray absorptiometry (DEXA) at the hip and lumbar spine [20]. Several randomized, placebo-controlled clinical trials have evaluated the effect of supplemental calcium in the preservation of BMD and the prevention of fracture risk in men and women aged 50 years and older. A meta-analysis of 15 randomized controlled trials (RCTs), including 1533 men and women >50 years of age, found that increasing calcium intake from dietary sources (i.e., milk, milk powder, dairy products, or hydroxyapatite preparations) increased BMD by 0.6–1% at the hip (+0.6%) and total body (+1.0%) after 1 year and by 0.7–1.8% at the lumbar spine (+0.7%), femoral neck (+1.8%), total hip (+1.5%), and total body (+0.9%) sites after 2 years [21]. A meta-analysis of 51 randomized controlled trials (RCTs) in 12,257 adults (>50 years) reported that BMD at all bone sites (lumbar spine, femoral neck, total hip, forearm) increased by 0.7–1.4% after 1 year and 0.8–1.5% after 2 years of supplemental calcium, alone or in combination with vitamin D [21]. Such modest increases may

help limit the average rate of BMD loss after menopause, but are unlikely to translate into meaningful fracture risk reductions. A meta-analysis of 20 RCTs that reported on total fracture risk found an 11% risk reduction associated with supplemental calcium with or without vitamin D [22]. Additionally, no reductions were found in risks of hip, vertebral, and forearm fractures with calcium supplementation [22]. Because estrogen withdrawal significantly impairs intestinal absorption and renal reabsorption of calcium, the level of calcium requirement might depend on whether post-menopausal women receive hormone replacement therapy [19].

The U.S. Preventive Services Task Force conducted a meta-analysis of 11 randomized placebo-controlled trials that included 52,915 older people (of whom 69% were post-menopausal women) and reported that the supplementation of vitamin D (300–1000 IU/day) and calcium (500–1200 mg/day) for up to 7 years resulted in a 12% reduction in the risk of any new fracture [23]. There was no significant effect of vitamin D without calcium [23]. A recently updated meta-analysis of randomized, placebo-controlled trials commissioned by the National Osteoporosis Foundation found a 15% reduction in risk of total fracture (eight studies) and a 30% reduction in risk of hip fractures (six studies) with calcium and vitamin D supplementation in older people [24]. The National Osteoporosis Foundation advises that adequate amount of calcium (1000–1200 mg/day) and vitamin D (800–1000 IU/day) be included in the diet of all middle-aged men and women [25].

The role and efficacy of vitamin D supplementation in strengthening bone and preventing fracture in older people remain controversial topics. The active form of vitamin D, 1,25-dihydroxyvitamin D, stimulates calcium absorption by promoting the synthesis of calcium-binding proteins in the intestine. While no amount of vitamin D can compensate inadequate total calcium intake, vitamin D insufficiency (circulating concentrations of 25-hydroxyvitamin D below 20 ng/mL) can lead to secondary hyperparathyroidism (SHPT) and an increased risk of osteoporosis [26]. Conversely, in post-menopausal women (aged 57–90 years) with adequate total calcium intakes (1400 IU/day), serum 25-hydroxyvitamin D concentrations ranging from 20 ng/mL to 66 ng/mL had little effect on calcium absorption (only 6% increase over the range) [27]. In a randomized, placebo-controlled trial, the supplementation of 1000 IU/day of vitamin D to post-menopausal women (mean age, 77.2 years) for 1 year was found to significantly increase circulating 25-hydroxyvitamin D concentrations by 34% from the baseline, but failed to enhance calcium absorption in the presence of high total calcium intakes (dietary plus supplemental calcium corresponding to an average 2100 mg/day) [28]. This study also reported no significant difference in measures of BMD at the hip and total body between placebo- and vitamin D-treated women. In addition, the pooled analysis of seven RCTs including 65,517 older individuals found that vitamin D (400–800 IU/day) could reduce the risk of any fracture only when combined with calcium (1000 mg/day) [29]. Interestingly, the results of a series of trials included in three recent meta-analyses [23, 30, 31] have suggested that supplemental vitamin D and calcium may have greater benefits in the prevention of fracture in institutionalized, older people who are also at increased risk of vitamin D deficiency and fractures compared to community dwellers [32, 33].

6.4.1.2 Nephrolithiasis

Approximately, 6% of women and 15% of men in industrialized countries will have a kidney stone during their lifetime. Most kidney stones are composed of calcium oxalate or calcium phosphate. Subjects with hypercalciuria are at higher risk of developing renal stones [34]. High urinary oxalate level is another risk factor for calcium oxalate stone formation. Most subjects with a history of kidney stones and/or idiopathic hypercalciuria have increased intestinal calcium absorption [35]. Although it was initially recommended to limit dietary calcium intake in these patients, a number of prospective cohort studies have reported associations between lower total dietary calcium intake and increased risk of incident kidney stones [36–38]. The prospective analyses of three large cohorts, including a total of 30,762 men and 195,865 women followed for a combined 56 years, have indicated that the risk of kidney stones was significantly lower in individuals in the highest versus lowest quintile of dietary calcium intake from dairy or non-dairy sources [39]. Additionally, a 5-year randomized intervention study that enrolled 120 men with idiopathic hypercalciuria (mean age, 45 years) reported that those assigned to a low-calcium diet (approximately, 400 mg/day) had a 51% higher risk of kidney stone recurrence compared to those on a normal-to-high calcium (1200 mg/day), low animal-protein, low-salt diet [40].

Mechanisms by which increased dietary calcium might reduce the risk of incident kidney stones are *not* fully understood. An inverse relationship was reported between total calcium intake and intestinal calcium absorption in the recent cross-sectional analysis of a cohort of 5452 post-menopausal women [35]. Moreover, women with higher supplemental calcium intake and lower calcium absorption were less likely to report a history of kidney stones [35]. Adequate intake of calcium with food may reduce the absorption of dietary oxalate and lower urinary oxalate through formation of the insoluble calcium oxalate salt [41, 42]. A recent small interventional study in 10 non-stone-forming young adults observed that the ingestion of large amounts of oxalate did *not* increase the risk of calcium oxalate stone occurrence in the presence of recommended level of dietary calcium [43].

On the other hand, a randomized, double-blind, placebo-controlled trial on 36,282 post-menopausal women reported that a combination of supplemental calcium (1000 mg/day) and vitamin D (400 IU/day) was associated with a significantly increased incidence of self-reported kidney stones during a 7-year treatment period [44]. However, a systematic review of observational studies and RCTs failed to find an effect of calcium supplementation on stone incidence [45]. A potential kidney stone risk associated with calcium supplementation may likely depend on whether supplemental calcium is co-ingested with oxalate-containing foods or consumed separately. Further research is needed to verify whether osteoporosis treatment drugs (e.g., bisphosphonates) rather than calcium supplements might influence the risk of stone occurrence [46].

Current data suggest that diets providing adequate dietary calcium and low levels of animal protein, oxalate, and sodium may benefit the prevention of stone recurrence in subjects with idiopathic hypercalciuria [47–49].

6.4.1.3 Hypertensive Disorders of Pregnancy

Pregnancy-induced hypertensive disorders including gestational hypertension, pre-eclampsia, and eclampsia, complicate approximately 10% of pregnancies and are a major health risk for pregnant women and their offspring [50]. *Gestational hypertension* is defined as "an abnormally high blood pressure that usually develops after the 20th week of pregnancy." *Pre-eclampsia* is characterized by poor placental perfusion and a systemic inflammation that may involve several organ systems, including the cardiovascular system, kidneys, liver, and hematological system [51]. Pre-eclampsia is also associated with the development of severe proteinuria and edema. *Eclampsia* is "the occurrence of seizures in association with the syndrome of pre-eclampsia" and is a significant cause of maternal and perinatal mortality.

Although patients with pre-eclampsia are at high risk of developing eclampsia, one-quarter of women with eclampsia do not initially exhibit pre-eclamptic symptoms. Risk factors for pre-eclampsia include genetic predisposition, advanced maternal age, first pregnancies, multiple pregnancies (e.g., twins or triplets), obesity, diabetes mellitus, and some autoimmune disorders [51]. While the pathogenesis of pre-eclampsia is *not* entirely understood, nutrition and especially calcium metabolism appear to play a role. Data from epidemiological studies noticed an inverse relationship between calcium intake during pregnancy and the incidence of pre-eclampsia [52]. Impairment of calcium metabolism when circulating vitamin D level is low and/or when dietary calcium intake is inadequate may contribute to the risk of hypertension during pregnancy. Secondary hyperparathyroidism due to vitamin D deficiency in young pregnant women has been associated with maternal hypertension and increased risk of pre-eclampsia [53]. The risk for elevated PTH concentration was also found to be increased in vitamin D-sufficient women with low-calcium intakes (<480 mg/day) during pregnancy when compared with adequate-to-high calcium intakes (≥1000 mg/day) [54]. Vitamin D deficiency may also trigger hypertension through inappropriate activation of the renin–angiotensin system.

Potential beneficial effects of calcium in the prevention of pre-eclampsia have been investigated in several randomized, placebo-controlled studies. The most recent meta-analysis of 13 trials in 15,730 pregnant women found that calcium supplementation with at least 1000 mg/day (mostly 1500–2000 mg/day) from about 20 weeks of pregnancy (34 weeks of pregnancy at the latest) was associated with significant reductions in the risk of hypertension, pre-eclampsia, and pre-term birth [52]. Greater risk reductions were reported among pregnant women at high risk of pre-eclampsia (5 trials; 587 women) or with low dietary calcium intake (8 trials; 10,678 women). Another meta-analysis of nine RCTs in high-risk women indicated that lower doses of calcium supplementation (≤800 mg/day), alone or with a co-treatment (vitamin D, linoleic acid, or antioxidants), could also lower the risk of pre-eclampsia by 62% [55]. Yet, based on the systematic review of high-quality RCTs, which used mostly high-dose calcium supplements, the World Health Organization (WHO) recently recommended that all pregnant women in areas of low-calcium intake (low-income countries with intakes around 300–600 mg/day) be

given 1.5–2 g (1500–2000 mg)/day of elemental calcium from the 20th week of pregnancy [56].

Because excessive calcium supplementation may be harmful, further research is required to verify whether calcium supplementation above the current U.S. Institute of Medicine (IOM) recommendation (1000 mg/day for pregnant women, aged 19–50 years) would provide greater benefits to women at high risk of pre-eclampsia. Finally, the lack of effect of supplemental calcium on proteinuria (reported in two trials only) suggested that calcium supplementation from mid-pregnancy might be too late to oppose the genesis of pre-eclampsia [57, 58].

6.4.1.4 Colorectal Cancer (CRC)

Colorectal cancer (CRC) is the most common gastrointestinal cancer and the second leading cause of cancer death in the USA [59]. It is caused by a combination of genetic and environmental factors. In individuals with familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer (HNPCC), the cause of CRC is almost entirely genetic, while modifiable lifestyle factors, including dietary habits, tobacco use, and physical activities, greatly influence the risk of sporadic (non-hereditary) CRC.

Prospective cohort studies have consistently reported an inverse association between dairy food consumption and CRC risk. Experimental studies in cell culture and animal models have suggested plausible mechanisms underlying a role for calcium, a major nutrient in dairy products, in preventing CRC [60]. In the multicenter European Prospective Investigation into Cancer and Nutrition (EPIC) prospective study of 477,122 individuals, followed for an average of 11 years, 4513 CRC cases were documented [61]. Intakes of milk, cheese, and yogurt were inversely associated with CRC risk. The highest versus lowest quintile of total dairy intake (≥490 vs. <134 g/day) was associated with a 23% lower risk of CRC. Similarly, CRC risk was 25% lower in those in the top versus bottom quintile of calcium intake from dairy food (≥839 vs. <308 mg/day). The 16-year follow-up of 41,403 women (aged 26–46 years at inclusion) from the prospective Nurses' Health Study II (NHS II) documented 2273 diagnoses of colorectal adenomas (pre-cancerous polyps). The analysis of the prospective cohort found that women with total calcium intake of 1001–1250 mg/day had a 76% lower risk of developing advanced adenomas compared to those with intakes equal to and below 500 mg/day [62]. In addition, a dose–response analysis using data from eight prospective studies (11,005 CRC cases) estimated that an increase of 300 mg/day in total calcium intake was associated with a 5% reduction in CRC risk [63]. Total daily intake of calcium ranged from 333 to 2229 mg in the examined studies. In addition, the dose–response analysis of six prospective studies (8839 CRC cases among 920,837 participants) showed 11% lower odds of high-risk adenomas for each 300 mg/day increment in total calcium [63].

However, the meta-analysis of seven randomized, double-blind, placebo-controlled studies found no evidence of an effect of calcium supplementation (≥500 mg/day) for a median period of 45 months on total cancer risk and CRC risk [64]. In addition, the re-analysis of the Women's Health Initiative placebo-controlled

trial failed to show a reduction in CRC risk in post-menopausal women supplemented with both vitamin D (400 IU/day) and calcium (1000 mg/day) for 7 years [65]. Finally, the results of the meta-analysis of four randomized, placebo-controlled trials have suggested that calcium supplementation (1200–2000 mg/day) may reduce the risk of adenoma recurrence by 13% over 3–5 years in subjects with a history of adenoma [66]. At present, it is not clear whether calcium supplementation is beneficial in CRC prevention.

6.4.1.5 Lead Toxicity

Children who are chronically exposed to lead, even in small amounts, are more likely to develop learning disabilities, behavioral problems, and to have low IQs. Deficits in growth and neurological development may occur in the infants of women exposed to lead during pregnancy and lactation. In adults, lead toxicity may result in renal damage and hypertension. Although the use of lead in paint products, gasoline, and food cans has been discontinued in the USA, lead toxicity continues to be a significant health problem, especially in children living in urban areas [67].

In 2012, the U.S. Centers for Disease Control and Prevention set the reference value for blood lead concentration at 5 mg/dL to identify children at risk [68]. Yet, there is no known blood lead concentration below which children are 100% safe. An early study of over 300 children in an urban neighborhood found that 49% of children aged 1–8 years had blood lead levels above the threshold of 10 mg/dL, indicating excessive lead exposure. In this study, only 59% of children aged 1–3 years and 41% of children aged 4–8 years met the recommended levels for calcium intakes [69].

Adequate calcium intake could be protective against lead toxicity in at least two ways. Increased dietary intake of calcium is known to decrease the gastrointestinal absorption of lead. Once lead enters the body it tends to accumulate in the skeleton, where it may remain for more than 20 years. Adequate calcium intake also prevents lead mobilization from the skeleton during bone demineralization. A study of circulating concentrations of lead during pregnancy found that women with inadequate calcium intake during the second half of pregnancy were more likely to have elevated blood lead levels, probably because of increased bone demineralization, leading to the release of accumulated lead into the blood [70]. Lead in the blood of a pregnant woman is readily transported across the placenta resulting in fetal lead exposure at a time when the developing nervous system is highly vulnerable. In a randomized, double-blind, placebo-controlled study in 670 pregnant women (≤14 weeks' gestation) with average dietary calcium intakes of 900 mg/day, daily supplementation of 1200 mg of calcium throughout the pregnancy period resulted in 8–14% reductions in maternal blood lead concentrations [71]. Similar reductions in maternal lead concentrations in the blood and breast milk of lactating mothers supplemented with calcium were reported in earlier trials [72, 73]. In post-menopausal women, factors known to decrease bone demineralization, including estrogen replacement therapy and physical activity, have been inversely associated with blood lead levels [74].

6.4.2 Disease Treatment

6.4.2.1 Overweight and Obesity

High dietary calcium intake is inversely related to body weight and central obesity [75]. A meta-analysis of 18 cross-sectional and prospective studies predicted a reduction in body mass index (BMI) of 1.1 kg/m^2 with an increase in calcium intake from 400 mg/day to 1200 mg/day [75]. Several mechanisms have been proposed to explain the potential impact of calcium on body weight [75]. The most-cited mechanism is that low calcium intake, through increasing circulating PTH and vitamin D, could stimulate the accumulation of fat (lipogenesis) in adipocytes [76]. Conversely, higher intakes of calcium may reduce fat storage, stimulate lipolysis, and drive fat oxidation. Another mechanism suggests that high-calcium diets may limit dietary fat absorption in the intestine and increase fecal fat excretion. Indeed, in the gastrointestinal tract, calcium may trap dietary fat into insoluble calcium soaps of fatty acids that are then excreted [77]. In addition, it has also been proposed that calcium might be involved in regulating appetite and energy intake [78].

To date, there is no consensus regarding the effect of calcium on body weight changes. A meta-analysis of 29 RCTs on 2441 participants (median age, 41.4 years) found that calcium supplementation was only associated with body weight and fat loss in short-term studies (<1 year) that used energy-restricted diets [79]. Another meta-analysis of 41 RCTs (n = 4802) found little-to-no effect of increased calcium intake from supplements or dairy foods for >12 weeks on body weight and body composition [80]. Finally, a meta-analysis of 33 RCTs (n = 4733) found no overall effect of calcium supplementation (from food or supplements) for >12 weeks on body weight changes. Yet, further subgroup analyses showed weight reductions in children and adolescents (mean, −0.26 kg), in adults (mean, −0.91 kg), and in those with normal BMI (mean, −0.53 kg). Supplemental calcium did *not* lead to weight loss in post-menopausal women or in overweight/obese individuals [81]. At present, additional research is warranted to examine the effect of calcium intake on fat metabolism, as well as its potential benefits in the management of body weight with or without caloric restriction [82].

6.4.2.2 Premenstrual Syndrome (PMS)

Premenstrual syndrome (PMS) refers to a cluster of symptoms, including, but not limited to, fatigue, irritability, moodiness/depression, fluid retention, and breast tenderness, that begins sometime after ovulation (mid-cycle) and subsides with the onset of menstruation [83]. A severe form of PMS called premenstrual dysphoric disorder (PMDD) has been described in 3–8% of women of child-bearing age. It interferes with normal functioning, affecting daily activities and relationships [84].

Low dietary calcium intakes have been linked to PMS in early reports, and supplemental calcium has been shown to decrease symptom severity [85]. A nested case-control study within the Nurses' Health Study II (NHS II) found that women in the highest quintile of dietary (but not supplemental) calcium intake (median of 1283 mg/day) had a 30% lower risk of developing PMS compared to those in the lowest quintile (median of 529 mg/day). Similarly, women in the highest versus

lowest quintile of skim or low-fat milk intake (≥4 servings/day vs. ≤1 serving/week) had a 46% lower risk of PMS [86].

In a randomized, double-blind, placebo-controlled clinical trial of 466 women with moderate-to-severe premenstrual symptoms, supplemental calcium (1200 mg/day) for three menstrual cycles was associated with a 48% reduction in total symptom scores, compared to a 30% reduction observed in the placebo group [87]. Similar positive effects were reported in earlier double-blind, placebo-controlled, crossover trials that administered 1000 mg of calcium daily [88, 89]. Recent small RCTs also reported that supplemental calcium (400–500 mg/day) for 3 weeks to 3 months reduced severity and/or frequency of symptoms in women with mild-to-moderate PMS [90–93]. Currently available data indicate that daily calcium intakes from food and/or supplements may have therapeutic benefits in women diagnosed with PMS or PMDD [94, 95].

6.4.2.3 Hypertension

The relationship between calcium intake and blood pressure (BP) has been investigated extensively over the past decades. A meta-analysis of 23 large observational studies found a reduction in systolic BP of 0.34 mmHg/100 mg of calcium consumed daily and a reduction in diastolic BP of 0.15 mmHg/100 mg calcium [96]. The DASH—Dietary Approaches to Stop Hypertension—study suggested that calcium intake at the recommended level (1000–1200 mg/day) may be helpful in preventing and treating moderate hypertension [97].

Yet, two large systemic reviews and meta-analyses of RCTs have examined the effect of calcium supplementation on blood pressure compared to placebo in either normotensive or hypertensive individuals [98, 99]. Neither of the analyses reported any significant effect of supplemental calcium on BP in normotensive subjects. A small but significant reduction in systolic BP, but not in diastolic BP, was reported in participants with hypertension. A more recent meta-analysis of 13 RCTs on 485 individuals with hypertension found a significant reduction of 2.5 mmHg in systolic blood pressure but no change in diastolic blood pressure with calcium supplementation [100]. The modest effect of calcium on BP needs to be confirmed in larger, high-quality, well-controlled trials before any recommendation is made regarding the management of hypertension.

Finally, a review of the literature on the effect of high calcium intake (dietary and supplemental) in post-menopausal women found either no reduction or mild and transient reductions in blood pressure [101].

6.5 Food Sources and Recommended Dietary Allowance

6.5.1 Food Sources of Calcium

Foods rich in calcium include mainly dairy products (e.g., yoghurt and cheese), sardine, salmon, soy products, kale, and fortified breakfast cereals [102]. Data analysis of the U.S. National Health and Nutrition Examination Surveys (NHANES)

2009–2010 and 2011–2012 found inadequate calcium intakes (intakes below the "estimated average requirement—EAR" in 37.7% of non-supplemented adults [aged ≥19 years] and 19.6% of adults taking multivitamin/mineral supplements) [103]. *Dairy foods* provide 75% of the calcium in the American diet. However, it is typically during the most critical period for peak bone mass (PBM) development that adolescents tend to replace milk with soft drinks [104]. Dairy products represent rich and absorbable sources of calcium, but *certain vegetables* and *grains* also provide calcium.

However, the bioavailability of calcium must be taken into consideration when addressing food sources of calcium. The calcium content in calcium-rich plants in the *kale family* (broccoli, bok choy, cabbage, mustard, and turnip greens) is as bioavailable as that in milk; however, other plant-based foods contain components that inhibit the absorption of calcium. Oxalic acid, also known as oxalate, is the most potent inhibitor of calcium absorption and is found at high concentrations in *spinach* and *rhubarb* and somewhat lower concentrations in *sweet potatoes* and *dried beans*.

Phytic acid (phytate) is a less potent inhibitor of calcium absorption than oxalate. Yeast possesses an enzyme (phytase) that breaks down phytate in grains during fermentation, lowering the phytate content of breads and other fermented foods. Only concentrated sources of phytate, such as *wheat bran* or *dried beans*, substantially reduce calcium absorption [105].

A number of calcium-rich foods along with their serving and calcium content are listed in Table 6.2.

6.5.2 Calcium Supplements

Most experts recommend obtaining as much calcium as possible from food because calcium in food is accompanied by other important nutrients that assist the body in utilizing calcium. However, calcium supplements may be necessary

Table 6.2 Some food sources of calcium

Food	Serving	Calcium (mg)
– Tofu prepared with calcium sulfate (raw)	½ cup	434
– Yogurt, plain, low-fat	8 ounces	415
– Sardines, canned	3.75 ounces (1 can)	351
– Cheddar cheese	1.5 ounces	303
– Milk	8 ounces	300
– White beans (cooked)	½ cup	81
– Chinese cabbage (bok choy/pak choi, cooked)	½ cup	79
– Figs (dried)	¼ cup	61
– Orange	1 medium	60
– Kale (cooked)	½ cup	47
– Pinto beans (cooked)	½ cup	39
– Broccoli (cooked)	½ cup	31
– Red beans (cooked)	½ cup	25

for those who have difficulty consuming enough calcium from food [106]. No multivitamin/mineral tablet contains 100% of the recommended daily value (DV) for calcium because it is too bulky, and the resulting pill would be too large to swallow. The "Supplement Facts" label, required on all supplements marketed in the USA, lists the calcium content of the supplement as elemental calcium. Calcium preparations used as supplements include calcium carbonate, calcium citrate, calcium citrate malate, calcium lactate, and calcium gluconate. *Calcium carbonate* is generally the most economical calcium supplement. To maximize absorption, no more than 500 mg of elemental calcium should be taken at one time. Most calcium supplements should be taken with meals, although calcium citrate and calcium citrate malate can be taken anytime. Calcium citrate is the preferred calcium formulation for individuals who suffer from achlorhydria or those treated with H_2 blockers or proton-pump inhibitors [107].

Many calcium compounds are *pharmaceuticals* in medicine, among others. For example, calcium bisphosphonates in hypercalcemia, and tricalcium phosphate in antacids and as a polishing agent in toothpaste. Calcium lactobionate is a white powder that is used as a suspending agent for pharmaceuticals [108]. Calcium is on the WHO list of essential medicines [109].

Lead in calcium supplements: Several decades ago, concern was raised regarding lead concentrations in calcium supplements obtained from natural sources (oyster shell, bone meal, and dolomite) [110]. In 1993, investigators found measurable quantities of lead in most of the 70 different preparations they tested [111]. Since then, manufacturers have reduced the amount of lead in calcium supplements to less than 0.5 μg/1000 mg of elemental calcium [112]. The U.S. Food and Drug Administration (FDA) developed provisional total tolerable intake levels (PTTI) for lead for specific age and sex groups [113]. Because lead is so widespread and long lasting, no one can guarantee entirely lead-free food or supplements. A study found measurable lead in 8 out of 21 supplements, in amounts averaging 1–2 mg/1000 mg of elemental calcium, which is below the tolerable limit of 7.5 mg/1000 mg of elemental calcium [114]. A more recent survey of 324 multivitamin/mineral supplements labeled for use in children or women found that most supplements would result in lead exposure ranging from 1% to 4% of the PTTI [115]. Calcium inhibits intestinal absorption of lead, and adequate calcium intake is protective against lead toxicity, so trace amounts of lead in calcium supplementation may pose less of a risk of excessive lead exposure than inadequate calcium consumption.

6.6 Abnormal Serum Levels of Calcium

It is important for the clinician to be aware of the causes of hypercalcemia and hypocalcemia because these diseases are potentially dangerous and either extreme may be life-threatening.

6.6.1 Calcium Deficiency

Hypocalcemia usually implies abnormal parathyroid function since the skeleton provides a large reserve of calcium for maintaining normal blood levels, especially in case of low calcium intake. It is often caused by inadequate secretion of PTH or defective PTH receptors in cells. Other causes of hypocalcemia include chronic renal failure, vitamin D deficiency, and hypomagnesemia, often observed with severe alcoholism. Magnesium deficiency can impair PTH secretion by the PTGs and lower the responsiveness of osteoclasts to PTH. Thus, magnesium supplementation is required to correct hypocalcemia in people who have hypomagnesemia.

Symptoms of hypocalcemia include neuromuscular excitability, which potentially causes tetany and disruption of conductivity in cardiac tissue. As calcium is required for bone development, many bone diseases can be traced to the organic matrix or the hydroxyapatite in molecular structure or organization of bone. Chronically low calcium intakes in growing individuals may prevent the attainment of optimal peak bone mass. Once peak bone mass is achieved, inadequate calcium intake may contribute to accelerated bone loss and ultimately to the development of osteoporosis [1]. *Osteoporosis* is a reduction in mineral content of bone per unit volume, and can be treated by supplementation of calcium, vitamin D, and bisulphonates [5, 6]. Inadequate amounts of calcium, vitamin D, or phosphates can lead to softening of bones (*osteomalacia*).

6.6.2 The Recommended Dietary Allowance (RDA)

Updated recommendations for calcium intake based on optimization of bone health were released by the Food and Nutrition Board of the Institute of Medicine (FNBIM) in 2011. The recommended dietary allowance (RDA) for calcium is listed in Table 6.3.

Table 6.3 Recommended dietary allowance (RDA) for calcium by life stage and gender

Life stage	Age	Males (mg/day)	Females (mg/day)
– Infants	0–6 months	200	200
	6–12 months	260	260
– Children	1–3 years	700	700
	4–8 years	1000	1000
	9–13 years	1300	1300
– Adolescents	14–18 years	1300	1300
– Adults	19–50 years	1000	1000
	51–70 years	1000	1200
	>70 years	1200	1200
– Pregnancy	14–18 years	–	1300
	19–50 years	–	1000
– Breast-feeding	14–18 years	–	1300
	19–50 years	–	1000

6.6.3 Calcium Excess—Safety

6.6.3.1 Toxicity

Primary hyperparathyroidism (PHPT) and malignancy are the most common causes of hypercalcemia [116]. Non-PTH-mediated hypercalcemia other than malignancy can be due to granulomatous disorders, pharmacological agents, endocrinopathies, and genetic causes. Excess intake of calcium may cause hypercalcemia. All these conditions result in excess calcium salts being deposited in the heart, blood vessels, or kidneys.

Hypercalcemia has *not* been associated with the overconsumption of calcium occurring naturally in food. Hypercalcemia has been initially reported with the consumption of large quantities of calcium *supplements* in combination with antacids, particularly in the days when peptic ulcers were treated with large quantities of milk, calcium carbonate (antacid), and sodium bicarbonate (absorbable alkali). This condition is termed *calcium-alkali syndrome* (formerly known as *milk-alkali syndrome*) and has been associated with calcium supplement levels from 1.5 to 16.5 g/day for 2 days to 30 years. The demographic of this syndrome has recently changed in that those at greater risk are now post-menopausal women, pregnant women, transplant recipients, patients with bulimia, and patients on dialysis, rather than men with peptic ulcers [117].

Supplementation with calcium (0.6–2 g/day for 2–5 years) has been associated with a higher risk of adverse gastrointestinal events like constipation, cramping, bloating, pain, and diarrhea [118]. Mild hypercalcemia may be asymptomatic or may result in anorexia, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, polyuria, dehydration, metabolic bone disease, and hypertension [116]. More severe hypercalcemia may result in confusion, delirium, coma, and, if not treated, death [3].

Because of concerns for long-term adverse *side effects*, both the U.S. Institute of Medicine (IOM) and the European Food Safety Authority (EFSA) set tolerable update intake levels (ULs) for combined dietary and supplemental calcium [119]. In 2011, the Food and Nutrition Board of the Institute of Medicine updated the tolerable upper intake level (UL) for calcium [120]. The UL is listed in Table 6.4 by age group.

Table 6.4 Tolerable upper intake level (UL) for calcium [120]

Age group	Age	UL (mg/day)
– Infants	0–66.6.3.4. months	1000
	6–12 months	1500
– Children	1–8 years	2500
	9–13 years	3000
– Adolescents	14–18 years	3000
– Adults	19–50 years	2500
	51 years and older	2000

Although the risk of *nephrolithiasis* is increased in individuals with hypercalciuria, this condition is *not* usually related to calcium intake, but rather to increased absorption of calcium in the intestine (excess PTH or vitamin D intake) or increased excretion by the kidneys [120]. Overall, increased dietary calcium intake has been associated with a decreased risk of kidney stones. Concerns have also been raised regarding the risks of prostatic cancer and vascular disease with high intakes of calcium.

6.6.3.2 Do High Calcium Intakes Increase the Risk of Prostate Cancer?

Prostate cancer is the second most common cancer in men worldwide [121]. Several observational studies have raised concern that high dairy intakes are associated with increased risk of prostatic cancer [122–124].

The analysis of a prospective cohort study (2268 men followed for nearly 25 years) conducted in Iceland, a country with a high incidence of prostate cancer, found a positive association between the consumption of milk (at least once daily) during adolescence and developing prostate cancer later in life [125]. Another large prospective cohort study in the USA followed 21,660 male physicians for 28 years and found that men with daily skim or low-fat milk intake of at least 237 mL (8 oz) had a higher risk of developing prostate cancer compared to occasional consumers [126]. The risk of low-grade, early-stage prostate cancer was associated with higher intake of skim milk, and the risk of developing fatal prostate cancer was linked to the regular consumption of whole milk [126]. In a cohort of 3918 male health professionals diagnosed with prostate cancer, 229 men died of prostate cancer and 69 developed metastasized prostate cancer during a median follow-up of 7.6 years [127]. The risk of prostate cancer death was found to be increased in men with high (>4 servings/week) versus low (≤3 servings/month) intakes of whole milk. However, no increase in risk of prostate cancer-related mortality was associated with consumption of "skim, low-fat, or total" *milk* or "low-fat, full-fat, or total" *dairy products* [127]. A recent meta-analysis of 32 prospective cohort studies found high versus low intakes of total dairy product (15 studies), total milk (15 studies), whole milk (6 studies), low-fat milk (5 studies), cheese (11 studies), and dairy calcium (7 studies) to be associated with modest, yet significant, increases in the risk of developing prostate cancer [128]. However, there was no increase in prostate cancer risk with non-dairy calcium (four studies) and calcium from supplements (eight studies). Moreover, high dairy intakes were *not* linked to fatal prostate cancer [128].

There is some evidence to suggest that milk consumption may result in higher circulating concentrations of insulin-like growth factor-I (IGF-I), a protein known to regulate cell proliferation [129]. Circulating IGF-I concentrations have been positively correlated to the risk of developing prostate cancer in a recent meta-analysis of observational studies [130]. Milk-borne IGF-I, as well as dairy proteins and calcium, may contribute to increasing circulating IGF-I in milk consumers [129]. In the large EPIC study, which examined the consumption of dairy products in relation to cancer in 142,520 men, the risk of prostate cancer was found to be significantly higher in those in the top versus bottom quintile of both protein and calcium intakes

from dairy foods [131]. Another mechanism underlying the potential relationship between calcium intake and prostate cancer proposed that high levels of dietary calcium may lower circulating concentrations of 1,25-dihydroxyvitamin D, the active form of vitamin D, thereby suppressing vitamin D-mediated cell differentiation [132]. However, studies to date have provided little evidence to suggest that vitamin D status can modify the association between dairy calcium and risk of prostate cancer development and progression [133–135].

In a multicenter, double-blind, placebo-controlled trial, 672 healthy men (mean age of 61.8 years) were randomized to daily calcium supplementation (1200 mg) for 4 years. While no increase in the risk for prostate cancer has been reported during a 10.3-year follow-up, calcium supplementation resulted in a significant risk reduction in the period spanning from 2 years after treatment started to 2 years after treatment ended [136]. In a review of the literature published in 2009, the U.S. Agency for Healthcare Research and Quality indicated that not all epidemiological studies found an association between calcium intake and prostate cancer [137]. The review reported that 6 out of 11 observational studies failed to find statistically significant positive associations between prostate cancer and calcium intake. Yet, in five studies, daily intakes of 921–2000 mg of calcium were found to be associated with an increased risk of developing prostate cancer when compared to intakes ranging from 455 to 1000 mg/day [137]. Inconsistencies among studies suggest complex interactions between the risk factors for prostate cancer, as well as reflect the difficulties of assessing the effect of calcium intake in free-living individuals. For example, the fact that individuals with higher dairy and/or calcium intakes were found to be more likely to be engaged in healthy lifestyles or more likely to seek medical attention can mitigate the statistical significance of an association with prostate cancer risk [138]. Until the relationship between calcium and prostate cancer is clarified, it is reasonable for men to consume a total of 1000–1200 mg/day of calcium (diet and supplements combined), which is recommended by the Food and Nutrition Board of the Institute of Medicine [120].

6.6.3.3 Do Calcium Supplements Increase the Risk of Cardiovascular Disease?

Several observational studies and RCTs have raised concerns regarding the potential adverse effects of calcium supplements on cardiovascular risk. The analysis of data from the Kuopio Osteoporosis Risk Factor and Prevention (OSTPRE) prospective study found that users of calcium supplements among 10,555 Finnish women (aged 52–62 years) had a 14% greater risk of developing coronary artery disease compared to non-supplement users during a mean follow-up of 6.75 years [139]. The prospective study of 23,980 participants (35–64 years old) of the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition cohort (EPIC-Heidelberg) observed that supplemental calcium intake was positively associated with the risk of myocardial infarction, but *not* with the risk of stroke or cardiovascular disease (CVD)-related mortality after a mean follow-up of 11 years [140]. Yet, the use of calcium supplements (≥400 vs. 0 mg/day) was associated with an increased risk of CVD-related mortality in 219,059 men, but *not* in 169,170

women, included in the National Institute of Health (NIH) American Association of Retired Persons (AARP) Diet and Health study and followed for a mean period of 12 years. CVD mortality in men was also found to be significantly higher with total (dietary plus supplemental) calcium intakes of 1500 mg/day and above [141].

In addition, the secondary analyses of two randomized, placebo-controlled trials initially designed to assess the effect of calcium on bone health outcomes also suggested an increased risk of CVD in participants daily supplemented with 1000 mg of calcium for 5–7 years [142, 143]. In the Auckland Calcium Study of 1471 healthy post-menopausal women (aged ≥55 years), calcium supplementation resulted in increased risks of myocardial infarction and of a composite cardiovascular endpoint, including myocardial infarction, stroke, or sudden death [142]. The analysis of data from 36,282 healthy post-menopausal women randomized to receive a combination of calcium (1000 mg/day) and vitamin D (400 IU/day) or a placebo in the Women's Health Initiative/Calcium-Vitamin D supplementation study (WHI/CaD study) initially reported no adverse effect on any cardiovascular endpoints with calcium (and vitamin D) compared to placebo [144]. A re-analysis was performed with data from 16,718 women who did not take personal calcium supplements (outside protocol) during the 5-year study [143]. Although criticized on the approach taken [118, 145], the investigators estimated that women supplemented with calcium and vitamin D had a 16% increased risk of clinical myocardial infarction or stroke and a 21% increased risk of myocardial infarction compared to those who received a placebo [143]. However, in another randomized, double-blind, placebo-controlled trial—the Calcium Intake Fracture Outcome Study (CAIFOS)—among elderly women (median age, 75.1 years), the supplementation of 1200 mg/day of calcium for 5 years was not found to increase the risk of vascular disease or related mortality [146]. The WHI/CaD data re-analysis also failed to show an increased risk of mortality due to myocardial infarction or coronary artery disease with calcium therapy [142]. Moreover, after an additional follow-up of 4.5 years at the end of the treatment period in the CAIFOS trial, the investigators reported fewer cases of heart failure-related deaths with supplemental calcium compared to placebo [146]. In another randomized, placebo-controlled trial of calcium and/or vitamin D_3 (RECORD trial), the evaluation of the effect of 1000 mg/day of calcium (alone or with 800 IU/day of vitamin D) reported no significant increase in the rate of mortality due to vascular disease in 5292 participants of ages 70 years and older [147]. A recent cross-sectional analysis of the Third National Health and Nutrition Examination Survey (NHANES III) evaluated the association between calcium intakes and cardiovascular mortality in 18,714 adults with no history of heart disease. No evidence of an association was observed between dietary calcium intake, supplemental calcium intake, or total calcium intake and cardiovascular mortality in either men or women [148].

A few prospective studies have reported positive correlations between high calcium concentrations in the blood and increased rates of cardiovascular events [149, 150]. Because supplemental calcium may have a greater effect than dietary calcium on circulating calcium concentrations, it has been speculated that the use of calcium supplements might promote vascular calcification by raising calcium serum

concentrations. In 1471 older women from the Auckland Calcium Study and 323 healthy older men from another randomized, placebo-controlled trial of daily calcium supplementation (600 mg or 1200 mg) for 2 years, serum calcium concentrations were found to be positively correlated with abdominal aortic calcification or coronary artery calcification [151]. However, there was no effect of calcium supplementation on measures of vascular calcification scores in men or women. Data from 1201 participants of the Framingham Offspring study were also used to assess the relationship between calcium intake and vascular calcification. Again, no association was found between coronary calcium scores and total, dietary, or supplemental calcium intake in men or women [152]. Nonetheless, in the Multi-Ethnic Study of Atherosclerosis (MESA), a US multicenter prospective study among 6814 participants followed for a mean 10 years, the greatest risk of developing coronary artery calcification was found in supplement users with the lowest total calcium intake (~306 mg/day of dietary calcium and ~ 91 mg/day of supplemental calcium), when compared to supplement users with higher total calcium intakes and non-users [153]. Finally, an assessment of atherosclerotic lesions in the carotid artery wall of 1103 participants in the CAIFOS trial was also conducted after 3 years of supplementation [154]. When compared with placebo, calcium supplementation showed no effect on carotid artery intimal medial thickness (CIMT) and carotid atherosclerosis. Yet, carotid atherosclerosis (but not CIMT) was significantly reduced in women in the highest versus lowest tertile of total (diet and supplements) calcium intakes (≥1795 vs. <1010 mg/day) [154].

The most recent meta-analysis of 18 RCTs, including a total of 63,563 postmenopausal women, found no evidence of an increased risk for coronary artery disease and all-cause mortality with calcium (≥500 mg/day) supplementation for at least 1 year [155]. Based on an updated review of the literature that included 4 RCTs, 1 nested case-control study, and 26 prospective cohort studies [156], the National Osteoporosis Foundation (NOF) and the American Society for Preventive Cardiology (ASPC) concluded that the use of supplemental calcium for generally healthy individuals was safe from a cardiovascular health standpoint when total calcium intakes did not exceed the "UL" [157]. Both, NOF and ASPC support the use of calcium supplements to correct shortfalls in dietary calcium intake and meet current recommendations [157].

6.6.3.4 Drug Interactions

Taking calcium supplements in combination with *thiazide diuretics* (e.g., hydrochlorothiazide) increases the risk of developing hypercalcemia due to increased reabsorption of calcium in the kidneys. High doses of supplemental calcium could increase the likelihood of abnormal heart rhythms in people taking *digoxin* (Lanoxin) for heart failure [158]. Calcium, when provided intravenously (IV), may decrease the efficacy of *calcium-channel blockers* [159]. However, dietary and oral supplemental calcium do *not* appear to affect the action of calcium-channel blockers [160]. Calcium may decrease the absorption of tetracycline, quinolone class *antibiotics*, *bisphosphonates*, *sotalol* (a β-blocker), and *levo-thyroxine* (El-troxin or Euthyrox); therefore, it is advisable to separate doses of these medications and calcium-rich

food or supplements by 2 h before calcium or 4 to 6 h after calcium [161]. Supplemental calcium can decrease the concentration of dolutegravir (Tivicay), elvitegravir (Vitekta), and raltegravir (Isentress), three *anti-retroviral medications*, in blood such that patients are advised to take them 2 h before or after calcium supplements [161].

Calcium should *not* be administrated IV within 48 h following IV ceftriaxone (rocephin), a cephalosporin antibiotic, since a ceftriaxone-calcium salt precipitate can form in the lungs and kidneys and be a cause of death [161]. Use of *H_2-blockers* (e.g., cimetidine) and *proton-pump inhibitors* (e.g., omeprazole) may decrease the absorption of calcium carbonate and calcium phosphate [162, 163], whereas *lithium* may increase the risk of hypercalcemia in patients [161]. The topical use of *calcipotriene*, a vitamin D analog, in the treatment of psoriasis places patients at risk of hypercalcemia if they take calcium supplements.

6.6.3.5 Calcium–Nutrient Interactions

Vitamin D

Vitamin D is required for optimal calcium absorption. Several other nutrients (and non-nutrients) influence the retention of calcium by the body and may affect the calcium nutritional status.

Iron

The presence of calcium decreases iron absorption from non-heme sources (i.e., most supplements and food sources other than meat). However, calcium supplementation up to 12 weeks has not been found to change iron nutritional status, probably due to a compensatory increase in iron absorption [3]. Individuals should take iron supplements 2 h apart from calcium-rich food or supplements to maximize iron absorption.

Zinc

Although high calcium intakes have *not* been associated with reduced zinc absorption or zinc nutritional status, an early study among 10 men and women found that 600 mg of calcium consumed with a meal halved the absorption of zinc from that meal [164].

Carotenoids

Supplemental calcium (500 mg calcium carbonate) has been found to prevent the absorption of lycopene (a non-provitamin A carotenoid) from tomato paste in 10 healthy adults randomized into a crossover study [165].

Sodium

Dietary sodium is a major determinant of urinary calcium loss [3]. High sodium intake results in increased loss of calcium in the urine, possibly due to competition between sodium and calcium for reabsorption in the kidneys or by an effect of sodium on PTH secretion. Every one-gram increment in sodium (2.5 g of sodium

chloride: NaCl salt) excreted by the kidneys has been found to draw about 26.3 mg of calcium into urine [3]. A study conducted among adolescent girls reported that a high-salt diet had a greater effect on urinary sodium and calcium excretion in White compared to Black girls, suggesting differences among ethnic groups [166]. In adult women, each extra-gram of sodium consumed/day is projected to produce an additional rate of bone loss of 1%/year if all of the calcium loss comes from the skeleton.

A number of cross-sectional and intervention studies have suggested that high sodium intakes are deleterious to bone health, especially in older women [167]. A 2-year longitudinal study in post-menopausal women reported that increased urinary sodium excretion (an indicator of increased sodium intake) is associated with decreased bone mineral density (BMD) at the hip [168]. Another study in 40 post-menopausal women found that adherence to a low-sodium diet (2 g/day) for 6 months was associated with significant reductions in sodium excretion, calcium excretion, and amino-terminal propeptide of type I collagen, a biomarker of bone resorption. Yet, these associations were only observed in women with elevated baseline urinary sodium excretions [169]. Finally, in a randomized, placebo-controlled study on 60 post-menopausal women, potassium citrate supplementation has been found to prevent an increase in calcium excretion induced by the consumption of a high-sodium diet (≥5000 mg/day of elemental sodium) for 4 weeks [170].

Protein

Increasing dietary protein intake enhances intestinal calcium absorption, as well as urinary calcium excretion [120]. The recommended dietary allowance (RDA) for protein is 46 g/day for adult women and 56 g/day for adult men [171]. It was initially thought that high-protein diets may result in a negative calcium balance (when the sum of urinary and fecal calcium excretion becomes greater than calcium intake) and thus increase bone loss [172]. However, most observational studies have reported either no association or positive associations between protein intake and BMD in children, adults, and elderly subjects [173]. The overall calcium balance appears to be unchanged by high dietary protein intake in healthy individuals [174], and current evidence suggests that increased protein intakes in those with adequate supplies of protein, calcium, and vitamin D do not adversely affect BMD or fracture risk [175].

Phosphorus

Phosphorus, which is typically found in protein-rich food, tends to increase the excretion of calcium in the urine. Diets with low calcium-to-phosphorus ratios (Ca: $p \leq 0.5$) have been found to increase PTH secretion and urinary calcium excretion [176, 177]. Intestinal absorption and fecal excretion of calcium and phosphorus are also influenced by calcium-to-phosphorus ratios of ingested food. In the intestinal lumen, calcium salts can bind to phosphorus to form complexes that are excreted in the feces. This forms the basis for using calcium salts as phosphorus binders to lower phosphorus absorption in individuals with renal insufficiency [178]. Increasing phosphorus intakes from cola soft drinks (high in phosphoric acid) and food additives (high in phosphates) may have adverse effects on bone health [179].

Table 6.5 Linus Pauling Institute recommendations of recommended dietary allowance [5]

Life stage	Age	RDA (mg/day)	Aim
Children and adolescents	9–18 years	1300	To promote attainment of maximal peak bone mass (PBM)
Adults			
• Women	19–50 years	1000	To promote the attainment of maximal PBM and to minimize bone loss later in life
• Men	19–70 years		
• Older women (post-menopausal)	>50 years	1200 +	To minimize bone loss and to ensure adequate calcium absorption
• Older men	>70 years	At least 10 μg (400 IU)/day of vitamin D	
Pregnant and breast-feeding women:			
• Adolescents	<19 years	1300	To promote maximal PBM and to minimize bone loss later in life
• Adults	≥19 years	1000	

Caffeine

Exposure to caffeine concentrations of ≤400 mg/day have led to increased urinary calcium content in two randomized controlled trials [180, 181]. However, caffeine intakes of 400 mg/day did not significantly change urinary calcium excretion over 24 h in pre-menopausal women when compared to a placebo [182]. A systematic review of 14 studies recently concluded that daily intake of ≤400 mg of caffeine was unlikely to interfere with calcium homeostasis, impact negatively BMD, or increase the risks of osteoporosis and fracture in individuals with adequate calcium intakes [183].

6.7 The Linus Pauling Institute Recommendations

The Linus Pauling Institute [5] supports the recommended dietary allowance (RDA: diet + supplement) set by the Food and Nutrition Board of the Institute of Medicine. Following these recommendations should provide adequate calcium to promote skeletal health and may also decrease the risks of some chronic diseases (Table 6.5).

6.8 Summary [5]

- Calcium is a major constituent of bones and teeth and also plays an essential role as a second messenger in cell-signaling pathways. Circulating calcium concentrations are tightly controlled by the parathyroid hormone (PTH) and vitamin D at the expense of the skeleton when dietary calcium intakes are inadequate.
- The recommended dietary allowance (RDA) for calcium is 1000–1200 mg/day for adults.

- The skeleton is a reserve of calcium drawn upon to maintain normal serum calcium in case of inadequate dietary calcium. Thus, calcium sufficiency is required to maximize the attainment of peak bone mass (PBM) during growth and to limit the progressive demineralization of bones later in life, which leads to osteoporosis, bone fragility, and an increased risk of fractures.
- High concentrations of calcium and oxalate in the urine are major risk factors for the formation of calcium oxalate stones in the kidneys. Because dietary calcium intake has been inversely associated with stone occurrence, it is believed that adequate calcium consumption may reduce the absorption of dietary oxalate, thus reducing urinary oxalate and kidney stone formation.
- Data from observation studies and RCTs support calcium supplementation in reducing the risk of hypertension and pre-eclampsia in pregnant women. The WHO advises all pregnant women in areas of low calcium intake (i.e., low-income countries with intakes around 300–600 mg/day) to receive supplemental calcium starting in the 20th week of pregnancy.
- Prospective cohort studies have reported an association between higher calcium intakes and lower risk of developing colorectal cancer (CRC); however, large clinical trials of calcium supplementation are needed.
- Current available data suggest that adequate calcium intakes may play a role in body weight regulation and have therapeutic benefits in the management of moderate-to-severe premenstrual symptoms.
- Adequate calcium intake is critical for maintaining a healthy skeleton. Calcium is found in a variety of foods, including dairy products, beans, and vegetables of the kale family. Yet, content and bioavailability vary among foods, and certain drugs are known to adversely affect calcium absorption.
- Hypercalcemia is usually due to malignancy or primary hyperparathyroidism (PHPT). However, the use of large doses of supplemental calcium, together with absorbable alkali, increases the risk of hypercalcemia, especially in postmenopausal women. Often associated with gastrointestinal disturbances, hypercalcemia can be fatal if left untreated.
- High calcium intakes—either from dairy foods or from supplements—have been associated with increased risks of prostatic cancer and cardiovascular events in some, but not all, observational and interventional studies. However, there is currently no evidence of such detrimental effects when people consume a total of 1000–1200 mg/day of calcium (diet and supplements combined), as recommended by the Food and Nutrition Board of the Institute of Medicine (FNBIM).

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Hyperparathyroidism (HPT)

7

7.1 Introduction

Hyperparathyroidism (HPT) was initially thought to be rare and always presenting with advanced renal and skeletal pathology. Nowadays, it is considered a common endocrine disorder with a rising incidence, four times more common in women than men. It is the third commonest endocrine condition after thyroid disease and diabetes mellitus, and is frequently diagnosed in asymptomatic patients [1].

A series of successful parathyroidectomy operations performed from 1925 onward, established surgery as the foremost treatment option of HPT, the position it still holds today. Parathyroid surgeons must adopt a pragmatic approach when choosing diagnostic tests (not to over-investigate), selecting right operations (simpler, better), aiming at providing excellent outcomes (to meet high patient expectations), and to achieve all of these in the most cost-effective way (government priority) [1].

7.2 Surgical Pathology

Hyperparathyroidism (HPT) is an abnormal state of calcium (Ca) homeostasis where one or many parathyroid glands (PTGs) secrete inappropriately large amounts of the parathyroid hormone (PTH).

7.2.1 Classification of Hyperparathyroidism (HPT)

Classification of HPT into primary, secondary, and tertiary reflects different mechanisms by which excess of PTH develops.

M. F. Sakr, *Parathyroid Gland Disorders*,
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1. *Primary HPT* (PHPT) is the commonest and indicates that abnormal changes occurred first within the PTG itself due to adenoma (single 80%, double 4%), hyperplasia (15%), and rarely cancer (1%). Distinction between hyperplasia and adenoma is difficult and is based on finding a rim on normal parathyroid tissue at the periphery of the adenoma [2, 3].
2. *Secondary HPT* (SHPT) is caused by prolonged hypocalcemia due to chronic renal disease, low vitamin D (rickets), or malabsorption. Low Ca stimulates the PTGs leading to compensatory hypertrophy and increase in the output of PTH. Despite high PTH levels, Ca remains low and in early stages SHPT can be reversed (e.g., by renal transplantation).
3. *Tertiary HPT* (THPT) is the result of long-lasting SHPT, which can lead to development of parathyroid nodules *autonomously* secreting PTH resulting in hypercalcemia.

7.2.2 Hyperparathyroidism: Sporadic or Familial?

Hyperparathyroidism could be *sporadic* or *familial*. Familial HPT (FHPT) accounts for 1–2% of cases of HPT in adults, but 25–45% in children. The FHPT is caused by inherited or de novo mutations of genes responsible for (1) multiple endocrine neoplasia (MEN; I and IIA), (2) HPT-jaw tumor syndrome (HPT-JT), and (3) familial isolated HPT (FI-HPT).

7.3 Primary Hyperparathyroidism (PHPT)

7.3.1 Epidemiology

Serum calcium is frequently measured during the work-up of other diseases or during investigation of ill-defined or vague symptoms, or in the course of routine biochemical screening in some countries. This led to changes in both, the mode of presentation and the incidence of PHPT. Before the era of widespread measurement of serum calcium, PHPT patients had been presenting with one or more of the known PHPT classical symptoms: frequently recurrent kidney stones and bone fractures, and frequently associated with moderate or severe hypercalcemia. However, in the last two decades, PHPT presentation has become most commonly asymptomatic, with hypercalcemia detected incidentally, and more frequently of mild severity.

Primary hyperparathyroidism is the third common endocrine disease after diabetes mellitus, and thyroid disorders, with its incidence generally rising globally. However, there have been remarkable well-defined secular trends related to calcium/bone density screening. In Mayo Clinic experience, the annual incidence increased from 16/100,000 per year before 1974 to a peak of 112/100,000 per year, after the introduction of multichannel biochemical screening, which included measuring serum calcium. Several years later, incidence declined due to elimination of

calcium from the automated chemistry panel. There was a second peak in the incidence of PHPT between 1998 and 2007 to 86/100,000, attributed to increased bone density measurements in the setting of osteoporosis screening [4]. Currently, the incidence of PHPT has been estimated to be 25/100,000 in the United Kingdom (UK), and prevalence has risen from 1.8 to 6.7/1000 between 1997 and 2006, implying that in the UK alone, about half a million people suffer from this condition and 12,000 develop it each year [5].

Primary HPT can occur at any age, but is more common in patients over the age of 50 years. Women are twice affected as often as men. One study looking at racial differences reported that the incidence of PHPT was highest among blacks, compared to other races [6].

7.3.2 Etiology of "PTH" Overproduction

Overproduction of PTH by the PTG results from parathyroid hyperplasia or parathyroid tumors of which nearly 90% are benign (adenoma) and 10% are malignant (adenocarcinoma; Fig. 7.1). Approximately, 90% of PHPT cases are sporadic (i.e., non-familial, non-syndromic). The exact etiology of sporadic disease is unknown in the majority of cases. However, some cases have been associated with certain environmental exposures and/or chromosomal defects. Familial disease usually occurs within a syndromic context and is associated with certain genetic alterations.

7.3.2.1 Radiation Exposure

Compared to people who did not have history of radiation exposure, PHPT has been reported to be more frequent among workers in Chernobyl power plant, atomic bomb survivors, and among patients who received head and neck irradiation for benign conditions. The increased risk is dose-dependent, and can exist up to 40 years after radiation exposure [7–9]. There are no clinically important differences between PHPT patients with and without history of radiation exposure. However, concurrent thyroid tumors were more common among the exposed patients, which can make management more difficult. Radiation exposure does *not* increase the risk of having multigland parathyroid disease and does *not* preclude a minimally invasive surgical approach in absence of a concomitant significant thyroid nodular pathology [10, 11]. Whether radioactive iodine (RAI) therapy is associated with increased risk of PHPT is still controversial [12, 13].

7.3.2.2 Calcium Intake

One prospective study has demonstrated an inverse association between oral calcium intake and the risk of developing PHPT. A possible explanation to this finding is that chronically low calcium intake may cause chronic stimulation of the PTG, therefore predisposing to PHPT; however, further studies are needed to confirm this association [14].

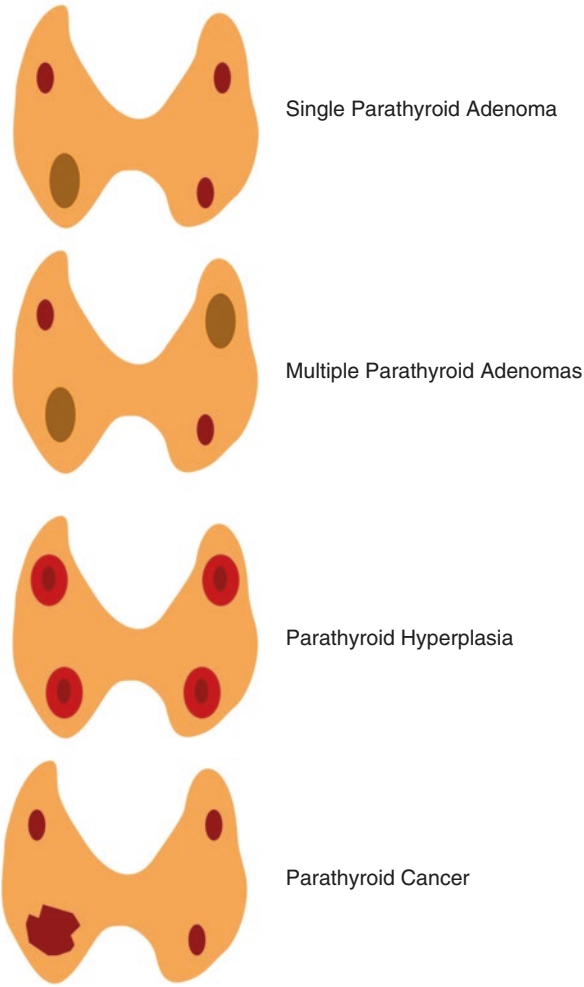

Fig. 7.1 Causes of primary hyperparathyroidism (PHPT): adenoma (single or multiple), hyperplasia, and carcinoma

7.3.2.3 Chromosomal Defects

Cyclin D1/PRAD1 Gene

Cyclin D1/PRAD1 gene is a proto-oncogene, located on chromosome 11, and encodes for cyclin D1, cell cycle (regulator). Rearrangement activation mutation in this gene has been reported in 8% of sporadic parathyroid adenomas, and is mediated through overexpression of cyclin D1, resulting in dysregulation of calcium-mediated PTH secretory control, with consequent parathyroid cell proliferation [15].

MEN-1 Gene

MEN-1 gene is a tumor-suppressor gene located on chromosome 11, and encodes protein menin, which acts as an inhibitor of Wnt/β-catenin, a

well-known tumorigenesis pathway. Various inactivation mutations in this gene have been reported in 20% of sporadic parathyroid adenomas and 90% of familial multiple endocrine neoplasia 1 (MEN-1) syndrome, although the exact menin-mediated tumor-suppressive activity is still an active area of research [16].

CDKI Genes

CDK N1B is a tumor-suppressor gene, located on chromosome 12, and encodes protein p27, one of cyclin-dependent kinase inhibitors, which are involved in cell cycle regulation. Various inactivation mutations in this gene have been reported in sporadic parathyroid adenomas and in familial multiple endocrine neoplasia-4 (MEN-4) syndrome [17].

RET Gene

RET gene is a proto-oncogene, located on chromosome 10, and encodes for tyrosine kinase receptor expressed at several stages of development in branchial arches and neural crest-derived cell lineages, including parathyroid chief cells, parafollicular C-cells, and adrenal medullary cells. Rearrangement activation mutations in this gene are associated with 20–30% of familial multiple endocrine neoplasia-2A (MEN-2A) syndrome [18].

CDC73/HRPT2 Gene

CDC73/HRPT2 gene is a tumor-suppressor gene located on chromosome 1, and encodes protein parafibromin, involved in regulation of other genes' transcriptions. Various inactivation mutations are associated with at least 50% familial HPT-JT syndromes as well about 20% of sporadic parathyroid carcinoma [19].

CaSR Gene

CaSR gene is a tumor-suppressor gene located on chromosome 3, and encodes G-protein transmembrane receptor, expressed mainly in parathyroid glands and kidney tubules, and is responsible for maintaining extra-cellular calcium ion level stability. Various inactivation mutations are associated with the extremely rare syndromes of familial neonatal severe hyperparathyroidism (NSHPT; homozygous), and familial hypocalciuric hypercalcemia (FHH; heterozygous), which mimic PHPT [20].

7.3.3 Surgical Pathology

Histological diagnosis of parathyroid pathology is usually *not* straightforward. Histological appearance of adenoma and hyperplasia frequently overlaps, and distinction may depend on whether other glands are involved. Additionally, not all cases of parathyroid cancer show frank histological malignant features, and clinical correlation is usually required.

7.3.3.1 Parathyroid Hyperplasia

Parathyroid hyperplasia has been reported in 10–15% of sporadic cases with PHPT; however, it is more common in familial cases. Diagnosis of hyperplasia typically entails multiple gland involvement (usually the four glands are involved), which may be a symmetrical or asymmetrical, diffuse or multinodular enlargement. There are two types of histological hyperplastic patterns. The first is *chief cell hyperplasia* pattern, which is the most common and can be found in both sporadic and familial PHPT. There is a positive family history and 25–35% has MEN-I or IIA, but *not* IIB. The second is the *clear cell hyperplasia*, which is rare and has *not* been reported in familial PHPT.

Hyperplastic glands are usually *not* fully encapsulated, with no rim of compressed normal tissue. The cell type and the amount of intra-glandular fat are variable. It is usually possible to distinguish an adenoma from hyperplasia, especially with biopsy of more than one gland. However, it is becoming less common for surgeons to biopsy apparently normal PTGs, so the final pathological diagnosis may have to include a caveat such as "the appearances are consistent with an adenoma provided that the other glands are normal." Some authors believe adenoma and hyperplasia are different morphological manifestations of the same process.

Under light microscopy, the cells in parathyroid hyperplasia are arranged in nests, sheets, trabeculae, or follicular structures. The nuclei are fairly uniform in size, with "salt and pepper" like chromatin as shown in Fig. 7.2. It may have some mitotic activity.

7.3.3.2 Parathyroid Adenoma

Adenoma is the commonest pathology seen in sporadic PHPT, with a reported incidence of 85–90%, while it tends to be less common in familial cases. Adenomatous change usually involves a single gland; however, involvement of two glands (double adenoma) or more has been reported in up to 20% of cases [21]. Criteria of *double adenoma* are: (1) enlargement of two glands, (2) the other two are normal, (3)

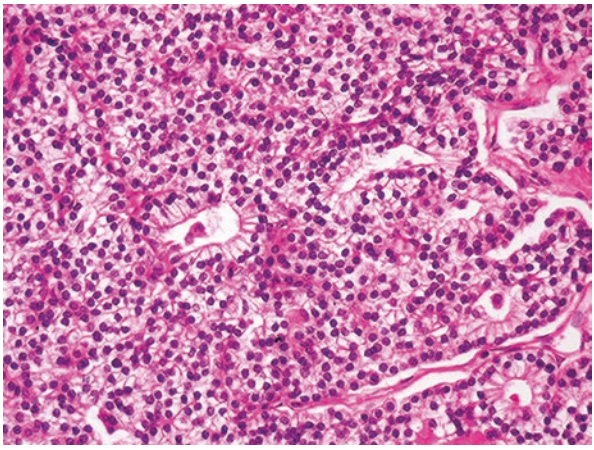

Fig. 7.2 High resolution of a micrograph: H&E stain showing parathyroid hyperplasia. Cells are arranged in nests, sheets, trabeculae, or follicular structures, and the nuclei are fairly uniform in size

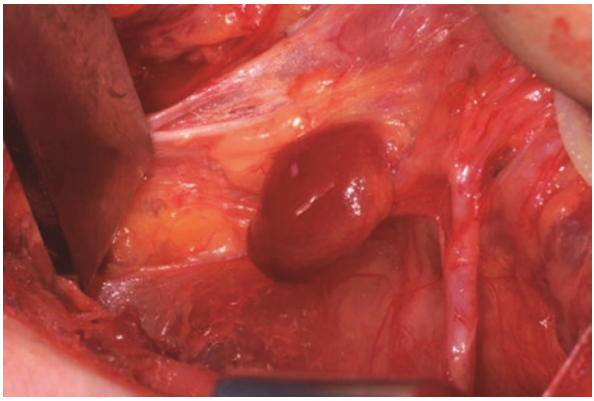

Fig. 7.3 A typical brick red globular appearance of a small parathyroid adenoma. This was an inferior gland that is seen just caudal to the inferior thyroid artery

negative family history, and (4) cure after excision of the two enlarged glands. The lower PTGs are usually affected (75%), whether right or left, more than upper glands.

Gross Appearance

Macroscopically, a parathyroid adenoma appears as a small well-encapsulated (well circumscribed) solid, oval, tumor (nodule), which is yellow/tan, dark red (Fig. 7.3), or grayish brown in color. It varies greatly in size, ranging from <1 cm to >10 cm. The term "micro-adenoma" has been used to describe tumors measuring <6 mm in size and <0.1 g in weight (it may lack the fibrous capsule). There is no invasion into adjacent structures [22].

Microscopic (Histological) Appearance

A typical parathyroid adenoma is well circumscribed, frequently with a thin fibrous capsule. Compressed non-neoplastic parathyroid tissue may be seen at the edge of the adenoma. Stromal adipocytes are either absent or reduced, i.e., there is little, if any, intra-cellular or extra-cellular fat. It is most commonly composed of *chief cells* (pure adenoma with round nucleus, little granular cytoplasm). Cells are arranged in cords, nests, sheets around blood vessels. Follicle formation is not rare. Mitoses and bizarre nuclei (endocrine atypia—nuclear pleomorphism) may be focally present (Fig. 7.4).

Variants of parathyroid adenoma include the following [23]:

- *Oxyphilic/oncocytic adenoma:* composed entirely of oncocytic cells with abundant, eosinophilic granular cytoplasm (Fig. 7.5).
- *Water-clear cell adenoma:* it is rare and cells have clear, glycogen-containing cytoplasm.
- *Lipoadenoma (hamartoma or mixed adenoma):* contains stromal (adipose) and parenchymal (usually chief cells) elements; most of the tumor is adipose tissue (Fig. 7.6).
- *Atypical adenoma:* contains borderline features concerning for (but not diagnostic of) malignancy; (1) dense fibrous bands with hemosiderin, (2) prominent

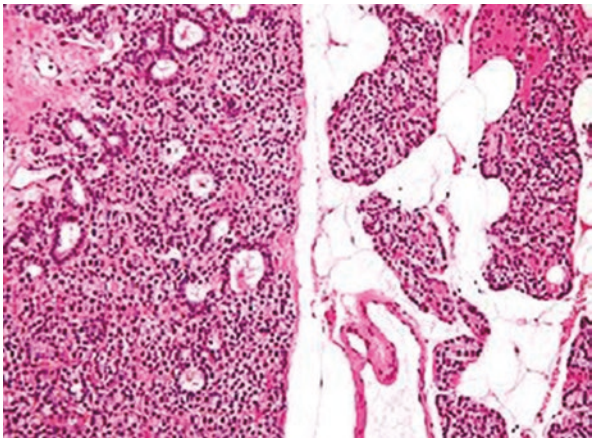

Fig. 7.4 A micrograph showing chief cell parathyroid adenoma (left of image) and unremarkable parathyroid gland (right of image). H&E stain. There is proliferation of chief cells, lacking adipose tissue, and with no invasion to surrounding structures

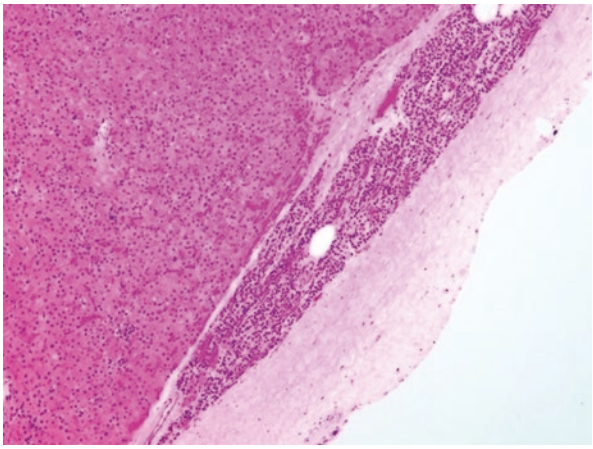

Fig. 7.5 A micrograph showing oxyphilic (oncocytic) cell parathyroid adenoma composed entirely of oncocytic cells with abundant, eosinophilic granular cytoplasm

nuclear atypia with spindled nuclei, (3) notable mitotic activity, (4) adherence to adjacent tissue, (5) necrosis, (6) solid or trabecular growth, and (7) no evidence of lympho-vascular invasion, perineural invasion, invasion into adjacent structures, or metastasis.

Cytology Description

Cellular aspirates show (1) uniform small cells in sheets, **three-dimensional** (3D) clusters, and trabecular arrangements (Fig. 7.7), (2) round dark nuclei with smooth nuclear borders and without nucleoli, (3) salt and pepper chromatin [24], (4) no colloid unless adjacent thyroid tissue is also aspirated, and (5) more monotony than normal thyroid tissue [25].

Electron Microscopy Description

Oxyphil cells are characteristically rich in mitochondria [26].

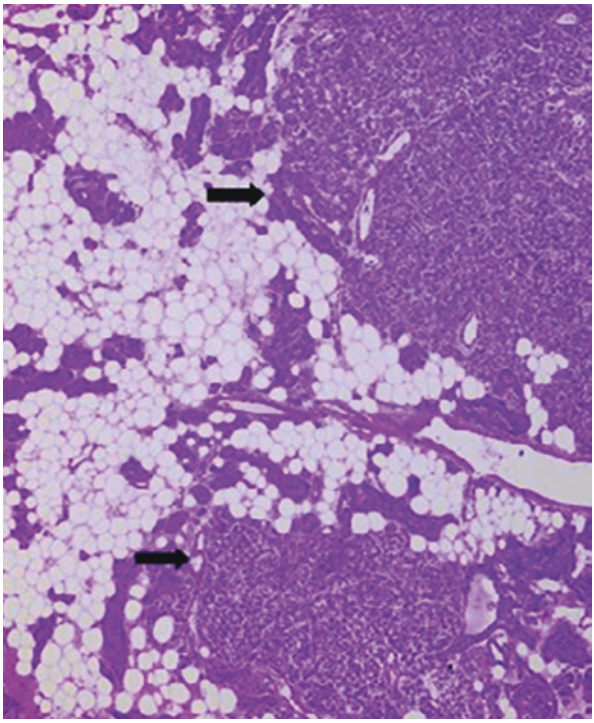

Fig. 7.6 A micrograph showing approximately 50% adipose tissue separating cords and nodular expansions of oxyphil cells (arrows), characteristic of parathyroid lipoadenomas (H&E stain: ×40)

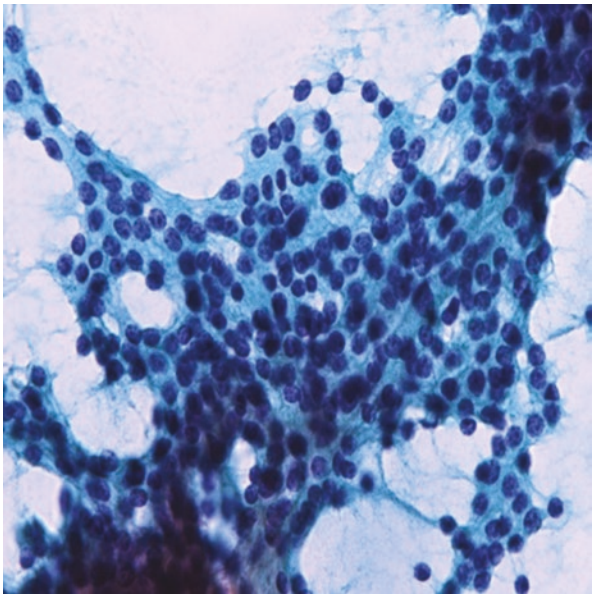

Fig. 7.7 Fine needle aspiration cytology (FNAC) of parathyroid adenoma showing chief cells arranged in sheets

Molecular/Cytogenetics Description

Molecular/cytogenetic studies are characterized by the following:

- *CDC73 (HRPT2)* in patients with hyperparathyroidism jaw tumor syndrome [22].
- *MEN1* in multiple endocrine neoplasia and sporadic adenomas.
- For fine needle aspiration samples, the Veracyte Afirma Gene Expression Classifier contains a cassette to distinguish parathyroid from thyroid tissue [25].
- Mutations in *CCND1* (cyclin D1), *ZFX*, and *EZH2* [23].

7.3.3.3 Parathyroid Carcinoma

Parathyroid carcinoma may occur with adenoma or chief cell hyperplasia and usually causes HPT. Suspicious pre-operative and intra-operative features should be communicated to the pathologist. Pre-operative features include severe hypercalcemia, evidence of regional nodal or distant metastasis, and recurrent laryngeal nerve (RLN) palsy. Intra-operative features include difficult dissection, thick capsule, and adhesion to or infiltration of thyroid gland. Parathyroid carcinoma spreads to cervical lymph nodes (LNs) and sends secondaries to liver, lung, bones, pancreas, and adrenals.

Histological features suggestive of a carcinoma that differentiate it from adenoma include thick fibrous capsule and septa; trabecular or rosette-like cellular architecture; frequent abnormal mitoses; capsular, vascular, or perineural invasion (although seen in only a few cases); and monotonous often bland nuclei.

7.3.4 Clinical Picture

A wide range of clinical symptoms is caused by prolonged over-secretion of PTH and hypercalcemia due to (A) parathyroid adenoma or (B) hyperplasia (Fig. 7.8). The clinical spectrum of PHPT has been long recognized by the historically famous mnemonic of "painful bones, kidney stones, abdominal groans, moans, thrones, and psychiatric overtones." However, in the last three decades, asymptomatic presentation has become the most frequently met clinical scenario. In addition, research in the field has revealed more insights on the association with cardiovascular and metabolic abnormalities.

The patient is usually between 30 and 60 years of age. The disease is rare before puberty. Women are more affected than men with a ratio of 3:1 or 4:1. The clinical presentation may include the following [1–3].

7.3.4.1 Classic Presentations

Skeletal Involvement

Bone disease is present in at least 15% of PHPT patients, and generally improves after parathyroidectomy. *Clinically*, skeletal involvement may be asymptomatic. Severe cases may manifest with (1) bone aches and tenderness, (2) deformities, e.g., kyphoscoliosis (due to vertebral collapse), (3) bone swellings (cysts in long bones or jaw), (4) pathological fractures, and (5) joint pains due to pseudo-gout (precipitation of calcium pyrophosphate crystals in the joint fluid). *Biochemically*, increased

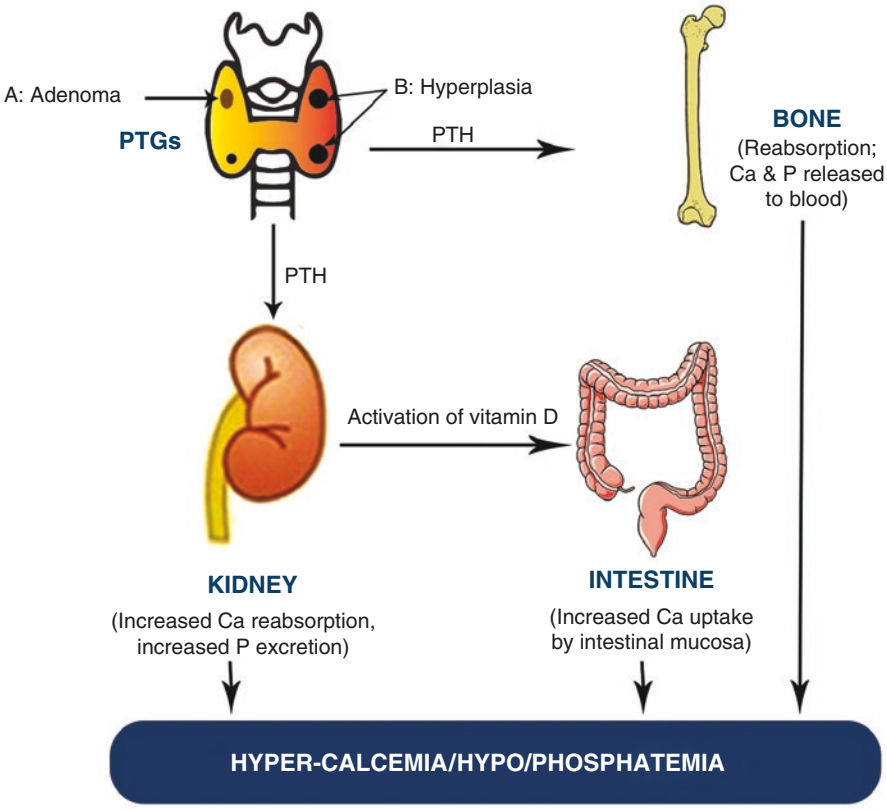

Fig. 7.8 In patients with PHPT, symptoms are caused by over-secretion of PTH from adenoma or hyperplasia and its action on target organs (bone, kidney, intestine) resulting in hypercalcemia. PHPT, primary hyperparathyroidism; PTH, parathyroid hormone

serum alkaline phosphatase is usually present, indicating increased bone turnover. *Radiological* features include the following:

1. *Decreased bone mineral density (BMD):* osteopenia and osteoporosis, in particular at more cortical sites (forearm and hip) as compared with more trabecular sites (spine).
2. *Osteitis fibrosa cystica* (*Von Recklinghausen's Disease):* rare, <5%, but pathognomonic.
   - Hand X-rays: subperiosteal resorption (most apparent on the radial aspect of the middle phalanx of the second and third fingers), bone cysts, and tufting of the distal phalanges (Fig. 7.9).
   - Skull X-rays: appears mottled (salt-and-pepper pattern) with a loss of definition of the inner and outer cortices (Fig. 7.10).
3. *Brown bone tumor* (very rare, <1.5%, but pathognomonic): focal, benign bony lesion caused by localized, rapid osteoclastic bone turnover, usually occurring in the mandible or maxilla (Fig. 7.11).

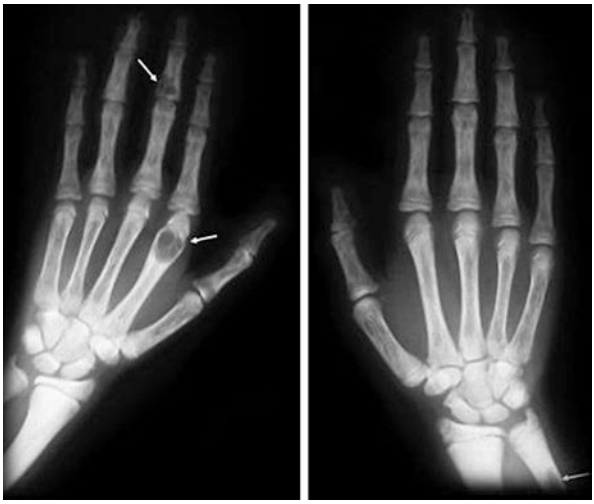

Fig. 7.9 Plain X-ray of the hands showing subperiosteal resorption and cyst formation (white arrows) in osteitis fibrosa cystica

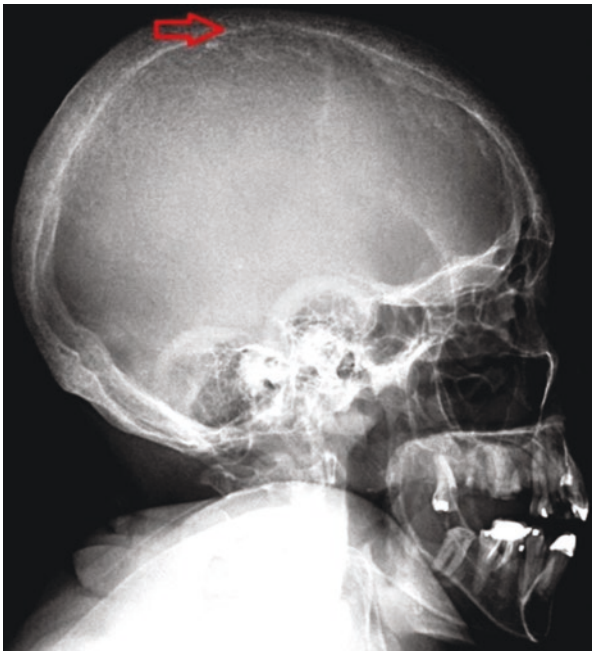

Fig. 7.10 Plain X-ray of the skull (lateral view) showing mottling with salt and pepper appearance (red arrow) in osteitis fibrosa cystica

Renal Involvement

Nephrolithiasis

Prevalence of symptomatic renal stones has decreased from 80% of patients in earlier series to 7–20% currently. Kidney stones occur with a similar prevalence in normo-calcemic (15%) and hypercalcemic (19%) patients with PHPT [27]. Hypercalciuria contributes to increased risk of renal stone formation (Fig. 7.12).

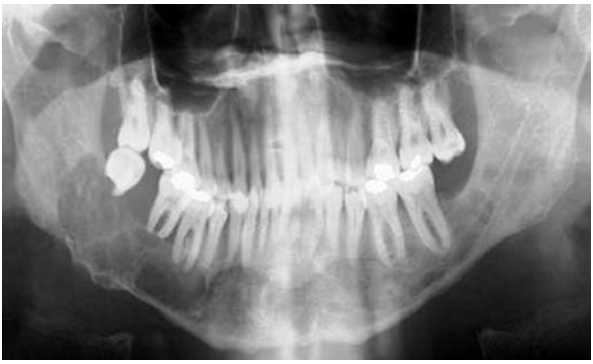

Fig. 7.11 Panoramic radiography showing a well-defined multilocular radiolucent lesion in the right mandibular body. It extends horizontally from the third molar to the second premolar and from the inferior border of the mandible to the alveolar ridge vertically

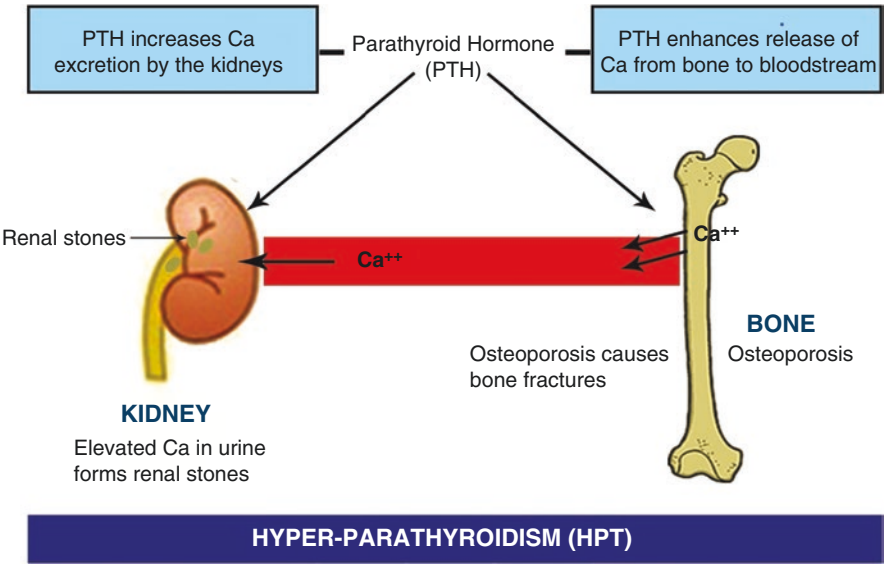

Fig. 7.12 Hypercalciuria in PHPT contributes to increased risk of renal stone formation. Osteoporosis occurs also in PHPT and may cause bone fractures. Ca, calcium

However, hypercalciuria by itself does not fully explain the increased risk [28]. Marked hypercalciuria is included as a guideline for surgery even in asymptomatic cases as risk of renal stones has been shown to be reduced by parathyroidectomy [29].

Deteriorated Renal Functions

Estimated glomerular filtration rate (eGFR) is inversely correlated with serum-intact PTH. Reduced renal function (GFR <70 vs. >70 mL/min) has been associated with greater reductions in bone mineral density (BMD). Reduced GFR, <60 mL/min, is included as a guideline for surgery even in asymptomatic cases. Successful surgery appears to prevent decline in renal function [30, 31].

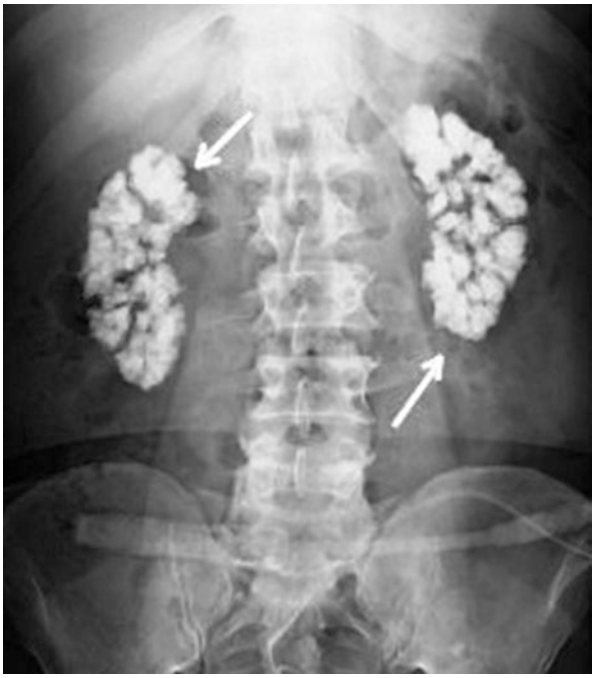

Fig. 7.13 Nephrocalcinosis appears on plain X-ray as calcified renal parenchyma (arrows)

Nephrocalcinosis

Nephrocalcinosis, once known as *Albright's calcinosis* after Fuller Albright, is a term originally used to describe "deposition of calcium salts—calcium oxalate and calcium phosphate—in the renal parenchyma due to HPT." It is now more commonly used to describe "diffuse, fine, renal parenchymal calcification on radiology" [32]. It appears as a fine granular mottling over the renal outlines on plain X-ray (Fig. 7.13).

Nephrocalcinosis is connected with conditions that cause hypercalcemia, hyperphosphatemia, and the increased excretion of calcium, phosphate, and/or oxalate in the urine. It is found in <5% of patients with PHPT [33]. It may contribute to progressive kidney dysfunction and hypertension. It may be severe enough to cause end stage kidney disease due to disruption of the kidney tissue by the deposited calcium.

Though this condition is usually *asymptomatic*, if symptoms are present they are usually related to the causative process (e.g., hypercalcemia). Some of the symptoms that can happen are hematuria, fever and chills, nausea and vomiting, and severe pain in the flanks, groin, or testicles. Renal colic is usually caused by preexisting nephrolithiasis, but can also result from calcified bodies moving into the calyceal system. Patients may also suffer from nocturia, polyuria, and polydipsia due to reduced urinary concentrating capacity (nephrogenic diabetes insipidus).

Renal Hypertension

Hypertension may occur due to renal impairment, hypercalcemia, and elevated renin levels. It appears to be more common in older patients and correlates with the magnitude of renal dysfunction, and is least likely to improve after parathyroidectomy.

Neuro-Muscular Involvement

Weakness and fatigue are common among patients with PHPT. A neuro-muscular syndrome characterized by atrophy of type II muscle fibers has been described in classical PHPT, though rarely seen today [34]. Neuro-muscular symptoms may improve after surgical cure [35].

Neuro-Psychiatric Involvement

Neuro-behavioral symptoms have been recognized in patients with PHPT although their prevalence is *not* well defined due to the lack of rigorous assessment for symptoms in many studies. These include lethargy, depressed mood, psychosis, decreased social interaction, and cognitive dysfunction. Exact pathogenesis is *not* known, but PTH may act on PTH receptors in the brain or reduce regional cerebral blood flow. Cellular apoptosis may be induced by intra-cellular calcium overload. Several studies showed improvement in these symptoms following surgical cure [36, 37].

Gastrointestinal (GIT) Involvement

The gastrointestinal manifestations of PHPT were described in the literature many decades ago as follows [38]:

- HPT causes smooth-muscle atony, resulting in upper and lower gastrointestinal symptoms such as nausea, heartburn (stomach atony), and constipation (colon atony).
- HPT may be associated with peptic ulcer due to hypercalcemia-induced hypergastrinemia. However, with the advent of proton pump inhibitors, such association is seen mostly in the context of MEN-1 (Zollinger-Ellison syndrome).
- Acute pancreatitis may occur due to precipitation of calcium salts in the pancreatic juice; distinction from secondary hyperparathyroidism is mandatory. Likewise, increased incidence of cholelithiasis may occur presumably due to an increase in biliary calcium.
- Finally, PHPT has been associated with increased incidence of malignancies, especially of the colon [39, 40].

The digestive manifestations of parathyroid malfunction are often overlooked. It has thus been suggested that serum calcium level must be included in the routine work-up for abdominal symptoms [41]. Significant reduction in symptom rates is found after parathyroidectomy. A summary of the classical manifestations of PHPT is depicted in Fig. 7.14.

7.3.4.2 Emergency Presentation (Parathyroid Crisis)

Parathyroid crisis (also known as *hypercalcemic crisis* and *acute hyperparathyroidism*) is a rare life-threatening PHPT complication, although it can also be the first evidence of parathyroid disease (i.e., presentation) [42]. It is currently defined as a "syndrome characterized by a serum calcium level of >3.5 mmol/L (>14–16 mg/dL) resulting from marked elevation of PTH with severe signs and symptoms of hypercalcemia."

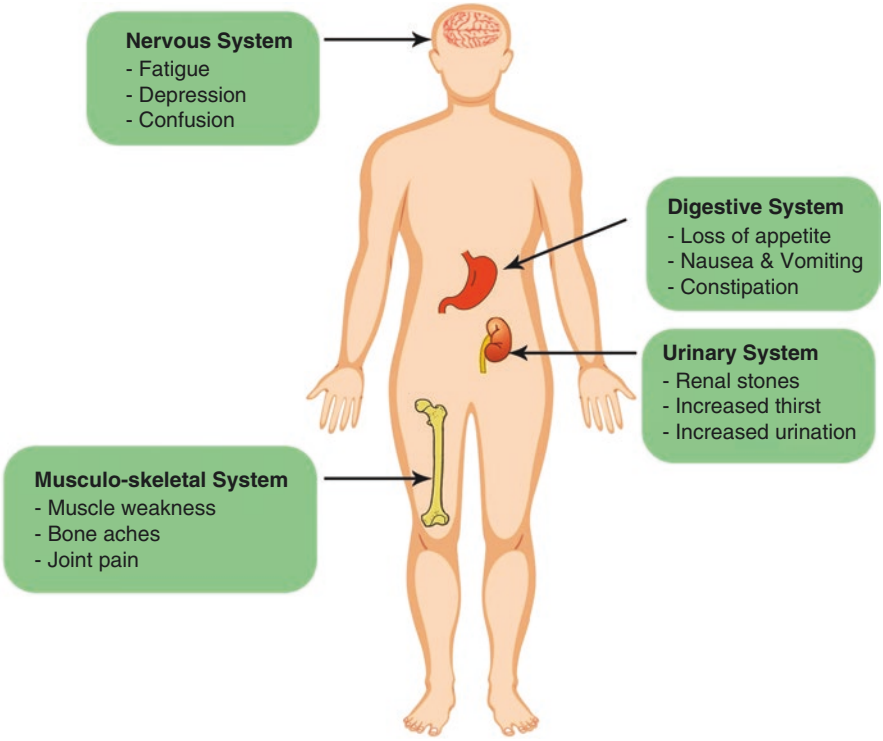

Fig. 7.14 Clinical manifestations of the classical presentation of primary hyperparathyroidism

Parathyroid crisis may present with lethargy, drowsiness, acute confusion, or coma associated with impaired renal function, profound dehydration, polyuria, thirst, nausea, vomiting, and constipation. Acute abdomen (perforated peptic ulcer, pancreatitis) and cardiac arrhythmias as well mortality have also been reported [43, 44].

7.3.4.3 Non-Classical Features

Cardiovascular Features

Hypertension

Hypertension is common in PHPT patients, even in mild disease [45] and normocalcemic disease [46]. In MEN-PHPT, association with pheochromocytoma accounts, at least in part, to the development of hypertension. In non-familial cases, pathogenesis is controversial; however, possible explanation includes renin–angiotensin–aldosterone axis dysfunction [47], enhanced vascular constriction in response to pressor hormones [48], or structural changes (vascular calcifications, increased intimal-media thickness) [49]. The effect of parathyroidectomy on hypertension is uncertain; although some studies reported maintained blood pressure reduction

[50], others did not [51]. Due to controversy of pathogenesis, and uncertainty of the effect of surgery, hypertension alone is *not* currently considered an indication of parathyroidectomy.

Cardiac Structure and Function

- Increased left ventricular mass (LVM), a predictor of cardiovascular mortality, has been reported in association with elevated PTH [52]. A recent meta-analysis concluded that LVM was reduced after parathyroidectomy, at least on short term [53].
- Increased risk of myocardial and valvular calcification has also been reported in patients with PHPT.
- Increased prevalence of arrhythmias (supraventricular and ventricular premature beats) has been reported in PHPT patients. These changes are related to short Q-T interval associated with hypercalcemia, and are significantly improved by parathyroidectomy [54].

Large Vessel Involvement

- Increased prevalence of abdominal aortic calcification has been reported in patients with PHPT [55].
- Increased carotid intima-media thickness (IMT), a predictor of cerebrovascular events, has been reported in PHPT patients, including those with mild disease. Worse carotid stiffness was correlated with higher PTH levels, suggesting its possible role in pathogenesis [56]. Whether IMT improves after parathyroidectomy is still controversial [57, 58].

Metabolic Abnormalities

Glucose Metabolism

An increased prevalence of impaired glucose tolerance, insulin resistance, and undiagnosed type-2 diabetes mellitus has been observed in PHPT patients [59]. The effect of curative parathyroidectomy on glucose metabolism is uncertain, with most studies reporting no change in insulin resistance post-operatively [60–63], while few others have demonstrated beneficial effect of surgery [58, 64, 65].

Body Weight and Lipid Profile

In a meta-analysis of 17 studies, PHPT patients have been observed to be heavier than age-matched controls [66]. Higher triglyceride levels as well as increased frequency of LDL-hypercholesterolemia were found in PHPT patients [67]. Both body mass index (BMI) and lipid profile did *not* change after parathyroidectomy in a study of 116 PHPT patients with a 2-year follow-up period [68].

Other Manifestations

Manifestations of Ectopic Calcification

Other symptoms may be present in patients with PHPT due to calcification in *other ectopic sites* such as (1) conjunctiva (blurring of vision), (2) around joints (pain), and (3) salivary glands (calculi).

Risk of Malignancy
Several studies have shown increased risk of malignancy in PHPT patients. Such increased risk appears to be unrelated to biochemical derangement of PHPT, since it persists even after parathyroidectomy. Possible etiological mechanisms include genetic predisposition to cancer or acquired disability to withstand environmental carcinogens in PHPT patients [69–71].

Risk of Mortality
Increased risk of "all-cause" mortality and "cardiovascular" mortality has been found in PHPT patients, including those with mild disease [72, 73]. The risk of death was lower in patients who had parathyroidectomy, compared to those who were conservatively managed [74].

Reduced Quality of Life (QOL)
Reduced QOL scores have been reported in PHPT patients. Patients who have been surgically cured experienced significant improvement in their QOL, although it remained lower than healthy controls [75].

7.3.4.4 Asymptomatic Primary Hyperparathyroidism

Definition
Asymptomatic PHPT is a term that describes those "patients who lack clear manifestations attributable to excess calcium PTH" [76].

Incidence
The introduction of the multichannel serum autoanalyzer in the 1970s, which included serum Ca measurement, led to the recognition of a group of individuals with asymptomatic hypercalcemia; evaluation led to the diagnosis of PHPT. Asymptomatic PHPT, presenting on routine biochemical screening, has become the most common presentation of PHPT in Europe and North America, accounting for up to 80–85% of PHPT presentations [77].

Natural History
Biochemical profile (serum Ca and PTH levels) remains stable in most patients, although they may increase over time in <15% of subjects. However, 27–37% of patients with asymptomatic PHPT may develop disease progression (development of at least one new indication for parathyroidectomy) in studies with 10–15 years of follow-up [1, 2, 78].

Biochemically
Biochemical changes seen in patients with asymptomatic PHPT may include [79]:

- Mild hypercalcemia, generally within 1 mg/dL of the upper limit of the normal range. Serum calcium may sometimes be intermittently normal.
- The PTH level is usually within 1.5–2-fold above the upper limit of normal.

- Unlike classical PHPT, serum phosphorus concentration is *not* usually low.
- Urinary calcium excretion is elevated in only about one-third of patients.

Clinically

Careful history-taking may reveal that some of these patients with presumed asymptomatic disease have some non-specific symptoms, such as fatigue, weakness, anorexia, mild depression, and intellectual weariness. Therefore, the differentiation between symptomatic and asymptomatic PHPT is *not* always clear.

Generally, neck examination in PHPT patients does *not* show any specific physical findings. Palpation of a neck mass in PHPT patient may indicate a concomitant thyroid nodule, rather than parathyroid pathology.

Densitometric and histo-morphometric studies in these patients commonly show reduced bone mineral density (BMD) at cortical sites (distal radius) with preserved cancellous sites (lumbar spine) [80].

7.3.5 Investigations

7.3.5.1 Diagnostic Studies

Biochemical Laboratory Tests

Diagnosis of PHPT is established by measuring serum Ca and PTH levels, which shows *hypercalcemia* (normal = 2.2–2.7 mmol/L) and *inappropriately high PTH levels*. Hyper-parathormonemia could also be produced by thiazide treatment, idiopathic hypercalcemia, or tumors producing PTH-like polypeptides. Conversely, some patients with PHPT may have normal levels of PTH. Laboratory tests may also show *hypophosphatemia* (normal = 3–4.5 mg/dL) and *hyperphosphaturia*. Routine assessment should include also *renal function tests* (serum urea and creatinine) and *vitamin D3* levels. *Serum alkaline phosphatase* is elevated if the bone is involved (normal = 3–13 KA units). It is *not* specific as it also rises in sarcoidosis, Paget's disease, and bone and hepatic malignancies.

Classical PHPT

Serum Calcium

About 45% of serum calcium is bound to proteins, mainly albumin. Consequently, total serum calcium concentration in patients with low or high serum albumin levels may *not* accurately reflect the biologically active (ionized) calcium. Therefore, serum calcium should be adjusted/corrected for albumin using the following calculation: "corrected calcium = measured calcium + (40-measured albumin) × 0.02," where calcium concentrations are in mmol/L and albumin is in g/L. In classic PHPT, serum albumin adjusted calcium is elevated. Reference range is 2.2–2.6 mmol/L, or 8.8–10.4 mg/dL. A single elevated serum calcium concentration should be repeated to confirm the presence of hypercalcemia.

Serum PTH

Serum PTH should be measured using either intact PTH (*second-generation PTH assay*) or whole (1–84) PTH assays (*third generation*). Serum albumin adjusted calcium should be measured concomitantly to enable interpretation of PTH result. Reference value for serum PTH varies according to the type and generation of the assay used, but it generally ranges from 1.6 to 6.9 pmol/L or 15 to 65 pg/mL [81]. Approximately 80–90% of PHPT patients have serum PTH concentrations above the normal range, often in the range of twice the upper limit of normal. Nearly 10–20% of patients have serum PTH values that are normal or only minimally elevated. These "normal" values in the presence of hypercalcemia are interpreted as "inappropriately non-suppressed." If the PTH concentration is low, PHPT diagnosis is unlikely, and further investigation is needed for non-PTH-mediated causes of hypercalcemia.

Assays recognizing N-truncated PTH fragments are actually measuring biologically inactive PTH fraction, an issue of concern in patients with renal impairment in whom C-terminal fragments significantly accumulate. The *first-generation PTH assay* described by Berson et al. in 1963 was a competitive immunoassay employing single radio-labeled antibodies directed either against N-terminal, mid-molecule, or C-terminal regions of the PTH peptide [82]. An important limitation of these assays was its low accuracy, which is attributed to their cross-reaction with biologically inactive PTH fragments. In 1987, Nussbaum et al. introduced the *second generation* of non-competitive immunoassays (aka: intact PTH assay), which employed the "sandwich technique" where two antibodies are directed against different regions of the PTH peptide [83]. A radio- or luminescence-labeled detector antibody is usually directed against the N-terminal region of the PTH peptide (1–34) and a capture antibody is attached to a solid phase and directed against the C-terminal region of the PTH peptide. Despite the improved accuracy of these assays, they still cross-react with the non-bioactive amino-truncated PTH fragment (7–84), mainly because of the low specificity of the amino-targeted antibodies. *Third-generation* (aka: bio-intact or whole PTH assay) immune assays have consequently been developed with a higher specificity of the N-terminal directed antibody, i.e., recognizing only the first four to six N-terminal amino acids thereby detecting at least theoretically only bioactive (1–84) PTH [84]. However, oxidative stress in patients with advanced renal disease may result in oxidation of methionine residues at positions 8 and 18 of PTH polypeptide, resulting in loss of biological activity. Such oxidized form may still be detected by third-generation assays; therefore, some authors have been questioning whether a *fourth-generation* assay may be needed to accurately reflect the level of functioning PTH in renal failure patients [85].

Such developments resulted in increased accuracy of PTH measurements, but they remained confined to the main hospital laboratory and used exclusively for routine diagnostics where long time to result (hours) was not a disadvantage. Timing of the assay became relevant when the concept of observing dynamic changes of PTH concentration during parathyroid surgery was introduced in 1988 by Nussbaum et al. [86]. They established that 40% or more reduction in PTH concentration of the baseline within 15 min of excision of pathological parathyroid correlated with operative

success. Therefore, manufacturers started to introduce more development into these assays to enhance "time-to-result" issue. Most of these assays utilize signal-generating "label-marked detector" antibody that recognizes a certain sequence in PTH peptide in the analyte (patients plasma), and capture antibody, attached to a slid phase, that recognizes another sequence in the PTH peptide. The strength of the signal is then measured and correlates with PTH concentration in the analyte [87].

24-Hour Urinary Calcium

Measurement of 24-h urinary calcium excretion is required after initial diagnosis of PHPT for two reasons:

(a) To assess the indications for surgery in biochemically confirmed but clinically asymptomatic PHPT. Since nephrolithiasis is, at least in part, predisposed by hypercalciuria, 24-h urine for calcium more than 400 mg/day is an indication for surgery [88].
(b) To differentiate between PHPT and familial hypocalciuric hypercalcemia (FHH), a rare cause of hypercalcemia and high PTH. In patients without vitamin D deficiency, an elevated urinary calcium concentration (>200 mg/day) or creatinine clearance ratio greater than 0.01 essentially excludes FHH. Vitamin D deficiency may reduce urinary calcium excretion; therefore, it should be repleted before diagnosis of FHH can be made [89].

Serum Vitamin D

Based upon current National Institute of Health and Care Excellence (NICE) Guidelines, vitamin D *insufficiency* is defined by "serum 25-hydroxyvitamin D concentrations between 25 and 50 nmol/L and vitamin D *deficiency* by concentrations below 25 nmol/L." 25-Hydroxyvitamin D should be measured in all patients with elevated (or inappropriately non-suppressed) PTH for two reasons:

(a) In case of elevated serum PTH with normo-calcemia, to differentiate secondary HPT from normo-calcemic PHPT. 25-Hydroxyvitamin D may be low in the former but should be normal in the latter.
(b) In case of elevated serum PTH with normal or low urinary calcium excretion, to differentiate between FHH and PHPT with vitamin D deficiency. Urinary calcium excretion increases with vitamin D repletion in PHPT, but it remains normal or low in FHH [90].

Other Laboratory Studies

- Renal function should be assessed because chronic kidney disease can also lead to increases in serum PTH level.
- Phosphate values may be low due to the phosphaturic effects of PTH.
- Markers of bone turnover do not need to be measured to confirm a diagnosis of PHPT.

Normo-Calcemic PHPT

Normo-calcemic PHPT is thought to be attributed to target organ resistance to PTH; when compared to hypercalcemia PHPT subjects, normo-calcemic patients showed less PTH suppression in response to oral calcium load [91]. Another theory is that it may represent initial stage in PHPT evolution. Approximately, 22% of symptomatic normo-calcemic patients developed hypercalcemia over mean follow-up of 4 years in the study by Bilezikian and Silverberg in 2010 [92].

Diagnostic Criteria

- Serum albumin adjusted calcium should be consistently normal. It is not uncommon that patients with classical PHPT may have occasionally or intermittently normal serum albumin adjusted calcium.
- Serum ionized calcium should also be normal.
- Other cases of elevated serum PTH should be excluded. These include vitamin D deficiency, reduced creatinine clearance, medications (hydrochlorothiazide and lithium), primary hypercalciuria, and calcium malabsorption [92].

Mild PHPT

The term "mild PHPT" is another term that has been frequently used in the literature. In fact, the term "mild PHPT" is a broad term that includes within its spectrum the previously defined term (normo-calcemic), and probably shares the same pathogenetic process, i.e., abnormality of PTH inhibition related to abnormal Ca-sensing mechanism, and/or it may just represent the initial (mild) phase of a disease with biphasic severity of natural history. There has, however, been a remarkable inconsistency regarding its definition as follows:

- Asymptomatic disease [93].
- Mildly elevated serum calcium (<2.72 mmol/L [94], ≤2.75 mmol/L [81], <2.85 mmol/L [95], or ≤2.87 mmol/L [96]).
- Mildly elevated serum calcium *and* mildly elevated serum PTH (PTH: 65–100 pg/mL and Ca: 10.4–11 mg/dL) [97].
- Normal baseline serum PTH concentration (<65 pg/mL), i.e., normo-hormonal PHPT [98].
- Normal pre-operative serum calcium <10.2 mg/dL; i.e., normo-calcemic PHPT [98].

Genetic Mutations

Genetic mutations causing HPT are rare in adults, but frequent in children. Positive genetic test is helpful in establishing diagnosis of familial HPT, planning treatment, and initiating biochemical and genetic screening of other members of family. In patients with a positive family history, testing for mutations should start with the MENIN gene [99] followed by parafibromin (HRPT2) gene [100–102] if the gland is an atypical adenoma or carcinoma. RET mutation analysis is recommended for patients with features consistent with MEN-2a [103].

Alternative to sequential genetic screening described above is to perform an analysis of all genetic mutations associated with HPT at once. Currently available panel of genetic tests include MEN-1 and 2; CaSR; CDC73; and CDKN 1A, 1B, 2B, and 2C, and is cheaper than performing these tests separately.

Imaging Studies

- *Plain X-ray of the bone* may show the following: (1) Subperiosteal resorption of bone demonstrated in the middle phalanx of the index and middle finger, outer third of the clavicle, distal ulna, tibia, neck of femur, symphysis pubis, and skull, (2) bone cysts or generalized osteoporosis, (3) deformities, e.g., wedged vertebrae, (4) pathological fractures, (5) moth-eaten ground glass appearance of the skull, and (6) other bone diseases such as osteoclastoma (Brown tum*o*r) may be detected.
- *Chest X-ray* may show kyphoscoliosis.
- *Plain radiology of the urinary tract* may show stones (stag-horn) or nephrocalcinosis.
- *Computed tomography* (CT) scan may be utilized to rule out other causes of hypercalcemia.

Other Studies

- *Bone Biopsy* (iliac crest) shows cortical resorption and osteolysis even if plain X-ray is normal.
- *Bone densitometry* can measure 5–10% reduction in bone density in patients with HPT.
- *ECG shows* shortened Q-T interval (hypercalcemia).
- *Slit-lamp examination* may show corneal calcification.

7.3.5.2 Localizing Studies

Rationale and Principles

In 1986, a classic statement was made by John Doppman: "in my opinion, the only localizing study indicated in a patient with untreated primary hyperparathyroidism is to localize an experienced parathyroid surgeon" [104, p. 117]. In fact, this statement has been widely accepted, in the era of bilateral neck exploration (BNE)-based parathyroidectomy, which proved high efficiency, with a cure rate of up to 97% in some published series [105]. Additionally, failed parathyroidectomy was due to missed multiglandular disease or small adenomas—two conditions in which imaging reliability is known to drop substantially. Another reason for failed surgery is ectopic gland location, a factor that can be mitigated if surgery is performed by a surgeon with knowledge and skills of exploring potential ectopic locations.

In the last two decades, technological advancement resulted in improved accuracy of PTG imaging localization. The concept of minimally invasive parathyroidectomy (MIP) has become gradually more appealing, and essentially become the gold standard for single gland disease (SGD). Thus, national guidelines currently recommend parathyroid imaging localization as a routine for patients who are candidates for

parathyroidectomy. Protocols for imaging however vary as there is marked regional variability in imaging accuracy. In the UK, for example, NICE guidelines state that ultrasound (US) is usually the first modality, and Technetium-99 m methoxyisobutylisonitrile (MIBI, aka as Sestamibi) scan is the second modality.

Imaging of abnormal PTGs is, nowadays, a critical part of the pre-operative work-up especially in patients with sporadic PHPT. Its main role is to identify the position of enlarged PTG in the neck or the mediastinum and to differentiate between single- and multiple-gland diseases. Imaging is less helpful in familial and renal HPTs when neck exploration and removal of multiple PTGs are usually required. In these situations, embarking on surgery without localization studies is acceptable [106].

Imaging Modalities

Ultrasound (US) of the Neck

Neck ultrasonography is usually done using a high frequency (7.5–15 MHz) transducer to enhance spatial resolution and allow detection of small glands and identification of their position. The patient should be supine with the neck hyperextended. Examination should proceed from the carotid bifurcation superiorly to the sternal notch inferiorly and the carotid artery/IJV laterally [107, 108]. Normal-sized parathyroid glands are usually not visualized with US. On gray-scale images, parathyroid adenomas appear as a discrete, oval, an-echoic, or hypoechoic masses (Fig. 7.15) located posterior to the thyroid gland, anterior to the longus colli muscles, and, frequently, medial to the common carotid artery. An echogenic line that separates the thyroid gland from the enlarged parathyroid gland can usually be seen [109]. Larger adenomas are more likely to have cystic change, lobulations, increased echogenicity due to fatty deposition, and occasional calcifications [110].

Color Doppler assessment is a useful tool for differentiating parathyroid lesions from other cervical masses. It has been used to localize enlarged PTGs. Parathyroid adenomas tend to be hyper-vascular lesions. An extra-thyroidal artery may lead to a

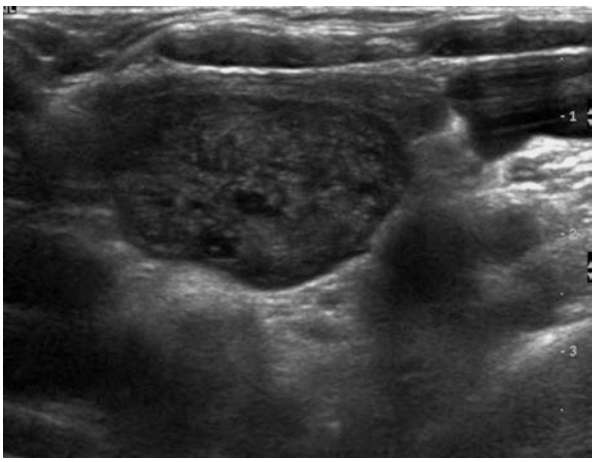

Fig. 7.15 Ultrasound image showing clearly an enlarged PTG as a homogenously an-echoic nodule

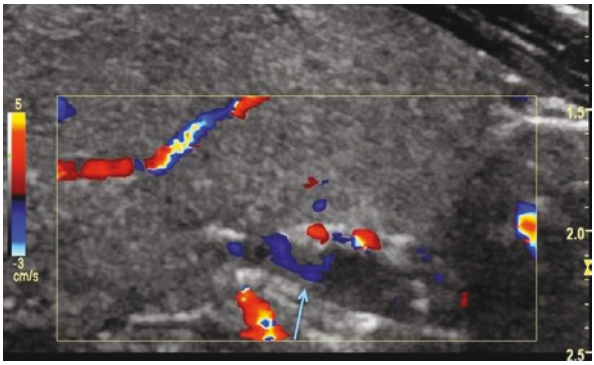

Fig. 7.16 Ultrasound imaging with color Doppler showing a hypoechoic lesion posterior to the thyroid gland with a polar vessel sign (arrow)

parathyroid adenoma in up to 83% of patients [111]. An extra-thyroidal feeding vessel may provide a roadmap to an otherwise inconspicuous gland. Characteristically, the extra-thyroidal artery enters at one pole of the gland (polar artery—a finding occasionally appreciated on **four-dimensional** [4D]-CT as well; Fig. 7.16). However, color Doppler sonograms of parathyroid adenomas may not show increased vascularity until the lesions are 1 cm in size.

The *specificity* of ultrasound in detecting parathyroid adenomas ranges from 40% to 98%, while the *sensitivity* has been reported to range from 55% to 83% [112]. Ultrasound is especially limited in the mediastinum, owing to a poor or absent acoustic window. A recent meta-analysis calculated pooled sensitivity to be 80% for detection of parathyroid adenoma, 35% for hyperplasia, and 16% for double adenomas [113]. *False-positive* findings result when thyroid nodules, enlarged lymph nodes, the esophagus, longus colli muscles, and perithyroid veins are mistaken for enlarged parathyroid glands. *False-negative* sonographic results are more likely to result from (1) small adenoma size, (2) ectopic locations lacking an adequate acoustic window, and (3) poor visualization of neck structures due to previous surgery, associated multinodular thyroid pathology (thyromegaly), or body habitus [108, 114].

Localization of adenomas in the mediastinum is limited because of the lack of an acoustic window and the difficulty in visualizing structures posterior to the air-filled trachea and esophagus. If an intra-thyroidal lesion is detected, the lesion cannot confidently be differentiated as a parathyroid adenoma or thyroid nodule. Aspiration biopsy is required.

Advantages of US include low cost, wide availability, absence of exposure to ionizing radiation, and ability to evaluate concomitant thyroid disease. *Disadvantages* include being operator-dependent, and inability to visualize retro-manubrial or mediastinal locations.

Nuclear Imaging (Scintigraphy)

Nuclear imaging is better than US at detecting ectopic adenomas. Technetium-99m (^{99m}Tc) methoxyisobutylisonitrile (MIBI), originally used for imaging of myocardial perfusion, was noted to be preferentially taken by PTGs, which is thought to be related to the rich mitochondrial content of parathyroid oxyphil cells. However, it

also accumulates significantly in the nearby thyroid tissue. The two most commonly used techniques to differentiate parathyroid from thyroid uptake are:

(a) *Dual radiotracer/digital subtraction approach* (dual-isotope technique or Technetium-Thalium Subtraction [TTS]): The thyroid is first scanned by intravenous (IV) injection of ^{99c}Tm. A bolus of ^{201}Thalium is then given and taken by both thyroid and parathyroid glands. The two images are recorded by a gamma camera and the thyroid image is subtracted from the combined image, leaving a parathyroid hot spot.
(b) *Dual-phase technique:* Images are obtained immediately after MIBI administration and then again approximately 2 h later. The tracer wash out more significantly and more rapidly from thyroid than from parathyroid adenoma due to higher mitochondrial content of the latter.

Single photon emission computed tomography (SPECT), which produces 3D images from two cameras, adds an anatomical perspective to the functional uptake, allowing better focal discrimination of MIBI retention in thyroid versus parathyroid tissue (Fig. 7.17) [115].

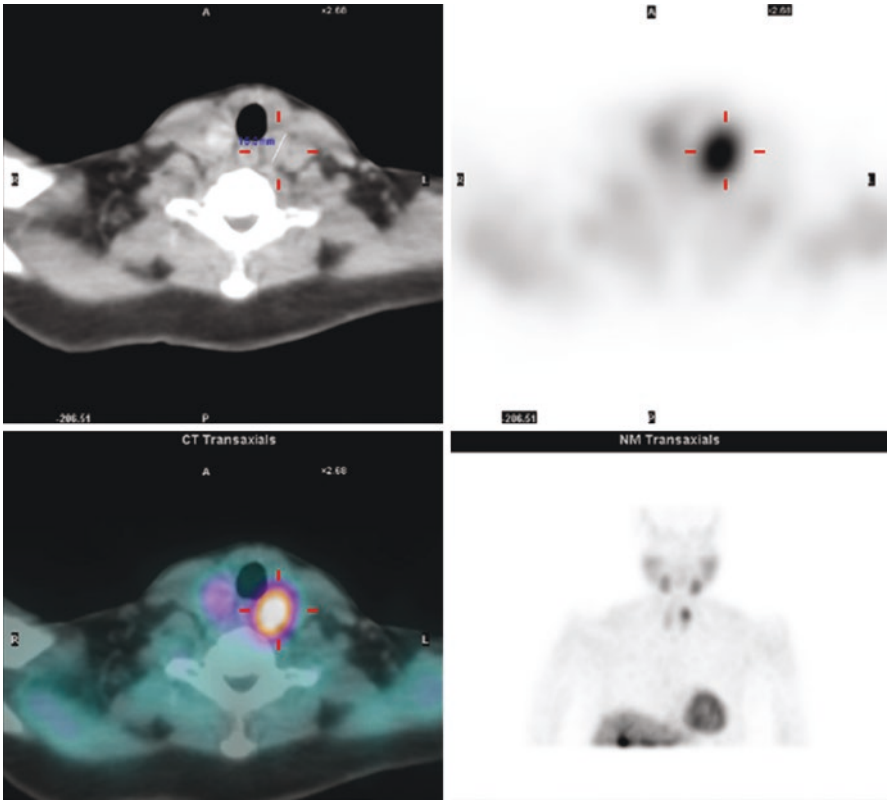

Fig. 7.17 CT/MIBI image showing an enlarged parathyroid in left upper position

Parathyroid adenomas and to lesser degree hyperplastic glands show higher tracer uptake in the early stage and delayed washout in the late image as compared to the surrounding thyroid tissue. The sensitivity of MIBI is reported to be 88% in detecting solitary adenomas, 44% in detecting hyperplastic glands, and 30% in detecting double adenomas [116]. In general, sensitivity of MIBI scan as a single modality for identifying adenomas ranges from 54% to 100%. A recent study reported that addition of SPECT improved sensitivity to 97%, compared to 63% for MIBI planar imaging alone [117]. *False-positive* results may happen in case of associated thyroid pathology, particularly chronic thyroiditis and Hurthle cell lesions. Small gland size and MGD are noted to increase *false-negative* results [118]. The main *advantage* of MIBI scintigraphy is the ability to assess ectopic locations including the mediastinum. *Disadvantages* include necessity of neck immobilization (in dual-tracer approach), and long scan time (in double-phase approach). Some studies showed no significant additional diagnostic yield of MIBI after neck US done with experience [119].

(11)C-methionine positron emission tomography/computed tomography (Met-PET/CT): In one study, *Met-PET/CT* raised the rate of correctly localized single parathyroid adenomas in patients with negative cervical ultrasonography and MIBI-SPECT/CT and increased the number of focused surgical approaches. Cervical US localized a single parathyroid adenoma in 10/17 patients (59%), while MIBI-SPECT/CT identified 11/17 single adenomas (65%). In the remaining six patients, Met-PET/CT identified five single adenomas. This step-up approach correctly identified single adenomas in 16/17 patients (94%) [120].

Computed Tomography (CT) Scan/Four-Dimensional CT (4D-CT)

Definition

Parathyroid four-dimensional CT (4D-CT) refers to multiphase computed tomography of the neck used to localize abnormal parathyroid glands (PTGs; i.e., adenoma, hyperplasia, or, rarely, carcinoma). The "4D" indicates that imaging is performed in multiple phases of contrast, with time being the fourth dimension in addition to the multiplanar format of CT; the number of phases is not necessarily four.

Technique

A typical protocol consists of scanning in three phases [121, 122]:

1. Non-contrast phase.
2. Arterial phase: 25–30 s after start of contrast injection.
3. Delayed phase: 60–80 s after start of contrast injection.

The axial coverage, at least for the post-contrast phases, includes the entire neck (up to the angle of mandible or maxilla) and the mediastinum (down to the carina) [121, 122].

Approach

A systematic approach is suggested based on anatomical and attenuation characteristics [121, 122]:

1. Typical morphology [121]:
   - Parathyroid lesions are usually oval or round, smooth or slightly lobulated.
   - Abnormal PTGs are usually supplied or drained by a prominent polar (as opposed to hilar) blood vessel.
2. Anatomical search pattern:
   - Search eutopic locations around the thyroid gland: Approximately, 85% of PTGs are eutopic, more frequent for superior glands and less frequent for inferior glands [2]. Superior glands are located posterior to the tracheo-esophageal groove and may fall caudally when enlarged, while inferior glands are anterior to the tracheo-esophageal groove.
   - Search ectopic locations in the para-pharyngeal space including carotid sheath, retro-pharyngeal/retro-esophageal space, thyrothymic ligament continuing into the anterior mediastinum (retro-sternal; Fig. 7.18), and tracheo-esophageal groove (Fig. 7.19) continuing into the posterior mediastinum. Approximately, 3% of superior PTGs are retro-pharyngeal/retro-esophageal and 28% of inferior PTGs are located along the thyrothymic ligament and anterior mediastinum [122].

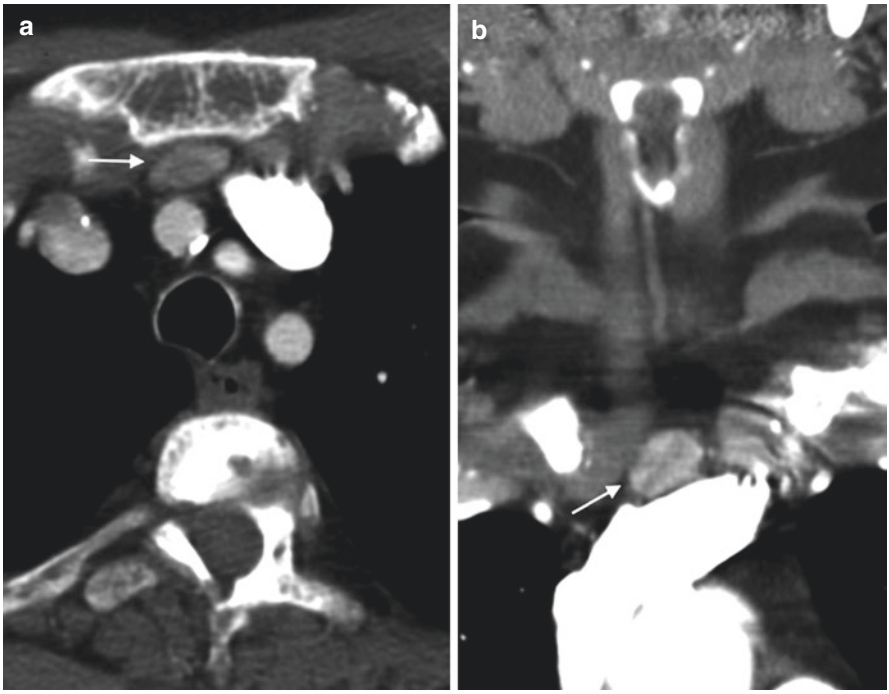

Fig. 7.18 4D-CT: Axial (**a**) and coronal (**b**) post-contrast imaging showing an enhancing retro-sternal ectopic parathyroid adenoma (arrows)

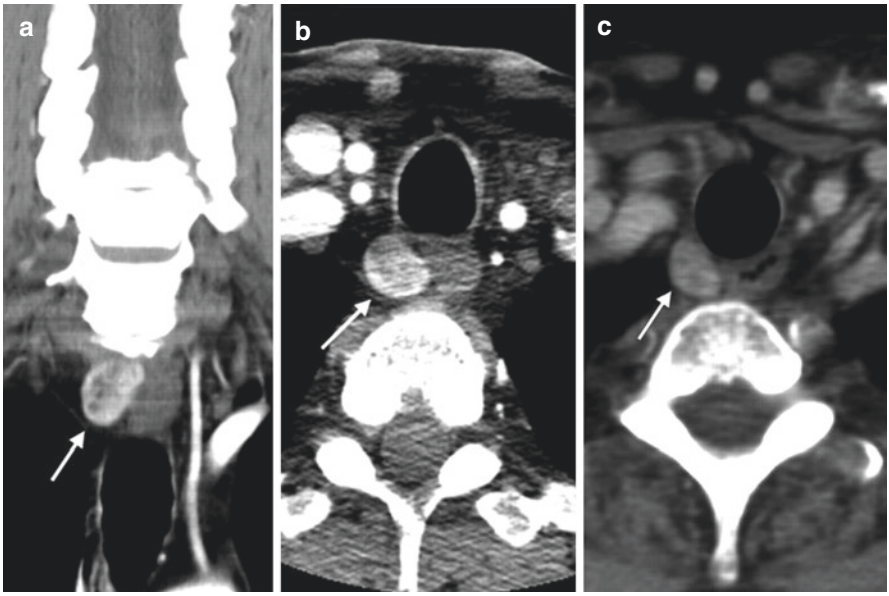

Fig. 7.19 4D-CT: Coronal early phase (**a**) post-contrast, axial early phase (**b**) and axial delayed phase (**c**) post-contrast images showing an early enhancing 1.3-cm nodule in the right tracheo-esophageal groove, with modest contrast washout denoting a right inferior PTG in the orthotopic location. Pathology showed a 3-g parathyroid adenoma (arrows)

- Evaluate the thyroid gland for intra-thyroid PTGs or thyroid nodules, which may appear similar on CT although the latter are much more common.

3. Contrast-phase search pattern.
   - Review arterial-phase images for lesions that avidly enhance, greater than thyroid. About 20% of parathyroid lesions are distinct on arterial phase (known as type A pattern) [123].
   - Review the delayed phase for lesions that have washed out contrast more than thyroid (whereas thyroid tissue and lymph nodes progressively enhance). Nearly, 57% of parathyroid lesions are distinct on delayed phase, but *not* arterial phase (known as type B pattern) [123].
   - Review the non-contrast phase for lesions that have lower attenuation than thyroid (whereas thyroid tissue has high attenuation). Approximately, 22% of parathyroid lesions are distinct on non-contrast phase, but *not* arterial or delayed phases (known as type C pattern) [123].
   - Recognize variants such as glands with areas of low attenuation due to cystic or fat components, or areas of high attenuation due to calcification.

Advantages

While conventional CT scan has only limited role in parathyroid disease localization, the 4D-CT protocol has become an increasingly used and powerful tool for pre-operative localization of abnormal PTGs in the setting of PHPT. Precise

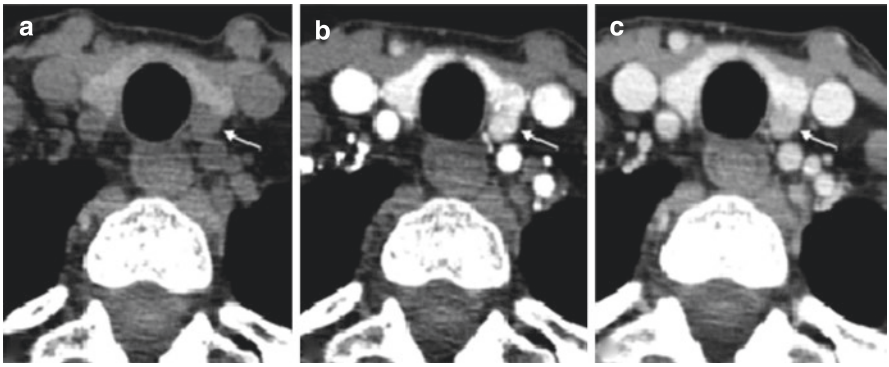

Fig. 7.20 Axial non-contrast (**a**), axial early phase post-contrast (**b**), and axial delayed phase post-contrast (**c**) images showing a hypoattenuated hypodense nodule contiguous with the left posterior thyroid gland, which demonstrates avid early contrast enhancement and washout. Pathology revealed a 600 mg parathyroid adenoma (arrows)

localization of a single adenoma (Fig. 7.20) facilitates minimally invasive parathyroidectomy, and localization of multiglandular disease aids bilateral neck exploration. In addition to the high-resolution visualization of 3D anatomic images, the 4D-CT protocol provides functional information related to the rapid uptake and washout of the contrast from the hyperfunctioning gland compared to thyroid and adjacent tissue.

Sensitivity of 4D-CT has been shown by Rodgers et al. (2006) to exceed that of US, and MIBI scan (88%, 57%, 65%, respectively, for lateralization, and 70%, 29%, 33%, respectively, for localization) [124]. However, current preferences for one modality or a combination vary by institution depending on expertise and experience.

The main advantages of 4D-CT are its demonstrated high sensitivity in detection of ectopic glands, small adenomas, and MGD, hence potential usefulness in disease localization in mild PHPT. Additionally, it has been reported to be effective in re-operative cases, those in which other modalities are negative [125–128].

The most important 4D-CT information to the surgeon includes the number, size, and specific location of candidate parathyroid lesions with respect to relevant surgical landmarks; the radiologist's opinion and confidence level regarding what each candidate lesion represents; and the presence or absence of ectopic or supernumerary parathyroid tissue, concurrent thyroid pathologic conditions, and arterial anomalies associated with a non-recurrent laryngeal nerve. Thus, the radiologist with the utilization of 4D-CT can substantially impact patient care by enabling the surgeon to develop and execute the best possible operative plan for each patient [8].

Disadvantages

The main *disadvantages* of 4D-CT are the high cost, increased radiation exposure, and requirement for a dedicated expert to interpret results [129].

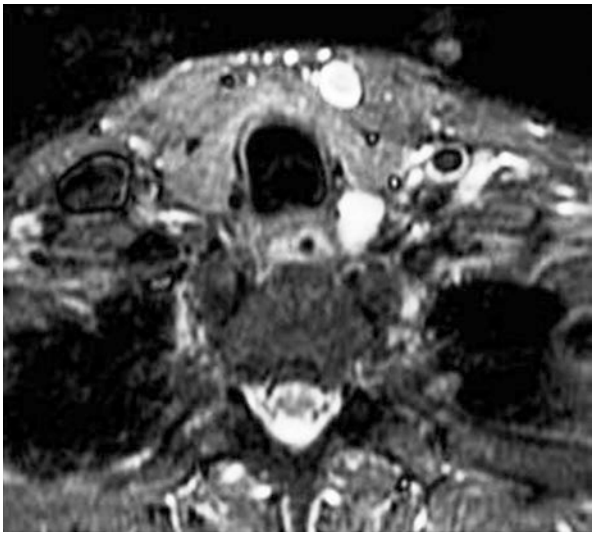

Fig. 7.21 Axial STIR image showing a T2 hyperintense lesion in the left tracheo-esophageal groove representing a parathyroid adenoma (at surgery)

Magnetic Resonance Imaging (MRI)/4D-MRI

A typical magnetic resonance imaging (MRI) protocol involves the acquisition of images through the neck and mediastinum. Axial, coronal, and sagittal views are typically acquired. A surface neck coil is used to image the neck and a chest coil for the mediastinum. Images are obtained from the hyoid bone to the lung apices by using T1- and T2-weighted spin-echo sequences. T2 acquisitions are typically fat-suppressed to increase conspicuity of the glands, with short tau inversion recovery (STIR), frequency-selective fat saturation, or DIXON-based fat-suppression techniques. A section thickness of 3 mm is typically acquired, with minimal intersection gap. Post-contrast T1 imaging is typically fat-suppressed to increase enhancement conspicuity [130].

Normal PTGs usually are not seen on MRI. Parathyroid adenomas are identified as soft tissue masses in the expected location of the parathyroid glands. They characteristically demonstrate low T1 signal, avid enhancement, and high T2 signal as shown in Fig. 7.21. Approximately, 30% of abnormal PTGs do not have the typical MRI signal intensity characteristics. Atypical patterns include (1) high signal intensity on T1-weighted images and low-to-medium signal intensity on T2-weighted images, (2) low signal intensity on both T1- and T2-weighted images, and (3) high signal intensity on both T1- and T2-weighted images. Low signal intensity on both T1- and T2-weighted images reflects cellular degenerative changes, old hemorrhage with hemosiderin-laden macrophages, and fibrosis in the abnormal gland. High signal intensity on both T1- and T2-weighted images has been associated with hemorrhage without significant degenerative or fibrotic changes [131].

Fat suppression can be problematic in the neck, requiring special attention to technique. There are little data supporting advanced MR techniques such as MR perfusion or dynamic contrast enhanced imaging.

Sensitivity of this modality (MRI) is generally inferior to 4D-CT, and ranges between 43 and 71%. However, MRI appears especially useful in detecting ectopic mediastinal glands, with sensitivities exceeding 80% [132].

False-positive findings are reported to result from the misidentification of the following as parathyroid adenomas: (1) enlarged lymph nodes, (2) thyroid nodules (adenomas and/or exophytic colloid cysts), (3) enlarged cervical ganglia, and (4) other neck masses such as sarcoid nodules and neuro-fibromas. Enlarged LNs have signal intensity characteristics similar to those of abnormal parathyroid glands. Abnormal PTGs are expected to be medial to the carotid sheath, whereas lymph nodes are most frequently situated around or lateral to the sheath.

False-negative findings most commonly result from small parathyroid glands. The mean volume of detected abnormal glands has been reported as 3.5 cm^3, while the mean volume of missed glands is 1.4 cm^3 [131]. Other reported false-negative findings result from concomitant thyroid disease, anatomical distortion due to previous surgery, ectopic glands (particularly intra-thyroidal glands), and atypical signal intensity characteristics. In a study of 11 patients with parathyroid adenoma in whom *four-dimensional MRI* (4D-MRI) was used, parathyroid adenomas were identified in 10 patients. In 9 patients, there was an exact match compared with ultrasound and sestamibi scan (MIBI). Sensitivity of 4D-MRI was 90%, and specificity was 100% [133].

Advantages of MRI include the lack of ionizing radiation rendering it suitable for pregnant women. It may also be a useful modality in imaging of re-operative cases, because of its high soft tissue definition.

Other Modalities

Several radiotracers (other than MIBI) have been studied in parathyroid imaging locations, e.g., ^{11}C methionine and ^{18}F fluoro-deoxy-glucose (FDG) [134]. Perhaps the most promising modality is *^{18}F-fluorocholine PET/CT*, which has demonstrated high diagnostic performance, in addition to being particularly useful in cases with negative traditional imaging [135]. Two recent studies have demonstrated 90% sensitivity of ^{18}F-fluorocholine PET/CT for parathyroid lesion localization [136, 137]. However, experience with choline scans is still limited and its use has not yet been recommended by national guidelines.

Although more common in the past, invasive procedures such as *parathyroid-selective arteriography* and/or *selective parathyroid venous sampling* are rarely performed and have now become almost completely obsolete [138]. The risks of parathyroid arteriography are stroke and spinal cord injury. The sensitivity of digital subtraction angiography (DSA) has been reported as 49% and that of parathyroid venous sampling ranges from 70% to 80% [139].

7.3.6 Differential Diagnosis

Hyperparathyroidism is the second common cause of hypercalcemia after *malignancy*.

7.3.6.1 Causes of Hypercalcemia

Endocrine Causes (PTH-Related)

Diseases that produce elevated PTH levels include the following:

1. *Hyperparathyroidism (HPT):*
   - PHPT: Increased PTH production by parathyroid adenoma, hyperplasia, or carcinoma.
   - SHPT: Through a negative feedback mechanism, hypocalcemia causes the release of PTH through the generation of cAMP. A reduction of 0.4 mg/dL in serum Ca doubles the PTH under physiological conditions.
   - MEN-1 syndrome (parathyroid adenoma, pituitary adenoma, pancreatic islet cell tumor).
   - Neonatal hyperparathyroidism.
2. *Hyperthyroidism:* Certain amines (epinephrine, dopamine, and histamine) may liberate PTH via the cAMP mechanism.
3. *Pheochromocytoma:* It may coexist with HPT as part of MEN-IIA. Alone, it can cause hypercalcemia secondary to Beta-adrenergic receptor activation and generation of cAMP with liberation of PTH.
4. *Familial hypocalciuric hypercalcemia*.
5. *PTH-related peptide (PTHrP)*: It is a protein member of the PTH family secreted by mesenchymal stem cells, occasionally by cancer cells. However, it also has normal functions related to "normal PTH" in bone, tooth, and vascular and other tissues. Tumors that secrete PTHrP cause hypercalcemia (considered a "paraneoplastic" phenomenon as it is sometimes the first sign of malignancy) [140]. PTHrP shares the same N-terminal end as PTH and thus it can bind to the same "Type I PTH receptor" (PTHR1), which is responsible for most cases of humoral hypercalcemia of malignancy. PTHrP can simulate most of PTH actions including increases in bone resorption and distal tubular Ca reabsorption, and inhibition of proximal tubular phosphate transport. PTHrP lacks the normal feedback inhibition as PTH [141]. It is less likely than PTH to stimulate 1,25-dihydroxy-vitamin D production. Therefore, PTHrP does *not* increase intestinal calcium absorption.
6. *Jansen's metaphyseal chondroplasia (JMC):* It is caused by a mutation in the *PTH-1R (receptor)* gene. Most cases are due to spontaneous mutation. Inheritance is autosomal dominant. It is extremely rare (as of 2007, there are fewer than 20 reported cases worldwide).

Malignancy

1. *Solid tumors with bone metastases* (osteolytic) from breast, thyroid gland, kidney, and gastrointestinal tract (GIT).
2. *Tumors producing PTH-like polypeptides (PTHrP):* Examples include breast cancer, certain types of lung cancer including squamous-cell lung carcinoma, in addition to kidney, urinary bladder, and pancreatic cancers.
3. *Hematological malignancies:* multiple myeloma, lymphoma, and leukemia.
4. *Ovarian small cell carcinoma* of the hypercalcemic type.

Calcitriol (Active Vitamin D)-Mediated

1. *Granulomatous* disease such as tuberculosis (TB) and sarcoidosis.
2. *Lymphoma* (ectopic calcitriol).
3. *Milk-alkali syndrome*: It is caused by excessive intake of calcium (usually as dietary supplements taken to prevent osteoporosis) and absorbable alkali (as are found in antacid drugs taken by patients with peptic ulcer who ingest large amounts of milk and antacids containing calcium carbonate) [142]. Among people hospitalized with hypercalcemia, milk-alkali syndrome is the third most common cause, after HPT and cancer [143]. In mild cases, full recovery is expected. In severe cases, permanent renal failure or death may result [142].
4. *Hypervitaminosis D:* Increased exogenous *vitamin D* (vitamin D intoxication).
5. *Dialysis* (exogenous vitamin D).
6. *Rebound hypercalcemia* after rhabdomyolysis.
7. *Subcutaneous fat necrosis:* It is a rare form of panniculitis most often seen in term infants following birth trauma or asphyxia, meconium aspiration, or therapeutic cooling [144]. Hypercalcemia is a potentially life-threatening complication that occurs in a subset of patients [143, 145–147].

Diseases Associated with Increased Ca^{++} Absorption or Resorption

1. *Sarcoidosis:* Hypercalcemia is probably due to increased sensitivity to vitamin D.
2. *Milk-alkali syndrome*.
3. *Vitamin D and vitamin A intoxication:* Increased absorption of Ca^{++} from the GIT as well as increased bone resorption.
4. *Prolonged rest (forced inactivity) and Paget's disease:* Hypercalcemia results from bone due to high bone turnover.
5. *Thiazide diuretics and Lithium intake:* Renal calcium excretion is reduced and bone turnover rates are increased.

Congenital Diseases

1. *Congenital hypophosphatemia.*
2. *Idiopathic hypercalcemia of infancy.*
3. *Jansen's metaphyseal chondroplasia* (JMC).

Diseases Associated with Hyper-Proteinemia

1. *Addison's disease.*
2. *Multiple myeloma.*

Renal Failure

1. Tertiary hyperparathyroidism (THPT).
2. Aluminum intoxication.
3. Milk-alkali syndrome.

Medications
1. Lithium.
2. Thiazides.
3. Vitamin D intoxication.
4. Vitamin A intoxication.
5. Aminophylline.
6. Retinoids.

Iatrogenic
1. Increased administration of calcium salts.

Miscellaneous
1. Acromegaly
2. Adrenal insufficiency
3. Zollinger–Ellison syndrome (ZES).

7.3.6.2 Differences between HPT and Malignancy

Common Primary Sites
The most common primary sites that cause bone secondaries are:

1. Cancer of the breasts, lungs, thyroid, suprarenals, and kidneys (osteolytic secondaries).
2. Cancer of the prostate and some breast scirrhous carcinomas (osteosclerotic secondaries).

Diagnosis
The clinical features of bone secondaries are pain, swelling, pathological fractures, cachexia, and evidence of the primary malignancy (if hidden as in the lungs or hypernephroma, diagnosis may be difficult). Differences between HPT and malignancy (bone secondaries) are summarized in Table 7.1 below.

An algorithm for the differential diagnosis of "hypercalcemia" is depicted in Fig. 7.22 below.

Table 7.1 Differences between HPT and malignancy

Criteria	HPT	Malignancy
• Onset and C/P	Long history of stone or peptic ulcer	Recent onset of symptoms
• Serum Ca level	↑ slightly (up to 12 mg/dL)	> 14 mg/dL
• Serum AP level	↑ (Osteitis fibrosa cystica only)	↑ without bone lesions
• PTH level	↑ (by RIA)	↑
• Anemia	–	+
• ESR	Normal	↑

AP alkaline phosphatase, *Ca* calcium, *C/P* clinical picture, *ESR* erythrocyte sedimentation rate, *PTH* parathyroid hormone

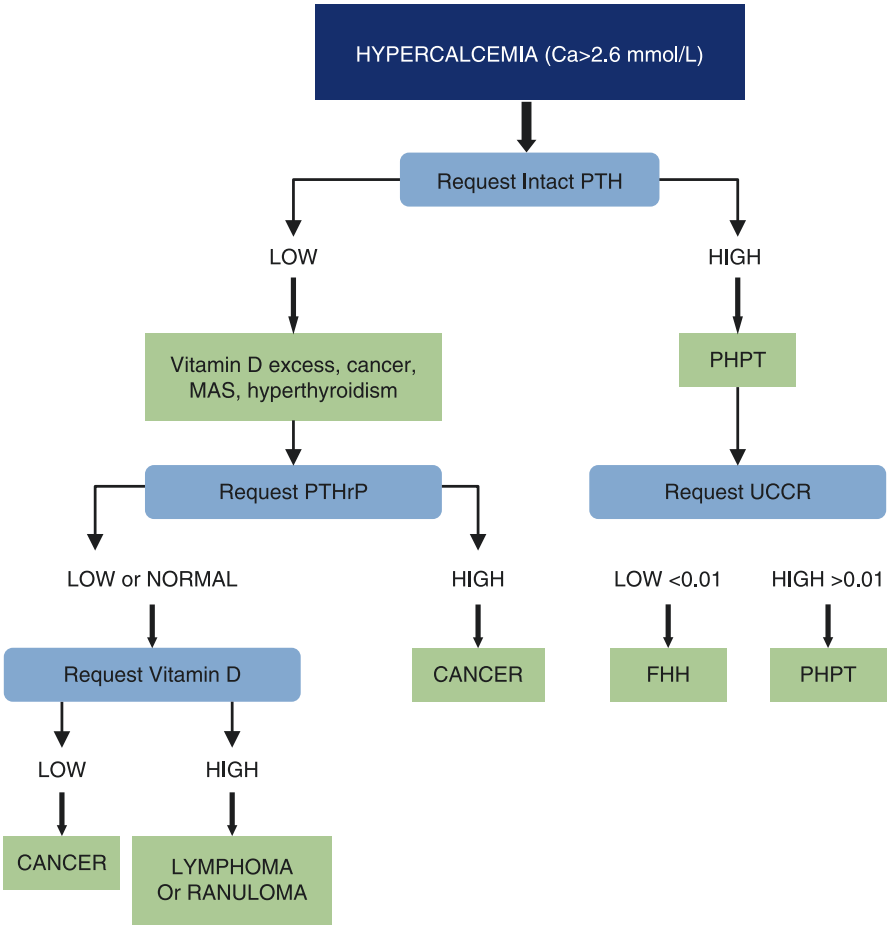

Fig. 7.22 Algorithm for differential diagnosis of hypercalcemia. FHH, familial hypocalciuric hypercalcemia; MAS, milk-alkali syndrome; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTHrP, parathyroid hormone-related peptide

7.3.7 Treatment

7.3.7.1 Surgical Treatment

Indications: When to Operate?

There is general consensus that *symptomatic* patients presenting with *end-PTG damage* such as renal stones, severe osteoporosis, or pancreatitis should be offered surgery. The decision to operate is more complex when faced with uncertainty whether subtler symptoms such as fatigue or depression are caused by PHPT or in 80% of patients who declare no symptoms at all.

Regularly updated National Institute of Health (NIH) Guidelines (UK) advice surgery in *asymptomatic* patients meeting any of the following criteria [88]: (1) age younger than 50 years, (2) when calcium level is >0.25 mmol/L (>1 mg/dL) above upper limit of the reference range for total serum calcium, (3) bone mineral density (BMD) T-score ≤ −2.5 at the lumbar spine, femoral neck, the total hip, or the distal third radius, or (4) creatinine clearance glomerular filtration rate (GFR) reduced to <60 mL/min or if further evaluation of asymptomatic patients with renal imaging and complete urinary stone risk profile (if urinary calcium excretion is >400 mg/day) show stone(s), nephrocalcinosis, or high stone risk.

Observational studies suggest that even subtle abnormalities of calcium and PTH levels are associated with adverse health outcomes. Between one-quarter and one-third of patients with asymptomatic PHPT left untreated for 10–15 years develop progressive disease with worsening hypercalcemia, hypercalciuria, and reduced bone density. Patients younger than 50 years have increased risk of disease progression. Patients who had parathyroidectomy had significant improvement in bone densitometry (BDM) at hip and lumbar spine but not forearm. Patients with untreated PHPT have increased mortality predominantly from cardiovascular disease but in patients who had surgery there was decline in mortality.

Evidence from randomized controlled trials showed that surgery reduces formation of renal stones, improves BDM, and reduces fractures. Dyslipidemia and diabetes mellitus are more prevalent in patients with PHPT. Although parathyroidectomy improves dyslipidemia, no overall improvement in cardiovascular events or decreased mortality has been observed.

The impact of surgery on quality of life and neuro-psychological outcomes of patients is still uncertain, as results of various studies are contradictory.

Aims of Surgery: Why Operate?

The aims of surgery in patients with PHPT are (1) immediate and permanent cure of abnormally high levels of calcium and PTH, (2) alleviation of the symptoms, and (3) prevention or reversal of end-organ damage.

The choice of operating technique depends on the underlying parathyroid pathology and imaging results indicating the number and location of the PTGs to be removed. In patients who need removal of one to three abnormal glands, normalization of calcium and PTH levels without post-operative supplementation is the goal. When all four glands are abnormal and have to be removed, the goal is normocalcemia maintained either by calcium and vitamin D3 supplementation or autotransplantation of parathyroid tissue.

Surgical Procedure: Which Operation?

Parathyroidectomy/Bilateral Neck Exploration (BNE)

Bilateral neck exploration (BNE) with visualization of all four parathyroid glands, irrespective of the underlying pathology, has been the *gold standard* surgical treatment for many past decades [148]. It is effective and safe, and able to cure 95% of patients with sporadic and 80–90% of patients with familial PHPT. Typically, BNE

is performed via a collar incision allowing exposure and dissection of all the parathyroid glands prior to deciding which glands should be removed. It not only allows direct visualization of the four glands but also enables exploration of sites of potential ectopic glands. *Mediastinal exploration* may be needed if the surgeon fails to find the parathyroid glands in the neck.

Deciding which glands are abnormal and need removing is based on prior knowledge of pre-operative imaging and the size of the glands observed during surgery. In case of parathyroid gland *hyperplasia*, subtotal parathyroidectomy is indicated, i.e., removal of three-and-half glands and marking the remaining part, or resection of the four glands (total parathyroidectomy) and implantation of one gland in the sternocleidomastoid muscle (SCM), deltoid, or brachioradialis muscle.

For PTG *adenoma*, excision of the affected gland only would suffice but ascertaining that other glands are normal is essential using BNE. For PTG *carcinoma*, excision of the tumor, ipsilateral thyroid lobe, and palpable lymph nodes (LNs), followed by adjuvant radiotherapy to reduce the recurrence rate are indicated. In addition, hypercalcemia should be controlled with mithramycin.

Bilateral neck exploration remains the operation of choice in three situations: first, in familial PHPT when multiple glands are expected to be abnormal; second, when all imaging is negative; and third, when minimally invasive parathyroidectomy (MIP) fails to identify the enlarged gland and thereby conversion to BNE is necessary. *Complication rate* after parathyroidectomy is not well quantified but expected to be below 4% with bleeding and infection accounting for 1% and transient or permanent recurrent laryngeal nerve (RLN) injury for 2–3%.

In patients with familial HPT (FHPT), the extent of parathyroidectomy depends on the underlying pathology.

- In *MEN-I*, a four-gland parathyroidectomy is often recommended as subtotal (<4 glands) parathyroidectomy is associated with high rates of recurrence requiring further surgery. Sometimes the decision is taken to remove 3 or 3½ parathyroids achieving immediate cure and accepting high risk of recurrence.
- In *MEN-IIa*, where frequently single gland is involved, removal of one to three glands can be curative without the risk of permanent hypocalcaemia. As the risk of PHPT in MEN-IIa is relatively low (10%), PTGs removed incidentally during prophylactic thyroidectomy should be re-implanted into muscle.
- *Hyperparathyroidism-jaw tumor (HPT-JT) syndrome* has a 15% risk of parathyroid carcinoma and surgical options include the removal of the single abnormal gland with subsequent annual surveillance of calcium and PTH levels, or prophylactic total parathyroidectomy to prevent future malignancy or recurrent HPT.
- *Familial Isolated HPT (FI-HPT)* is a complex disease associated with mutations in different genes including CaSR, MEN1, and *HRPT2* genes. The current recommendation is to remove one to four abnormal PTGs using intra-operative PTH monitoring and consider auto-transplantation.
- In neonates with *neonatal severe hyperparathyroidism (NS-HPT)*, parathyroidectomy of the four glands (total parathyroidectomy) is essential to achieve cure as removal of <4 glands results in persistently high levels of calcium and PTH.

Parathyroid auto-transplantation is frequently considered when multiple PTGs are removed. First described in 1926, it is a common and established practice when normal PTGs are incidentally removed during thyroidectomy. Auto-transplanting abnormal parathyroid tissue is controversial and presents a dilemma. It is potentially desirable, since there is no direct hormonal replacement therapy available for the PTH, and the medical management of post-operative hypoparathyroidism requires vitamin D and calcium supplementation. However, transplanted abnormal parathyroid tissue could cause recurrence requiring more surgery. If auto-transplantation is pursued, it can be carried out either during the primary procedure or after cold storage (cryopreservation in −135°C) usually within 24 months. The excised gland is divided to multiple small pieces (1 mm thick) and placed in the sternocleidomastoid (SCM) or forearm (brachioradialis) muscles. Alternative procedure involves intra-muscular injections of PTG tissue. Good PTG graft function has been reported in 86–100% of adult patients [149].

Minimally Invasive Parathyroidectomy (MIP)

Minimally invasive parathyroidectomy (MIP) was introduced two decades ago and represents a significant development in surgical management of PHPT. Growing acceptance of MIP as a procedure of choice is due to realization that solitary adenomas are responsible for majority of cases of sporadic HPT [150]. Improved accuracy of pre-operative imaging allows precise localization of the adenoma and enables its targeted removal, without the need for dissection of remaining parathyroid glands. The majority of patients could be now selected for MIP and benefit from the surgery performed through smaller incisions, better scars, less pain, and reduced hospital stay.

There are two distinctive techniques of MIP. The first is a "mini-incision parathyroidectomy," which usually involves a one-inch or smaller lateral incision overlying the affected PTG [151]. Dissection is carried out between the SCM and strap muscles toward the lateral border of thyroid, which is retracted medially and upward with retractors. Blunt dissection allows direct visualization of the enlarged PTG and important landmarks such as carotid vessels, inferior thyroid artery, and recurrent laryngeal nerve. If the enlarged parathyroid gland is not found in position indicated by pre-operative localization, dissection could be carried toward the upper or lower pole through the same incision. If the abnormal gland is on the opposite side, the incision is extended horizontally across the midline and bilateral neck exploration is performed. The advantage of this technique is its simplicity, speed, and no need for special equipment [152, 153].

The second MIP technique is endoscopic, known as "video-assisted parathyroidectomy." The endoscope is introduced either in the midline, laterally between the carotid sheath and strap muscles, or via a trans-axillary approach. Space is created either by insufflation of CO_2 or gasless retraction, and instruments are introduced through the same or separate incisions. *Disadvantage* of this approach is requirement for videoscopic equipment and increase in operating time [154]. *Robotic parathyroidectomy* using trans-axillary approach keeps the scar away from neck but its cost is unnecessarily high and it is unlikely to become commonly used. Mini-invasive parathyroidectomy, irrespective of technique employed, can cure as many as 98% of patients with sporadic PHPT; the success rate is similar to bilateral neck exploration.

Intra-Operative Techniques Aiding Localization and Confirmation of Cure of PHPT

Failure of surgery to cure HPT (5–10%) is predominantly due to either (1) multigland disease (hyperplasia, double adenomas) unrecognized by pre-operative localization studies, or (2) the inability to find PTGs in unusual locations (ectopic glands). Various operative adjuncts are commonly used to overcome these problems and improve cure rate. These include the following.

Frozen-Section

Frozen-section of resected specimens is the oldest and most widely used technique. It has 99% accuracy in differentiating parathyroid from non-parathyroid tissue. Limitations include inability to determine whether remaining PTGs function normally, i.e., unable to confirm cure.

Methylene blue injected intravenously 1 h before surgery has been widely used; however, it did not demonstrate significant improvement in cure rate or recurrence.

Fluorescence-Guided Parathyroidectomy

Fluorescence-guided parathyroidectomy is used to locate and differentiate normal and enlarged PTGs. Patients take oral aminolevulinic acid (ALA) 4 to 5 h prior to surgery. The operating field is illuminated with violet-blue light (405 nm wavelength), to which the PTGs selectively demonstrate red fluorescence.

Radio-Guided Parathyroidectomy (RGP)

Radio-guided parathyroidectomy (RGP) involves pre-operative MIBI injection and the use of a portable γ-probe to localize the abnormal PTG in vivo and determine ex vivo radioactivity count after the excision. Reported success rates for RGP are 93–97%.

Intra-Operative Parathyroid Hormone (IOPTH) Monitoring

Intra-operative parathyroid hormone (IOPTH) monitoring is possible because, in patients with normal renal function, PTH has a biological half-life of <5 min. Therefore removal of the abnormal, hypersecreting PTG results in rapid reduction in PTH levels. Blood sampling is done before, and at 5 and 10 min after excision of the abnormal PTG and biochemical cure is confirmed by 50% reduction in PTH compared to the highest pre-excision level.

More details of intra-operative adjuncts during parathyroidectomy to aid in PTG localization and confirmation of cure are mentioned in Chap. 17.

7.3.7.2 Conservative Treatment

Candidates

- Asymptomatic PHPT patients who do not meet guideline indications for surgery.
- Patients who are unable or unwilling to undergo surgery.

Outlines of Conservative Treatment

Monitoring

- Serum calcium, annually.
- Skeletal: bone mineral density (BMD), at three sites, every one to 2 years, by dual-energy X-ray absorptiometry (DEXA).
- Renal: eGFR, and serum creatinine, annually. Renal imaging and 24-h urine biochemical stone profile, if renal stones are suspected.

Vitamin D Repletion

Target serum concentration of 25(OH) vitamin D should at least be >50 nmol/L and preferably >75 nmol/L; because there is evidence that levels >75 nmol/L may be associated with reduction in PTH levels. Generally, 800 IU/day is a useful starting dose [88].

Antiresorptive Therapy

Bisphosphonates have been shown to increase hip and lumbar spine BMD, similar to the improvements seen after surgery. The best evidence is for the use of alendronate 10 mg/day, which improves bone mineral density without significantly altering the serum Ca and PTH concentrations [155].

Calcimimetic Agent

Calcimimetic agents increase the sensitivity of the CaSRs to extra-cellular calcium, thereby reducing serum calcium level, but have only a modest effect on serum PTH. With cinacalcet, serum calcium normalizes in 70–80% of patients with PHPT. However, serum calcium increases to baseline levels when treatment is stopped, and it does not impact BMD or lower biochemical markers of bone turnover [156].

7.3.7.3 Special Situations of PHPT Disorder

Special situations of PHPT discussed herein include PHPT in children, in pregnancy, in the elderly, and in patients with intra-thoracic parathyroid glands, in addition to parathyroid cancer in PHPT and re-do parathyroidectomy.

PHPT in Children

Primary HPT in children differs from that in adults in that it is 100 times less frequent, equally common in boys and girls, more frequently familial, and almost always symptomatic at presentation. Neonates are exclusively affected by CaSR mutations causing neonatal severe HPT (NS-HPT). Older children have higher proportion of familial to sporadic disease and routine genetic testing is recommended. Despite these differences, biochemical and genetic testing as well as pre-operative localization studies have the same accuracy and value in both children and adults. Similar to adults, sporadic PHPT in children is caused in great majority of cases by single parathyroid adenoma and can be cured by minimally invasive parathyroidectomy. Children with familial PHPT should undergo BNE and removal of multiple abnormal parathyroid glands [154].

PHPT in Pregnancy

Primary hyperparathyroidism in pregnancy carries a risk to the mother and baby and is frequently diagnosed late. It presents as dehydration, hyperemesis, and pre-eclampsia and is associated with a 3.5-fold increase in spontaneous abortion and stillbirth. Fetal effects are intra-uterine growth retardation, low birthweight, hypocalcaemia, and tetany in the neonate. Medications to lower calcium could be used, but parathyroidectomy in the second trimester is safe and considered the best treatment [157].

PHPT in the Elderly

Primary hyperparathyroidism in the elderly affects approximately 2% of elderly population, and about one-quarter of parathyroidectomies for PHPT are performed in patients older than 70 years. Parathyroidectomy in the elderly is safe and should be considered as it offers significant improvement in symptoms and cardiovascular and skeletal health [158].

PHPT with Intra-Thoracic Parathyroids

Intra-thoracic PTGs can be found in nearly 10% of patients with PHPT. Glands located above the aortic arch can almost always be removed through the cervical approach. Adenomas situated deeper might require an open approach such as thoracotomy or partial/full sternotomy or their minimally invasive alternatives (video-assisted thoracoscopy or mediastinoscopy). Angiographic or chemical ablation can also be used [159].

Parathyroid Cancer in PHPT

Parathyroid cancer is found in approximately 1% of patients with PHPT and could present as a hard palpable mass. It should be also suspected in patients with normal examination but very high levels of calcium and PTH. Infiltrating tumors should be resected with adjacent thyroid and involved soft tissue. If diagnosis is made post-operatively on histology, a second operation and hemi-thyroidectomy should be considered. Local recurrence develops in about 10% of patients and the 5- and 10-year survival rate has been reported to be 86% and 49%, respectively. Distant metastases and associated hypercalcemia should be treated with a combination of ablation procedures and systemic therapy to control calcium (cinacalcet) and chemotherapy [160].

Re-Do Parathyroidectomy

Re-do parathyroidectomy is necessary in approximately 5–10% of patients with recurrent or persistent PHPT. The commonest causes of surgical failure include the following:

1. Wrong diagnosis and/or suboptimal imaging.
2. Ectopic glands.
3. Familial disease.
4. Inexperienced surgeon.

If re-operation is necessary, it is essential that diagnosis of PHPT is confirmed and imaging, operating notes, and histology of the previous surgery reviewed. Additional imaging and relevant genetic tests should be carefully planned. Most re-do operations are BNEs sometimes combined with sternotomy, but MIP or thoracoscopy should also be considered. Re-operations have higher risks of postoperative complications, but success rate is high at 90–95% [161, 162].

7.4 Secondary Hyperparathyroidism (SHPT)

7.4.1 Definition

Secondary hyperparathyroidism (SHPT) is defined as the "medical condition characterized with excessive secretion of parathyroid hormone (PTH) by the parathyroid glands (PTGs) with resultant hyperplasia of these glands in response to hypocalcemia, hyperphosphatemia, or decreased active vitamin D" [163]. The increased PTH secretion, in turn, causes increased calcium in the blood by acting on bones, intestines, and kidneys [163].

7.4.2 Epidemiology

The common causes of SHPT are vitamin D deficiency and chronic renal disease [164]. About 50% of the world population is affected by vitamin D insufficiency [165]. Chronic renal disease affects about 15% of the population in the United States [166]. Increased PTH levels are seen in chronic renal disease, and there is a strong correlation between the prevalence and stage of chronic renal disease with increasing prevalence in advanced disease [167].

7.4.3 Etiology

1. *Renal disease:* Examples include chronic renal failure (most common cause) and renal/tubular acidosis [164]. Failing kidneys do not convert enough vitamin D to its active form, and they do not adequately excrete phosphate [167]. Consequently, insoluble calcium phosphate forms in the body and removes calcium from the circulation. Both processes lead to hypocalcemia and hence SHPT with hyperplasia of all PTGs.
2. *Malabsorption syndrome* (due to gastrectomy, chronic pancreatitis, small bowel disease, or malabsorption-dependent bariatric surgery): In such cases, fat-soluble vitamin D cannot get reabsorbed leading to hypocalcemia and subsequent increase in PTH secretion [167].
3. *Osteomalacia* (vitamin D deficiency or phosphate depletion): It is prevalent in lactating women with poor diet causing bone softening, deformity, bending, and fractures. Causes of vitamin D deficiency include (1) poor diet, (2) inadequate

exposure to sunlight, (3) malabsorption, (4) inhibited conversion of vitamin D to active metabolites as in renal disease, (5) end-organ resistance, and (6) disorders of vitamin D metabolism [167].

4. *Other causes:* A few other causes of SHPT can stem from inadequate dietary intake of calcium, steatorrhea [1], or pseudo-hypoparathyroidism (a condition associated primarily with resistance to PTH. Those with the condition have a low serum calcium and high phosphate, but PTH is appropriately high [due to the low level of calcium in blood]. Its pathogenesis has been linked to dysfunctional G-proteins, particularly the Gs-alpha subunit) [167].

7.4.4 Pathophysiology

Hypocalcemia is the most important stimulus for increased secretion of PTH from PTGs in SHPT resulting also in parathyroid hyperplasia. Increased PTH results in increased calcium and phosphate absorption from the gut. PTH acts as a stimulus for increased osteoclast activity, which results in calcium and phosphorus resorption from the bone [164]. PTH activates vitamin D in the kidneys to its active form. Vitamin D increases calcium and phosphorus absorption from the gut and calcium and phosphorus reabsorption in renal tubules [164]. Vitamin D suppresses also PTH secretion from the parathyroid glands and regulates the calcium and phosphorus levels [164].

Fibroblast growth factor-23 (FGF-23) is secreted by osteocytes and plays an important role in phosphorus homeostasis by increasing phosphorus clearance in the renal tubules [164]. The FGF-23 also inhibits 1,alpha-hydroxylase activity, and thus the active form of vitamin D [164]. On the other hand, FGF-23 is *not* known to modulate PTH secretion directly, but may do so indirectly through regulating phosphate and vitamin D metabolism [168].

In chronic kidney disease, decreasing glomerular filtration rate (GFR) leads to increased secretion of PTH. Decreasing GFR leads to decreased phosphate clearance and hyperphosphatemia, which stimulates the PTGs to secrete PTH [169]. Also, hyperphosphatemia causes hypocalcemia (phosphorus forms complexes with calcium) and stimulates FGF-23 and increased PTH secretion [169].

7.4.5 Pathology

In CRF, there is an increase in the ability of parathyroid cells to synthesize and secrete, which is responsible for an increase in serum PTH concentration at first; this results in hyperplasia of the gland linked to both cell hypertrophy and increased cell proliferation, which is still potentially inhibitable by therapeutic measures. As renal function deteriorates, the expression of calcium, vitamin D, and FGF-23 receptors gradually decreases in the PTG, which leads to PTG hyperplasia [170]. Clones appear as nodular hyperplasia, which gives rise to true autonomic adenomas, thus causing tertiary HPT [171].

Parathyroid hyperplasia is classified into four categories: (1) diffuse hyperplasia, (2) diffuse and multinodular hyperplasia, (3) multinodular hyperplasia, and (4) simple nodular hyperplasia [172, 173].

Renal osteodystrophy compromises a group of bone mineral disorders. There are five types based on histological classification [174]:

1. *Mild disease*: A state of slightly increased bone remodeling and usually seen in early or treated SHPT [174].
2. *Osteitis fibrosa cystica*: A state of high bone turnover from increased osteoclast activity and bone destruction and resorption caused by the high PTH levels [169]. It is characterized by peritrabecular fibrosis [174].
3. *Osteomalacia*: It is the softening of the bone due to inadequate osteoid or insufficient mineralization of the osteoid, depending upon the rate of bone remodeling. The problems with mineralization arise due to abnormal calcium and phosphorus metabolism [175].
4. *Mixed disease*: It has features of both osteomalacia and osteitis fibrosa and is associated with aluminum deposition [174].
5. *Dynamic bone disease:* Administration and overuse of vitamin D analogs, calcimimetics, and phosphate binders decrease PTH levels, which in turn leads to a state of low bone turnover with normal mineralization known as adynamic bone disease [169].

7.4.6 Clinical Picture

In SHPT, the disorder of phosphocalcic metabolism affects the different systems of the body and manifests by specific clinical signs. Primarily bone and then soft tissues (e.g., visceral and vascular calcifications, which are responsible for cardiovascular morbidity and mortality) are affected. Skin can also be affected.

7.4.6.1 Osseous Manifestations

In SHPT, bone remodeling and mineralization are affected [175]. Bony skeletal deformities are secondary to bone remodeling [175]. This leads to bone deformation, bone pain, and bone fractures in extreme cases. Chest wall deformity and kyphoscoliosis can be noted due to abnormal mineralization and bone remodeling [176]. Pelvic bones, hip joints, and bones of lower extremities can be deformed, and increased stress from weight-bearing can lead to fractures [176]. In children, bone deformities in SHPT can lead to rickets [177].

7.4.6.2 Extra-Osseous Manifestations

Extra-osseous manifestations are also seen. Calcifications affect the arterial walls, viscera, periarticular tissue, cutaneous tissue, and the eye (cornea and conjunctiva). They are thus responsible for muscle weakness, red-eye syndrome, and intense pruritus [175]. Pruritus is especially seen in advanced renal disease and is due to the deposition of calcium and phosphorus in the skin. Calcifications can occur in the

heart, myocardium, aortic, and mitral valves and can lead to increased cardiovascular events such as ischemia, left ventricular dysfunction, congestive heart failure, arrhythmias, and death [178, 179].

Calciphylaxis can be seen as ulceration of the skin, resulting from arterial obstruction, with cutaneous necrosis of the extremities [175]. Calciphylaxis is caused by high levels of PTH, calcium, and phosphorus induced by high levels of calcium in dialysate and phosphate binders [176]. In calciphylaxis, there is calcification of small arterioles and venules with severe intimal hyperplasia and can be complicated by thrombosis leading to painful skin necrosis [176]. Increased risk of infections, sepsis, and ischemia contributes to increased mortality risk in calciphylaxis [176].

Other manifestations in secondary hyperparathyroidism include *malnutrition* as well as *psychological*, *neurological* disturbances [180].

7.4.7 Evaluation/Diagnosis

7.4.7.1 Laboratory Tests

Evaluation in SHPT consists of monitoring of laboratory values of serum PTH, calcium, phosphorus, vitamin D levels, and renal function. Serum calcium level is characteristically *low* and PTH is elevated due to decreased levels of calcium or 1,25-dihydroxy-vitamin D_3.

Since it can present as bone mineral disorder and affects the musculoskeletal system, "Kidney Disease for Improving Global Outcomes" (KDIGO), 2017, recommends systematically performing bone mineral density (BMD) in dialysis patients with bone mineralization disorders to assess the risk of pathological fracture [181].

7.4.7.2 Imaging

There are certain striking radiological features in renal osteodystrophy. Osteosclerosis is increased bone density, especially in the axial skeleton, but bone is structurally weak and prone to stress fractures [182]. "Rugger jersey" spine sign is a hallmark sign of osteosclerosis in SHPT [183]. Osteomalacia is softening of the bone due to poor mineralization of the newly formed osteoid and is characterized by the presence of looser zones on imaging [182].

The brown tumor in SHPT is a lytic bone lesion caused by increased osteoclastic activity and proliferation of fibroblasts [184]. On a standard radiograph, it presents itself as a well-defined hypodense lesion. These tumors are located more commonly in hands, feet, facial bones, and skull [184]. Brown tumor represents the terminal stage of bone mineral disorder in SHPT [185]. Brown tumors can be misdiagnosed as neoplasm on imaging [185].

Osteitis fibrosa cystica is revealed on standard radiographs by subperiosteal resorption, especially at the distal phalanges, clavicles, distal ulna, and skull [183]. Cortical thinning in long bones, bone cysts, and densification of the trabecular bone are also seen [183].

Periarticular, vascular, and, more rarely, visceral metastatic calcifications can also be seen [175]. There are no clear guidelines regarding laboratory or diagnostic testing for vascular calcifications in SHPT [186].

7.4.8 Differential Diagnosis

Primary or tertiary hyperparathyroidism is always in the differential diagnosis of secondary hyperparathyroidism. In PHPT, there is increased secretion of PTH, which leads to increased calcium and phosphate levels [187]. In SHPT, there is hypocalcemia and hyperphosphatemia, which leads to increased PTH levels [169]. In THPT, the PTH levels are excessively high, and the calcium and phosphorus levels are high as well [169].

7.4.9 Treatment

Despite improvements in medical treatment, surgical treatment of SHPT is often necessary, especially in refractory cases [188]. Renal transplantation is a therapeutic alternative but is frequently followed by the persistence of HPT [189].

7.4.9.1 Medical Treatment

If the underlying cause of the hypocalcemia can be addressed, the hyperparathyroidism will resolve. Management in SHPT targets abnormal phosphocalcic metabolism. Maintaining the serum calcium and phosphorus levels within the normal range along with control of PTH and vitamin D levels is the key in management of SHPT. The U.S. National Kidney Foundation (NKF) proposed the "Kidney Disease Outcomes Quality Initiative" (KDOQI) guidelines and established targets for biomarkers (calcium, phosphorus, and PTH levels) to lower SHPT-related mortality [190]. The "Kidney Disease Improving Global Outcomes" (KDOGI) proposed clinical practice guidelines to address the management of chronic kidney disease–mineral bone density (CKD-MBD) in dialysis patients [190]. However, most of these targets are difficult to achieve in the long term.

Phosphate binders, vitamin D, and calcimimetics have been reported in the management of calcium and phosphate levels in patients with chronic renal disease. In addition, patients are advised to restrict dietary intake of phosphorus by limiting phosphate-rich foods such as beverages, meat, cheese, and dietary products [164].

Phosphate Binders

Phosphate binders include aluminum hydroxide, sevelamer hydrochloride, sevelamer carbonate, and lanthanum carbonate [164]. Phosphate binders can be calcium-containing or calcium-free. Calcium-containing phosphate binders are known to increase vascular and soft tissue calcification and are associated with lower survival as compared to calcium-free phosphate binders [191].

Vitamin D Metabolites

Vitamin D metabolites include cholecalciferol (1,25-dihydroxy-vitamin D3) and ergocalciferol, which is vitamin D2. Vitamin D analogs such as calcitriol, paricalcitol, alfacalcidol, and doxercalciferol are grouped under vitamin D receptor activators (VDRA) based on their site of action. Vitamin D could have a possible survival benefit in patients with chronic renal disease [192]. Vitamin D analogs' use in chronic renal disease has been shown to decrease PTH levels and are likely associated with reduced inflammation, decreased tubulo-interstitial fibrosis, improved endothelial function, inhibition of renin–angiotensin system, prevention of vascular calcification and decreased cardiovascular outcomes, reduced hospitalizations, and improved mortality [192]. However, the crux of these observations is from observational studies, and randomized control trials (RCTs) are needed to validate the outcomes [192].

Calcimimetics

Calcimimetics are agents that increase the sensitivity of calcium-sensing receptors (CaSR) in the parathyroid gland and lead to decreased PTH production. Cinacalcet is a calcimimetic that is commercially available and extensively used in dialysis patients. Etelcalcetide is another calcimimetic. Important side-effects of calcimimetics include hypocalcemia, Q-T prolongation, arrhythmias, worsening heart failure, and convulsions [164, 193]. Calcimimetics have been shown to suppress PTH levels but do *not* increase calcium or phosphorus levels [192]. Cinacalcet, along with low-dose vitamin D, minimizes the risk of calcification while offering the benefits of PTH-lowering therapy [194].

In Evaluation of Cinacalcet Therapy to Lower Cardiovascular Outcomes (EVOLVE) study, Cinacalcet did *not* improve survival or cardiovascular outcomes in dialysis patients, but offered significant benefits in terms of lowering PTH, calcium, phosphate, and FGF-23 levels [193]. More RCTs are needed to explore the full range of benefits of calcimimetics.

7.4.9.2 Surgical Treatment

Indications

The main indications of surgery include (1) unsuccessful or refractory medical therapy (2) pathological fractures, (3) symptomatic secondary HPT such as bone pain, ectopic (extra-skeletal) calcification, calciphylaxis, refractory pruritus, and anemia hyporesponsive to erythropoietin, (4) severe hypercalcemia (serum calcium >10.2 mg/dL) or hyperphosphatemia (serum phosphorus >5.5 mg/dL), (5) persistent and symptomatic hypercalcemia in prospective renal transplantation patients, and (6) progressive hypercalcemia in patients with functioning renal transplants [164, 195]. Other useful indications for operations include: (1) a marked elevation of PTH level >800 pg/mL (for more than 6 months despite medical therapy), and (2) elevation of the $Ca \times PO_4$ product above 70 [164, 195].

The PTGs in SHPT are characterized by asymmetric enlargement and nodular hyperplasia. Assessment of parathyroid mass is an important factor in predicting the response to medical management. Glands larger than 1 cm in size or greater than

500 mm^3 on ultrasound represent glandular hyperplasia and are usually refractory to medical treatment [195]. It is estimated that surgery will be required in about 15% of patients in 10 years and 38% of patients in 20 years after the initiation of dialysis [196]. Following the introduction of calcimimetics, there appears to have been a reduction in parathyroidectomy rates [195].

Surgical Techniques

Surgical techniques include subtotal parathyroidectomy and total parathyroidectomy with or without auto-transplantation [197]. Subtotal parathyroidectomy involves leaving a remnant part of the gland while total parathyroidectomy removes all the glandular tissue. Sometimes, in total parathyroidectomy, small amounts of the PTG could be autografted post-surgery. There are no major differences between subtotal parathyroidectomy and total parathyroidectomy regarding outcomes such as complications, re-admissions, and 30-day mortality [198]. However, subtotal parathyroidectomy has been associated with lower extended hospital stay post-surgery and a lower incidence of post-operative hypocalcemia [199].

Most people with HPT secondary to CRF will improve after renal transplantation, but many will continue to have a degree of residual HPT (tertiary hyperparathyroidism) post-transplant with associated risk of bone loss. Subtotal hyperparathyroidism is preferred in renal transplant patients with tertiary hyperparathyroidism due to a lower risk of recurrence [200]. Total parathyroidectomy with auto-transplantation is preferred for patients who cannot undergo repeat neck surgeries due to conditions such as coexisting thyroid disorders requiring surgery, history of repeated neck surgeries, recurrent laryngeal nerve injury, or patients with significant perioperative comorbidities [195].

An interesting post-operative complication of surgery is the hungry bone syndrome with the lack of osteoclastic activity causing decreased PTH, leading to hypocalcemia [195]. It can be prevented by administering high doses of calcium and using a high calcium dialysate post-surgery [195].

7.4.10 Pertinent Studies and Ongoing Trials

- In patients on hemodialysis, the "Dialysis Outcomes and Practice Patterns Study" (DOPPS) has shown increased cardiovascular and all-cause mortality with calcium level greater than 10 mg/dL, phosphorus level greater than 7 mg/dL, and PTH level >600 pg/mL [201].
- Evaluation of the "Cinacalcet Therapy to Lower Cardiovascular Outcomes" (EVOLVE) study is the largest, double-blinded, placebo-controlled clinical trial conducted in dialysis patients with SHPT. The study showed that cinacalcet therapy did *not* offer survival benefit or improve cardiovascular outcomes in patients on hemodialysis [202].
- In the ADVANCE study, cinacalcet with low-dose vitamin D analogs as compared to flexible vitamin D dosing showed a positive trend in decreasing vascular calcification, although the study was inconclusive [193].

- The OPTIMA study is a multicenter, open-label study that showed cinacalcet-based treatment algorithms were compared with conventional therapy in dialysis patients and have shown an increase in the achievement of KDOQI targets [203].
- Observational studies have shown that parathyroidectomy is beneficial in dialysis patients as it can lead to normalization of calcium and phosphorus, reduced fracture rate, improved health-related quality of life, and decreased all-cause mortality [195]. However, randomized controlled trials are lacking to validate these benefits. More prospective trials are needed to look at the outcomes of calcimimetics and parathyroidectomy.

7.4.11 Prognosis

Secondary hyperparathyroidism can have a significant impact on life due to complications such as bone and mineral disorders, cardiovascular complications, and calciphylaxis. Quality of life (QOL) can be affected by symptoms such as muscle pain, bone pain, and fractures in extreme cases. Although medical therapy has been aimed to achieve target levels per Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, there is not much clinical evidence from prospective studies suggesting an improvement in survival due to vitamin D analogs or calcimimetics [204]. Calcimimetics have been shown to improve certain outcomes such as improvement in rates of parathyroidectomy, fractures, cardiovascular hospitalizations, and certain health-related quality of life parameters [204].

Parathyroidectomy is indicated in medically refractory disease. In CRF patients on hemodialysis, the incidence of parathyroidectomy goes up with time, with about 15% of these patients undergoing surgery in 5–10 years from initiation of dialysis [195]. A study showed that parathyroidectomy, regardless of the technique used, significantly relieved most of the initial functional signs within 7 days of the procedure, but patients continued to experience mild to moderate symptoms over a 6-month follow-up [205]. Surgery and calcimimetics can offer improved survival in the initial stages of chronic renal disease resistant to the standard therapy [206]. Surgery has not been shown to offer improved cardiovascular morbidity or mortality benefit in case of secondary hyperparathyroidism patients on hemodialysis [206].

7.5 Tertiary Hyperparathyroidism (THPT)

7.5.1 Definition

Tertiary hyperparathyroidism (THPT) refers to the "condition in which SHPT appears to become *autonomous*," i.e., there is persistent HPT with autonomous release of PTH in the face of normal or increased serum calcium (hypercalcemia state) [167, 171, 207].

7.5.2 History

In 1962, Dr. C.E. Dent reported that autonomous hyperparathyroidism may result from malabsorption syndromes and chronic kidney disease [208]. The term "tertiary hyperparathyroidism" was first used in 1963 by Dr. Walter St. Gaur to describe a case reported on at Massachusetts General Hospital [208]. This case involved a patient who had presented with autonomous parathyroid adenoma causing hypercalcemia with a background of parathyroid hyperplasia. Further reports were recorded in 1964, 1965, and 1967 of suspected tertiary hyperparathyroidism. In 1968, Davies, Dent, and Watson produced a historic case study where they reviewed 200 cases of previously diagnosed PHPT and found the majority of these cases should be reclassified as tertiary [208]. These were important findings as it allowed an understanding into distinguishing features of primary, secondary, and tertiary hyperparathyroidism, which then allows appropriate medical treatment.

It is now understood that tertiary hyperparathyroidism is defined as the presence of hypercalcemia, hyperphosphatemia, and parathyroid hormone due to terminally biased parathyroid-bone-kidney feedback loop [167]. Although there is still conjecture as to whether tertiary hyperparathyroidism is also due to adenomatous growth or hyperplasia, it is clear that tertiary hyperparathyroidism presents with some form of tissue enlargement in all four parathyroid glands [209, 210].

7.5.3 Etiology

The main role of PTGs is calcium homeostasis [211, 212]. They monitor blood calcium levels via the calcium-sensing receptors, a g-coupled protein receptor [211]. Parathyroid hormone is responsible for the induction of increased calcium absorption in the gastrointestinal tract (GIT) and in the kidney. It also induces calcium and phosphate resorption from the bone by osteoclasts [207, 213]. Additionally, PTH also plays a role in activating vitamin D from its pro-form to its active form [213]. Vitamin D is also responsible for increased blood calcium levels and works in conjunction with PTH. Vitamin D is also partly responsible for the inhibition of PTH release by binding vitamin D receptors at the PTG [207].

Hyperparathyroidism (HPT), in general, is caused by either neoplastic growth in one or more PTGs or a prolonged hypocalcaemia, which in turn stimulates the production of PTH release from the PTGs. Many of the mechanisms that cause the development of tertiary HPT are due to outcomes of SHPT, and so the tertiary from is said to be a continued progressive HPT [171, 207]. Secondary hyperparathyroidism occurs mainly in those who suffer chronic renal disease or vitamin D deficiencies, both of which lead to malabsorption of calcium and phosphate resulting in decreased blood calcium levels and inducing HPT. Hyperphosphatemia in SHPT, due to increased PTH, is thought to act directly on parathyroid glands and induce a hyperplasia of the chief cells in particular [207]. At the same time, the hyperplasic PTGs have reduced fibroblast growth factor-23 (FGF-23) and vitamin D receptor

expression. FGF-23 is partly responsible for phosphate homeostasis and provides negative feedback to the PTG as does vitamin D [207, 214, 215].

During prolonged SHPT, increased blood phosphate levels drive hyperplasia of the PTG and this acts to reset calcium sensitivity at the calcium-sensing receptors leading to tertiary HPT after resolution of the secondary form with the continued release of PTH in the presence of hypercalcemia [207]. Thus, unlike PHPT, hypercalcemia in the tertiary form is thought to be the result of resolution of SHPT rather than adenoma formation alone [167, 171, 207].

7.5.4 Risk Factors and Genetics

An elevated risk of developing tertiary HPT exists when late stage kidney disease is not corrected timely [167, 209]. This is due to a hyperphosphatemia acting directly on the PTGs. Genetically, those who suffer an X-linked dominant disorder that disrupts phosphate transport at the renal tubules (X-linked hypophosphatemic rickets) and are receiving oral phosphate treatment have shown to be at high risk of developing tertiary HPT in the absence of SHPT [216]. Recurring tertiary HPT is generally seen to be caused by incomplete parathyroidectomy without renal transplant and the risk is increased when the parathyroid tissue left after surgery is that of a nodular type [209].

Other risk factors of tertiary HPT include an elevated risk of developing acute pancreatitis, mainly due to the hypercalcemia associated with the HPT [217]. Other studies have shown a significant increase in the risk of developing malignancies of the urinary tract and renal system with women being more at risk [218]. Though there is some conjecture as to the correlation between HPT and thyroid carcinoma development, there is however a correlation between the two, which is thought to be due to prolonged irradiation of the head and neck for parathyroid adenomas and increased PTH hormone [219].

Other studies have found some correlation in the development of renal disease following parathyroidectomy. However, the mechanism for this effect remains unknown [220].

7.5.5 Pathophysiology

Tertiary HPT is almost always related to end stage kidney disease and SHPT [167, 210, 221]. Physiological changes due to the kidney damage adversely affect feedback loops that control secretion of PTH. Renal management of phosphate is impaired in SHPT, which results in hyperphosphatemia [167, 208].

Primary hyperplasia of the PTGs results from both hypocalcaemia and increased phosphate levels by decreasing expression of calcium-sensing receptors and vitamin D receptors at the PTG [167, 221]. These reductions in receptor expression lead to hyperfunctioning of the PTG, which is thought to exacerbate primary hyperplasia, which evolves further to a secondary more aggressive hyperplasia. Histologically,

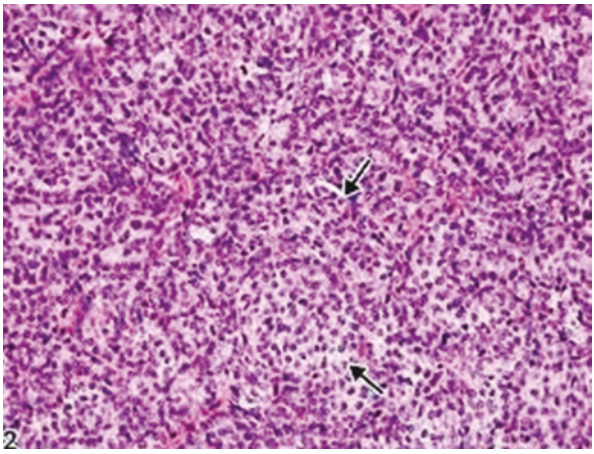

Fig. 7.23 Diffuse (non-nodular) hyperplasia of the parathyroid gland (black arrows). H&E stain

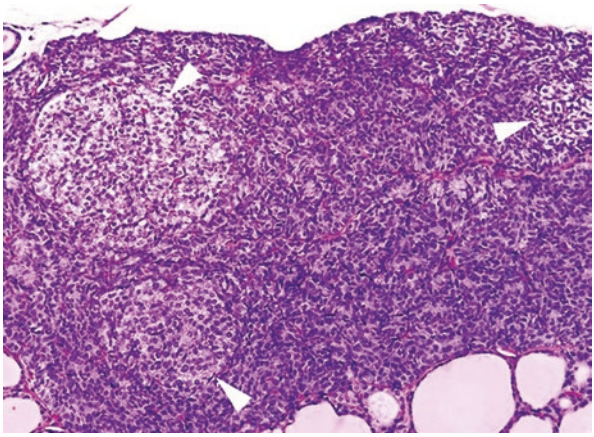

Fig. 7.24 Multifocal (nodular) hyperplasia (white arrow-heads) of chief cells in parathyroid glands. The focal areas of increased cellularity are poorly demarcated and not encapsulated from adjacent parathyroid parenchyma. H&E stain

these hyperplasic glands can be either diffuse (Fig. 7.23) or nodular (Fig. 7.24) [210]. Primary hyperplasia, usually resulting in diffuse polyclonal growth, is mainly related to reversible SHPT. Secondary hyperplasia of the PTG is more often a nodular, monoclonal growth that sustains SHPT and is the catalyst in the progression to tertiary HPT. Nodular hyperplastic glands in tertiary HPT are distinctly larger in both absolute size and weight; up to 20–40-fold increases have been reported [210, 222, 223].

Biochemically, there are changes in function between normal and nodular hyperplastic PTGs. These changes involve proto-oncogene expression and activation of proliferative pathways while inactivating apoptotic pathways [224]. In nodular parathyroid tissue, increased expression of TGF-a, a growth factor, and EGFR, its receptor, results in aggressive proliferation and further downregulation of vitamin D receptors, which act to suppress hormone secretions [221, 222, 224]. Furthermore, the proliferative marker, Ki-67, is seen to be highly expressed in the secondary

nodular hyperplastic state [222, 224]. Tumor-suppressor genes have also been highlighted as being silenced or degraded in nodular hyperplastic parathyroid tissue [221, 224]. One such gene, p53, has been shown to regulate multiple tumor-suppressor pathways and in tumorigenesis can be degraded by β-catenin. This pathway, in some aspect, is mediated by CACYBP, which is highly expressed in nodular parathyroid hyperplasia [224].

7.5.6 Clinical Presentation

Symptoms in tertiary HPT are generally those seen in relation to hypercalcemia [221, 225]. Tertiary HPT shares many symptomatic features with that of PHPT, as the two are defined by hypercalcemia. These symptoms can vary greatly from asymptomatic to conditions leading to decreased quality of life [167, 225].

Non-specific symptoms include feeling tired and thirsty; mood changes, including feeling blue, weak, and irritable; along with other symptoms such as itching, headache, joint pain, forgetfulness, and abdominal pain [167, 221, 225, 226].

More *specific symptoms* related to elevated blood calcium and phosphate levels include bone pain (osteodynia) and tenderness, which are common and related to proximal muscle tenderness. Other clinical manifestations may include pancreatitis, renal stones, corneal calcifications, thinning of long bones (Fig. 7.25), and hypodermic calcifications, which may be palpable in some patients [167, 225, 227].

Calciphylaxis, though uncommon, can develop in patients with THPT. The product of elevated calcium and phosphate forms crystal structures that are then deposited in blood vessels. These crystals cause an inflammatory response and cause occlusion of smaller vessels. Further complications like secondary infections and necrosis can develop from this and can be fatal for some, making the monitoring of blood calcium and phosphate levels necessary [221, 225].

Conditions due to bone loss such as osteopenia, osteoporosis, and pathological fractures are common in tertiary HPT. Pseudo-clubbing of the digits can also be indicative of a severe tertiary HPT due to excess resorption at the distal phalanges [221, 225].

7.5.7 Investigations/Diagnosis

Diagnosis of THPT includes clinical, laboratory, and radiological investigations.

- *Clinical examination* can include grading of muscle weakness, which is done by asking the patient to stand from a seated position with their hands folded across their chest [167, 221].
- *Laboratory tests* include evaluating blood calcium and alkaline phosphatase, which are always increased in THPT. Other common results would include decreased vitamin D levels, elevated blood PTH, and hyperphosphatemia [167, 221, 225, 226].

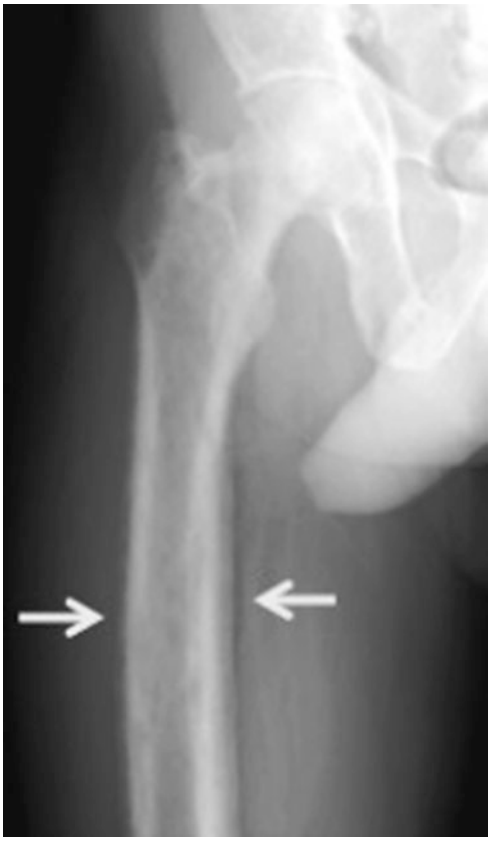

Fig. 7.25 Thinning of long bones (femur) due to tertiary hyperparathyroidism (white arrows)

- *Radiological investigations* include looking for signs of bone loss in both the hands and pelvis, which is characteristic of THPT [221].

7.5.8 Treatment

Early *pharmaceutical* treatment of THPT may include supplementing vitamin D and the use of cinacalcet [167, 225, 226], which increases the sensitivity of the calcium-sensing receptors to calcium leading to a reduction in PTH release; however, its use has limited impact in patients with THPT and are more likely only transient therapies before *parathyroidectomy* [226].

Indications of *surgery* in THPT commonly involve the development of chronic, severe conditions including osteopenia, persistent severe hypercalcemia, bone pain, and pathologic fracture [167, 209, 225, 227, 228]. Other indications include development of conditions such as calciphylaxis [225]. Rarely, nephrocalcinosis or renal calculi (15–30%) may threaten the function of the transplanted kidney, and *surgical treatment* of tertiary HPT must be entertained in these cases.

Table 7.2 Familial causes of primary hyperparathyroidism (PHPT)

Condition	Inheritance and mutation	Organs affected
MEN-1	Autosomal dominant (AD), MEN-1 gene on chromosome 11	*PTGs* (90%), neuroendocrine tumors (NET) of *pancreas* and GIT (60%), *pituitary* adenomas (30%), NET of the thymus and bronchus, adrenal hyperplasia and adenomas, lipomas, leiomyomas, and skin disorders such as angio-fibromas and collagenomas
MEN-2A	AD, MEN-2A gene on chromosome 10	*PTGs* (20–30%), medullary *thyroid* carcinoma (MTC), and *adrenal* pheochromocytomas
JT-HPT	AD, HRPT-2 gene on chromosome 1	Mainly *HPT* and *fibro-osseous* lesions of mandible and maxilla; risk of PTG carcinoma in 10–15%; associated with renal lesions—Renal cell carcinoma, Wilms' tumor, hamartomas, and cysts
FI-HPT	Different mutations: MEN1, CaSR, HRPT2	*Parathyroid glands*
FHH/ NS-HPT	AD, CaSR gene	*Parathyroid glands*

FHH familial hypercalciuric hypercalcemia, *FI-HPT* familial isolate hyperparathyroidism, *GIT* gastrointestinal tract, *JT-HPT* jaw tumor-hyperparathyroidism, *MEN* multiple endocrine neoplasia, NS-HPT neonatal severe hyperparathyroidism, *PTG* parathyroid gland

Surgical options for THPT include subtotal parathyroidectomy (three-and-half of total tissue) and total parathyroidectomy with auto-transplantation of resected tissue [209, 225, 227]. Outcomes of surgery are generally favorable and a return to normalized blood calcium levels and parathyroid function is seen [225].

7.6 Familial HPT in "Men" Syndromes

Familial HPT is caused by inherited or de novo mutations of genes responsible for multiple endocrine neoplasia type I and IIa (MEN-I and MEN-IIa), hyperparathyroidism jaw tumor syndrome ((HPT-JT), and familial isolated HPT (FI-HPT) as shown in Table 7.2 [229, 230].

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Osteitis Fibrosa Cystica

8

8.1 Overview

Osteitis fibrosis cystica (OFC), also known as *osteitis fibrosa, osteo-dystrophia fibrosa,* and *von Recklinghausen's disease of bone* (not to be confused with von Recklinghausen's disease, neurofibromatosis type I), is a skeletal disorder characterized by loss of bone mass, weakening of bones due to replacement of their calcified supporting structures with fibrous tissue (peri-trabecular fibrosis), and formation of cyst-like brown tumors in, and around, the bone.

Osteitis fibrosa cystica is caused by hyperparathyroidism (HPT), which is a surplus of parathyroid hormone (PTH) that results from over-active parathyroid glands (PTGs). This surplus stimulates the activity of osteoclasts, which break down bone, in a process known as "osteoclastic bone resorption." Hyperparathyroidism can be triggered by hereditary factors, parathyroid adenoma, hyperplasia, or carcinoma in addition to renal osteo-dystrophy. Osteoclastic bone resorption releases minerals, including calcium, from bone into the bloodstream, causing both hypercalcemia and structural changes that weaken the bone. Symptoms of the disease are the consequences of both the general softening of bones and the excess calcium in blood, and include bone fractures, kidney stones, nausea, and moth-eaten appearance in the bones, as well as loss of appetite and loss of weight.

First described in the nineteenth century, OFC is currently detected through a combination of blood testing, X-rays, and tissue sampling. Before 1950, around half of those diagnosed with HPT in the United States progress to OFC, but with early identification techniques and improved treatment methods, instances of OFC in developed countries are increasingly rare. Where treatment is required, it normally involves addressing the underlying HPT before commencing long-term treatment; depending on its cause and severity, this can range from just hydration and exercise to pharmacological treatment to surgical intervention.

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8.2 History

Osteitis fibrosa cystica was first described by *Gerhard Engel* in 1864 and *Friedrich Daniel von Recklinghausen* in 1891, though *William Hunter*, who died in 1783, is credited with finding the first example of the disease [1, 2]. "von Recklinghausen's disease" (without the qualification "of bone") is a completely unrelated disorder, nowadays termed as "neurofibromatosis." In 1884, *Davies Colley* delivered a presentation to the Pathological Society of London that detailed the manifestation of HPT into a brown tumor of the mandible, as well as the histological make-up of the tumor [3].

The discovery and subsequent description of the PTGs is credited to *Ivar Sandstrom*, though his publication, *On a New Gland in Man and Several Mammals-Glandulae Parathyroideae*, received little attention at that time. *Gustaf Retzius* and *Eugene Glay* compounded their research; the latter is credited with discovery of PTG function [3]. That research resulted in the first surgical removal of a parathyroid tumor by *Felix Mandel* in 1925. A 64 × 38 mm tumor was removed from the thyroid gland of a man suffering from advanced OFC. The patient's symptoms disappeared, only to return in approximately 6 years as a result of renal stones that were diagnosed only after the patient had died. In 1932, blood tests on a female patient suffering from renal stone-based OFC revealed extremely high hypercalcemia. *Fuller Albright* diagnosed and treated the woman, who suffered from a large tumor of the neck as well as renal stones.

The first published literature to describe a brown tumor, which was linked to OFC, was published in 1953, though clinical reports published before 1953 do draw a correlation between the disease and tumors previous to that publication [4].

The advent of the multichannel autoanalyzer in the 1960s and 1970s led to an increase in early diagnosis of primary hyperparathyroidism (PHPT), resulting is a sharp decline in the prolonged manifestation of the disease and a drop in the number of patients with OFC. Before this invention, the diagnosis of PHPT was generally prolonged until the emergence of severe manifestations, such as OFC.

8.3 Epidemiology

Osteitis fibrosa cystica has long been a rare disease [5]. Today it appears in only 2% of individuals diagnosed with PHPT, which accounts for 90% of instances of the disease [6]. Primary hyperparathyroidism is three times more common in individuals with diabetes mellitus (DM) than those without DM [7].

Hospitalization rate of HPT in the United States in 1999 was 8.0 out of 100,000 [8]. The disease has a definite tendency to affect younger individuals, typically appearing before the age of 40 years, with a study in 1922 reporting that 70% of cases display symptoms before the age of 20 years, and 85% before the age of 35 years. Both, PHPT and OFC, are more common in Asian countries. Before treatment of HPT improved in the 1950s, half of those patients diagnosed with HPT had its progress into OFC [9].

Rates of OFC increase alongside cases of unchecked PHPT. In developing countries, such as India, rates of disease as well as case reports often mirror those published in past decades in the developed world [10, 11]. The other 10% of cases are primarily caused by parathyroid hyperplasia. Parathyroid carcinoma accounts for less than 1% of all cases [6], occurring most frequently in individuals around 50 years of age (in stark contrast to OFC as a result of PHPT) and showing no gender predilection [6]. Approximately, 95% of HPT caused by genetic factors is attributed to multiple endocrine neoplasia (MEN) type-I. This mutation also tends to affect younger individuals [12].

Despite the prevalence of hyperparathyroidism, PHT-related brown tumor is extremely rare, while patients with brown tumors caused by secondary hyperparathyroidism (SHPT) are increasingly reported in the literature, especially for those with definite diagnosis of chronic renal failure [13]. Since HPT can be diagnosed and treated effectively at an early stage [14], brown tumors are more commonly seen in patients with SHPT, accounting for up to 13% of all cases [15–17]. In contrast, the incidence of brown tumors is <5% in PHPT patients [18, 19].

8.4 Etiology

Osteitis fibrosa cystica is the result of unchecked HPT, or overactivity of PTGs, which results in persistent over-production of PTH that causes the release of calcium from bones into the blood, and reabsorption of calcium in the kidney, resulting in hypercalcemia. Hyperparathyroidism may be primary, secondary, or tertiary.

8.4.1 Primary Hyperparathyroidism (PHPT)

There are four major causes of PHPT that result in OFC; parathyroid adenoma, parathyroid hyperplasia, parathyroid carcinoma, and hereditary factors [20].

8.4.1.1 Parathyroid Adenoma

Parathyroid adenoma is the main cause of PHPT, being present in about 90% of the primary-form cases and in 80–85% of all documented cases of HPT [12]. It is more commonly found in adults, especially in females above the age of 50 years, at a female-to-male ratio of 2:1. It is characterized by prevalent proliferation of main cells forming a metabolically active tumoral nodule, usually isolated, and rarely in more than one gland (multi-glandular disease—MGD) [21]. Its prevalence in two glands is approximately 6% [22]. It has a small size (1–3 cm wide), weighs 10 g at most, and is well outlined by a connective tissue strap from the organ's capsule. When sectioned, the adenoma is homogenous, pinkish, and soft. According to Lloyd et al. (1968), an adenoma's weight is proportional to the severity of HPT and bone changes, and its weight may reach 50 g or more [23]. Treatment consists of surgical excision of the PTGs with adenoma(s). For being a slow-progression disease that could remain for years, this surgical excision can provide a definitive cure. If bone

repercussions and renal changes due to nephrocalcinosis are very severe, the patient's life may be threatened.

8.4.1.2 Parathyroid Hyperplasia

Parathyroid hyperplasia is an increase of the number of cells in one or more PTGs, rarely in all four, and is the second most frequent cause of PHPT, reported in as many as 7% of cases of unknown etiology [24]. In most cases, proliferation of the "chief" cells is seen, with a variable amount of clear and oxyphil cells. At early stages, cells are arranged as small isles, which progressively replace the gland as ropes or with an acinar arrangement, with increased size and weight. The histological differential diagnosis with adenoma, when examining only one gland, is particularly difficult, especially if the test is made through frozen-section biopsy during the surgical procedure.

Not rarely, primary parathyroid hyperplasia is included in the picture of type-I multiple endocrine neoplasia (MEN-I) when associated to Langerhans' isles tumor of the pancreas and hypophyseal tumor, and in type-II when associated with medullary thyroid carcinoma and with medullary pheochromocytoma of the suprarenal gland [24].

8.4.1.3 Parathyroid Carcinoma

Parathyroid carcinoma is the rarest cause of OFC, accounting for about 0.5–1% of all cases of HPT. It is the cause of PHPT in about 2.9% of cases [24]. Osteitis fibrosa cystica onset by parathyroid carcinoma is difficult to diagnose [12]. The criteria for microscopic diagnosis of parathyroid carcinoma should be well assessed by the pathologist since the presence of only a dis-arrangement and cell and nucleus polymorphism with mitosis is *not* absolute for diagnosis. Organ capsule invasion, appearance of atypical mitosis characterizing anaplasia, and identification of neoplastic cells in the lumen of blood and/or lymphatic vessels contribute to the diagnosis of carcinoma [24]. Sometimes still, these criteria are *not* enough to differentiate adenoma, which, in some cases, shows marked cellular polymorphism, inducing a wrong diagnosis of carcinoma. On the other hand, certain cases diagnosed as adenoma only started to be interpreted as such after patient's evolution with metastasis to lungs.

8.4.1.4 Hereditary Factors

Approximately, 1 in 10 documented cases of HPT are a result of hereditary factors. Disorders such as familial hyperparathyroidism (fHPT), MEN Type-I, and hyperparathyroidism-jaw tumor (HPT-JT) syndrome can, if left unchecked, result in OFC [12]. MEN Type-I, an autosomal dominant disorder, is the most common hereditary form of HPT, affecting about 95% of genetic cases of OFC, and also tends to affect younger patients than other forms. Major mutations which can lead HPT generally involve PTH receptor, G-proteins, or adenylate cyclase [25, 26]. Certain genetic mutations have been linked to a higher rate of parathyroid carcinoma occurrence, specifically mutations of the gene HRPT2, which codes for the protein "parafibromin" [27].

8.4.2 Secondary Hyperparathyroidism (SHPT)

8.4.2.1 Renal Complications

Osteitis fibrosa cystica is a common presentation of renal osteo-dystrophy (renal rachitis), which is a term used to refer to the "skeletal complications of end-stage renal disease (ESRD)." The most common abnormalities are SHPT and OFC, with extensive bone marrow fibrosis and increased osteoclastic bone resorption. Osteitis fibrosa cystica occurs in approximately 50% of patients with ESRD in which the kidneys fail to produce calcitriol, which assists in the absorption of calcium into bones [28]. When calcitriol levels decrease, PTH levels increase, halting the storage of calcium, and triggering, instead, its removal from bones [29]. The concept of renal osteo-dystrophy is currently included into the broader term chronic kidney disease-mineral and bone disorder (CKD-MBD) [30]. On X-ray studies, areas of more or less condensation are seen, which, at gross examination, are characterized by thinner (osteopenia) and demineralized (osteomalacia) bone girders. Brown tumors are rare [31]. Less frequently, these changes are seen in cases of bone resistance to PTH action and in malabsorption syndromes of the bowel [32].

8.4.2.2 Fluoride Intoxication

Osteitis fibrosa cystica was noticed in the early years of community fluoridation to be at higher risk when water supplies were fluoridated. Indeed, death rates which in some cases were gruesomely dramatic during dialysis quickly brought attention to the fact that fluoride in water during dialysis was a health hazard. Modern dialysis takes pains to de-fluoridate water in order to minimize bone disease including OFC. The 2006 National Research Council confirmed kidney patients are a subpopulation particularly susceptible to ill effects from fluoride exposure, which manifest in bones [33–35].

8.4.3 Tertiary Hyperparathyroidism (THPT)

In spite of controversies, HPT is regarded as "tertiary" when caused by autonomous proliferation of cells in patients with SHPT developing to hypercalcemia at the re-establishment of renal function [36]. Molecular studies suggest that the progression of tertiary hyperthyroidism (THPT) is associated with the loss of chromosome allele [37], consistent with monoclonal proliferation that is found with previous parathyroid hyperplasia.

8.5 Pathophysiology

Bone tissue shows no interstitial growth. It grows at the expense of the apposition of a new matrix over the previously existent one, by osteoblastic activity, which produced the matrix. These cells are identical to fibroblasts that produce collagen fibers on soft tissues. On bones, the collagen of the matrix has the ability to

mineralize by depositing hydroxyapatite crystals, which, under normal conditions, does *not* occur on other tissues. Matrix reabsorption is performed by osteoclasts, having characters of multiple nucleated giant cells [20].

Osteoclasts act under direct stimulus of PTH and local agents such as the transforming growth factor-alfa (TGF-α), tumor necrosis factor (TNF) and interleukins (ILs) [38]. Approximately, 95% of the bone matrix is constituted of collagen fibers. The remaining 5% are on cement or reverse lines, which mark the apposition ranges over the pre-existent ones, and are constituted of glycosaminoglycans (hyaluronic acid and chondroitin sulfate). Several factors contribute to matrix formation and maintenance, especially an appropriate protein intake, vitamins A and C, hormonal stimuli of the pituitary, thyroid and supra-renal glands, as well as gonads, and muscular exercise, which is essential for osteoblastic activity. Matrix mineralization depends on nutritional factors such as calcium and vitamin D intake, exposure to sun rays and normal bowel activity for calcium absorption, also under PTH action.

Bone turnover, apposition and reabsorption, persists throughout life. It is higher during intra-uterine and first decade of life, becoming progressively lower with aging, but always present until older ages. The skeleton is an important metabolic homeostasis factor for proteins and minerals in the body [36].

Parathormone in excess (HPT) will cause imbalance of bone maintenance, acting on osteoclasts that, through enzymes (hyaluronidase and collagenase), absorb the matrix and make calcium soluble. The effects of OFC on bone are largely dependent on the duration of the disease and the level of PTH produced, which is responsible for maintaining a homeostatic calcium concentration in blood [39]. It activates the PTH-related protein receptor located on osteoclasts and osteocytes, both of which are responsible for the breakdown and maintaining of bone. Abnormalities affecting the PTGs cause a surplus of PTH, which, in turn, increases the activity and frequency of osteoclasts and osteocytes [40]. Increased PTH levels trigger the release of stored calcium through the dissolution of old bone, as well as the conservation of serum calcium through a cessation in the production of new bone. Generally, the first bones to be affected with osteitis fibrosa cystica are the fingers, facial bones, ribs, and pelvis [6, 9]. Long bones are also among the first affected [6]. With progression of the disease, any bone in the body may be involved [39].

8.6 Clinical Presentation

The major symptoms of OFC are bone pain and/or tenderness, bone fractures, swelling (brown tumors) (Fig. 8.1), and skeletal deformities such as bowing of bones. The underlying HPT may cause kidney stones, nausea, constipation, fatigue, and weakness due to hypercalcemia. Plain radiography may show thin bones, fractures, bowing, and cysts. Fractures are most commonly localized in the arms, legs, or spine [41].

The addition of weight loss, appetite loss, vomiting, polyuria, and polydipsia to the aforementioned symptoms may indicate that OFC is the result of parathyroid carcinoma [42], which is generally indicated by serum calcium levels higher than

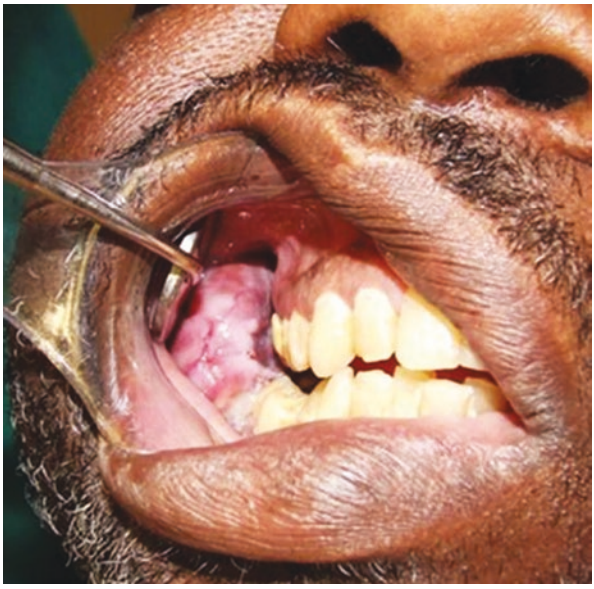

Fig. 8.1 Brown tumor causing intra-oral expansion of the mandible in a 49-year-old gentleman with end-stage renal disease and secondary hyperparathyroidism

usual, even in comparison to the high serum calcium levels that OFC generally presents with. Symptoms are also often more severe [43]. The presence of a palpable neck mass (lymphadenopathy) is also generally, indicative of malignancy, occurring in approximately 50% of sufferers, but virtually non-existent in individuals with OFC with a different origin [44].

Muscles in patients afflicted with OFC can either appear unaffected or "bulked-up." If muscular symptoms appear upon the onset of HPT, they are generally sluggish contraction and relaxation of the muscles. Identification of muscular degeneration or lack of reflex can occur through clinical testing of deep tendon reflexes, or via photomotogram (an Achilles tendon reflex test). Deviation of the trachea in conjunction with other known symptoms of OFC can point to the diagnosis of parathyroid carcinoma [6].

8.7 Investigations/Diagnosis

Osteitis fibrosa cystica may be diagnosed using a variety of techniques including laboratory tests, imaging studies, and cytology/histology.

8.7.1 Laboratory Tests

The first biochemical sign is "hyperphosphaturia" by the action of parathormone on renal tubules, inhibiting phosphorus reabsorption. For maintaining the calcium × phosphorus product in the blood around 36 in adults, increased bone reabsorption

will occur, which is translated into "hypercalcemia," to 10 or more mg/% (normal 8.5–10.2 mg/dL). As a result of hyperphosphaturia, "hypophosphatemia" of 3 mg/% or less will occur. Although bone histology remains the best method for differentiating between the forms of renal osteodystrophy, serum levels of PTH are commonly used for diagnosing SHPT and OFC. High serum PTH levels generally above 250 pg/mL, as opposed to the "normal" upper-range value of 65 pg/mL [45], and alkaline phosphatase (normal 20–140 IU/L) [46] will confirm the presence of the disease [47, 48].

8.7.2 Imaging Studies

Since bone radiological abnormalities associated with ESRD often appear late, and because radiographic findings are less sensitive than PTH levels, the use of radiographic images for *screening* purposes has been *abandoned*, and nowadays is reserved for symptomatic patients only [49]. However, in patients with very high levels of PTH, radiographs have some clinical indications, such as ruling out dialytic amyloidosis [50], and identifying several common complications of SHPT, such as skeletal lesions and heterotopic calcifications. Other important issues related to X-ray images include (1) localization of brown tumors, thus leading to actions for preventing fragility fractures, (2) detection of osteosclerosis in vertebral bodies or calcification of abdominal vessels, in order to correctly interpret over-estimated bone mineral density at such sites [51], (3) detection of metastatic calcifications, thus requiring more rigid control over the calcium-phosphate product, including indication of parathyroidectomy [50], (4) diagnosis of vertebral deformities and fractures, thus pointing toward better control over SHPT [50], and (5) possible prediction of the severity of hungry bone syndrome (post-parathyroidectomy hypocalcemia) based on the severity of the changes of bone structures [52].

Osteitis fibrosa cystica is characterized by several features of radiographic findings, which can be used to diagnose the disease. Usually, plain X-rays will show extremely thin bones, which are often bowed or fractured. However, such findings are also associated with other bone diseases, such as osteopenia or osteoporosis [53].

8.7.2.1 Bone Resorption

Bone resorption occurs because of increased osteoclastic activity and affects all bone surfaces at different skeletal sites. It may be subperiosteal, intra-cortical, endosteal, trabecular, sub-chondral, sub-ligamentous, or sub-tendinous [54]. *Subperiosteal bone* resorption is the most characteristic radiographic feature of HPT and is found in the phalanges (Fig. 8.2), humerus, and distal epiphysis of the clavicles [55, 56]. Hand radiographs probably remain the most commonly requested type of radiograph [50], since they can detect several typical changes in bone structure in severe forms of OFC [57]; they allow detection of bone resorption, deformities (acro-osteolysis), brown tumors, and vascular calcification [58]. Since subperiosteal resorption of the phalanges is considered to be the most sensitive

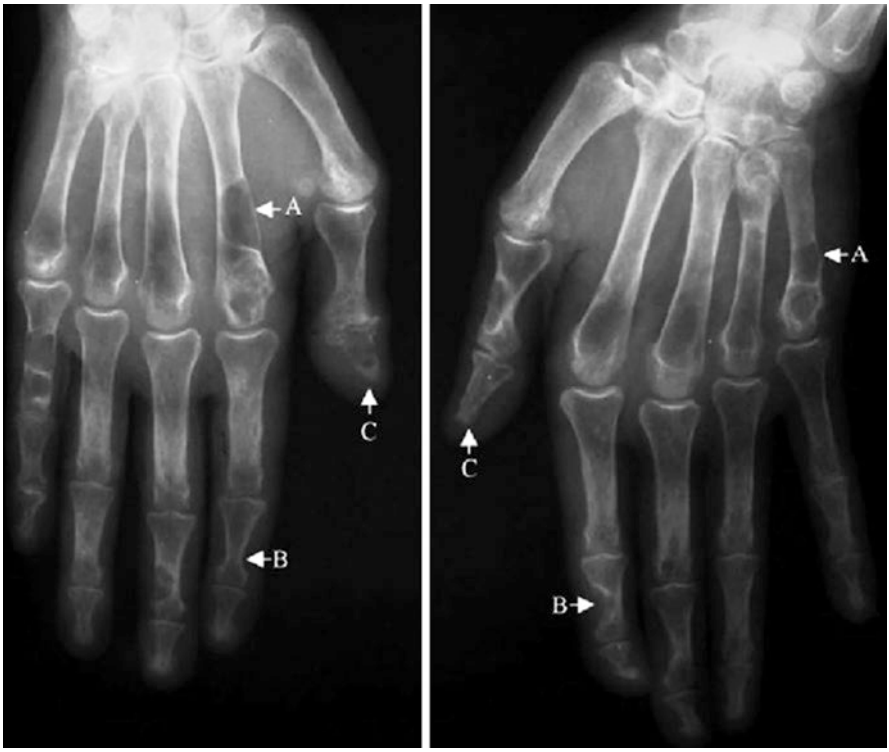

Fig. 8.2 Radiograph of both hands (frontal view) showing (**A**) multiple and bilateral brown tumors, (**B**) marked subperiosteal resorption, and (**C**) distal phalangeal resorption (acro-osteolysis). Note also diffuse osteopenia

radiographic sign of OFC [59], its absence would rule out bone resorption at other frequently affected sites [52, 54].

Hand radiographs are useful not only for early radiological diagnosis, but also for monitoring the effect of treatment of SHPT [49, 52]. With disease progression, bone changes become increasingly evident, until they reach more severe stages. When subperiosteal reabsorption foci start to compromise long bones, cystic lesions of variable sizes appear (Fig. 8.3).

When resorption is *sub-chondral*, like in the sacro-iliac joints, it can mimic the widening of the pubic symphysis, leading to "pseudo-widening" of the joint [60]. It occurs in different joints, particularly the sacro-iliac, sterno-clavicular, and acromio-clavicular joints [54]. *Intra-cortical* and *endosteal* resorption can cause scalloped defects of the inner cortical contour. Association of *trabecular* resorption (which causes loss of definition) and granular texture leads to a "salt and pepper" or "ground glass" appearance of the skull (Fig. 8.4) [61]. *Sub-ligamentous* and *sub-tendinous* bone resorption also occurs at many sites, such as the ischial tuberosities, femoral trochanters, and insertions of the coraco-clavicular ligaments [54]. Losses of lamina dura of the *teeth* are also usually due to bone resorption (Fig. 8.5).

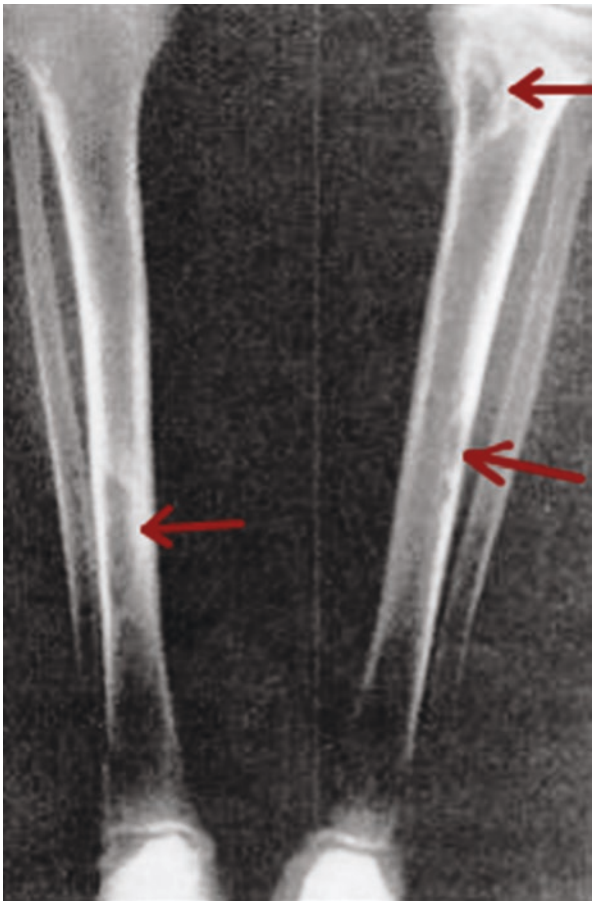

Fig. 8.3 Osteitis fibrosa cystica (OFC) of the tibia. The red arrows point to cystic lesions of variable sizes, which are typically present in bones of patients with OFC

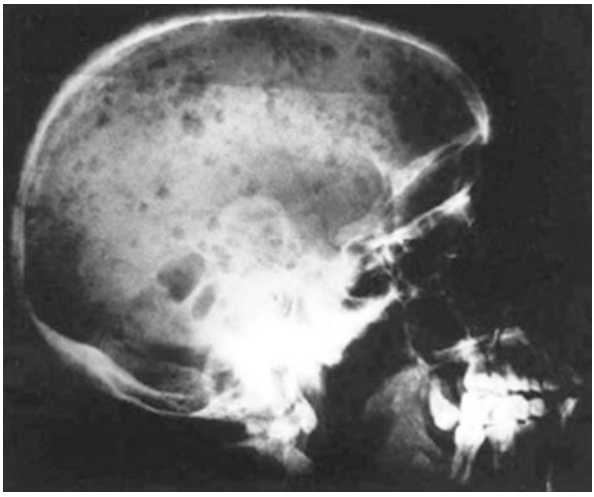

Fig. 8.4 Plain X-ray of the skull showing "salt and pepper" appearance with multiple punched out lesions: classical of osteitis fibrosa cystica (OFC) due to primary hyperparathyroidism (PHPT)

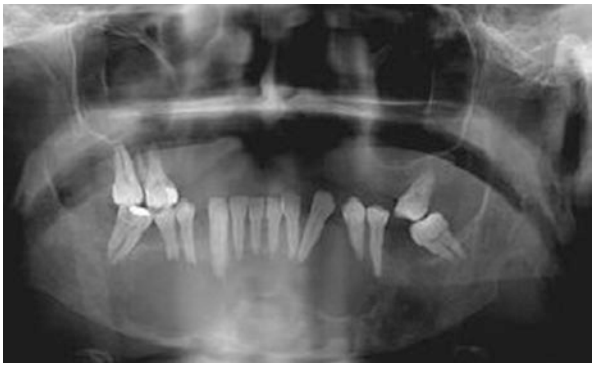

Fig. 8.5 Panographic radiograph showing a radiolucent image extending from tooth 20 to the region of 30 and in the mandibular angle in a patient with hyperparathyroidism (HPT)

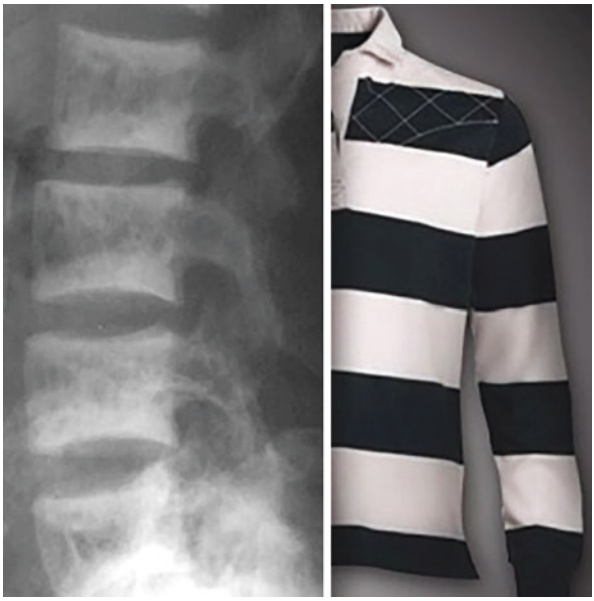

Fig. 8.6 Rugger jersey spine—prominent vertebral subendplate densities due to hyperparathyroidism, usually secondary to chronic renal failure

8.7.2.2 Osteosclerosis

Osteosclerosis can also occur in SHPT. Such changes are frequently found despite the presence and predominance of resorption. They are related either to excessive osteoblastic cellular function in response to bone resorption, or to increased production of mineralized osteoid [54]. Increased amounts of trabecular bone predominate in the axial skeleton, such as in the pelvis, ribs, spine, and skull. One of the typical findings is broad osteosclerosis located below the endplates of the *vertebral bodies*, representing accumulations of excess osteoid, with normal density in the middle parts. This finding is called "rugger jersey spine sign" (Fig. 8.6) [62], which is almost diagnostic of *osteosclerosis* associated with SHPT [62]. Thoracic and lumbar column radiographs are very useful for detecting "rugger jersey spine" sign (35.1%), thoracic deformities (91.7%), brown tumors (22.2%), fractures (60.0%) as well as vascular calcification (51.1%) [58, 63].

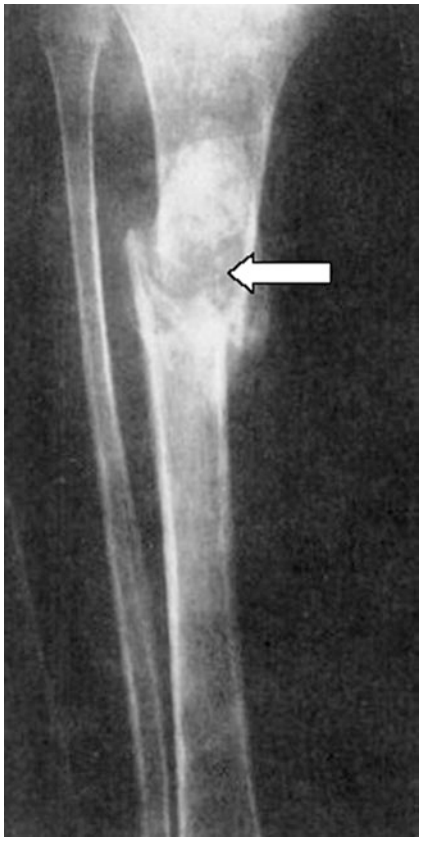

Fig. 8.7 Osteitis fibrosa cystica (OFC) of the tibia. The arrow points to a pathological fracture of the right tibia in a patient with OFC

Another typical example is sclerosis of the cortical surface of the *cranium*. Despite very high prevalence, sclerosis of the cranium is *not* specific for SHPT and does *not* cause complications for the patients. For these reasons, cranial radiographs are *not* useful. On the other hand, the finding of osteosclerosis in vertebral bodies is useful in clinical practice, since it may interfere with bone densitometry at this site.

8.7.2.3 Bone Deformities and Fragility (Pathological) Fractures

In severe cases of OFC, some bone deformities and fragility (pathological) fractures may appear (Fig. 8.7) [20]. Detection of pathological fractures is also crucial, since they are a marker for severity of OFC, which is a classical indication for parathyroidectomy. Such fractures may cause several complications, including inability to walk and dependence on other people for basic daily tasks as well as the risk of increased mortality. *Vertebral fractures* are associated not only with increased morbidity, such as height loss, kyphosis, back pain, functional impairment, and depression [64, 65], but also with increased risk of hospitalization [66] and relative risk of mortality [67–69], which may be almost nine times greater [70]. Only about 25% of vertebral fractures are clinically recognized [71]. For this reason, the lateral view of the lumbar column is useful for evaluating this complication.

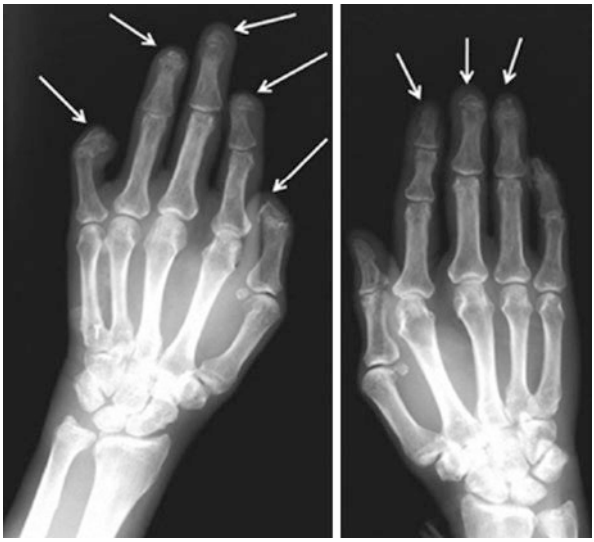

Fig. 8.8 Radiograph of the hands showing terminal resorption of the distal phalanges (acro-osteolysis) without any erosion of the articular surfaces (arrows)

Excessive resorption of the terminal phalanges may cause a deformity named *acro-osteolysis* (Fig. 8.8) [54]. Severe resorption in the sacro-iliac joint may cause great damage to the pelvis, thus leading to deformities that can impair the ability to walk. *Thoracic vertebral fractures* increase the antero-posterior diameter and enlarge the base, and thus the thorax can take on a "bell mouth" shape. In cases of thoracic kypho-scoliosis, abnormal curvature, and vertebral rotation may lead to chest deformity [58].

8.7.2.4 Brown Tumors

Fragility fractures sometimes occur at the sites of brown tumors. These lesions are caused by bone demineralization with rapid osteoclastic activity and peritrabecular fibrosis, and sometimes blood pigments (hemosiderin deposits) due to micro-hemorrhages, which lend to the notion of "brown tumors" because of their typical color. The name *tumor* is a misnomer because the lesion, although invasive in some instances, does not have a neoplastic potential and should be differentiated from true giant cell tumors of bone [72]. Brown tumors are very similar to giant cell tumors, but in the context of HPT they are considered "reparative granulomas" [73]. They are usually well-defined purely lytic lesions with the cortex thinned and expanded but *not* penetrated (Fig. 8.9) [20]. Radiographic findings can mimic bone malignancy, while the synchronous involvement of multiple skeletal segments can be interpreted as diffuse metastatic disease [53].

Since brown tumors are usually painless, clinical diagnosis is commonly made when the patient presents a fracture. However, a brown tumor may cause spinal cord compression when it involves the vertebral column, or it may cause breathing or swallowing difficulties when it deforms the face where it can be mis-diagnosed as being malignant [53, 74, 75].

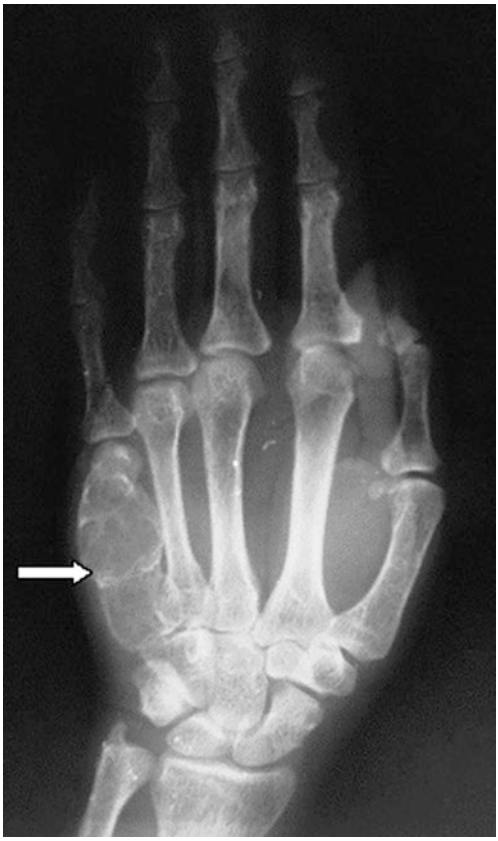

Fig. 8.9 Hand radiography showing a "brown tumor," consisting of a cystic, expansile, well-defined lesion, with the cortex thinned and expanded, but not penetrated in the fifth metacarpal (arrow)

Brown tumors appear mostly at the pelvis, ribs, clavicles, mandible and extremities [75]. They are considered to be the most pathognomonic of the many skeletal changes that accompany SHPT [76] and their incidence in patients with CRF ranges from 1.5% to 13% [74, 77]. Femoral radiographs are very important for showing brown tumors (Fig. 8.10), which in some cases cause fragility fractures that can be detected at this site. Vascular calcifications are also frequently seen in the femur. Therefore, this location should also be evaluated in hemodialysis patients with very high levels of PTH [58].

8.7.2.5 Metastatic (Ectopic) Calcification

Metastatic calcification occurs when the calcium/phosphate solubility product in extracellular fluid is exceeded [78]. Its presence has become a very important sign since Block et al. (1998) demonstrated the positive correlation between the risk of mortality and plasma calcium-phosphate product [79], especially due to vascular calcification, including coronary arteries. At autopsy, metastatic calcifications have been detected in 60–80% of patients who had undergone dialytic therapy [55]. Other types of soft-tissue calcifications, such as visceral and peri-articular calcifications, are also frequently seen in patients undergoing long-term hemodialysis [80, 81].

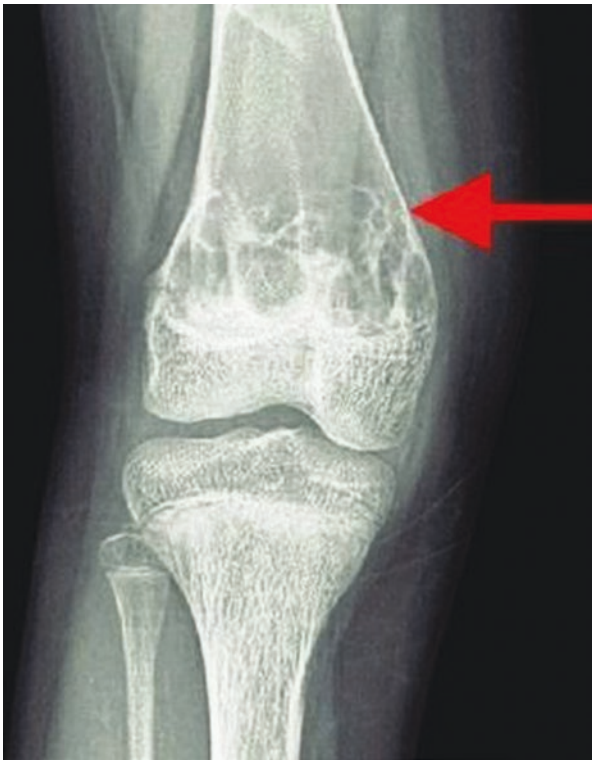

Fig. 8.10 Plain radiography showing a brown tumor measuring 87 × 44 mm in size (red arrow) in the distal metaphysis of the right femur

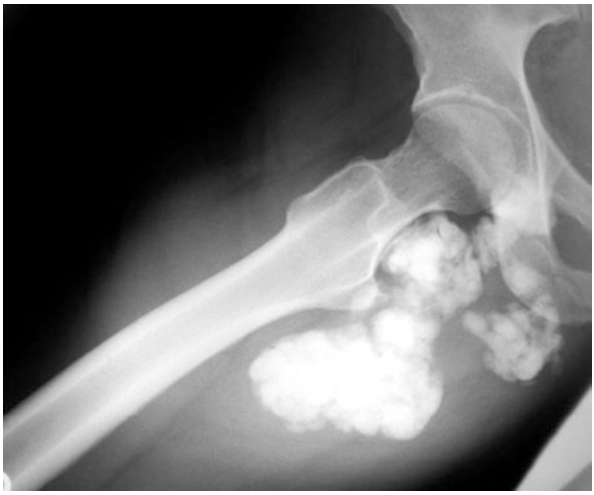

Fig. 8.11 Amorphous, cystic, lobular (circular or oval) well-demarcated calcification in the peri-articular location of the hip. Direct involvement of the bones or joints is rare

Tumoral calcinosis is the calcification of peri-articular subcutaneous tissues around the major joints. Typically, the hips (Fig. 8.11) and shoulders (Fig. 8.12) are affected, although additional joints such as the elbows, feet, hands, and wrists can become involved [82].

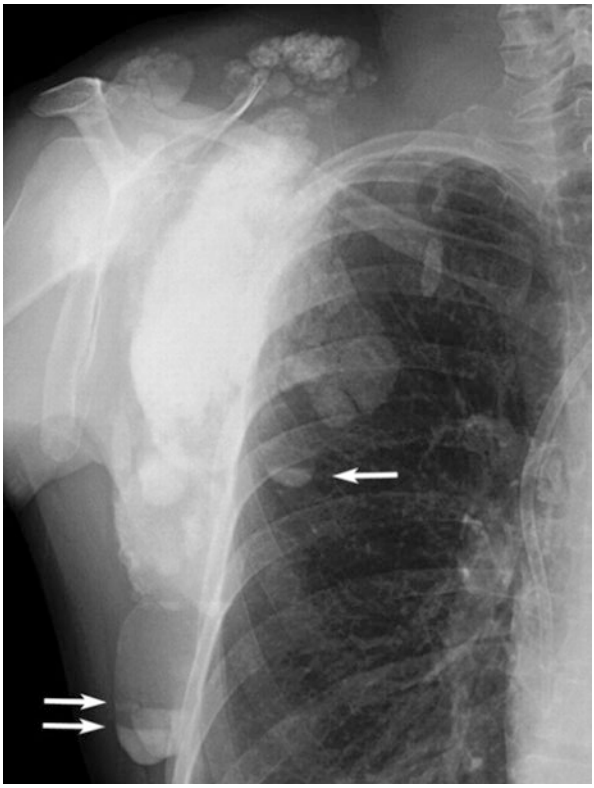

Fig. 8.12 Tumoral calcinosis of the shoulder girdle. Antero-posterior radiograph shows multiple rounded calcified masses, some of which demonstrate sedimentation (arrows)

8.7.3 Cytology/Histology

Fine needle aspiration (FNA) can be used to biopsy bone lesions, once found on an X-ray or other scan. Such tests can be vital in diagnosis and can also prevent unnecessary treatment and invasive surgery [83]. Conversely, FNA biopsy of tumors of the PTG is not recommended for diagnosing parathyroid carcinoma and may in fact be harmful, as the needle can puncture the tumor, leading to dissemination and the possible spread of cancerous cells [84].

Microscopically, bones show a reduced girder thickness (osteoporosis) and reduced mineralization (osteomalacia) around fibrous proliferation. On bone girders' edges reabsorption gaps are numerous, with a variable number of osteoclasts, sometimes as "reabsorption fronts" [85]. Lesions behaving as "brown tumor" on X-ray result from hemorrhagic foci, which, after red blood cells' disintegration, will make cumulative hemosiderin deposits to appear, permeated by numerous multiple nucleated giant cells with osteoclasts characters (Fig. 8.13), corresponding to "hyperparathyroidism brown tumors," which

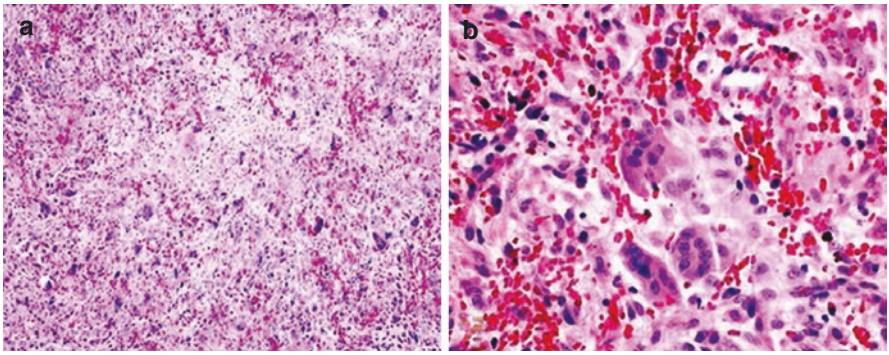

Fig. 8.13 Microscopic aspect of brown tumor of hyperparathyroidism (BTH). (**a**) Lower magnification showing a dense cellular lesion consisting of mesenchymal and multinucleated giant cells, with erythrocytes extravasation (hematoxylin-eosin [H&E] × 50 magnification). (**b**) Higher magnification illustrating the multinucleated giant cells typical of BTH (H&E×200 magnification)

Table 8.1 Biochemical comparison of different bone pathologies

Condition	Calcium	Phosphate	AP	PTH	Comments
Osteitis fibrosa cystica	Elevated	Decreased	Elevated	Elevated	Brown tumors
Osteopenia	Unaffected	Unaffected	Normal	Unaffected	Decreased bone mass
Osteopetrosis	Unaffected	Unaffected	Elevated	Unaffected	Thick dense bones also known as marble bone
Osteomalacia and rickets	Decreased	Decreased	Elevated	Elevated	Soft bones
Paget's disease of bones	Unaffected	Unaffected	Variable (depends on stage of disease)	Unaffected	Abnormal bone architecture

AP alkaline phosphatase, *PTH* parathyroid hormone

is "pseudo-neoplastic" [6]. These cells are characteristically benign, with a dense, granular cytoplasm, and a nucleus that tends to be ovular in shape, enclosing comparatively fine chromatin. Nucleoli also tend to be smaller in size than average [39].

8.7.4 Differential Diagnosis/Comparison of Bone Pathology

Osteitis fibrosa cystica (OFC) should be differentiated from other pathological bone lesions. Table 8.1 summarizes the differences in biochemical parameters (serum calcium, phosphate, alkaline phosphatase, and PTH) between OFC, osteopenia, osteopetrosis, osteomalacia and rickets, as well as Paget's disease of bones.

8.8 Management

8.8.1 Medical Treatment

Medical management of OFC consists of vitamin D treatment, generally alfacalcidol or calcitriol (Rocaltrol), delivered intravenously (IV), and Cinacalcet (a calcimimetic). Arabi (2006) reported that in cases of OFC caused by either end-stage renal disease (ESRD) or primary hyperparathyroidism (PHPT), this method is successful not only in treating the underlying HPT, but also in causing the regression of brown tumors and other symptoms of OFC [86].

8.8.2 Surgical Treatment

In especially severe cases of OFC, parathyroidectomy, or complete removal of PTGs, is the treatment of choice. Parathyroidectomy has been shown to result in the reversal of bone resorption and the complete regression of brown tumors in primary cases [86]. In situations where parathyroid carcinoma is present, surgery to remove the tumors has also led to the regression of HPT as well as the symptoms of OFC [87].

For brown tumors with HPT, managing the cause of HPT is the primary treatment [88, 89]. *Surgical interventions* including removing the offending parathyroid mass can be effective. Parathyroid surgery rapidly decreases the excessive amount of PTH and thus achieving complete regression of the lesions with remineralization. Medical treatment may also be used together. Normalizing serum calcium level should be the goal to stabilize the micro-environment of bone. Bisphosphonates are also recommended for treatments [90].

Surgical resection of a brown tumor is generally *not* recommended and should only be considered if the patient wants quick resolution, if the bony lesion is compromising body functions or promoting facial deformation, or if the lesion fails to regress after 1–2 years of follow-up [91]. *Bone transplants* have proven successful in filling the lesions caused by OFC. Brand and Richard (2008) reported that in 8 out of 11 instances where cavities caused by OFC were filled with transplanted bone, the lesion healed and the transplanted bone blended rapidly and seamlessly with the original bone [92].

As for brown tumors of the *spine*, treatment varies according to the situation. Pathological fractures require surgical intervention. After parathyroidectomy, spinal instrumentation and fusion are indicated to maintain stability [93]. Surgical decompression should be taken immediately on occasion of spinal cord compression to preserve neural function. In 2015, Sonmez et al. [94] and Alfawareh et al. [15] reported that decompressive surgery at an early stage can be effective to improve life quality apparently in relieving pain and paralysis. In the literature, most patients underwent both spine surgery and parathyroidectomy. In 2019, Jimbo et al. reported that without unstable fracture or spinal cord compression the outcome is similar, without statistical significance, between patients who underwent parathyroid adenoma resection with or without spine surgery [95].

8.9 Prognosis

Almost all patients who undergo parathyroidectomy experience increased bone density and repair of the skeleton within weeks. Additionally, those with OFC who have undergone parathyroidectomy begin to show regression of brown tumors within 6 months [11, 96]. Gibbs et al. (1996) found that following parathyroidectomy, hypocalcemia is common. This results from a combination of suppressed PTGs due to prolonged hypercalcemia, as well as the need for calcium and phosphate in the mineralization of new bone [97].

Gupta et al. (2001) reported that 30% of patients with OFC-like tumors caused by metastatic parathyroid carcinoma and undergo surgery experience local recurrence of symptoms. The post-surgical survival rate hovers around 7 years, while patients who do not undergo surgery have a survival rate of around 5 years [6].

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Hypoparathyroidism

9

9.1 Overview

Hypoparathyroidism is a condition characterized by absence or inappropriately low concentrations of circulating parathyroid hormone (PTH), leading to hypocalcemia, hyperphosphatemia, and elevated fractional excretion of calcium in the urine, with tendency toward chronic tetany [1, 2].

The mechanism of action of PTH was first described by Collip et al. in 1912 [3] when parathyroidectomized dogs that developed tetany were given purified oxen (bovine) PTH with resolution of symptoms. They concluded that PTH plays an important role in maintaining normal blood calcium (Ca) and phosphorus levels in the body. The full sequence of PTH was later described [4, 5].

The role of parathyroid glands (PTGs) is to regulate Ca levels in the blood by release of PTH by sensing low serum Ca level through calcium-sensing receptors (CaSRs) located on the parathyroid cells. Parathyroid hormone regulates Ca homeostasis by a tightly controlled system; it plays an important role in mobilizing Ca from bone where it is primarily stored and increasing Ca absorption from the intestine by increasing synthesis of calcitriol (1,25-dihydroxy-vitamin D) by conversion of 25-hydroxy-vitamin D in the proximal renal tubule of the kidney. Parathyroid hormone also increases Ca reabsorption from the thick ascending limb of the nephrons and facilitates the excretion of phosphorus through the kidneys.

Calcium is sensed by the CaSR, a 7-transmembrane G protein-coupled receptor found on the PTGs, which stimulates PTH release in response to low serum Ca, and suppresses PTH release in response to high serum Ca. The CaSR is also expressed in several other tissues including renal tubular cells, where it regulates Ca reabsorption, as well as bone and intestinal cells. In hypercalcemia, the filtered Ca load overcomes the renal tubular ability to reabsorb Ca resulting in decrease in Ca and sodium transport in the loop of Henle with an associated decrease in urinary concentrating ability to reduce Ca absorption through the kidneys.

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When PTH production is reduced or absent, normo-calcemia and normo-phosphatemia cannot be maintained resulting in hypocalcemia, hyper-phosphatemia, and low PTH ensue. The most common cause of hypoparathyroidism is inadvertent damage to the PTGs during thyroid surgery [6–8]. Other causes of hypocalcemia that need to be ruled out include magnesium (Mg) deficiency and vitamin D deficiency. Magnesium is needed for the secretion of PTH by the PTGs and its depletion or excess may cause hypoparathyroidism and subsequent hypocalcemia. This is thought to be due to the lack or excess Mg playing a role in defective cyclic AMP generation in the PTGs interfering with PTH synthesis and secretion [9].

Symptoms of hypoparathyroidism are the result of low serum Ca effect on the internal organs and correlate strongly with the acuteness of the low serum Ca and the absolute level. Presenting symptoms are variable. Mild symptoms include numbness and tingling of the extremities and perioral region, muscle cramps, and fatigue, and in severe cases, tetany, seizure, altered mental status, cardiac rhythm disturbances, refractory congestive heart failure, bronchospasm, and laryngospasm can be seen [1, 10]. In most patients, symptoms develop when the albumin-corrected serum calcium is less than 7.5–8.0 mg/dL [9].

9.2 Epidemiology

The incidence of hypoparathyroidism in the United States, Denmark, and Italy are relatively close, in the range of 23–37 per 100,000 individuals [11–13], but the prevalence in some other countries is reported to be lower [14]. The variation between countries might be explained by differences in surgical outcomes, as the majority of cases are the consequence of surgery. Further research is needed to define the prevalence and incidence of hypoparathyroidism outside the United States and Europe, as no such studies have been reported from South America, Asia, Africa, or Australia.

Although the prevalence of inherited causes of hypoparathyroidism is similar between men and women [15], post-surgical hypoparathyroidism is more common in women than in men, 75% versus 25, respectively, [12, 16] because women are more likely to have thyroid disease and hence undergo thyroidectomy [17]. About 75% of these patients are aged 45 years or older, and roughly 75% of cases are due to neck surgery and 25% are reported to be due to non-surgical causes.

9.2.1 North America

The best estimate of the prevalence of hypoparathyroidism in North America is based on analysis of a large US health plan claims database over a 12-month period from 2007 to 2008 [16]. Population prevalence of hypoparathyroidism is estimated at 77,000 adults in the United States. An alternative approach based on the incidence of neck surgeries and the incidence of chronic hypoparathyroidism as a surgical complication using the same database led to similar estimates [16]. Another

estimate of the prevalence of hypoparathyroidism was based on the longitudinal population-based Rochester Epidemiology Project. In this database, hypoparathyroidism resulted from neck surgery in 78% of cases, other secondary causes in 9%, familial disorders in 7%, and was idiopathic in 6% [18].

9.2.2 Europe

The prevalence of hypoparathyroidism in *Denmark* was estimated using the Danish National Patient Registry [12, 15, 19]. These studies also assessed mortality and comorbidities by comparing patients with hypoparathyroidism with age-matched and sex-matched population-based controls. A total of 1849 individuals with post-surgical hypoparathyroidism and 180 individuals with non-surgical hypoparathyroidism were identified. The estimated prevalence of post-surgical hypoparathyroidism was 22 per 100,000 individuals and non-surgical hypoparathyroidism was 2.3 per 100,000 individuals. The incidence of post-surgical hypoparathyroidism was estimated to be 0.8 per 100,000 person-years [19]. Of the post-surgical cases, indications for surgery included malignancy (primarily thyroid cancer) in 30%, simple goiter in 37%, toxic goiter in 25%, and primary hyperparathyroidism in 8% [19]. The prevalence of hypoparathyroidism in *Norway* is about half that of the estimates for Denmark, at 10.2 per 100,000 individuals [20]. The mean hospitalization rate for hypoparathyroidism in *Italy* was 5.9 per 100,000 individuals per year [21].

9.3 Etiology/Pathophysiology

The most common cause of hypoparathyroidism is surgical destruction or injury of the parathyroid glands (PTGs); other causes are autoimmune diseases or genetic disorders affecting PTG development or the biosynthesis or release of PTH.

9.3.1 PTH and Mineral Homeostasis

The PTGs control extra-cellular calcium homeostasis by secreting PTH (Fig. 9.1). In the parathyroid cell, PTH is synthesized as a 115-amino-acid precursor peptide [pre-proPTH(1–115)], which later matures into full-length PTH containing 84 amino acids [PTH(1–84)]. PTH is stored in secretory granules and released by the PTGs when circulating ionized calcium concentrations are reduced. These changes in serum calcium levels are detected by CaSR, a G protein-coupled receptor that is highly expressed on the surface of parathyroid cells [22]. A decrease in the levels of extra-cellular calcium reduces CaSR signaling via $G_{11}\alpha$ and $G_q\alpha$, which induces a marked increase in PTH release from the PTGs. The secreted PTH circulates in the bloodstream and acts on the G protein-coupled PTH1 receptor (PTH1R) [23] in bone and the kidneys to increase serum calcium levels, which leads to feedback inhibition of PTH secretion from the PTGs [22].

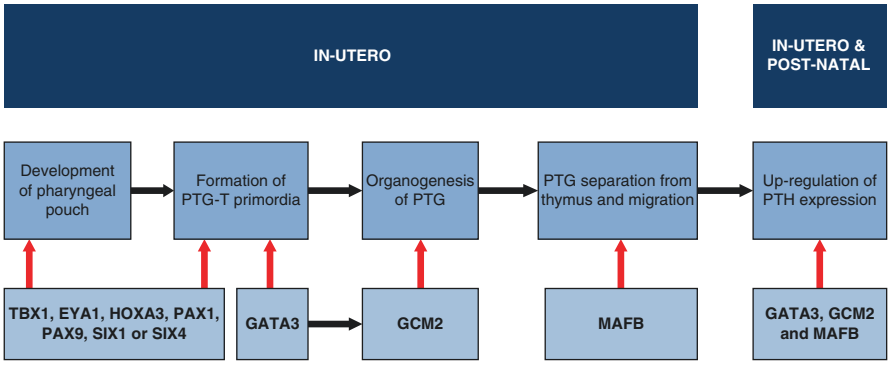

Fig. 9.1 Transcription factors involved in parathyroid gland development and function. EYA1, eyes absent homologue 1; HOXA3, homeobox A3; PAX, paired box; SIX, Sine oculis homeobox homologue; PTG-T, parathyroid gland-thymus

Parathyroid hormone acts on the PTH1 receptor (PTH1R) in the kidneys and bone. In bone, PTH1R activation in osteoblasts and osteocytes results in the release of cytokines that stimulate osteoclast activity, thereby enhancing bone resorption and the release of calcium from the skeleton [23]. In the kidney, PTH increases tubular calcium reabsorption, phosphate excretion and stimulates the 25-hydroxyvitamin D 1-α-hydroxylase (CYP27B1) enzyme, which promotes the conversion to active 1,25-dihydroxyvitamin D (calcitriol) metabolite from its precursor (25(OH)D).

Calcitriol acts on the intestine to increase the absorption of dietary calcium via the vitamin D receptor (VDR) [23]. The increase in calcium and calcitriol levels mediated by PTH causes the PTGs to induce feedback inhibition of further PTH secretion [22].

Parathyroid hormone also regulates circulating phosphate levels. A rise in circulating phosphate levels stimulates the secretion of PTH, which in turn acts on the kidneys to inhibit tubular phosphate reabsorption [24]. Phosphate homeostasis is further regulated by fibroblast growth factor 23 (FGF23), an osteocyte-derived hormone that inhibits renal tubular phosphate reabsorption and the renal synthesis of calcitriol (also known as 1,25-dihydroxyvitamin D ($1,25(OH)_2D$)) [25].

In the setting of *hypoparathyroidism*, absence or low circulating levels of PTH lead to hypocalcemia by impairing osteoclast activity, which diminishes the efflux of calcium from bone, by enhancing urinary calcium excretion and by inhibiting the renal synthesis of calcitriol, which impairs the intestinal absorption of dietary calcium [26]. Deficiency of PTH also causes hyperphosphatemia, owing to an increase in the renal tubular reabsorption of phosphate, and chronic hyper-phosphatemia has been shown to be associated with increases in serum FGF23 levels in patients with hypoparathyroidism [27].

Parathyroid hormone is also involved in magnesium homeostasis; it increases magnesium reabsorption in the kidney [28], whereas severe and prolonged hypomagnesemia results in hypocalcemia through inhibition of PTH secretion and PTH end-organ resistance [29, 30]. Hypermagnesemia may also inhibit PTH release through activation of CaSR, thus promoting hypocalcemia [31, 32].

9.3.2 Post-surgical Hypoparathyroidism (Extirpation of the PTG—Parathyroidectomy)

The most common cause of acquired hypoparathyroidism is anterior neck surgery accounting for approximately75% of all cases of hypoparathyroidism [1, 13, 33]. Surgeries associated with the development of hypoparathyroidism are (1) parathyroid surgery (e.g., treatment of adenoma or hyperplasia), (2) thyroid surgery (inadvertent PTG removal, intra-operative trauma to the PTGs or gland devascularization during thyroidectomy, being more common after total thyroidectomy, or treatment of recurrent goiters [completion thyroidectomy]), and (3) head or neck cancer surgery (e.g., radical or modified radical neck dissection) [1, 16, 26].

Transient post-surgical hypoparathyroidism, which is defined as absence of PTH or low PTH levels lasting <6 months, affects up to 25–30% of patients following total thyroidectomy, whereas permanent post-surgical hypoparathyroidism (hypoparathyroidism for >6 months) affects only up to 3% of patients [6, 16, 20, 34–36]. The risk of hypoparathyroidism after anterior neck surgery depends on the experience of surgeon, presence of multigland disease (MGD), long-standing history of HPT resulting in hungry bone syndrome, and in malabsorption resulting from weight loss surgeries (in particular Roux-en-y gastric bypass surgery, which affects Ca and vitamin D absorption) [6].

Low pre-operative levels of serum calcium, low intra-operative PTH concentrations, auto-transplantation of one or more PTGs, and longer duration of surgery have been identified as independent predictors of *transient* hypoparathyroidism post-thyroidectomy [37]. Risk factors of *permanent* hypoparathyroidism following thyroid surgery include extent of the surgery; a pre-operative diagnosis of Graves disease; failure to identify ≥2 PTGs during surgery; serum calcium levels of ≤7.5 mg/dL (normal range: 8.5–10.5 mg/dL) at 24 h post-surgery; and re-operation for bleeding [37]. Vitamin D deficiency prior to surgery can also result in post-operative hypocalcemia and most experts recommend vitamin D replacement to maintain vitamin D level >20 ng/dL prior to surgery. Vitamin D level should be individualized and corrected with caution in patients with primary hyperparathyroidism (PHPT) undergoing parathyroidectomy to prevent the risk of hypercalcemia [38].

Rarely, post-surgical hypoparathyroidism can present years after neck surgery [39]. The mechanism underlying this delayed presentation is unclear, but may be caused by the effects of age-related changes to the vasculature of the marginally functional, residual parathyroid tissue present post-surgery [1].

9.3.3 Inherited (Genetic) Causes of Hypoparathyroidism

Hypoparathyroidism has a genetic etiology in <10% of cases [13]. However, chromosomal micro-deletions and monogenic abnormalities represent the major cause of hypoparathyroidism in children [40]. Genetic forms of hypoparathyroidism occur as (1) a component of *syndromic* disorders, (2) as a *solitary endocrinopathy*, which is referred to as isolated hypoparathyroidism, or (3) as *autosomal dominant hypocalcemia*, which can be considered a distinct type of hypoparathyroidism. Genetic forms of PTH resistance are a distinct set of diseases referred to as "pseudo-hypoparathyroidism" (parathyroid hormone resistance of the kidneys and bone, presenting with high PTH and low calcium serum levels) that is rarely seen. There are several types or forms of pseudo-hypoparathyroidism, which include type1a, type 1b, type 1c, and type 2. Pathogenesis of pseudo-hypoparathyroidism has been linked to dysfunctional G-proteins (in particular, Gs-alfa-subunit).

Inherited (genetic) causes of hypoparathyroidism, both syndromic and non-syndromic forms (isolated hypoparathyroidism and autosomal dominant hypocalcemia), are depicted in Table 9.1, which summarizes the mode of inheritance, the responsible genes/proteins, and abnormal chromosomal location.

9.3.3.1 Pathophysiology of Inherited Causes of Hypoparathyroidism

Variations in the levels of extracellular calcium are detected by the calcium-sensing receptor (CaSR), which is expressed by cells in the parathyroid gland, kidney, and bone. CaSR signals via the guanine-nucleotide-binding protein q/11α ($G_{q/11}\alpha$) to stimulate phospholipase C (PLC), which catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate ($PtdIns(4,5)P_2$) to inositol 1,4,5-trisphosphate ($Ins(1,4,5)P_3$), thereby increasing the levels of intracellular calcium. CaSR also signals via the $G_i\alpha$ protein, which inhibits adenylyl cyclase (AC), thereby leading to a reduction in the formation of cAMP from ATP. In parathyroid cells, these proximal signals modulate downstream pathways, which lead to alterations in the synthesis and secretion of PTH. Secreted PTH acts on the PTH1 receptor (PTH1R) in target tissues, which mediates signaling via the $G_s\alpha$ and $G_{q/11}\alpha$ proteins. Abnormalities in several genes and encoded proteins in these pathways involved in calcium-sensing and G protein function, mitochondrial activity and tubulin formation, as well as in gene transcription and chromatin remodeling have been identified in patients with genetic hypoparathyroid disorders [26].

As demonstrated in Fig. 9.1, PTGs in humans are derived from the endoderm of the third and fourth pharyngeal pouches [42]. Studies using mouse models have shown that a network of transcription factors mediates patterning of the third pharyngeal pouch and the formation of the common parathyroid–thymus primordia [42, 43]. These transcription factors act in a spatio-temporal manner. For example, T box 1 (TBX1), expressed in the pharyngeal endoderm, is required for the development of the third pharyngeal pouch [44], whereas GATA-binding factor 3 (GATA3), which is expressed later than TBX1 in the common parathyroid–thymus primordia, mediates the differentiation and survival of PTG and thymus progenitor cells [42, 45]. Moreover, GATA3 regulates the expression of glial cells missing homologue 2

(GCM2), which is expressed in the parathyroid domain of the common primordia and mediates the initial stages of PTG organogenesis [42, 45]. MAFB is also expressed in the parathyroid domain and facilitates the separation of PTGs from the thymus and their migration towards the thyroid [43]. GATA3, GCM2, and MAFB act synergistically to upregulate the expression of PTH [46].

9.3.3.2 Individual Hereditary Causes

Autoimmune Polyendocrine Syndrome—Type 1 (APS-1)

Autoimmune polyendocrine syndrome type 1 (APS-1), which is also referred to as "autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy syndrome," is an autosomal recessive disorder characterized by immune deficiency and autoimmune destruction of endocrine organs, such as the PTGs, adrenal cortex, and ovaries [37] (Table 9.1). APS-1 is caused by mutations in autoimmune regulator (*AIRE*), which is expressed in thymic medullary epithelial cells [47] and promotes immunological tolerance to self-antigens by deleting clones of auto-reactive T-cells within the thymus [48]. Autoimmune polyendocrine syndrome type 1 mechanism also indicates that affected individuals' autoantibodies have considerable reactions with both interferon omega and interferon alfa.

The APS1 is clinically defined by the presence of at least two components of a triad that consists of muco-cutaneous candidiasis (a *Candida* spp. infection of the skin, mucous membranes or nails), hypoparathyroidism, and adrenal insufficiency (Addison's disease) [49]. However, the disorder can also be associated with various other autoimmune disorders, such as gonadal failure (primary hypogonadism), autoimmune thyroid disease, alopecia, malabsorption, pernicious anemia, vitiligo, cataract, and type 1 diabetes mellitus (DM), and can present with isolated hypoparathyroidism [50]. Patients can have ectodermal dystrophies (skin, nails, and tooth enamel) [51], and are at higher risk of developing oral cancer [52].

Autoimmune polyendocrine syndrome type 1 (also known as Bizzard's syndrome) is a subtype of autoimmune polyendocrine syndrome (autoimmune polyglandular syndrome) in which multiple endocrine glands dysfunction as a result of autoimmunity. The main differences between type 1 and type 2 (also known as Schmidt's syndrome) are summarized in Table 9.2.

Autoimmune polyendocrine syndrome type 1 treatment is based on the symptoms that are presented by the affected individual. Additionally, there is hormone replacement, systemic anti-fungal treatment, and immuno-suppressive therapy.

DiGeorge Syndrome: Type 1

DiGeorge syndrome was first described in 1968 by American physician Angelo DiGeorge. In late 1981, the underlying genetics were determined. The syndrome occurs in about 1 in 4000 live-births.

DiGeorge syndrome presents with hypoparathyroidism (hypocalcemia), congenital heart problems (cardiac outflow tract malformations), facial dysmorphia (abnormal facies), and deformities of the ear, nose, and mouth, psychiatric illness, palatal dysfunction (cleft palate), immuno-deficiency, and thymic hypoplasia/aplasia [40].

Table 9.1 Inherited causes of hypoparathyroidism [41]

Disease	Inheritance	Gene/Protein	Abnormal chromosome
Syndromic forms			
Auto-immune poly-glandular syndrome type 1 (APS-1)	AR	*AIRE*	21q22.3
DiGeorge syndrome type I (22q11.2 deletion syndrome)	AD	*TBX1, NEBL*	22q11.2
DiGeorge syndrome type 2	AD	*NEBL*	10p13–14
CHARGE syndrome	AD	*CHD7, SEMA3E*	8q12.1–q12.2,7q21.11
Hereditary deafness and renal dysplasia (HDR) syndrome (hypoparathyroidism, sensori-neural deafness, and renal disease syndrome)	AD	*GATA3*	10p15
Kenny–Caffey syndrome type I	AR	*TBCE*	1q42.3
Kenney–Caffey syndrome type 2	AD	*FAM111A*	11q12.1
Sanjad–Sakati syndrome	AR	*TBCE*	1q42.3
Gracile bone dysplasia[a]	AD	*FAM111A*	11q12.1
Kearns–Sayre syndrome (KSS)	Maternal	Mitochondrial genome *(DNA)*	NA
Mitochondrial encephalo-myopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome	Maternal	Mitochondrial genome *(DNA)*	NA
Mitochondrial trifunctional protein (MTP) deficiency syndrome (MTPDS)	AR	*HADHB*	2p23
Non-syndromic forms			
Isolated hypoparathyroidism			
– Autosomal hypoparathyroidism	AD or AR	*PTH, GCMB*	11p15,6p24.2
– X-linked hypoparathyroidism	X-linked	*SOX3*[b]	Xq26–27
Autosomal dominant hypocalcemia type 1 (ADH1), Bartter syndrome type 5[c]	AD	CaSR	3q21.1
Autosomal dominant hypocalcemia type 2 (ADH2)	AD	*GNA11*	19p13.3

AD autosomal dominant, *AR* autosomal recessive, *AIRE* autoimmune regulator 1, *GCM2* glial cell missing 2, *CaSR* calcium-sensing receptor, *TBX1* T-box 1, *NEBL* nebulette, *CHD7* chromo-domain helicase DNA-binding protein 7, *SEMA3E* semaphorin 3E, *GATA3* GATA-binding protein 3, *TBCE* tubulin folding cofactor E, *FAM111A* family with sequence similarity 111 member A, *GCMB* glial cell missing gene, *SOX3* Sry-related HMG box, *GNA11* G protein subunit alfa 11, *ADH* autosomal dominant hypocalcemia, *MELAS* mitochondrial encephalopathy, *MTPDS* mitochondrial trifunctional protein deficiency syndrome, *PTH* parathyroid hormone, *NA* not applicable

[a]Bone dysplasia and short stature

[b]The causative role of *SOX3* in X-linked hypoparathyroidism is uncertain

[c]Bartter syndrome type 5 is a variant of autosomal dominant hypocalcemia type 1

Table 9.2 Differences in major components of APS type1 and APS type 2

APS-1 (Bizzard's syndrome)	APS-2 (Schmidt's syndrome)
– Chronic muco-cutaneous candidiasis	– Autoimmune thyroid disease
– Hypoparathyroidism	– Diabetes mellitus—Type 1
– Addison's disease	– Addison's disease
– Other endocrinopathies and features	– Other endocrinopathies and features

DiGeorge syndrome is most commonly caused by a heterozygous 3-Mb micro-deletion of chromosome 22q11.2 [53], which is referred to as DiGeorge syndrome type 1 (also known as 22q11.2 deletion syndrome) (Table 9.1). The deleted region encompasses *TBX1*, which encodes T box protein 1, a transcription factor involved in the development of the PTGs and thymus from the embryonic pharyngeal region [44]. Abnormalities in the function of TBX1 explain all of the main phenotypical features of DiGeorge syndrome type 1 [54].

Although there is no cure, treatment can improve symptoms. This often includes a multidisciplinary approach with efforts to improve the function of the potentially many organ systems involved. Long-term outcomes depend on the symptoms present and the severity of the heart and immune system problems. With treatment, life expectancy may be normal.

DiGeorge Syndrome: Type 2

Some patients harbor chromosome 10p deletions [26] referred to as DiGeorge syndrome type 2. Deletion of the gene encoding the actin-binding protein nebulette (NEBL) is probably responsible for this disorder [55] (Table 9.1), but how deficiency in NEBL causes hypoparathyroidism is currently unclear.

CHARGE Syndrome

CHARGE syndrome is a congenital condition that affects many areas of the body. "CHARGE" stands for **c**oloboma, **h**eart defect, **a**tresia **c**hoanae (also known as choanal atresia), **r**estricted growth and development, **g**enital abnormality, and **e**ar abnormality. Some patients with DiGeorge syndrome have features of CHARGE syndrome, which is characterized clinically by coloboma (a hole in one or more ocular structures), heart abnormalities, choanal atresia (a congenital nasal airway abnormality), anosmia, growth retardation, gonado-tropin deficiency, and genito-urinary, and/or ear anomalies [56]. Signs and symptoms vary among people with this condition; however, infants often have multiple life-threatening medical conditions.

CHARGE syndrome is caused, in more than 50% of all cases, by heterozygous mutations in chromodomain helicase DNA-binding 7 (*CHD7*) [56], (Table 9.1), which is expressed within the pharyngeal ectoderm [57] and may play a part in the development of the pharyngeal region. When caused by a mutation in the *CHD7* gene, CHARGE syndrome can be inherited in an autosomal dominant pattern; although most cases result from new (de novo) mutations in the gene and occur in people with no history of the condition in their family. Although there is no specific

treatment or cure, there may be ways to manage the symptoms. A multidisciplinary team (MDT) is often needed to figure out the treatment options for each individual patient.

Hypoparathyroidism, Sensorineural Deafness and Renal Disease (HRD) Syndrome

The HDR syndrome is an autosomal dominant disorder in which patients often have hypocalcemia and undetectable or low serum PTH concentrations [58, 59]. Moreover, HDR syndrome is associated with bilateral symmetrical sensori-neural deafness and renal abnormalities consisting mainly of cysts that compress the glomeruli and tubules, thereby leading to renal impairment [59]. In addition, there may be other malformations such as uterine or vaginal atresia, Hirschsprung's disease, eye changes such as retinopathia pigmentosa, nystagmus, pseudo-papillary edema, ptosis, or developmental delays.

HDR syndrome is caused by germline heterozygous mutations in GATA-binding factor 3 (*GATA3*) [60] (Table 9.1). This dual zinc-finger transcription factor mediates *PTH* expression (Fig. 9.2) and is involved in the embryonic development of the common parathyroid–thymus primordia [42, 43, 45, 46] (Fig. 9.3). Diagnosis of HRD syndrome arises from the combination of clinical findings, and treatment relates to the respective key findings.

Mitochondrial Disorders Associated with Hypoparathyroidism

Hypoparathyroidism has been reported to occur in three disorders associated with mitochondrial dysfunction, namely, (1) Kearns–Sayre syndrome (KSS), (2) mitochondrial encephalo-myopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome, and (3) mitochondrial trifunctional protein (MTP) deficiency syndrome [61–63] (Table 9.1, Fig. 9.2).

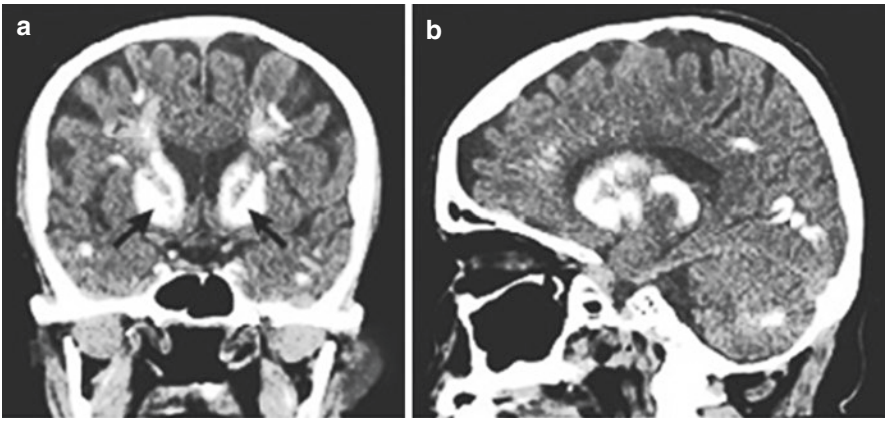

Fig. 9.2 Extra-skeletal calcifications. Coronal (**a**) and sagittal (**b**) CT images of the head of an individual with hypoparathyroidism show extensive symmetrical calcifications involving the subcortical white matter, basal ganglia (arrows), and cerebellar hemispheres. The clinical relevance of CNS calcifications seen in patients with long-standing

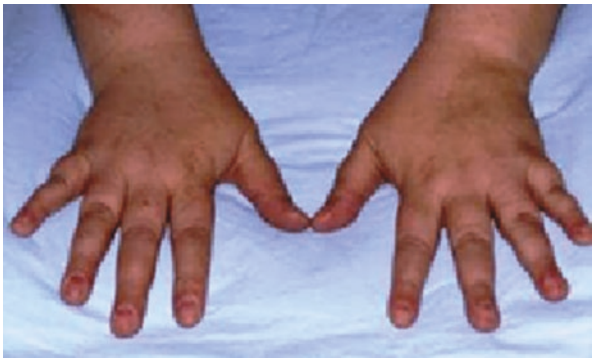

Fig. 9.3 Patient with pseudo-hypoparathyroidism (PHP) showing shortened fourth metacarpals

Kearns–Sayre syndrome (oculo-craniosomatic disorder or oculo-cranion-somatic neuro-muscular disorder with ragged red fibers) is characterized by progressive external ophthalmoplegia and bilateral pigmented retinopathy occurring at <20 years of age and cardiac conduction abnormalities [62]. KSS is a more severe syndromic variant of chronic progressive external ophthalmoplegia (CPEO), a syndrome that is characterized by isolated involvement of the muscles controlling movement of the eyelid (levator palpebrae, orbicularis oculi) and eye (extra-ocular muscles). This results in ptosis and ophthalmoplegia, respectively. Other symptoms may include cerebellar ataxia, proximal muscle weakness, deafness, DM, growth hormone deficiency, short stature, hypoparathyroidism, and other endocrinopathies. In both of these diseases, muscle involvement may begin unilaterally, but always develops into a bilateral deficit, and the course is progressive. Currently there is no cure for KSS.

Deletions, duplications, and missense substitutions in mitochondrial DNA cause Kearns–Sayre syndrome and MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) syndrome [26, 40, 61], whereas MTP deficiency syndrome, which is a disorder of fatty acid oxidation in the mitochondria associated with cardiomyopathy (cardiac conduction abnormality), peripheral neuropathy, pigmentary retinopathy and liver dysfunction, is caused by mutations in *HADHB*, which encodes the trifunctional enzyme β-subunit [63]. The mechanism(s) leading to hypoparathyroidism in these mitochondrial disorders is currently not understood.

There is no curative treatment for MELAS syndrome. It remains progressive and fatal. Patients are managed according to what areas of the body are affected at a particular time. Enzymes, amino acids, anti-oxidants, and vitamins have been used.

Inherited Bone Dysplasias Associated with Hypoparathyroidism

Inherited bone dysplasias associated with hypoparathyroidism include (1) Kenny–Caffey syndrome (types 1 and 2), (2) Sanjad–Sakati syndrome, and (3) gracile bone dysplasia.

Hypoparathyroidism occurs in >50% of patients with *Kenny–Caffey syndrome* [26], which is also characterized by short stature and osteosclerotic bone dysplasia. Kenny–Caffey syndrome can be inherited as an autosomal recessive (type 1) or

dominant (type 2) disorder [26]. Sanjad–Sakati syndrome, which is also known as the "hypoparathyroidism–retardation–dysmorphism syndrome," affects Middle Eastern populations and has a similar phenotype to that of Kenny–Caffey syndrome [64].

Sanjad–Sakati syndrome and Kenny–Caffey syndrome type 1 are caused by mutations in tubulin-specific chaperone E (*TBCE*) [65], which encodes a chaperone protein that is required for the correct folding of α-tubulin subunits [65] and is postulated to have a role in parathyroid gland migration [66]. On the other hand, Kenny–Caffey syndrome type 2 is caused by heterozygous missense mutations of family with sequence similarity 111 member-A (*FAM111A*), which encodes a protein involved in DNA replication and chromatin maturation and may be involved in embryonic development [67, 68].

A *FAM111A* mutation, Ser342del, has been shown to cause gracile bone dysplasia, which occurs in association with hypoparathyroidism and represents a perinatally lethal condition [68] (Fig. 9.2; Table 9.1).

Autosomal Dominant Hypocalcemia

Autosomal dominant (AD) hypocalcemia type 1 and type 2 are genetically distinct disorders that were found to be associated with germline gain-of-function mutations of CaSR and $G_{11}\alpha$ proteins, respectively [22, 69, 70] (Fig. 9.2; Table 9.1). Type 1, which is the most common type of AD hypocalcemia, is associated with hypocalcemia, PTH levels ranging from undetectable to normal, and elevated fractional excretion of calcium, which can lead to frank hypercalciuria even in the setting of low serum calcium concentrations [22, 70–72]. Ectopic calcifications of the kidneys or basal ganglia affect approximately 35% of patients with AD hypocalcemia type 1 [22, 70, 73]. Some patients with AD hypocalcemia type 1, associated with severe gain-of-function mutations of CaSR, may also have a Bartter-like syndrome (*Bartter syndrome type 5*) characterized by hypokalemic alkalosis, renal salt wasting, and hyper-reninemic hyper-aldosteronism, in addition to hypocalcemia and hypoparathyroidism [22, 74].

Autosomal dominant hypocalcemia type 2 has a similar serum biochemical phenotype to that of type 1 [20, 69, 75], but usually a milder renal phenotype, with considerably less urinary calcium excretion [76]. Moreover, some patients with AD hypocalcemia type 2 have short stature caused by postnatal growth insufficiency [76, 77].

9.3.3.3 Autosomal Forms of Hypoparathyroidism

Glial cells missing homologue 2 (GCM2) is a parathyroid-specific transcription factor (Fig. 9.2) that has a crucial role in extra-cellular calcium homeostasis by promoting development of the PTGs [42, 45, 78] and by interacting with the GATA3 and MAFB transcription factors to increase PTH expression [43, 46] (Fig. 9.3). Germline *GCM2* mutations (Table 9.1) are often associated with severe hypocalcemia and low or undetectable serum PTH concentrations [79]. Homozygous *GCM2* mutations

cause an autosomal recessive form of isolated hypoparathyroidism by impairing nuclear localization, DNA binding, and/or transactivation activity of the GCM2 transcription factor [79], whereas heterozygous *GCM2* mutations cause AD hypoparathyroidism by exerting a dominant-negative effect on GCM2 transactivation activity [80, 81].

Germline *PTH* gene abnormalities are a rare cause of autosomal dominant and recessive forms of isolated hypoparathyroidism (Table 9.1). These abnormalities, which comprise missense, nonsense, or splice-site mutations, mainly affect exon 2 (encoding the signal peptide region of the pre-pro-PTH(1–115) peptide) and are predicted to impair PTH biosynthesis and secretion [26, 82–84] (Fig. 9.2). A mutation affecting the mature PTH(1–84) peptide was recently identified in a family with an autosomal recessive form of hypocalcemia and was shown to impair binding of PTH to PTH1R [84]. Affected family members showed either high or low plasma PTH levels depending on the type of PTH assay used. The mutation (Arg25Cys) was subsequently revealed to interfere with some PTH immunoassays that used antibodies raised against PTH(1–34) and PTH(13–34) fragments, thus explaining why some assays were unable to detect the mutant PTH peptide [84].

X-Linked Recessive Hypoparathyroidism

X-Linked recessive hypoparathyroidism only affects men and is associated with infantile hypocalcemic seizures [85]. Molecular deletion–insertions involving chromosome 2p25 and Xq27 have been identified, and these structural alterations may alter the expression of the nearby gene *SOX3* [86, 87]. *SOX3* encodes a high-mobility group box transcription factor, which is expressed in the PTGs during embryogenesis and may play a part in the development of PTGs from the pharyngeal pouches [77] (Fig. 9.3).

9.3.4 Non-hereditary Causes (Rare)

Some cases of *isolated* hypoparathyroidism, in which no other cause can be identified, are presumed to be caused by *autoimmune destruction of the PTGs*. No formal diagnostic criteria and no established laboratory tests are available to confirm this diagnosis. Severe and *prolonged hypomagnesemia* can also lead to functional hypoparathyroidism [88, 89].

Rarely, *infiltrative diseases* such as hemochromatosis, Wilson disease, granulomas, and metastasis can cause hypoparathyroidism [2]. The mechanism for this is thought to involve inhibition of parathyroid cellular function by iron (primary iron excess in hemochromatosis and secondary iron overload owing to blood transfusions in thalassemia (a group of inherited blood disorders associated with abnormal hemoglobin production), copper (in Wilson disease), and replacement of functional parathyroid tissue by tumor cells (in metastases). Parathyroid tissue is relatively

radiation-resistant. Although cases of *radiation-induced hypoparathyroidism* have been reported; this etiology is very rare [2]. Other rare non-hereditary causes of hypoparathyroidism include neonatal hypocalcemia of prematurity or secondary to maternal hypercalcemia, hypo- or hypermagnesemia.

9.4 Clinical Manifestations

The clinical manifestations of hypoparathyroidism are variable and can involve almost any organ system. The classic symptom of hypoparathyroidism is neuromuscular irritability due to hypocalcemia. Other manifestations can result from episodes of hypercalcemia and hyperphosphatemia (e.g., extra-skeletal calcification), but the cause of some symptoms (e.g., neuro-psychiatric symptoms) remains poorly understood [2].

9.4.1 Occult Condition

Hypoparathyroidism may be "occult" presenting with general ill-health and mental depression only.

9.4.2 Peripheral Nervous System: Manifestations of Tetany

9.4.2.1 Overt Tetany

Hypocalcemia partially depolarizes the resting membrane potential of a neuron, thereby increasing the probability of triggering action potentials [90]. This leads to neuro-muscular irritability—the hallmark symptom of hypocalcemia from any cause. Sensory neuron irritability manifests as *paresthesia* in the extremities and in the peri-oral and oral area. Motor neuron irritability can manifest as muscle spasms or *tetany*, ranging from the classic carpopedal spasm (spastic muscle contractions of the forearm, hand, lower leg, and/or feet) to life-threatening laryngospasm [91, 92].

9.4.2.2 Latent Tetany

Signs of neuro-muscular excitability include the following [93].

- *Chvosteck's Sign:* Gentle tap to the facial nerve in front of the external auditory meatus causes brisk muscular twitches of ipsilateral facial muscles. Contractions range from the upper lip and nose to the entire half-face when severe and significant hypocalcemia is present. Chvostek's sign is positive in 15% of individuals with normal serum Ca.
- *Trousseaus' Sign:* Inflating a blood pressure cuff to > the systolic pressure for 3 min, thereby occluding the brachial artery, results in tetany due to the combination of absence of blood flow and muscular hyper-excitability due to hypocalcemia.
- *Erb's Sign:* Characteristic tetanic response to a weak electric current (rarely used).

9.4.3 Central Nervous System (CNS)

9.4.3.1 Seizures

Severe hypocalcemia can precipitate seizures (epilepsy), which can be "focal" or "generalized" (tonic–clonic type). Occasional spasm of the muscles of respiration may also occur. Spasm of intra-ocular muscles causing early blurring of vision has been reported. Recent studies showed increased risk of posterior subcapsular cataracts, likely due to elevated calcium × phosphorus product occurring in lenses in the eyes. Papilledema and raised intracranial tension may be encountered and may be mistaken for a brain tumor.

Although seizures were frequently observed in the past, prevalence rates of seizures in patients with hypoparathyroidism were only 4–8% in two recent studies [19, 94]. Possible explanations might be selection bias of the earlier studies or better control of serum calcium levels in the later studies.

9.4.3.2 Ectopic Calcifications

Central nervous system (CNS) calcifications (Fig. 9.2) are a common finding in patients with hypoparathyroidism, with prevalence rates of 52–74% in cohort studies from the United States [94] and India [95]. The study, by Goswami et al. (2012) [95], of a large Indian cohort of patients with idiopathic hypoparathyroidism reported a high prevalence of basal ganglia calcifications (73.8%) and showed that the risk of progression over time was associated with a lower serum calcium–phosphate ratio, which suggests that altered phosphate metabolism may play a key part in ectopic calcifications [95]. Calcifications are most commonly seen in the basal ganglia, but can also occur in the gray and white matter junction, the cerebellar parenchyma, the thalamus, and the dentate nucleus.

Notably, two genes (sodium-dependent phosphate transporter 2 (*PIT2*; also known as *SLC20A2*) and xenotropic and polytropic retrovirus receptor 1 (*XPR1*)) were found to be associated with familial idiopathic basal ganglia calcification (Fahr syndrome). They encode proteins involved in phosphate transport, which supports the hypothesis that abnormal phosphate homeostasis has a role in ectopic calcifications in chronic hypoparathyroidism [96, 97].

Hypoparathyroidism is unclear. Symptoms including "parkinsonism" (a neurological movement disorder characterized by tremors, bradykinesia, rigidity, and postural instability) and "dystonia" (a neurological movement disorder associated with twisting or abnormal fixed postures) have been reported in hypoparathyroidism, but at a much lower prevalence than basal ganglia calcifications [94, 95, 98]. In addition, the relationship between the extent and location of calcification with neurological findings is conflicting [99, 100].

9.4.4 Cardiovascular System

Increased risks of cardiac arrhythmias and cardiovascular diseases have also been reported by several authors [12, 94]. Cardiac manifestations include prolonged QT interval on electrocardiogram and prominent U-wave and T-wave abnormalities

[101], acute cardiomyopathy, and congestive heart failure (CHF) due to decreased cardiac contractility related to low serum Ca and possibly PTH deficiency, as there are PTH receptors in cardiac myocytes. Hypocalcemia-associated dilated cardiomyopathy is typically reversible with treatment [102]. However, a recent case report of an infant with severe hypocalcemia suggested a non-reversible disorder [103]. Despite the numerous case reports, the prevalence of cardiomyopathy is very low in cohorts of patients with hypoparathyroidism, suggesting that there is a subset of vulnerable patients with as yet undefined risk factors [19, 94].

9.4.5 Renal System: Impairment Manifestations

Impaired renal function is the most common complication seen in patients treated for hypoparathyroidism. It is related to age of the patient, duration of the disease, and level of hypercalcemia during treatment. Absence of PTH results in inability of the renal tubules to reabsorb Ca, resulting in hyper-calciuria and nephrocalcinosis. In addition, patients with underlying renal disease such as renal dysgenesis in DiGeorge syndrome are in particular at higher risk of nephrolithiasis. Over-treatment of hypoparathyroidism with calcitriol and Ca can lead to nephrocalcinosis and nephrolithiasis, thus monitoring of renal Ca excretion is necessary.

The reported prevalence rates of nephrocalcinosis in patients with hypoparathyroidism who are treated with calcium and calcitriol is 12–57% [73, 104, 105]. The hazard ratio of developing kidney stones (nephrolithiasis) is 4.82 in a large Danish case–control study of patients with post-surgical hypoparathyroidism [19]. Patients with hypoparathyroidism on conventional treatment have a significantly increased risk of chronic kidney disease. In a US cohort [94], 41% of patients had an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73 m^2 (normal = eGFR of ≥90 mL/min/1.73 m^2), which was 2–17-fold higher than age-adjusted normal values [94]. In two Danish case–control studies [15, 19], the hazard ratios for diagnosed renal insufficiency were 3.10 and 6.01 for patients with surgical and non-surgical hypoparathyroidism, respectively, compared with age-matched controls.

Underbjey et al. (2013) reported that the risk of hospitalization related to renal causes (kidney stones or chronic kidney disease) was higher in adult hypoparathyroid patients than in normal controls [19]. The same finding was also recently reported in children by Levy and colleagues in 2015 [105].

9.4.6 Musculo-Skeletal and Dental System

9.4.6.1 Bones

Patients with hypoparathyroidism typically have higher bone density due to low bone turnover (the active process of coupled bone formation and bone resorption), which is linked to normal or increased bone mineral density and distorted bone

micro-architecture [1, 8, 106–110]. The reduction in bone formation is demonstrated by the profound reduction of tetracycline labeling in bone biopsies compared with controls [111–113]. The activation frequency (a marker for the number of times/year a specific bone site undergoes bone formation) is decreased by 50–80% in patients with hypoparathyroidism compared with controls. In addition to the overall reduction in bone remodeling, the depth and number of resorption pits are reduced, suggesting a reduction in bone resorption. Bone formation rate, osteoid (unmineralized bone matrix) surface and osteoid width are consistently and substantially reduced. The reduction in bone formation is reflected in reductions in mineralizing surface and mineral apposition rate. In hypoparathyroidism, the decrease in bone turnover leads to a situation where more bone is deposited than removed after each remodeling cycle is completed [109]. This observation explains the increase in bone mineral density and cortical thickness that has been reported in some studies. These skeletal abnormalities are detected in trabecular and cortical bone, and these changes are confirmed by micro-computed tomography (CT) of the bone biopsies [114–116].

The impact, if any, of the skeletal abnormalities associated with hypoparathyroidism on osteoporosis and fracture risk remains unclear. In the Danish case–control studies [1, 16], no differences in overall fracture rate compared with the general population were detected. Analyses of specific fracture types showed that patients with non-surgical hypoparathyroidism had an increased hazard ratio for upper extremity fractures (1.94) compared with controls and that patients with post-surgical hypoparathyroidism had a lower hazard ratio for the same fracture (0.69) [12, 117]. In several case reports, hypoparathyroidism has also been associated with a spondylo-arthropathy characterized by ligament ossification and syndesmophyte formation [118]. Goswami et al. (2008) reported the presence of clinically overt spondyloarthropathy in 3 out of 40 patients with hypoparathyroidism, with radiological changes being identified in 14 out of 40 [119].

9.4.6.2 Skeletal Muscles

Myopathy of skeletal muscles, characterized by increased serum levels of creatine phosphokinase and histological abnormalities in muscle biopsies, is also seen in hypoparathyroidism and seems to be related to the severity of hypocalcemia [120, 121]. Compared with age-matched and sex-matched controls, patients with hypoparathyroidism have a significant reduction in muscle strength and maximal force production; they also require a longer time to complete tests of physical function [122].

9.4.6.3 Teeth

Dentition can be affected in patients with non-surgical hypoparathyroidism, with symptoms including shortened roots, delayed and irregular eruption, ridges, punctate holes, and falling, in addition to hypoplastic enamel and hypoplastic or absent teeth [117, 123].

9.4.7 Ophthalmological System

Blurring of vision due to spasm of ocular muscles (early) or subcapsular *cataract* (late) can be seen in patients with hypoparathyroidism. The increased risk of cataracts is reflected with the reported high prevalence rates of 27–55% [124–126]. In the Danish case–control studies, non-surgical hypoparathyroidism was associated with an increased hazard ratio of 4.21 compared with controls, but the risk of cataracts in patients with post-surgical hypoparathyroidism was not significantly different from that in the general population. This suggests that age of onset and/or duration of hypoparathyroidism are important contributing factors [15, 19]. In a recent case–control study of patients with cataracts, those with hypoparathyroidism were significantly younger than typical patients with cataracts who did not have hypoparathyroidism and had evidence of more-severe posterior capsule disease and a higher rate of anterior capsule disease [126]. In addition, hypoparathyroidism is predominantly associated with cortical cataracts (gradual clouding starting in the periphery of the lens), whereas typical age-related cataracts are more likely to be nuclear (gradual clouding of the central portion of the lens) [125]. The etiology of the cataract formation is unclear, although preclinical studies suggest that it may be a consequence of chronic hypocalcemia [127].

Papilledema (swelling of the optic disc caused by increased intra-cranial pressure) can also be seen in patients with hypoparathyroidism and typically improves with correction of hypocalcemia [128].

9.4.8 Dermatological System

Skin and skin appendages are affected by hypoparathyroidism. Dermal changes include dry, coarse and scaly skin, spotty alopecia, liability to moniliasis in addition to deformed nails with increased brittleness and risk of onycholysis (separation of the nail from the nail bed) [129]. Some studies have suggested an increased incidence of infection in these individuals, although the mechanism is not clear [12].

A rare and severe type of psoriasis (generalized pustular psoriasis associated with pus-filled blisters) has been described in numerous case reports; in all cases, pustular psoriasis was associated with profound hypocalcemia and improved with treatment [130, 131].

9.4.9 Neuro-Psychiatric System

Hypoparathyroidism is associated with an increased risk of neuro-psychiatric diseases [10]. In the Danish cohort, the risk of being hospitalized due to neuro-psychiatric diseases, such as depression or bipolar affective disorders, was significantly increased in post-surgical (hazard ratio: 2.01) and non-surgical hypoparathyroidism (hazard ratio: 2.45) compared with age-matched and sex-matched controls [12].

9.5 Investigations/Assessment

9.5.1 Biochemical Tests

Biochemical investigations are required to confirm the clinical diagnosis of hypoparathyroidism. Albumin-corrected serum calcium or ionized calcium and $1,25(OH)_2D$ are typically below the laboratory normal range (<8.5 mg/dL or 2.12 mmol/L), with an elevated serum phosphorus level. Intact PTH is typically low, but can be inappropriately normal for the degree of hypocalcemia. This is the hallmark of hypoparathyroidism and helps to differentiate it from other disorders associated with hypocalcemia, such as pseudo-hypoparathyroidism. Twenty-four-hour urine calcium is most often increased, but may be normal or low before calcium supplementation is started, depending on calcium intake and bone turnover [132].

For biochemical diagnosis of hypoparathyroidism, PTH value has to be considered in relation to the serum calcium value drawn simultaneously. In patients with hypocalcemia, PTH levels that are within normal laboratory range are inappropriate, as they would be elevated if the function of the PTG was intact. In patients with a positive family history of hypoparathyroidism and in children with non-surgical hypoparathyroidism, a search for a possible genetic defect should be considered, with appropriate pretest counseling and informed consent.

9.5.1.1 Measurement of Serum PTH Levels: Generations of PTH Assay

Circulating PTH peptides include full-length, active PTH(1–84) peptides, and several forms of truncated, mostly carboxyl-terminal fragments, the majority being PTH(34–84) and PTH(37–84) [133, 134]. These truncated fragments cannot bind to and activate the classic PTH1 receptor (PTH1R). Although the plasma half-life of intact PTH(1–84) is only a few minutes, renal clearance of PTH fragments is slower. Thus, under normo-calcemic conditions, only about 20% of the PTH peptides are intact, biologically active PTH [135].

To improve the clinical performance of the *first-generation PTH assay* [136], which detected not only intact PTH, but also truncated fragments, the two-site immunoradiometric assay (IRMA) was introduced in 1987 [137]. This sandwich assay uses a C-terminal capture antibody linked to a solid phase and an amino-terminal detection antibody, making the measurement of PTH(1–84) more accurate. The *second-generation assay*, which does not detect the majority of C-terminal fragments, is the most widely used intact PTH assay to date.

In 1999, a *third-generation* PTH assay was introduced [138], called the "whole PTH" or "biointact PTH" assay. This assay uses a C-terminal capture antibody similar to that of the second-generation test, but an *N*-terminal detection antibody that detects only the extreme *N*-terminal region of PTH [i.e., PTH(1–6)]. Despite being theoretically better, this test has not been proven to be superior in clinical practice, although studies are limited [139, 140].

9.5.2 Imaging Studies

Plain X-ray may show calcification of the basal ganglia, arteries, and external ear. It can also exclude rickets (in children) and osteomalacia (in adults). Ultrasonography of the kidneys may detect the presence of early-stage nephrocalcinosis [141].

9.5.3 Electrocardiographic (ECG) Changes

The electrocardiographic (ECG) changes encountered in hypoparathyroidism include mainly prolongation of the Q-T interval due to hypocalcemia.

9.5.4 Monitoring

Patients should be monitored at regular intervals, for potential complications of hypoparathyroidism [20, 142]. In addition to measuring the levels of total calcium and albumin, or ionized calcium, biochemical tests should include serum *phosphate* levels, *creatinine* levels, with calculation of eGFR to detect renal impairment, and serum *magnesium* concentrations, particularly in patients with autosomal dominant hypocalcemia. The calcium–phosphate product should be kept below 55 mg^2/dL^2 in order to avoid renal calcifications [1, 20]. This target *calcium–phosphate product* is used by nephrologists in patients with chronic kidney disease to reduce the risk of arterial calcification. However, the value of using the calcium–phosphate product level in hypoparathyroidism to predict the risk of calcifications that may lead to renal insufficiency remains controversial [143, 144] and requires further evaluation.

Patients should be asked whether they have experienced symptoms such as flank pain or hematuria (to detect renal stones), blurred vision (to detect cataracts), and neuro-psychiatric symptoms (to detect depression and anxiety). Measurement of 24-h urinary calcium once a year should be considered for monitoring of hypercalciuria. Patients with a greater tendency to hypercalciuria might require more frequent monitoring. In children, 24-h urine calcium measurements should be adjusted for body surface area or body weight. Renal imaging should be considered periodically [145] or if a patient has symptoms of renal stone disease or if serum creatinine levels start to rise [20].

Renal ultrasonography is a safe modality to detect the presence of early-stage nephrocalcinosis and was shown in one study to be superior to CT scan [141]. As hypoparathyroidism treated by conventional therapy is associated with low bone turnover, patients are not especially prone to developing osteoporosis. Dual energy X-ray absorptiometry (DXA) scans to determine bone mineral density (BMD) are not needed specifically for patients with hypoparathyroidism, but may be performed according to guidelines for the diagnosis and monitoring of osteoporosis (e.g., screening in populations at risk). Owing to the uncertain clinical relevance of calcifications in the CNS, brain imaging using CT scan should be performed only in case of unexplained neurological manifestations [20, 145].

9.6 Differential Diagnosis

Hypoparathyroidism should be differentiated from other causes of ***tetany*** which include:

1. *Renal Failure:* It is the only other condition with hypocalcemia and hyperphosphatemia. Blood urea nitrogen (BUN) level is elevated.
2. *Alkalosis:* There is a reduced level of ionized Ca, while total blood Ca level is normal.
3. *Rickets and osteomalacia:* Hypocalcemia, normal, or reduced phosphorus levels.
4. *Malabsorption:* due to steatorrhea or gastrectomy.
5. *Hypomagnesemia.*

9.7 Management

The goal of therapy is to control symptoms while minimizing complications. Laboratory testing should involve measurements of serum total and ionized Ca, albumin, phosphorus, Mg, creatinine, intact PTH, and 25-hydroxyvitamin D levels.

Albumin-corrected total calculation: Corrected total Ca = measured total Ca + 0.8 × (4.0 − serum albumin), where Ca is measured in mg/dL and albumin in g/dL.

9.7.1 Screening

As most cases of hypoparathyroidism are post-surgical, patients should be evaluated for hypocalcemia following neck surgeries, but no guidelines exist with regard to the diagnostic tests and timing. In familial forms of hypoparathyroidism, biochemical screening of first-degree relatives may be offered. In several patients with seizures, including children presumed to be suffering from febrile convulsions, not measuring serum calcium concentrations can cause a delay in the diagnosis of hypoparathyroidism [146].

9.7.2 Prophylaxis

To avoid *post-surgical hypoparathyroidism*, surgical experience in neck surgery is crucial. Careful surgical planning in patients with HPT with pre-operative localization may reduce the likelihood of post-operative PTG dysfunction. If an extensive surgery is undertaken, preservation with reimplantation of parathyroid tissue (autotransplantation) should be done. Pre-operative optimization of vitamin D is helpful, given that vitamin D deficiency is very common in the older population and patients undergoing parathyroid surgery. Some studies showed that vitamin D supplementation improves bone health in these individuals [6]. However, too much vitamin D could worsen hypercalcemia so it should be gives with caution.

In *non-surgical hypoparathyroidism* with a known genetic etiology, genetic counseling should be offered. To avoid lengthy episodes of hypocalcemia or hypercalcemia, patients with hypoparathyroidism should be aware of the symptoms of low and high circulating calcium concentrations, to allow for early detection and adjustment of treatment. Of note, serum calcium levels may fluctuate without obvious reasons in patients being treated for chronic hypoparathyroidism. Likewise, patients should be familiar with potential complications of their disease to enable early detection.

9.7.3 Conventional Therapy

To date, three guidelines on the management of hypoparathyroidism have been published, including those of the International Consensus Conference guidelines based on the first international conference on hypoparathyroidism held in Florence, Italy, in May 2015, the European Society of Endocrinology clinical guidelines, and the American Association of Clinical Endocrinologists, and the American College of Endocrinology Disease State Clinic Review [6, 20, 142]. In addition, three papers were recently published (2016) on presentation, epidemiology, diagnosis, and management of hypoparathyroidism [8, 13, 145]. These guidelines address management of acute and chronic hypoparathyroidism.

9.7.3.1 Emergency Treatment (Acute Hypoparathyroidism)

Symptomatic (acute) hypocalcemia is a medical emergency that requires acute intravenous (IV) administration of calcium. Ten milliliter of 10% *calcium gluconate* diluted in 100 mL 5% dextrose is infused IV over 5–10 min. This can be repeated until patient's symptoms resolve. Administration of a calcium gluconate drip for longer periods may be required, particularly with persistent hypocalcemia [20, 142].

The aim should be to raise the serum ionized calcium concentration into the low normal range (8.0–9.0 mg/dL), preserve it at this level and control the patient's symptoms. Calcium gluconate is the preferred IV calcium salt because *calcium chloride* irritates the veins and should be avoided. Oral calcium supplementations and vitamin D analogues should also be started. Intravenous administration of calcium could cause arrhythmias and patients should be under continuous electrocardiographic (ECG) monitoring [20, 142].

9.7.3.2 Long-Term Treatment (Chronic Hypoparathyroidism)

Patients with *chronic hypocalcemia* can often tolerate severe hypocalcemia with minimal or no symptoms. Serum calcium levels can be restored with *oral* calcium and vitamin D supplementations in patients who are asymptomatic or have mild symptomatic hypocalcemia.

Long-term management of hypoparathyroidism should keep serum Ca within the low-normal range, with serum phosphorus within the high-normal range, and avoid significant hypo- or hypercalcemia. The goal is to reduce symptoms, minimize risk of kidney stones or dysfunction, and prevent ectopic soft tissue Ca deposition. With

Table 9.3 Medications used in management of chronic hypoparathyroidism

Medication	Typical dose
Calcium preparations	
Calcium carbonate	1000–9000 mg elemental calcium/day in 2–4 divided doses
Calcium citrate	1000–9000 mg elemental calcium/day in 2–4 divided doses
Vitamin D preparations	
Ergocalciferol (D_2) or cholecalciferol (D_3)	Total 25-hydroxyvitamin D level ≥ 30 ng/mL
Calcitriol [1,25$(OH)_2D_3$]	0.25–2.0 μg/day
Alfacalcidol (1-alfa OH-vitamin D_3)	0.5–4.0 μg/day (not available in USA)
Thiazide diuretics/others	
Hydrochlorothiazide	12.5–100 mg/day
Chlorthalidone	25–100 mg/day longer duration
Indapamide	1.25–5 mg/day
Amiloride	5 mg daily (alone or combined with hydrochlorothiazide)

low or absent PTH, Ca absorption is dependent on daily Ca and active vitamin D intake, so patients with hypoparathyroidism require daily consistent Ca and active vitamin D intake necessary to achieve goal serum Ca level. Intake of other medications such as iron can interfere with Ca absorption. Standard treatment consists of adequate Ca, vitamin D2 or D3, active vitamin D (1,25-dihydroxyvitamin D3), and Mg supplementation as needed (Table 9.3).

Calcium Preparations

The goal of therapy is to maintain serum Ca level at 8.0–9.0 mg/dL range while normalizing urinary Ca. Patients often require a minimum of 1 g of elemental calcium in doses divided throughout the day. *Calcium carbonate* (contains 40% elemental Ca) and *calcium citrate* (contains 21% elemental Ca) are the most commonly preparations used, typically 1–3 g of elemental Ca in divided doses 2–4 times/day. Calcium carbonate is the least expensive formulation. As it depends on an acidic gastric pH for efficient absorption, it should be taken with meals. Calcium citrate, calcium gluconate, or calcium lactate are alternatives for calcium carbonate, but more tablets are needed for these, owing to their relatively low content of elemental calcium. For patients with hypo- or achlorhydria due to use of antacids or proton pump inhibitors, or elderly patients with low gastric acid secretion, Ca citrate is preferred as it is easily absorbed without stomach acid and can be given on an empty stomach while calcium carbonate requires an acidic gastric environment for digestion and absorption and should be taken with food [20, 142].

Lower serum calcium predisposes the patient to symptoms of hypocalcemia and cataract if the phosphate level is also high. When serum calcium concentrations are in the upper normal range hyper-calciuria may occur and this is related to nephrolithiasis, nephrocalcinosis, and chronic renal insufficiency. Levels of serum calcium,

phosphorus, and creatinine should be measured weekly to monthly during initial dose adjustments, with twice-yearly measurements once the regimen has been stabilized. A 24-h urine calcium should be determined at least once a year once stable doses of supplements are established and should be <4 mg/kg/24 h. All patients should be tested with slit-lamp and ophthalmoscopic examination annually to monitor for the development of cataracts.

Magnesium (Mg) Supplements

Magnesium (Mg) supplements may be necessary if serum Mg is low, as normal serum Mg is required for normal secretion of PTH [147].

Vitamin D (Metabolites and Analogues)

In patients with hypocalcemia, vitamin D_2 (ergo-calciferol) or vitamin D_3 (cholecalciferol) or vitamin D metabolites, (calcitriol or 1,25-$(OH)_2$ vitamin D or 1 ∞-OH vitamin D), are usually required. Although a high dose of the vitamin D precursors ergo-calciferol (vitamin D_2) and cholecalciferol (vitamin D_3) can be used [148], such treatment is *not* common and can lead to prolonged hypercalcemia owing to the long half-life of these precursors. The use calcitriol ($1,25(OH)_2D$) the active form of vitamin D, or alfacalcidol ($1\alpha(OH)D_3$) which is quickly converted to $1,25(OH)_2D_3$ in vivo—is favored, because of its direct action on the gastrointestinal tract to increase intestinal calcium absorption and its shorter onset of action and half-life [149]. Both alfacalcidol and calcitriol are titrated to achieve desired serum calcium concentrations within or slightly below the low-normal range.

Calcitriol is administered over a wide dosing range (0.25–2.0 μg/day) and can raise serum calcium levels significantly within 3 days. The analog *alfacalcidol* (1-∞-hydroxy-vitamin D_3) can be useful in clinical practice. Vitamin D therapy can be related to hyperphosphatemia, since active vitamin metabolites and analogs also increase intestinal phosphate absorption. In such cases, the hyperphosphatemia may be reduced by lessening dietary intake of phosphate (e.g., in meats, eggs, dairy products, and cola beverages), whereas phosphate binders can be used in severe situations. Infants and young children should receive calcitriol (weight-based dosing, 0.01–0.04 μg/kg/day); some centers will also give calcium carbonate supplements (20–40 mg/kg/day), divided into two or three doses. Older children usually receive adult doses of activated vitamin D [150].

Thiazide Diuretics

Thiazide-type diuretics (hydrochlorothiazide, chlorthalidone, and indapamide) and sodium restriction may be added (as an adjunct treatment) to reduce urine Ca if hyper-calciuria is present [151–154]. A study in dogs with hypoparathyroidism treated with chlorothiazide demonstrated a progressive decrease in the fractional clearance of calcium, with increased clearance of sodium [155]. Thus, a high-salt diet would override any reduction in calciuria associated with thiazides, and dietary restriction of sodium is required. Indeed, a study in seven patients with

mild post-surgical hypoparathyroidism reported that oral chlorthalidone in combination with a low-salt diet was effective in lowering urinary calcium levels [20, 156].

Furosemide and other *loop diuretics* should be avoided because they increase urinary calcium excretion and, thus, might decrease serum calcium levels. Other factors that may precipitate hypocalcemia are *glucocorticoids* that can antagonize the action of vitamin D and its analogues. Hydrochlorothiazide may assist to limit the amount of vitamin D and calcium supplements that are required to maintain normal calcium levels in post-thyroidectomy hypocalcemia. Limitations of thiazide diuretics are associated with the risk of developing hypokalemia and/or hyponatremia and, thus, low-sodium diet could be helpful [20].

Thiazides lead to urinary magnesium losses. Thus, patients with autosomal dominant hypocalcemia type 1, who have abnormally high urinary magnesium excretion and hypomagnesemia, should avoid thiazide diuretics [157]. Likewise, patients with autoimmune polyendocrine syndrome type 1 and adrenal insufficiency should not take thiazide diuretics, to avoid the resulting increase in urinary sodium excretion [158].

Despite standard therapy, some individuals remain symptomatic with some requiring multiple hospitalizations for the treatment of hypocalcemia or its complications. For those, new adjunctive therapy options are available [142, 145].

Diet Control

Treatment of hypoparathyroidism is facilitated by a diet rich in calcium. To manage hyperphosphatemia, dietary phosphate restriction and phosphate binders are sometimes prescribed in hypoparathyroidism. Simply avoiding foods with phosphate additives and limiting commercially prepared foods, which are often high in sodium and phosphate, effectively limits phosphate intake but enables dairy intake, which provides important nutrients, especially in children. All patients, particularly if risk factors for kidney stone formation are present, should be counseled regarding adequate fluid intake to decrease the risk of renal calcifications [41].

9.7.4 Emerging Treatments

Although conventional therapy with activated vitamin D and calcium supplements can restore serum calcium levels, it does not restore other actions of PTH, such as bone turnover or renal calcium reabsorption. In addition, conventional treatment is associated with hypercalciuria, which increases the risk of developing nephrocalcinosis and kidney stones. To establish a more physiological alternative to conventional therapy, studies aimed at PTH replacement were first initiated with synthetic human PTH(1–34) (hPTH(1–34)), the biologically active amino-terminal fragment of the full-length PTH peptide. Both the active *N*-terminal fragment and the full-length 84-amino-acid peptide bind to and activate PTH1R [41].

9.7.4.1 PTH Therapy: PTH 1–34 and PTH 1–84

Teriparatide (PTH 1–34) or (hPTH 1–34)

Teriparatide (PTH 1–34) is a truncated molecule of synthetic PTH approved by the US FDA in 2002 for the treatment of osteoporosis in adults. hPTH(1–34) The restrictions on the length of treatment to 2 years and the exclusion of its use in children render this peptide not practicable for use in long-term replacement therapy of hypoparathyroidism as an "off-label" drug.

Synthetic hPTH was used in the first clinical trials testing hormonal replacement therapy of hypoparathyroidism. In these studies, the biologically active fragment hPTH(1–34) was formulated in the pharmacy at the study site, as there was no commercially available hormone when the studies were initiated in 1992. Synthetic hPTH(1–34) was given alone, without calcitriol, thiazide diuretics or phosphate binders, and titrated to maintain serum calcium levels within or slightly below the low-normal range and normal urine calcium excretion. Various hPTH(1–34) regimens were evaluated in short-term or long-term studies [71, 72, 159–163].

Teriparatide has been evaluated in a number of studies in adult and pediatric patients with post-surgical hypoparathyroidism [164] and permanent hypoparathyroidism from other causes [71, 72, 160–162] and appears to be safe and effective. Initial studies confirmed the advantages of once-daily subcutaneous (SC) hPTH(1–34) injection over calcitriol conventional therapy [160, 162]. The phosphaturic and calcium-retaining effects of hPTH(1–34) on the kidney reduced serum phosphate levels and urinary calcium excretion compared with conventional therapy over a period of 10 weeks [162]. hPTH(1–34) replacement compared with conventional therapy was further investigated in a randomized controlled study over a 3-year period in both adults and children [159, 161].

Comparisons of once-daily and twice-daily hPTH(1–34) therapy in both adults and children demonstrated that an increased frequency of injections significantly reduced the total daily dose needed [72, 160]. In a study of 14 children, twice-daily injections resulted in lower markers of bone turnover and more physiological serum calcium and magnesium profiles with less fluctuation in the later portion of the day compared with once-daily hPTH(1–34) injections [160].

A 3-year randomized controlled trial in children compared conventional therapy to twice-daily subcutaneous hPTH(1–34) injection therapy, with doses titrated to specific target serum and urine levels [161]. In both treatment groups, mean serum calcium levels were slightly below the normal range; mean urine calcium excretion, lumbar spine and whole-body bone mineral density, as well as height and weight percentiles, were within the normal range and did not differ between groups [159, 161]. Serum calcitriol levels were higher in children receiving twice-daily hPTH(1–34) injections than in those receiving conventional therapy [161]. This study shows that treatment with hPTH(1–34) is safe and effective in maintaining stable calcium homeostasis in children with hypoparathyroidism and allowed for normal linear growth over a 3-year period.

In 27 adults with hypoparathyroidism, conventional treatment was compared with twice-daily injections of hPTH(1–34) in a 3-year randomized open-label trial [159]. Serum calcium levels were maintained slightly below the normal range in both groups. Although mean urinary calcium excretion was consistently within normal range in the hPTH(1–34) group and above the normal range in the conventional treatment arm, the levels were not significantly different between groups. Bone mineral content and bone mineral density, measured twice yearly, were not different between the groups [159]. Treatment with hPTH(1–34) for 3 years was safe and effective in maintaining serum calcium at the slightly low to low-normal range without hypercalciuria in adults with hypoparathyroidism.

To further improve metabolic control, pump delivery of hPTH(1–34) was studied in adults and children with various hypoparathyroidism etiologies and compared with twice-daily injections [71, 163]. hPTH(1–34) microboluses (0.1 μg) were delivered at intervals ranging from 2–8 pulses/h and corresponded to a dose range of 4.8–19.2 μg daily, which is approximately one-third of the average daily hPTH(1–34) dose required during twice-daily injection therapy. Pump delivery of hPTH(1–34) led to less fluctuation of serum calcium levels and a >50% reduction in urine calcium levels in adults with post-surgical hypoparathyroidism compared with twice-daily delivery [163]. Moreover, serum magnesium concentrations were higher and bone resorption markers lower in the pump group [163]. Although pump delivery has clinical advantages, it requires a skilled provider with expertise in the management of hypoparathyroidism and in pump devices.

In children with congenital hypoparathyroidism (autoimmune polyendocrine syndrome type 1 or a mutation in *CASR*), pump delivery of hPTH(1–34) compared with twice-daily injections resulted in near normalization of mean serum calcium levels (2.02 ± 0.05 mmol/L vs. 1.88 ± 0.03 mmol/L; $p < 0.05$), a non-significant reduction of mean urine calcium excretion (5.17 ± 1.10 mmol/24 h vs. 6.67 ± 0.76 mmol/24 h; $p = 0.3$) and a significant reduction in the levels of bone turnover markers [71]. Pump therapy increased serum magnesium levels, lowered the urinary magnesium excretion, and permitted the reduction in magnesium supplements [71, 163].

Three children with hypoparathyroidism (two siblings with autoimmune polyendocrine syndrome type 1 and one child with idiopathic hypoparathyroidism) refractory to conventional therapy were successfully treated with continuous SC administration of hPTH(1–34) over a 3-year period. The two patients with autoimmune polyendocrine syndrome type 1 required substantially higher doses than the child with idiopathic hypoparathyroidism [165]. Improvement in mental and physical health has also been reported with PTH 1–34 treatment [163].

Sudden discontinuation of treatment with hPTH(1–34) may lead to hypocalcemia, and patients may require significantly higher than baseline doses of calcium and calcitriol [166]. Weaning hPTH(1–34) may be a safe approach for patients transitioning to conventional therapy.

Natpara (Recombinant Human PTH) (rhPTH) 1–84

The full-length form of rhPTH (1–84; *Natpara*) was the first form of PTH approved by the FDA in Jan 2015 for adjunctive therapy in individuals not adequately controlled with Ca, active vitamin D, thiazide-diuretics, and/or Mg therapy as needed. Natpara is given as once a day SC injection based on phase 1 clinical trial data in adults with hypoparathyroidism [167].

An open-label trial of 27 patients treated with rhPTH 1–84 every other day 100 μg/dose for 4 years showed that all patients had stable serum Ca and were able to reduce their Ca and active vitamin D supplements significantly [168]. The 24-h urine Ca was also reduced at 4 years with treatment, and serum phosphorus declined [168]. Six-year data from this cohort was recently published, extending these findings [169]. The long-term efficacy of PTH replacement therapy on kidney function preservation is not yet known.

Markers of bone turnover are typically reduced, reflecting low bone turnover, along with higher bone density due to increased trabecular and cortical bone volume, in individuals with untreated hypoparathyroidism, but it is not yet clear whether this denser bone translates into increased bone strength [114, 168]. Treatment with rhPTH 1–84 increased lumbar spine bone mineral density (BMD), but did not change femoral neck or total hip BMD, whereas the 1/3 distal radius BMD declined at 2 years, but remained stable at 4 years [168]. Paired trans-iliac bone biopsies before and after treatment with rhPTH (1–84) showed that 1-year treatment resulted in reduction in bone mineralization and high bone turnover, but these parameters returned to baseline at 2 years [170, 171]. At baseline, hypoparathyroidism patients have low to low-normal bone turnover markers. rhPTH (1–84) therapy, there was a threefold elevation in markers of bone resorption (e.g., tartrate-resistant acid phosphatase 5b and collagen type 1 cross-linked C-telopeptide), and bone formation markers (e.g., bone specific alkaline phosphatase, osteocalcin and total pro-collagen type 1 *N*-terminal pro-peptide), peaking at 6–12 months, with a slow decline to steady state by 30 months, but remaining higher than pretreatment values [168].

hPTH(1–34) for osteoporosis is subcutaneously (SC) injected into either the thigh or the abdomen. Full-length rhPTH(1–84) is associated with a longer calcemic effect when injected into the thigh than when injected into the abdomen [172]. One single-center study tested subcutaneous rhPTH(1–84) injection in the thigh in 33 patients over a 6-year period compared with baseline [170]. The initial dose was 100 μg SC every other day, but most patients transitioned later to once-daily injections, with doses ranging from 25 to 100 μg daily. Compared with baseline, serum calcium levels were stable over 6 years, and serum phosphate and urinary calcium levels decreased significantly at several of the measured time-points. Bone mineral density (BMD) at the spine mildly increased, whereas it decreased at the hip and the distal radius. The required calcium dose was reduced by 53% and calcitriol dose by 67%. Adverse events included hypercalcemia (12 episodes in 9 patients), hypocalcemia (5 episodes), musculoskeletal symptoms, infections, fractures (8 fractures in 6 patients), and renal stones (3 patients). This study by Rubin et al. [170] concluded that treatment with rhPTH(1–84) is safe and effective for at least 6 years and allows a reduction in the dose of conventional therapy.

In another single-center study, 62 patients with hypoparathyroidism were randomized (1:1) to either placebo or rhPTH(1–84) (100 μg daily) for 24 weeks as an add-on to conventional therapy [173]. Supplements were titrated to achieve normal serum calcium levels and 24-h urine calcium excretion. Daily doses of calcium and activated vitamin D decreased by 75% and 73%, respectively, in patients randomized to rhPTH(1–84) compared with placebo. Bone turnover markers increased, and BMD of the hip and spine decreased, with rhPTH(1–84) therapy compared with placebo.

"REPLACE" was, the pivotal double-blind, multi-national, randomized placebo-controlled trial for 24 weeks conducted with 134 adults with hypoparathyroidism randomized 1:2 to placebo or rhPTH 1–84 [7, 174]. Subjects were injected once daily with rhPTH 1–84 versus placebo with dose titration from 50 to 75 or 100 μg/day [5]. The trial showed that 53% of treated subjects were able to reduce their supplemental Ca and active vitamin D doses by ≥50%, with 43% able to completely stop all active vitamin D and reduce their Ca dose to 500 mg/day or less, while maintaining normal serum Ca level. Urinary calcium levels did not change with rhPTH(1–84) therapy [7], but serum phosphate levels decreased significantly compared with placebo [174]. Adverse events were similar between the two groups and included hypocalcemia, muscle spasm, paresthesia, headache and nausea. After the end of treatment with rhPTH(1–84), hypocalcemia was reported in a higher proportion of patients in the rhPTH(1–84) group than in the placebo group [7].

Conventional treatment does little to alter the marked static and dynamic abnormalities of bone in hypoparathyroidism [145]. By contrast, use of rhPTH(1–84) has shown reversal and recovery of many of these abnormalities. Transiliac crest bone biopsies have demonstrated a rapid and marked increase in tetracycline-labeled surfaces, representing an increase in bone formation, as early as 3 months after rhPTH(1–84) administration [112]. Within 1 year of treatment, improvements in both cortical and trabecular bone were observed, including, for example, a reduction in trabecular width and an increase in trabecular number [112]. Intratrabecular tunneling (bone resorption in trabecular packets) was demonstrated in more than half of the biopsies [115]. These micro-structural changes demonstrate that one of the functions of PTH in bone is to maintain ongoing turnover and repair bone.

The FDA approved rhPTH(1–84) in 2015 as an adjunct to calcium and vitamin D for the treatment of adults with hypoparathyroidism who cannot be well-controlled on conventional therapy. In 2017, the European Commission granted Conditional Marketing Authorization for rhPTH (1–84) in Europe.

Expert opinion of the First International Conference on the Management of hypoparathyroidism to guide the use of full-length recombinant human parathyroid hormone (rhPTH(1–84)) [142]. Long-term effects of Natpara are unknown. Given the lack of such data, *indications* of considering the use of rhPTH (1–84) therapy in treatment of hypoparathyroidism should be restricted to the following:

1. Inadequate control of serum calcium with hypocalcemia, or erratic swings to hypocalcemia or hypercalcemia on conventional therapy.
2. Doses of supplemental calcium of >2.5 g, or of activated vitamin D of >1.5 μg calcitriol or >3.0 μg alfacalcidol daily needed.

3. Evidence for renal involvement with hypercalciuria, nephrocalcinosis, nephrolithiasis or reduced creatinine clearance on conventional therapy.
4. Hyperphosphatemia or a calcium–phosphate product of >55 mg^2/dL^2 (or >4.4 $mmol^2/L^2$) on conventional therapy.
5. A gastrointestinal disorder or post-bariatric surgery, associated with malabsorption.
6. Reduced quality of life on conventional therapy.

9.7.4.2 Safety of PTH Treatment

Quality of life among patients treated with rhPTH (1–84) 100 μg every other day for 5 years assessed by the SF-36 showed an improvement compared to untreated individuals [112]. On the contrary, there was no change in muscle strength, postural stability or quality of life at 6 months in the phase III randomized controlled trial of hypoparathyroid patients receiving rhPTH (1–84) [175].

Long-term data on the safety and efficacy of PTH in any form beyond 7 years is not available. In the REPLACE trial, a single subject taking PTH (1–84) 100 μg each day had *hypercalcemia*, which required dose reduction to 50 μg each day, and did not require discontinuation of treatment. Muscle spasm, hypocalcemia, paresthesia, headache, and nausea were the most common *adverse events* reported in those receiving rhPTH (1–84) compared to placebo, most of which occurred during dose titration at the beginning of the study [7]. Cusano et al. reported 11 episodes of mild hypercalcemia in 8 subjects over 4 years of treatment with PTH (1–84) 100 μg every other day, most of which occurred within the first 6 months of treatment during dose titration, and corrected with adjustment of calcium and vitamin D intake [168].

Longer term studies are needed to address the potential safety concerns related to *osteosarcoma* seen in the Fisher 344 strain of rat treated with rhPTH 1–34 in preclinical studies. The osteosarcomas were dose-dependent and duration-dependent and most evident in animals receiving the highest dose (75 μg/kg) [176]. Similar rodent carcinogenicity studies demonstrated an increased osteosarcoma risk associated with pharmacological doses of subcutaneous rhPTH (1–84) injections [177]. Subsequent data in non-human primates receiving high doses of hPTH(1–34) (5 μg/kg) for 18 months showed increased bone mass, but no osteosarcoma or bone proliferative lesions were evident after the therapy was discontinued or during a subsequent 3-year observation period [178]. Despite the rat toxicity data, an important observation in humans is that long-standing HPT is not associated with the development of osteosarcomas despite chronically elevated PTH levels [179]. Furthermore, no increased rate of osteosarcoma has emerged despite extensive use of hPTH(1–34) in patients with hypoparathyroidism or osteoporosis over >20 years, although most of the latter were treated for only 2 years [180, 181].

Recently, guidelines of the European Society of Endocrinology [5], based on a systematic review of literature, were published to aid clinicians in the management of hypoparathyroidism as shown in Table 9.4.

Table 9.4 Goals of hypoparathyroidism management according to European Society of Endocrinology

Therapeutic goal	Parameter to monitor	Complications to be prevented	Frequency of monitoring	Comments
Serum Ca in the low to the low-normal range	Albumin-corrected total serum Ca levels of 8.0–8.5 mg/dL. Serum ionized Ca levels in the lower part of, or slightly below, the reference range	– Hypocalcemia (tetany and mental status changes) – Hypercalcemia (dehydration, renal dysfunction, and mental changes)	Every 3–6 months	During adjustments of treatment with Ca and vitamin D, clinical assessment and serum biochemistry should be done weekly or every other week
Prevent hypercalciuria	Urinary Ca levels corrected for BSA below the sex-specified normal range (<250 mg daily for women; <300 mg daily for men; <4 mg/kg/day for both sexes)	– Hypercalciuria – Nephrocalcinosis – Kidney stones – Renal insufficiency	Once a year or every second year	NA
Serum phosphate levels within normal	Serum phosphate levels within or close to age-adjusted reference range‡	Ectopic soft tissue calcifications (brain, kidney, vascular system, and other tissues)	Every 3–6 months	After a change in therapy, monitor every week or other week
Control calcium–phosphate product levels	Serum calcium–phosphate levels of <55 mg^2/dL^2 (<4.4 $mmol^2/L^2$)	Ectopic soft tissue calcifications in the brain, kidneys, and vascular system	Every 3–6 months	After a change in therapy, monitor weekly or every other week
Serum mg within normal	Serum magnesium levels within reference range	Hypomagnesemia	Every 3–6 months	NA
eGFR within reference range	Creatinine levels in serum and urine. Aim for a level of 90–120 mL/min/1.73 m^2	Renal insufficiency	Every 3–6 months	After a change in therapy, monitor weekly or every other week
Vitamin D adequacy	Serum 25(OH)D of >20 ng/mL (>50 nmol/L)	Non-skeletal effects of vitamin D deficiency, including myopathy	Yearly	Vitamin D levels should be maintained within the normal range

(continued)

Table 9.4 (continued)

Therapeutic goal	Parameter to monitor	Complications to be prevented	Frequency of monitoring	Comments
Prevention of kidney stones and/or nephrocalcinosis	Urine levels of kidney stone risk markers and renal imaging (mainly ultrasonography)	– Flank pain infection – Renal insufficiency, others	If symptoms or kidney stones occur or if renal function starts to decline	Renal imaging if renal stone symptoms are present or serum creatinine levels start to increase
Improved QOL and absence of symptoms	QOL, Well-being and symptoms	Impaired QOL	Every 3–6 months	No specific instrument used to assess QOL
Maintain bone mass	BMD by dual energy X-ray absorptiometry	– Osteoporosis – Fractures	Not routinely recommended	NA

BSA body surface area, *eGFR* estimated glomerular filtration rate, *NA* not applicable, *QOL* quality of life, *BMD* bone mineral density

9.8 Quality of Life

Patients with hypoparathyroidism on conventional therapy with calcium and calcitriol often have complaints suggestive of reduced QOL [1, 2]. These complaints include (1) physical symptoms, such as fatigue; (2) neuro-muscular complaints, such as weakness, cramps, paresthesia and seizures; (3) inability to concentrate or to focus (brain fog); and (4) emotional difficulties, which encompass, among others, anxiety, depression, and personality disorders.

Recent studies have attempted to define the nature and prevalence of QOL impairments in hypoparathyroidism [10, 14, 122, 125, 182]. When compared with healthy controls or with patients who have had thyroid surgery, but retained normal parathyroid function, patients with post-surgical hypoparathyroidism had significantly higher global complaint scores [125], lower physical summary scores on the 36-Item Short Form Health Survey (SF-36) and decreased muscle function [122]. Lower QOL scores have also been observed in patients with hypoparathyroidism in registries and surveys from Norway [14], Denmark [12, 15], and the United States [10]. Finally, patients who developed post-surgical hypoparathyroidism had lower QOL scores than anticipated by healthy individuals given the description of the disease and by experienced (endocrine) surgeons [182].

When hPTH(1–34) and rhPTH(1–84) became available, there was a hope that replacing the missing hormone would restore QOL in patients with hypoparathyroidism. Indeed, many patients treated with synthetic hPTH report improved well-being compared with baseline (conventional treatment). However, despite such laudable anecdotal reports, findings from the studies of synthetic hPTH on QOL have been inconsistent. In an open-label, uncontrolled study from Columbia University, New York, USA, QOL, as assessed by SF-36, was low in all domains at baseline despite acceptable control of serum calcium levels through conventional

therapy [175, 183]. All domains improved significantly in response to rhPTH(1–84) at one and 2 years [183]. In individuals who completed 5 years of therapy, QOL improved for the duration of the study [175]. Similar improvements were reported in an Italian study that used twice-daily injection of hPTH(1–34) [167]. However, many patients in this study had hypocalcemia at baseline, which was corrected during the study [167]. Thus, it is possible that improved well-being may be at least in part due to better calcemic control.

In contrast to the strikingly positive results of the open-label studies described above, a Danish double-blind, placebo-controlled study that enrolled relatively well-controlled patients with hypoparathyroidism found that patients receiving rhPTH(1–84) had less improvement in SF-36 scores than those who received placebo and actually had worse performance on at least some muscle function tests [176]. However, many patients treated with rhPTH(1–84) in that study developed hypercalcemia, which may have negatively affected their well-being. Preliminary analysis of the REPLACE study revealed improved QOL scores (SF-36) with rhPTH(1–84) treatment, but not with placebo. However, the between-group differences were not statistically significant [184].

Further studies are needed to better understand the nature and the degree of QOL impairments, individual differences, and the relationship to biochemical variables (if any) and treatment modalities. Developing better and hypoparathyroidism-specific instruments to assess QOL will be crucial in achieving this goal.

9.9 Outlook

Since the first studies of synthetic hPTH therapy were initiated, our knowledge of hypoparathyroidism has increased markedly. For a rare disease, the stimulus to conduct further research emerged from the fact that hypoparathyroidism was one of the last of the classic endocrine deficiency diseases for which the replacement hormone was not available. This is "ironic," as the primary amino acid sequence of PTH was delineated in the late 1960s [185] and it was the second peptide hormone, after insulin, for which a sandwich immunoassay was developed [137]. Almost 50 years later, we now have an approved replacement therapy for hypoparathyroidism.

The recent interest in this disorder has resulted in more information about the incidence, prevalence, and natural history of hypoparathyroidism. Our understanding of the underlying genetics of many of the rare variants has been enhanced greatly. Such insights not only have added to our knowledge of rare genetic mutations that cause hypoparathyroidism, but also have given us insight into the molecular actions of PTH and its cellular functions under normal circumstances.

The experience with rhPTH(1–84) as a treatment of hypoparathyroidism provides evidence for the maintenance of the serum calcium levels, at doses of supplemental calcium and calcitriol that are substantially lower than pre-treatment values. Only modest effects on urinary calcium excretion, restoration of abnormal skeletal histo-morphometric parameters and QOL have been observed. Experts have

galvanized new knowledge of hypoparathyroidism by offering guidelines for the diagnosis and management of this disease [20, 142].

As we look to the future, several issues require greater insight and knowledge, including questions related to which patients should be considered for treatment with the newly approved rhPTH(1–84) therapy. Although patients with mild disease can often be managed with oral calcium and/or calcitriol, patients with more-severe manifestations require higher doses of calcium and calcitriol, which raises concerns about long-term sequelae, such as soft tissue calcifications in the kidneys, brain, and joints. Moreover, conventional therapy does not restore the underlying hormonal deficiency. Some experts also consider the reduced QOL, now substantiated in many studies using generic metrics, such as the SF-36 QOL scale, as being due, at least in part, to the lack of PTH.

Indications for the use of FDA-approved rhPTH(1–84) target patients with hypoparathyroidism who cannot be well-controlled on conventional therapy. Although the wording of the FDA term "well-controlled" is subject to interpretation, the First International Conference on the Management of Hypoparathyroidism considered six specific situations, any one of which could lead to rhPTH(1–84) therapy [145]. Data on the efficacy of rhPTH(1–84) therapy in preventing long-term complications of hypoparathyroidism are sparse, and safety data in large cohorts of patients, especially in children, are missing. The current costs of rhPTH(1–84) therapy and compliance with the Injectable form are potential hurdles for its use.

Long-term, multicenter, controlled trials are necessary to determine the best possible treatment for patients with hypoparathyroidism. In addition, more-detailed analysis of the skeleton with newer technologies, such as high-resolution peripheral quantitative CT, trabecular bone score and reference point indentation, might yield insights into altered bone quality in hypoparathyroidism.

To understand the long-term impact of rhPTH(1–84), more insight into the natural history of hypoparathyroidism, skeletal dynamics, bone quality, renal function, QOL, and known complications of the disease is needed. With regard to long-term studies, the idea that rhPTH(1–84) might have an effect to reverse or mitigate ectopic calcifications in soft tissues is worthy of study. Another direction that is likely to be of importance is the feasibility and applicability of new delivery systems (including the trans-dermal patch, continuous infusion pump and oral hPTH formulations), as well as PTH analogues and mimetics [180, 181].

9.10 Pseudo-Hypoparathyroidism (PHP)

Pseudo-hypoparathyroidism (PHP) is a heterogeneous group of rare endocrine disorders associated primarily with resistance to the parathyroid hormone (PTH) [186]. Patients with this condition have a low serum calcium and high phosphate, but the PTH is appropriately high (due to the low level of calcium in blood), which differentiates it from hypoparathyroidism.

9.10.1 Epidemiology

The estimated overall prevalence of PHP is 7.2/1000,000 or approximately 1/140,000. The estimated prevalence of PHP type 1a, type1b, and PPHP is 1/150,000 in Italy [187]. In Japan, the estimated prevalence of PHP type 1a and type 1b is 1/295,000 [187, 188]. Mantovani et al. (2016) reported that PHP occurs approximately twice as frequently in females as in males and that the onset of endocrine symptoms occurs during childhood, although cases with severe hypothyroidism at neonatal screening have been reported [187].

9.10.2 Etiological Classification

In 1942, Fuller Albright first introduced the term "pseudo-hypoparathyroidism." There are five variants (types) of pseudo-hypoparathyroidism: PHP type 1a (PHP-1a), PHP type 1b (PHP-1b), PHP type 1c (PHP-1c), PHP type 2 (PHP-2), and pseudo-pseudo-hypoparathyroidism (PPHP) (Table 9.5). PHP type 1a is the most common subtype and represents 70% of cases [189].

9.10.2.1 Type 1a (PHP-1a)

Several other peptide hormones, including thyroid-stimulating hormone (TSH), anti-diuretic hormone (ADH), gonadotropins, glucagons, adrenocorticotropin, and growth hormone-releasing hormone (GHRH), use the α subunit of stimulatory G

Table 9.5 Appearance and biochemical features of hypoparathyroidism, pseudo-hypoparathyroidism, and pseudo-pseudo-hypoparathyroidism

Condition		Appearance	PTH levels	Calcitriol	Calcium	Phosphate	Imprinting
Hypoparathyroidism		Normal	Low	Low	Low	High	Not applicable
Pseudo-hypoparathyroidism	Type 1A	Skeletal defects	High	Low	Low	High	Gene defect from mother (GNAS1)
	Type 1B	Normal	High	Low	Low	High	Likely a gene defect from mother (GNAS1 and STX16), but it can also result from an imprinting issue of (GNAS1) due to mother and father in equal measure
	Type 2	Normal	High	Low	Low	High	?
Pseudo-pseudo-hypoparathyroidism		Skeletal defects	Normal	Normal	Normal [54]	Normal	Gene defect from father

protein to enhance cAMP production. Patients with PHP-1a can present with resistance to the effects of any of these hormones, although in most patients, responses to corticotropin and glucagon are clinically unaffected.

The dominant pattern of inheritance of PHP-1a has been attributed to haplo-insufficiency of *GNAS1* (heterozygous inactivating mutations on the maternal *GNAS* allele*),* meaning that the protein produced by a single normal $G_s\alpha$ allele cannot support normal function, although it may suffice for survival [190]. The single normal $G_s\alpha$ allele preserves the responses to hormones such as corticotropin and glucagon. The haplo-insufficiency of the *GNAS1* gene is tissue specific, which may explain the selective resistance to hormones and the characteristic habitus of patients with PHP-1a.

In addition to PTH resistance, patients with this type have a characteristic phenotypic appearance (Albright's hereditary osteodystrophy—AHO), including developmental delay, short stature, stocky habitus obesity [191], round facies, dental hypoplasia, subcutaneous or soft tissue calcification/ossification and brachy-dactyly (shortening of fingers [brachy-metacarpalis] or toes [brachy-metatarsalis]) [192]. It is most likely an autosomal dominant disorder.

9.10.2.2 Type 1b (PHP-1b)

Pseudo-hypoparathyroidism type 1b lacks the characteristic physical appearance of type 1a, but is biochemically similar. *Familial* PHP-1b is caused by heterozygous deletions in *STX16*, NESP55, and/or AS exon. Sporadic PHP-1b is characterized by complete loss of methylation at the NESPas, XLas, and A/B promoters. In some cases, paternal 20q disomies have been found [193]. Absence of PTH resistance in the mother and maternal grandfather who carried the same mutation was consistent with current models of paternal imprinting of the *GNAS1* gene [110]. The molecular defect of the more-common *sporadic* form of the disease is still unresolved [194, 195].

9.10.2.3 Type 1c (PHP-1c)

Aldred (2006) referred to a "type 1c" pseudo-hypoparathyroidism [196]. The phenotype of this type is the same as in type 1a, but red blood cells (RBCs) show normal $G_s\alpha$ activity in vitro [197]. PHP-1c appears to be a variant of PHP-1a, in which the specific *GNAS* mutation disrupts receptor-mediated activation of adenylyl cyclase but does not affect receptor-independent activation of the enzyme. This accounts for the inability to demonstrate reduced activity of solubilized $G_s\alpha$ with conventional assays [13, 198]. It is *not* clear whether it should be considered an entity separate from type 1a [186].

9.10.2.4 Type 2 (PHP-2)

Pseudo-hypoparathyroidism type 2 also lacks the physical appearance of type 1a. Since the genetic defect in type 2 is further down the signaling pathway than in type 1 in which cAMP responses to PTH are blunted, there is a normal cAMP response to PTH stimulation in type 2 despite the inherent abnormality in calcium regulation. The specific gene is *not* identified. Pseudo-hypoparathyroidism type 2 may, in some

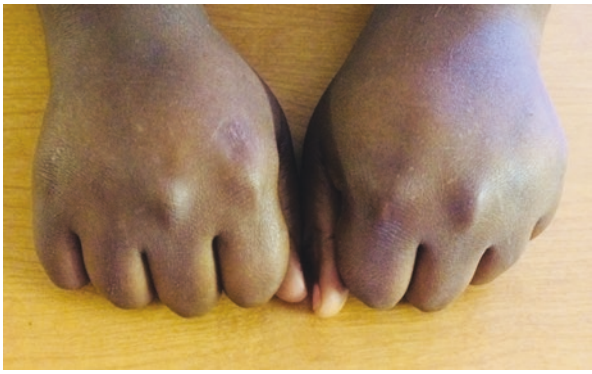

Fig. 9.4 *Archibald's metacarpal sign*: The hand characterized by a shortening of the fourth and/or fifth metacarpals when the fist is clenched

cases, be explained by vitamin D deficiency [199]. While biochemically similar, type 1 and 2 disease may be distinguished by the differing urinary excretion of cAMP in response to exogenous PTH.

As $G_s\alpha$ is expressed from both alleles in the distal renal tubule where it is not imprinted, urinary calcium reabsorption is normal in the distal tubule, and patients with pseudo-hypoparathyroidism are not at increased risk for nephrocalcinosis.

9.10.2.5 Pseudo-Pseudo-Hypoparathyroidism (PPHP)

Pseudo-pseudo-hypoparathyroidism (PPHP) is caused by *GNAS* mutations on paternally inherited alleles. It is characterized by the AHO phenotype, but without obesity, neuro-cognitive abnormalities and hormonal resistance (Table 9.5).

Paternal inheritance accounts for differences in the same family where some patients with a defective *GNAS1* gene inherited maternally have resistance to PTH (PHP-1a), whereas others with PPHP share with them the habitus of AHO but are not resistant to PTH.

9.10.3 Pathophysiology

9.10.3.1 Genetics

A heterozygous mutation of the *GNAS* gene that encodes the G stimulatory α subunit ($G_s\alpha$) of guanine nucleotide-binding protein leads to a loss of expression or function of the $G_s\alpha$, which impairs the transmission of stimulatory signals to adenylate cyclase, limiting cyclic AMP (cAMP) generation necessary for hormone action. *GNAS* mutations on maternally inherited alleles (PHP-1a and PHP-1c) manifest resistance to PTH, TSH, GHRH, and gonadotropins, as well as the phenotypic features of Albright hereditary osteodystrophy (AHO) [13].

GNAS mutations on paternally inherited alleles (PPHP) have only the phenotypic features of AHO without hormonal resistance [13]. Davies et al. reported an analysis of pedigrees of families that included patients with PHP and PPHP, suggesting that patients who inherit the defective gene from the father have PPHP, because the mutant gene is not expressed and the product of a single maternally inherited *GNAS1*

gene preserves normal responses to PTH and thyrotropin [200]. However, the occurrence of AHO in patients with PPHP indicates that one *GNAS1* gene is not sufficient in all tissues.

Those with PHP-1b lack typical features of AHO but may have mild brachydactyly. *Familial PHP-1b* displays an isolated loss of methylation at exon A/B associated with a recurrent 3-kb deletion in the *STX16* gene. NESP55 and NESPAS deletions have also been described leading to the loss of all maternal GNAS imprints (epimutations). *Sporadic PHP-1b* is characterized by complete loss of methylation at the NESPas, XLas, and A/B promoters. In some cases, paternal 20q disomies have been found [193, 198]. PHP-2 is associated with renal resistance to PTH action and the absence of AHO phenotype; however, the genetic abnormalities causing PHP-2 remain to be identified [13].

9.10.3.2 Testotoxicosis

Testotoxicosis with PHP-1a can occur. Gonadotropin-independent sexual precocity has been reported in two boys who presented in infancy with classic PHP-1a. Usually, patients with PHP-1a show resistance to luteinizing hormone (LH), which could lead to primary testicular insufficiency. The paradoxical presentation of testotoxicosis in these boys resulted from an identical point mutation in the *GNAS1* gene, which caused both a loss and gain of Gsα function.

PHP-1a, characterized by a loss of $G_s\alpha$ function, is caused by thermal inactivation of the mutant protein at body temperature. Testotoxicosis indicates an organ-specific gain of $G_s\alpha$ function, resulting from the expression of the mutant protein. The lower temperature of the testes protects the mutant protein from thermal inactivation.

9.10.3.3 Growth Plate Defects

A study by Sanchez et al. found that an imprinting defect in *GNAS* may lead to growth plate defects in patients with PHP-1b, including brachydactyly and Madelung deformity. This suggests that *GNAS* signaling has a more extensive role in chondrocyte maturation than was previously believed [201].

9.10.4 Clinical Presentation

9.10.4.1 History (Symptoms)

Patients with PHP can present in infancy, especially if significant hypocalcemia occurs. Patients may present with features of *hypocalcemia* including paresthesias, carpo-pedal muscular spasms, cramping, tetany, and if the calcium deficit is severe, generalized seizures. Hypocalcemia in children or adolescents is often asymptomatic [202].

Patients with *PHP type 1a* present with a characteristic phenotype, collectively called Albright hereditary osteodystrophy (AHO). Patients with PHP-1a may also have disturbances in taste, smell, vision, and hearing, and they may be hypo-responsive to the biological effects of other peptide hormones that use $G_s\alpha$ to enhance

cAMP production (TSH, ADH, GHRH, gonadotropins, glucagon, and adrenocorticotropin). Patients should be evaluated for signs and symptoms suggestive of deficiencies of any of these hormones.

Primary hypothyroidism occurs in most patients with PHP-1a [203, 204]. In addition, *reproductive dysfunction* commonly occurs in persons with PHP-1a. Women may have delayed puberty, oligomenorrhea, and infertility. Features of hypogonadism may be less obvious in men. Testes may show evidence of maturation arrest or may fail to descend normally. Fertility appears to be decreased in men with PHP-1a. Within the spectrum of PHP-1a, variability exists in osteoclast responsiveness to PTH. Some patients may have osteopenia and rickets. *Mentation* is impaired in approximately half of patients with PHP-1a and appears to be related to the $G_s\alpha$ deficiency rather than to chronic hypocalcemia, because patients with other forms of PHP and hypocalcemia have normal mentation.

Unusual presenting manifestations include neonatal hypothyroidism, Parkinson disease, and spinal cord compression. An interesting association between PHP-1a and hyper-calcitoninemia without any evidence of medullary thyroid carcinoma (MTC) has been described [205]. An increased prevalence of sleep apnea in children with PHP-1a has also been reported [206].

9.10.4.2 Physical Examination

Physical examination may reveal signs of hypocalcemia, including positive Chvostek sign (twitching of facial muscles after tapping the facial nerve just in front of the ear) and/or Trousseau sign (carpal spasm after maintaining an arm blood pressure cuff at 20 mmHg above the patient's systolic blood pressure for 3 min). Occasionally, cataracts or papilledema is present.

Patients with *PHP type 1b* present with hypocalcemia without AHO. The severity of hypocalcemia can vary greatly among family members of the same kindred. Patients with pseudo-PHP (PPHP) have the phenotype of AHO, but with normal biochemical parameters. Patients with PPHP are often found in the same kindreds as those with PHP type 1a.

9.10.4.3 Albright Hereditary Osteodystrophy

Obesity is a common feature of AHO, although brachydactyly is the most reliable sign in the diagnosis of this condition. The brachydactyly may be symmetrical or asymmetrical and may involve one or both hands (Fig. 9.3) or feet.

Shortening of the metacarpals in PHP type 1 causes shortening of the digits, particularly the fourth and fifth digits and may be recognized during physical examination as dimpling or blunting over the knuckles of a clenched or closed fist. This is known as "Archibald sign" or "Archibald metacarpal sign" (Fig. 9.4). Moreover, shortening of the distal phalanx of the thumb is evident as a thumb in which the ratio of the width of the nail to its length is increased (so-called *murderer's thumb* or *potter's thumb*).

Several other skeletal deformities have been described in AHO, including short ulna, bowed radius, deformed elbow, or cubitus valgus and coxa vara, coxa valga, genu varum, and genu valgum deformities.

9.10.5 Work-Up/Investigations

9.10.5.1 Laboratory Tests

Pseudo-hypoparathyroidism (PHP) can be diagnosed by blood and urine tests to measure the levels of calcium, phosphorous, and PTH. Diagnosis of PHP is defined by the coexistence of hypocalcemia and hyperphosphatemia with elevated PTH levels in the presence of normal vitamin D values and normal renal function and the absence of hypercalciuria [202]. When the serum concentration of PTH in a hypocalcemic patient is increased, the patient has either a form of PHP or secondary hyperparathyroidism (SHPT).

Assessment of skeletal and renal responsiveness to PTH is accomplished by measurement of changes in serum calcium, phosphorus, cAMP, and calcitriol concentrations and in urinary cAMP and phosphorus excretion after administration of the biosynthetic *N*-terminal fragment of PTH.

Other laboratory tests to consider include thyroid function tests and measurement of gonadotropin and testosterone or estrogen levels. Assessment of growth hormone function with insulin-like growth factor-1 should also be considered.

Freson et al. (2008) concluded that platelet-based testing can effectively be used in the diagnosis of $G_s\alpha$ defects. They reported that platelet aggregation responses varied according to $G_s\alpha$ signaling defects, thus providing a reflection of a patient's phenotype and genotype [207]. Todorova-Koteva et al. (2012) demonstrated the use of commercially available recombinant PTH injections and concomitant measurement of cAMP in urine to diagnose PTH resistance, especially in non-phenotypically evident PHP [208].

9.10.5.2 Imaging Studies

Radiography of the hand may show a specific pattern of shortening of the bones, in which the distal phalanx of the thumb and the third through fifth metacarpals are shortened most severely. Radiography may also show small soft tissue opacities (calcifications/ossifications). Computed tomography (CT) scanning may reveal calcification of the basal ganglia.

9.10.5.3 Other Tests

Electrocardiogram (ECG) may reveal prolongation of the QT-interval secondary to hypocalcemia. Patients with PHP type 1b may be evaluated for parathyroid-related bone disease such as bone mineral density (BMD) testing [209].

9.10.5.4 Genetic Testing

Genetic testing and analysis of the *GNAS1* gene can confirm diagnosis and identify the different variants or subtypes of PHP [189]. Patients affected by PHP-1b require testing for *GNAS* methylation changes; some laboratories will analyze exon A/B only as a screen, because the loss of methylation of this DMR on the maternally derived *GNAS* allele is present in all reported cases of both inherited and sporadic forms of PHP-1b. Patients with PHP-1b can be further analyzed for paternal

uni-parental isodisomy of chromosome 20q or small deletions within *STX16* and *GNAS*; these tests have furthermore been shown to identify deletions within *GNAS* as the cause of some PHP-1a cases [13].

9.10.6 Differential Diagnosis

There have been case reports of vitamin D deficiency mimicking PHP. The clinical presentation and biochemical features of stage 1 of vitamin deficiency rickets (VDR) and PHP type 2 are quite similar.

In 2005, Mahmud et al. described two sisters who were initially identified as having paroxysmal dyskinesia, but who, on subsequent testing, showed hypocalcemia, hyperphosphatemia, and elevated PTH levels consistent with PHP type 1b [210].

Other conditions to consider in the differential diagnosis of PHP include secondary hyperparathyroidism (SHPT) and autoimmune polyglandular syndromes. Some forms of PHP may remain unnoticed or undiagnosed if patients do not have hypocalcemia and/or features of Albright hereditary osteodystrophy (AHO).

9.10.7 Treatment

9.10.7.1 Approach Considerations

The goals of pharmacotherapy are to correct calcium deficiency, prevent complications, and reduce morbidity. Maintain serum total and ionized calcium levels within the reference range is essential to avoid hypercalciuria and to suppress PTH levels to normal. This is important because elevated PTH levels in patients with PHP can cause increased bone remodeling and lead to hyperparathyroid bone disease.

Intravenous calcium is the initial treatment for all patients with severe symptomatic hypocalcemia. Administration of oral calcium and 1alfa-hydroxylated vitamin D metabolites, such as calcitriol, remains the mainstay of treatment and should be initiated in every patient with a diagnosis of PHP; it is usually needed in larger dose than for treatment of hypoparathyroidism. Maintaining serum total and ionized Ca levels within the reference range discourages hypercalciuria and suppresses PTH levels to normal. Blood chemistries should be monitored frequently and urinary calcium excretion monitored occasionally [15, 36].

In adults, approximately 100 mg of elemental calcium are infused over 10–20 min. If this measure does not alleviate the clinical manifestation, 100 mg/h of elemental calcium can be infused (in *adults*), with close monitoring of calcium levels. Calcium should *not* be infused rapidly because of the possible adverse effects of cardiac conduction defects; cardiac monitoring may help to guide therapy. The two most readily available formulations for IV use are calcium chloride and calcium gluconate; a 10-mL ampoule of 10% calcium chloride contains 360 mg of elemental

calcium, and a 10-mL ampoule of 10% calcium gluconate contains 93 mg of elemental calcium. For *neonates, infants,* and *children*, the recommended initial dose is 0.5–1 mL/kg of 10% calcium gluconate, administered over 5 min.

Patients with PHP type 1b could develop tertiary hyperparathyroidism (THPT) and/or hyperparathyroid bone disease. Therefore, it is important to treat them with sufficient doses of Ca and vitamin D to maintain serum Ca and PTH levels within the normal range [211].

Patients with intra-cranial calcifications may experience seizures related to chronic neuropathic changes, and they may need anti-epileptic medications [15, 36].

Rarely, extra-skeletal osteomas require surgical removal to relieve pressure symptoms. Parathyroidectomy is the treatment of choice in patients with THPT.

Therapy should be monitored by regular serum and urinary calcium measurements and caution should be exercised to avoid renal or hypercalcemic complications. In addition, serum PTH levels are monitored with the goal of maintaining serum PTH levels within normal range.

9.10.7.2 Calcium Salts

These agents are used for calcium electrolyte supplementation.

- *Calcium chloride:* it improves nerve and muscle performance by regulating the action potential excitation threshold affected by calcium deficiency.
- *Calcium gluconate* (Cal-G, Cal-GLU): it moderates nerve and muscle performance and facilitates normal cardiac function. It can be initially given IV, and calcium levels can be maintained with a high-calcium diet. Some patients require oral calcium supplementation.
- *Calcium carbonate* (Oystercal, Caltrate, Os-Cal, Tums): it is used for supplementation of IV therapy in hypocalcemia. It moderates nerve and muscle performance by regulating the action potential excitation threshold.

9.10.7.3 Vitamins (Fat-Soluble)

Calcitriol (Calcijex, Rocaltrol, Vectical) increases calcium levels by promoting calcium absorption in the intestines and retention in kidneys.

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Metabolic Syndromes of Parathyroid Failure

10

10.1 Definitions of Parathyroid Failure Syndromes

10.1.1 Post-operative Hypocalcemia

There is consensus that the diagnosis and treatment of post-operative hypocalcemia must precede the development of symptoms and that PTH and/or serum calcium should be monitored after total thyroidectomy (TT) in order to start treatment before symptoms occur. Alternatively, some authors have proposed to give calcium and vitamin D supplements to all patients (*preventive therapeutic strategy*) and do not pay much consideration to the biochemical parameters [1]. In some registries, Ca and vitamin D replacement are used as surrogate variables for post-operative hypocalcemia [2–4].

The cutoff value and timing of blood sampling used to define post-operative hypocalcemia differs. Most authors [5–9] agree on the biochemical diagnosis of hypocalcemia as a "total serum calcium concentrations <8 mg/dL or 2 mmol/L." Total serum calcium is cheap and easy to interpret and is preferable to ionized calcium concentrations which are highly dependent on blood sampling, transport and pH. A cutoff of 8 mg/dL (2 mmol/L) corrects for recumbency and mild hemodilution, and only exceptionally are symptoms of hypocalcemia observed above this value. Other authors [10, 11] define hypocalcemia as a *serum calcium < 1.8 or 1.9 mmol/L,* but this risks to underestimate the diagnosis of hypocalcemia since patients may develop symptoms when s-Ca drops below 2 mmol/L. Finally, raising the cutoff up to *2.1 mmol/L* may lead to an over-estimation of hypocalcemia rates and over-treatment [12].

Timing of s-Ca measurement after thyroidectomy is critical because it has an impact on the prevalence of hypocalcemia rates: the closer the blood sampling is performed to surgery the lower the rates of hypocalcemia will be. On the other hand, if s-Ca is determined too late, patients may develop clinical symptoms before treatment is commenced. It is thus advisable to adhere to the definition of post-operative

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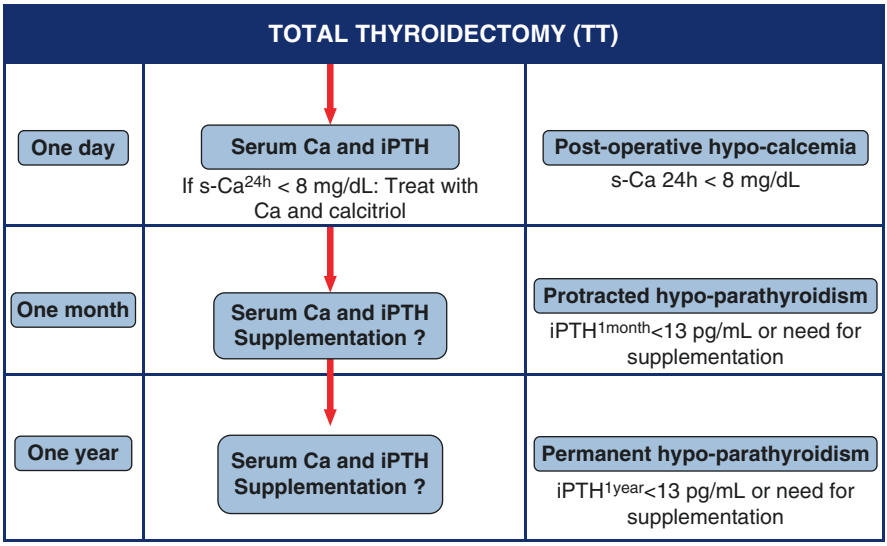

Fig. 10.1 Recommended time points for classification of patients developing hypocalcemia after total thyroidectomy (TT)

hypocalcemia as a "*serum calcium <8 mg/dL (2 mmol/L) 24 hours after TT*" [7] and that oral treatment with Ca and calcitriol be started if serum Ca drops below this value. This "selective therapeutic strategy" allows for patients to be discharged home early on the next day and minimizes over-treatment of the normo-calcemic patients.

In addition, a second blood test including intact parathyroid hormone (iPTH) is recommended to be obtained the morning following surgery. This post-operative iPTH concentration is used as a reference value to check parathyroid function recovery during patient follow-up. If PTH is low or undetectable, calcium and calcitriol supplements are continued when the patient is seen the next week in the outpatient clinic. All patients with post-operative hypocalcemia should be followed up with regular checks of serum-Ca and iPTH until recovery or a final diagnosis of permanent hypoparathyroidism [7] is madras demonstrated in Fig. 10.1.

10.1.2 Protracted Hypoparathyroidism

Parathyroid function recovery can be expected in at least two-thirds of patients with post-operative hypocalcemia within 1 month of thyroidectomy. Those who need treatment beyond this time period suffer from *protracted hypoparathyroidism*. Promberger et al. [13] proposed the concept of protracted hypoparathyroidism for those patients requiring replacement therapy 2 weeks after thyroidectomy. This period of time, however, may be a little too short to diagnose early parathyroid function recovery. Other authors assessed the hypoparathyroidism rates around *1 month* after surgery.

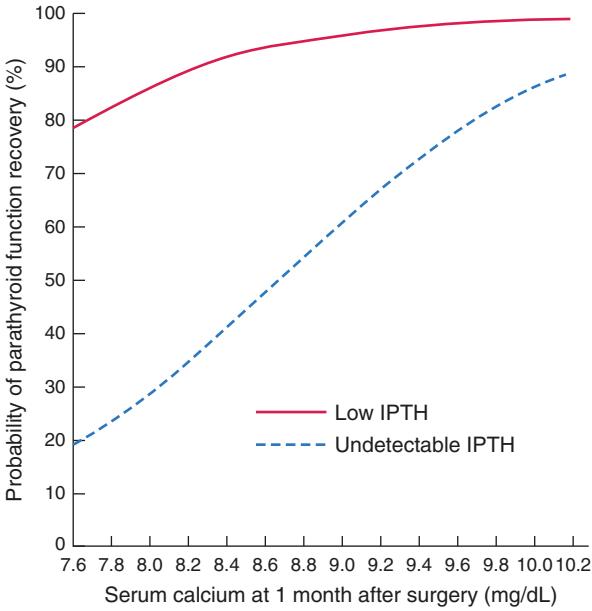

Fig. 10.2 Probability of recovery of parathyroid function in patients with protracted hypoparathyroidism according to serum calcium and iPTH concentrations 1 month after total thyroidectomy

Hallgrimsson et al. [4] reported a 9.1% of protracted hypoparathyroidism assessing the need for vitamin D supplements at *6 weeks* after surgery. Bergenfelz et al. [3] reported continuation of calcium, vitamin D, or both in 7.8%, 2.6%, and 7.3% of patients, respectively, 6 weeks after bilateral (not always total) thyroidectomy. In agreement with these two teams, it is conceivable to propose the following *definition of protracted hypoparathyroidism*: "a subnormal iPTH concentration (<13 pg/mL) and/or need for calcium replacement with or without calcitriol at four to six weeks after thyroidectomy" [7].

A proper definition of protracted hypoparathyroidism has clinical relevance as a predicting tool when informing patients. If the patient is hypoparathyroid 1 month after surgery, the probability of recovering the parathyroid function during the next 12 months is 75%. In addition, the chances of parathyroid function recovery after 1 month are better if iPTH is detectable (4–14 pg/mL) that when it is undetectable (Fig. 10.2) [7].

10.1.3 Permanent Hypoparathyroidism

Permanent hypoparathyroidism is defined as "the need for replacement therapy 6 months [14] or 1 year after thyroidectomy" [5, 7]. The 1-year deadline is proposed herein since according to the data of Lorente-Poch and colleagues (2015) [15], about 20% of patients who recover from protracted hypoparathyroidism do so after 6 months. Subnormal iPTH concentration (<13 pg/mL) is the rule in these cases.

A closer look at permanent hypoparathyroidism allows for a sub-classification of this syndrome into three conditions:

1. *Aparathyroidism* (undetectable PTH, high PO_4);
2. *Hypoparathyroidism* (detectable but subnormal iPTH concentrations, normal phosphate);
3. *Relative parathyroid insufficiency* (normal iPTH levels but insufficient to maintain serum Ca within normal limits).

Broadly speaking, aparathyroidism always requires vitamin D supplementation, hypoparathyroidism can often be managed with Ca salts alone, and relative parathyroid insufficiency is seen in patients with associated conditions (treatment with bisphosphonates, malabsorption, bowel resection, gastric bypass) impairing Ca absorption or resorption in whom there is an insufficient parathyroid functional reserve to respond to hypocalcemia. The secretory response of parathyroid glands (PTGs) is impaired in some patients' long-term after TT despite PTH levels being within normal limits [16]. After a hypocalcemic stimulus with $NaHO_3$ infusion, PTH levels increased in TT patients but to a lesser degree compared with non-thyroidectomized patients.

The best vitamin D substitute for treatment of permanent hypoparathyroidism is controversial. Calcifediol is generally favored because it is cheap, non-nephrotoxic, and can be usually started as one ampoule (10,000 UI, 266 mg) twice a week. Once diagnosed and stabilized, patients with permanent hypoparathyroidism should be controlled twice a year.

Serum Ca, P, iPTH levels, 25-hydroxyvitamin D and 1,25-hydroxyvitamin D (particularly if calcitriol is being administered) are determined to adjust replacement therapy and prevent hypo- and hypercalcemia.

10.2 Risk Factors of Parathyroid Failure

10.2.1 Post-operative Hypocalcemia

A recent meta-analysis [17] isolated as predictive factors for *transient hypocalcemia biochemical parameters* such as pre-operative Ca levels, peri-operative PTH, and 25-OHvit.D levels and post-operative magnesium. Predictive *surgical factors* were reoperation for recurrent goiter or for bleeding. Graves' disease [2] and thyroid cancer [18] were associated with higher rates of post-thyroidectomy hypocalcemia. *Patient-related factors* are younger age and female gender [2, 19, 20].

Lower peri-operative levels or a larger decline in serum calcium [9, 20, 21], lower intra-operative or post-operative PTH levels [21, 22], and also larger decline in intra-operative [6, 21] and post-operative PTH [23–25] appear as biochemical factors associated with post-operative hypocalcemia as well as low pre-operative vitamin D [9, 26], low post-operative magnesium [27], high pre-operative alkaline phosphatase and bone turnover markers [9, 20], which is consistent with hungry bone syndrome.

With regard to surgical factors, increased risk of transient hypocalcemia is mainly associated with the extent of surgery, central compartment lymph node (LN) dissection [3, 7, 8], redo operations, re-operation for bleeding, and wound infection

[3, 4]. Some authors found that a lower hospital volume and therein, less experimented endocrine surgery team leads to an increase in hypocalcemia rates [4]. Regarding surgical technique, few PTGs maintained in situ due to inadvertent parathyroid excision [7, 8, 28, 29] and/or auto-transplantation [3, 4, 7, 8, 10, 13, 18] emerges as a major post-thyroidectomy hypocalcemia risk factor. Gland injury and accidental parathyroid excision may be facilitated by failure to identify properly the PTGs during total thyroidectomy [2, 3]. Hence, it is our routine practice to look for PTGs in their orthotopic position. Nevertheless, some authors have suggested that parathyroid gland identification has no influence on post-operative hypocalcemia [4, 24], whereas others have considered it as a risk factor for hypocalcemia [30, 31].

10.2.2 Protracted Hypoparathyroidism

Protracted hypoparathyroidism is associated with (1) weight of the resected thyroid gland, (2) lymph node dissection, (3) re-operation for bleeding, (4) wound infection, (5) sternotomy, (6) few PTGs identified, and (7) auto-transplantation.

Multivariate analysis of the data of Lorente-Poch et al. (2015) [32] revealed the presence of a linear influence of the *number of PTGs remaining* in situ on protracted hypoparathyroidism rates. At this stage, demographic and clinical variables, as well as the extent of surgery were much less relevant. The prevalence of protracted hypoparathyroidism doubled in patients who received auto-transplantation [32].

10.2.3 Permanent Hypoparathyroidism

Despite attempts to predict permanent hypoparathyroidism on the basis of biochemical parameters at the time of hospital discharge the fact is that no single post-operative variable can be used to accurately predict it [33, 34]. The following factors have been identified as independent predictors of permanent post-operative hypoparathyroidism [17]; (1) a serum calcium level < 1.88 mmol/L at 24 h after surgery, (2) identification of fewer PTGs during the surgery [2, 3], (3) reoperation for bleeding [10], (4) Graves' disease, and (5) heavier thyroid specimens [35].

Parathyroid function recovery, however, is a dynamic event and cannot be predicted early after thyroidectomy. Lorente-Poch et al. (2015) [32] reported that the best predictors of iPTH recovery in patients with protracted hypoparathyroidism are the number of PTGs remaining in situ and the serum calcium concentration at 1 month after surgery.

Whether parathyroid auto-transplantation prevents permanent hypoparathyroidism is a very controversial issue. All authors admit that auto-transplantation results in higher rates of post-operative hypocalcemia but some have proposed that in the long term it prevents permanent hypoparathyroidism [33, 36–40]. Several studies, however, have found a strong association between auto-transplantation and permanent hypoparathyroidism [5, 7, 10, 18].

Lorente-Poch et al. (2015) [32] showed that parathyroid auto-transplantation in the sternocleido-mastoid (SCM) muscle using the fragmented tissue technique

proposed by Olson et al. [40] resulted in a threefold increase of permanent hypoparathyroidism; 3% in non-transplanted versus 9% in transplanted patients. Interestingly, in patients with three glands remaining in situ, the rate of permanent hypoparathyroidism was the same whether the fourth gland was auto-transplanted or was found in the specimen in the pathology laboratory.

10.3 Likelihood of Recovery of Parathyroid Function

Post-operative hypocalcemia is usually (>60–70%) a transient phenomenon and calcium supplements can be stopped within 1 month after surgery. If calcium and calcitriol supplements are still required after 1 month, the chance to develop permanent hypoparathyroidism is 25%. Clinical and surgical variables (age, gender, extension of surgery, diagnosis) do lose predictive significance and calcium and calcitriol dosage at hospital discharge, high serum calcium and low but detectable iPTH levels 1 month after surgery become the most relevant predictive variables [7]. Higher serum calcium concentrations associated with higher calcium and calcitriol dosages at the time of hospital discharge have a positive effect on parathyroid function recovery. This phenomenon has been described as "*parathyroid splinting*," meaning that the injured and ischemic PTGs are allowed to rest in a normal-high serum calcium environment. Parathyroid splinting has a synergistic effect with the number of PTGs remaining in situ to facilitate recovery of the parathyroid function [32].

10.4 Summary

The approach to post-thyroidectomy hypoparathyroidism may be facilitated by the understanding of the three different metabolic syndromes of parathyroid failure. Selective calcium/vitamin D replacement therapy of post-operative hypocalcemia at the time of hospital discharge is recommended. A detectable iPTH, all PTGs remaining in situ and high levels of serum calcium 1 month after surgery increase the likelihood of recovery from protracted hypoparathyroidism. Permanent hypoparathyroidism can be managed according to iPTH levels. Aparathyroidism with undetectable iPTH requires vitamin D supplementation whereas hypoparathyroidism (detectable but subnormal iPTH) can often be managed with calcium salts alone. Associated conditions such as malabsorption, gastric bypass, or treatment with bisphosphonates may cause a relative parathyroid insufficiency.

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Hungry Bone Syndrome (HBS)

11

11.1 Definitions

11.1.1 Hungry Bone Syndrome

Hungry bone syndrome (HBS) most often appears in the post-operative period of patients who have undergone parathyroidectomy (e.g., for hyperparathyroidism) or thyroidectomy (e.g., for toxic goiter); however, it has also been shown to be a possibility in patients with osteoblastic metastases [1–4]. Although HBS does not have a consensus definition, most resources define it as "profound hypocalcemia of less than 8.4 mg/dL that persists for more than four days post-operatively" [1–3].

Hungry bone syndrome results from rapid increase in bone remodeling [5]. If the stimulus is removed (thyroid hormone or parathyroid hormone), there is a dramatic increase in bone formation; hypocalcemia can occur if the rate of skeletal mineralization exceeds the rate of osteoclast-mediated bone resorption. This syndrome can be associated with severe and diffuse bone pain [5].

11.1.2 Factitious Hypocalcemia

Decreased serum albumin levels caused by hemodilution due to excessive fluid transfusion [6], or the release of anti-diuretic hormone (ADH) in response to surgical stress and the consequent retention of water, can cause a decreased total, but *not* ionized calcium, which has no clinical significance because the active fraction (ionized) is *not* affected [7].

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11.2 "HBS" After Parathyroidectomy and Thyroidectomy

11.2.1 Introduction

Hungry bone syndrome (HBS) refers to the rapid, profound, and prolonged hypocalcemia associated with hypophosphatemia and hypomagnesemia, and is exacerbated by suppressed parathyroid hormone (PTH) levels, which follows parathyroidectomy in patients with severe primary hyperparathyroidism (PHPT) and pre-operative high bone turnover. It is a relatively uncommon, but a serious adverse effect of parathyroidectomy.

Patients with primary hyperparathyroidism (PHPT) who undergo parathyroidectomy demonstrate a rapid decrease in serum calcium levels after successful removal of one or more hyperactive PTG(s). This decrease in serum calcium levels is usually mild and maximal 2 to 4 days post-operatively, and independent of the size of hyperactive glands or pathological diagnosis [8–14]. Persistence of hypocalcemia for more than 4 days after parathyroidectomy may be due to intentional (PTG disease) or accidental (TT with removal of all PTGs, devascularization or trauma to residual PTGs), but is also often due to long-term suppression of residual non-pathological PTGs [3, 8, 14, 15].

The term "hungry bone syndrome" (HBS) has been coined to the profound (serum calcium <2.1 mmol/L) and prolonged (longer than fourth day post-operatively) hypocalcemia, which follows parathyroidectomy for severe HPY. This is usually associated with skeletal manifestations, reflected by high pre-operative indices of bone turnover, osteitis fibrosa cystica, and/or "brown tumors." The severe hypocalcemia is believed to be due to the greatly increased skeletal usage of calcium, thought to occur as a result of removal of the effect of high circulating PTH levels on bone, with immediate arrest of bone resorption in the face of continuing and enhanced bone formation, although there is no good documentation for this.

11.2.2 Pathophysiology of HBS

Parathyroid hormone (PTH) is released from the parathyroid chief cells when the calcium-sensing receptor (CaSR) notes a low serum calcium level and thus initiates a cascade of reactions leading to both bone resorption and bone formation, to raise serum calcium levels. Small or sporadic exposures to PTH lead to net bone formation, but in continuous exposure states such as hyperparathyroidism (HPT), there is net bone resorption [16].

A study performed by Yanfei et al. investigated the catabolic effects of PTH given as a continuous infusion to rodents. Over time, steady PTH exposure led to increased levels of receptor activator of nuclear factor-kappa-B; ligand (RANK-L) and decreased levels of Osteoprotegerin (OPG). Typically, RANK-L leads to osteoclastogenesis and subsequent increased osteoclast activity. As a counter-regulatory mechanism, OPG can bind to RANK-L, leading to decreased differentiation of cells

to osteoclasts, ultimately leading to a net osteoblastic activity state. This evidence suggests that with constant exposure to PTH, bone resorption would predominate [17].

Bone remodeling consists of a series of cellular events on the bone surface, the function of which is to remove damaged bone through the process of osteoclastic bone resorption, and replacing it with new bone through the process of osteoblastic bone formation. The process of bone resorption, which lasts about 2 weeks is followed by a reversal phase of 2 to 3 weeks duration, before new bone is formed, which lasts about 3 months. The remodeling space is the total amount of bone that at any time has been resorbed by osteoclasts, but not yet reformed by osteoblasts during the coupled remodeling process because of the delay between resorption and formation. This space depends on the activation frequency of new remodeling sites, which is considerably increased in PHPT, leading to mineral depletion of bone and significantly contributing to the hypercalcemia of PHPT [17–21].

In those patients with pre-operative high rates of bone turnover, successful parathyroidectomy curbs osteoclastic resorption, leading to a decrease in the activation frequency of new remodeling sites and to a decrease in remodeling space leading to a consequent gain in bone mass. This is believed to be the cause of the rapid, profound, and sometimes prolonged decrease in serum calcium, phosphate, and magnesium levels. The duration of the HBS is defined as the "duration of post-operative hypocalcemia or time required for normalization of serum calcium following successful parathyroidectomy, which parallels normalization of bone turnover and may last for up to nine months, but exceptionally longer in cases of parathyroid carcinoma following radical excision of the tumor." The duration of the hypocalcemia may be determined by the height of the increased bone turnover pre-operatively as well as by the time required for recovery of normal function of residual non-pathological parathyroid tissue.

Ge et al. assessed retrospectively the bone turnover markers in patients with HBS post- parathyroidectomy for secondary hyperparathyroidism (SHPT), finding that prior to parathyroidectomy there was statistically significant less osteocalcin, a marker of bone formation, and statistically significant more Tartrate-resistant acid phosphatase (TRAP-5b), a bone resorption marker, in patients who had HBS compared to those who did not. Additionally, post- parathyroidectomy for all patients, there was a statistically significant shift in the bone markers in that all markers of formation increased (osteocalcin, calcitonin, and c-terminal peptide) and the markers of resorption decreased (TRAP-5b). During this process, the shift in bone metabolism from resorption to net formation leads to an influx of minerals into the bone with the levels of calcium and phosphate depleting in the blood [22].

Karunakaran et al. prospectively evaluated the rate of HBS in the post-thyroidectomy state for thyrotoxicosis and proposed that the mechanism for HBS in those cases is related to increased bone turnover in the hyperthyroid state that will take months to reverse, even if biochemical evidence of euthyroid state gets achieved before surgery [4].

11.2.3 Clinical Manifestations: Symptoms and Physical Examination

Patients with HBS will present, if symptomatic, with signs and symptoms of hypocalcemia. Severe hypocalcemia (serum calcium concentration $\leq$ 2.1 mmol/L) is associated with neuro-muscular irritability, clinically manifested by seizures, tetany, paresthesias, and numbness or tingling sensation in the perioral area, hands or feet, as well as carpopedal spasms, arrhythmias, cardiomyopathy, and laryngospasm [5, 23–33]. Patients can also develop generalized convulsions, which can lead to pathological fractures [34, 35] and ultimately if remaining uncorrected to coma and even death. Congestive heart failure, which is reversible after normalization of serum calcium concentration, has also been reported [23, 36].

Physical examination may show a fracture, bone deformities depending on the length of uncontrolled HPT, recent surgical scar after parathyroid or thyroid gland removal, and in some cases, there might be signs of nerve hyper-excitability due to hypocalcemia with more prominent Trousseau or Chvostek signs [1, 2].

11.2.4 Epidemiology/Prevalence of HBS After Parathyroidectomy

Data on the prevalence of HBS have been scarce and conflicting after original publications in the 1980s of large case series suggesting that the syndrome develops post-operatively in up to 13% of patients with PHPT [3, 9, 37]. The prevalence of HBS has decreased in the Western World over the last two decades, most likely due to the early detection of still asymptomatic PHPT by routine calcium screening before the effects of high circulating levels of PTH on the skeleton, such as high bone turnover, osteoporosis, or osteitis fibrosa cystica, become evident [38, 39] although exact numbers are missing. Recent case series from Asia reported much higher prevalence rates of 24–87% [40–43], whereas a case series from Saudi Arabia documented a prevalence rate of only 4%, which likely mirrors a rate closer to the current expectation in the USA [44]. Regarding cases post-parathyroidectomy for secondary hyperparathyroidism (SHPT), the prevalence ranges between 20% and 70% [1, 2]. Data regarding prevalence in tertiary HPT are scarce.

It is noted, in one prospective study, that the prevalence of HBS in an Indian cohort of thyrotoxic patients post-thyroidectomy was approximately 39%. Instances of hypocalcemia not due to post-surgical hypoparathyroidism post-thyroidectomy were also noted in a study of post-operative patients in Singapore with a rate of 53%, although this study did not explicitly clarify or was able to elucidate if these were instances of HBS [4, 45]. For HBS in metastatic prostatic cancer, only few case reports are available in the literature [46].

11.2.5 Etiology

Hungry bone syndrome occurs in the post-operative period after parathyroidectomy for PHPT or SHPT, after total thyroidectomy (TT) for thyrotoxicosis, and it can also occur in the case of metastatic prostate cancer. Hungry bone syndrome in

post-surgical cases occurs after prolonged exposure to parathyroid hormone (PTH) or thyrotoxicosis that leads to high bone turnover rates with net bone resorption that then has a sudden marked shift toward osteoblastic activity after the removal of the hormone excess takes place. It can also present in men with increased osteoblastic activity in metastatic prostate cancer, leading to increased use of mineral building blocks for excess bone formation [1–4, 46].

11.2.6 Risk Factors of Development of HBS

Multiple risk factors have been postulated and noted to correlate with HBS in retrospective studies, case reports, and case series reviews (Table 11.1). *Common risk factors* include elevated levels of parathyroid hormone (PTH), alkaline phosphatase (ALK-P), body mass index (BMI), blood urea nitrogen (BUN), and increased size of resected glands. Radiological evidence of bone diseases such as brown tumors, fractures, and osteitis fibrosa cystica with higher osteoclast numbers on bone biopsy have also correlated with an increased risk of HBS. On the other hand, there have been *divergent risk factors* noted in the incidence of HBS, like older age and high pre-operative calcium levels in PHPT versus younger age and lower pre-operative calcium levels, respectively, in the patients with SHPT [1–3, 47–49].

11.2.6.1 Age at Time of Surgery

Older age at time of surgery is a risk factor for HBS [3]. Brasier and Nussbaum (1988) [3] showed that in a group of 198 patients with PHPT, those who developed HBS were 10 years older than patients with an uncomplicated post-operative course (61 ± 3 vs. 51 ± 1, $p < 0.05$). With older age being more often associated with vitamin D deficiency, a decrease in renal 1α-hydroxylase activity and lower dietary calcium intakes [3]; all three factors potentially contribute to a negative calcium balance and clinical bone disease [10].

Table 11.1 Summary of risk factors for development of HBS

Common risk factors	Divergent risk factors
1. Elevated PTH	1. PHPT
2. Elevated ALK-P	– Older age
3. Radiological evidence of bone disease	– Higher preoperative calcium levels
4. Higher BMI	2. SHPT
5. Larger volume or weight of PTGs removed	– Younger age
6. A higher number of osteoclasts on bone biopsy	– Lower preoperative calcium levels
7. Higher BUN levels	3. Thyrotoxicosis
	– Lower lumbar spine bone mineral density

PTH parathyroid hormone, *ALK-P* alkaline phosphatase, *BMI* body mass index, *PTGs* parathyroid glands, *BUN* blood urea nitrogen, *PHPT* primary hyperparathyroidism, *SHPT* secondary hyperparathyroidism

11.2.6.2 Laboratory Investigations Before Surgery

Patients who developed HBS had higher pre-operative levels of *serum calcium*, and almost twofold increased levels of *PTH* and *alkaline phosphatase* (ALK-P) compared with those who had an uncomplicated post-operative course [3, 10, 50].

Serum Calcium

However, Lee et al. (2006) [51] were not able to demonstrate a significant difference in pre-operative serum levels of calcium, PTH, or ALK-P between nine patients who developed HBS post-operatively and 14 patients who did not. Serum magnesium and albumin levels were found to be significantly decreased in patients who subsequently developed HBS [3].

Serum PTH

Unfortunately, thus far, there has been no specific level of PTH at which the risk for HBS is proportional to suggest the creation of a clinical calculator or indicator. However, more often, the levels of PTH elevation in PHPT are more subtle in the range of 300–400 pg/mL as compared to 700–1000 pg/mL range in patients with SHPT.

Alkaline Phosphatase

There are no available data on the predictive value of pre-operative bone markers other than *ALK-P*, such as procollagen type 1 amino-terminal propeptide (P1NP, a marker of bone formation) and β-crosslaps (β-CTX, a marker of bone resorption). Pre-operative serum ALK-P levels reflect the state of bone turnover and, therefore, the degree of osteoclast activity and bone resorption. It has been suggested that pre-operative serum ALK-P concentrations may predict the degree and duration of hypocalcemia after successful parathyroidectomy [52].

Vitamin D

Depleted *vitamin D* status (low levels of 25(OH)D and $1,25(OH)_2D$) has been suggested to be a risk factor for the development of HBS by some, but not all, authors [3, 10, 38].

11.2.6.3 Radiological Bone Disease Before Surgery

Radiological evidence of *PHPT-related bone disease* has been reported to be an important risk factor for the development of HBS [10, 24, 25, 31, 34, 53]. Fourteen of 18 case reports on HBS indeed report skeletal abnormalities, such as subperiosteal erosions, lytic lesions, brown tumors, and multiple fractures [5, 23–27, 29–34, 36, 54–58]. Osteitis fibrosa cystica was observed in 47–100% of patients who develop HBS [40, 50] and the syndrome was reported in 25–90% of patients with radiological evidence of PHPT-related bone disease compared with only 0–6% of patients without skeletal involvement [10, 40, 53]. It has been shown that patients with osteitis fibrosa cystica have lower levels of $1,25(OH)_2D$ than expected, which

may be due to high levels of serum calcium directly inhibiting renal 1α-hydroxylase production, or to hypercalcemia-induced renal impairment with resulting further decreases in 1α-hydroxylase activity [13]. A testable hypothesis for the development of bone disease, and for the development of HBS, relates to the possibility that low circulating levels of $1,25(OH)_2D$ with resultant decreased fractional absorption of calcium, leads to under-mineralization of the skeleton [3, 10]. Low levels of $1,25(OH)_2D$ may thus represent a measurable risk factor for the development of HBS, independently of age, although 25(OH)D deficiency has been proposed to be the more significant risk factor [38].

11.2.6.4 Volume and Weight of Resected Pathological Parathyroid Gland(s)

A large study on 198 patients with PHPT demonstrated that the volume and weight of the removed adenomas were significantly greater in patients who developed HBS compared with patients who had an uncomplicated post-operative course (5 ± 1 vs. 1 ± 0.2 cm^3, $p < 0.05$ and 4 ± 1 vs. 2 ± 0.2 g, $p < 0.05$, respectively) [3]. Zamboni and Folse (1986) [9] confirmed this finding, by demonstrating that 11 of 16 patients with a single adenoma of >2 g developed transient post-operative hypocalcemia versus only 3 of 21 patients with a single adenoma of <1 g ($p < 0.001$). There are no available data on the relationship between histological characteristics of the resected pathological glands (adenoma vs. hyperplasia) and the development of HBS.

Diagnosis of hungry bone syndrome hinges on a profound and persistently low calcium level of less than 8.4 mg/dL (2.1 mmol/L) for more than 4 days post-operatively along with hypo-phosphatemia and normal PTH levels. Hungry bone syndrome is also often associated with hypomagnesemia and hypercalciuria [1–3].

11.2.7 Biochemical Changes Associated with HBS

A rapid decrease in serum PTH levels to a mean of 1.7 ± 0.4 pmol/L follows successful parathyroidectomy in all cases of PHPT [3]. Serum calcium levels drop to <2.1 mmol/L within the first 3 to 4 days but decrease further after the fourth post-operative day in patients with HBS [3]. Serum phosphate levels decrease post-operatively and remain so for the duration of the syndrome [3, 25, 34, 38–40, 51, 52, 54]. Hypomagnesemia is frequently encountered [50]. Serum alkaline phosphatase levels increase significantly post-operatively and remain elevated sometimes for up to 9 months after surgery [3, 25, 34, 38, 40, 47, 54, 56, 59].

Agarwal et al. (2002) [40] also reported increased levels of osteocalcin, a marker of bone formation, and decreased urine crosslaps, a marker of bone resorption, in 51 patients 1 week after surgery, with serum osteocalcin levels normalizing only 6 months after successful parathyroidectomy [40]. In 3 of 51 patients with extreme osteopenia, bone turnover markers remained elevated for 1 year after successful parathyroidectomy [40].

11.2.8 Radiological Changes Associated with HBS

Removal of the excessive circulating levels of PTH shuts off bone-resorptive activity and leads to a rapid increase in bone mineral density. Case reports show an increase in bone mineral density of the lumbar spine of 17% at 10 weeks, 10% at 6 months and 27–65% at one year after parathyroidectomy [13, 39, 57, 59] and an increase in bone mineral density of the greater trochanter of 33% at 6 months and of 35–131% at 1 year after surgery [13, 59].

Bone mineral density (BMD) increased post-operatively by a remarkable 332% within 1 year in Indian patients with overt skeletal disease and/or osteitis fibrosa cystica [40]. Follow-up radiographs show recovery of subperiosteal resorption and remineralization of brown tumors, osteolytic lesions and fracture sites [13, 24, 34, 40]. Skeletal scintigraphy shows increased radioactive isotope uptake 1 month after parathyroidectomy, known as "flare phenomenon," which reflects a healing response due to a significant increase in bone formation and consequent mineralization and high influx of calcium into the skeleton [24, 27]. A moderately increased uptake can still be seen 8 months after parathyroidectomy [26] and a decrease in number of lesions and normalization of uptake in the remaining lesions 1 year after parathyroidectomy [24].

11.2.9 Differential Diagnosis

The differential diagnosis of HBS includes the following:

- Post-surgical (thyroidectomy) devascularization of parathyroid glands.
- Accidental removal of all PTGs with permanent post-surgical hypoparathyroidism.
- Long-term suppression of non-pathological PTGs.

When considering the possible etiologies for hypocalcemia, specifically in the post-operative period, the state of the PTGs glands requires evaluation. Post-surgical devascularization or accidental destruction and removal of the remaining PTGs are possibilities. In other cases, the remaining PTGs need time to recover from the previous constant over-production of PTH from the hyperactive adenoma that was suppressing their production of PTH. In those instances, in contrast to HBS, although hypocalcemia will be evident, the PTH level will be low, and the phosphorus level will be high [3].

11.2.10 Management of HBS: Calcium, Vitamin D, and Magnesium

The treatment of HBS is aimed, in the short term, primarily at replenishing the depleted skeletal calcium stores. The first case reports of an HBS, which appeared

in the late 1970s, described the difficulties encountered in the management of this severe complication of parathyroidectomy before active metabolites of vitamin D and their synthetic analogues became available for clinical use [23, 30, 33, 34]. Persistence of severe hypocalcemia (≤1.3 mmol/L) was thus reported despite treatment with very high doses of calcium, magnesium, and cholecalciferol [23, 33, 34]. The reported amount of *calcium* supplementation required to treat the severe hypocalcemia varies between 6 and 12 g/day [25, 29, 31, 36, 57, 58].

If the serum calcium level is less than 7.6 mg/dL (1.9 mmol/L), if the patient is symptomatic, or if there are ECG changes such as QTc prolongation noted, any of these indicates treatment with intravenous (IV) calcium. Calcium chloride and calcium gluconate are the two forms of calcium available for IV administration. Calcium gluconate is more common, although 1 g of calcium chloride has three times more elemental calcium; this is mainly because calcium gluconate has a lower osmolarity and is far less irritating and damaging if it extravasates into surrounding tissues during infusion and also it does not require a central line as calcium chloride does [60, 61].

The regimen should begin with a bolus of 10% calcium gluconate 10–20 mL in 50–100 mL of D5% IV fluids given over 5–10 min; this is equivalent to approximately 100–200 mg of elemental calcium. After that, a continuous infusion should start. A 100 cc dose of 10% calcium gluconate in 1 L of D5W equates to approximately 1 mg/mL of elemental calcium. It can start at 50 mL/h and follow calcium, phosphorus, and magnesium levels every 4 to 6 h titrating to achieve a normal level; the aim should be a rate of 0.5–1.5 mg of elemental calcium/kg/h. Simultaneously, while giving IV calcium, once the patient can tolerate medications by mouth, oral supplementation should also begin with concomitant use of adequate doses of active metabolites of *vitamin* D (calcitriol) or alfacalcidol (2–4 μg/day) [25, 29–31, 37, 56–58], and with replenishment of *magnesium* stores as required. When calcium-containing solution is given IV, administration into large veins or via a central venous catheter is recommended to minimize the risk of local irritation or tissue necrosis by accidental extravasation in surrounding tissues. Electrocardiographic (ECG) monitoring is recommended as dysrhythmias may occur in case of too rapid correction of the hypocalcemia [62].

In prescribing oral calcium preparations, it is important to realize that different calcium preparations contain different amounts of elemental calcium. Calcium carbonate and calcium citrate are the most commonly used oral preparations. Calcium carbonate has 400 mg of elemental calcium/1 g (40%) versus calcium citrate has 211 mg of elemental calcium/1 g (approximately, 20%). Other calcium preparations are also available (calcium lactate—13%, calcium gluconate—9%, and calcium glubionate—6.6%), although they do not contain sufficient elemental calcium per tablet and compliance may be affected by the large number of tablets required to be taken orally to achieve the same calcium level [28].

Calcium carbonate requires a smaller number of pills to achieve supplementation overall and is the preferred agent for this reason. However, calcium citrate does not require an acidic environment for absorption, as calcium carbonate does. Thus, citrate is the better option in hypochlorhydria states such as with chronic

proton-pump inhibitor or histamine-2 blocker use, after gastric bypass surgery or in elderly patients. The appropriate amount of daily calcium supplementation required in HBS patients can be vast and varied. In case reports, the amount required was as low as 800 mg of elemental calcium in a patient with parathyroid adenoma versus 36 g of elemental calcium per day in a patient who experienced HBS after parathyroidectomy for SHPT [63, 64].

Magnesium should be repleted as needed because persistent hypomagnesemia will hinder efforts for calcium replacement as it can alter the ability of PTH to exert its effects and lead to a state resembling hypoparathyroidism. In other words, hypocalcemia does not resolve until the magnesium deficiency has been corrected. The amount of magnesium required to correct hypomagnesemia has not always been reported, and supplementation has been variably given IV as magnesium chloride or sulphate or orally as magnesium sulphate [23, 25, 27, 30, 33, 38, 57]. If high doses of magnesium are required for the treatment of hypomagnesemia, this should only be given IV in adequate dilutions of magnesium sulphate, and *not* intramuscularly (IM) or orally. Lower doses of magnesium can be supplemented as magnesium oxide orally or magnesium sulphate IM [9, 23, 33, 35, 39].

Hypophosphatemia should *not* prompt repletion as its treatment can lead to precipitation with calcium and further reduce calcium levels, overall worsening the effort of replacement.

11.2.11 Preventive Option of HBS

When considering the possibilities for reducing the risk for HBS, research thus far has investigated the use of bisphosphonate agents as well as vitamin D supplementation.

11.2.11.1 Pre-operative Treatment with Vitamin D

Depleted vitamin D status has been postulated to be a risk factor for the development of HBS and it has generally been recommended to supplement vitamin D to normalize 25(OH) vitamin D levels, although there are so far no available data to support the premise that this would contribute to the prevention or blunting of HBS [3, 38].

11.2.11.2 Pre-operative Treatment with Bisphosphonates

Bisphosphonates are anti-resorptive agents, widely used in the management of osteoporosis and bone disorders associated with increased bone turnover, such as Paget's disease of bone or metastatic bone disease. In hyperparathyroid bone disease these agents inhibit osteoclastic bone resorption and decrease activation frequency of remodeling sites, thus resulting in refilling of remodeling space and increasing mineralization of bone [38, 65, 66]. In this context, pre-operative bisphosphonate treatment would have a potential beneficial effect on the severity and duration of HBS by significantly decreasing or normalizing bone turnover before surgery is attempted [38, 67]. In contrast, short-term pre-operative treatment

may exacerbate post-operative hypocalcemia by just reducing bone resorption, without allowing time for a coupled decrease in bone formation. There are as yet no prospective studies or randomized control trials addressing the use of bisphosphonates in the prevention or limitation of duration of HBS. Data from case reports and small case series on the beneficial effect of preoperative treatment with bisphosphonates on the HBS in patients with hyperparathyroid bone disease [13, 36, 45, 53] or with long-standing severe PHPT [67] are conflicting [31, 34, 44, 50, 51].

Two case reports of patients with extensive hyperparathyroid bone disease demonstrated that pre-operative treatment with IV pamidronate given at a dose of 30 mg for 2 consecutive days or as a single infusion of 60 mg, resulted in a pre-operative decrease in serum calcium and in a decrease (just 1500 mg calcium orally/day) or no post-operative calcium requirements [13, 68]. One case report showed that a patient with a history of severe PHPT for longer than 8 years, who was treated with alendronate for 6 years, in addition to receiving a pre-operative total dose of 180 mg pamidronate IV, did not develop HBS post-operatively [67].

In a retrospective study, Lee et al. (2006) [51] also demonstrated that none of six patients who had received bisphosphonates pre-operatively (either oral clodronate 400–1600 mg/day or IV pamidronate 60 mg/day) developed HBS post-operatively, compared with 9 of 17 patients who had not been pre-operatively treated with bisphosphonates. There was no significant difference in pre-operative mean serum calcium (3.00 ± 0.15 vs. 3.01 ± 0.04 mmol/L), PTH (34.8 ± 11 vs. 33.4 ± 10 pmol/L), or alkaline phosphatase (224 ± 50 vs. 174 ± 60 U/L) levels between groups. A retrospective case series of 46 patients with severe bone disease, who were treated with IV zoledronate pre-operatively, also reported a low frequency of post-operative HBS of only 4% [44]. Another retrospective case series of six patients with radiological features of osteitis fibrosa cystica, who were pre-operatively treated with bisphosphonates (oral alendronate 20–30 mg/day for 4 to 6 weeks or a single dose of pamidronate 90 mg or ibandronate 150 mg IV), reported that none of the patients needed post-operative IV calcium supplementation [59].

In contrast, a case report of a patient with severe, prolonged, and extensive bone involvement (florid radiological bone changes) has shown that a single dose of 60 mg IV pamidronate combined with calcitriol 1–2 μg/day was able to significantly decrease (but not normalize) serum alkaline phosphatase levels (1600 to 420 U/L) but was not able to completely prevent HBS [56]. Four other case reports also show that treatment of severe HPT with alendronate (70 mg/week), pamidronate (twice 90 mg or 5 × 15 mg IV), or zoledronate (twice 4 mg IV) was unable to completely prevent HBS [31, 38, 57, 58].

11.2.11.3 Pre-operative Treatment with Active Metabolites of Vitamin D

Because low levels of $1,25(OH)_2D$ are a risk factor for the development of post-operative HBS [3, 10], it has also been hypothesized that preoperative supplementation of $1,25(OH)_2D$ could shorten symptomatic hypocalcemia and hospital course [3, 13, 69]. Data on preoperative $1,25(OH)_2D$ supplementation in patients undergoing parathyroidectomy for severe PHPT are also conflicting [10, 69]. Early in 1977,

Boyle et al. [69] showed that pre-operative treatment of severe HPT with $1,25(OH)_2D$ (calcitriol) at a dose of 2 μg/day for 1–10 weeks significantly decreased pre-operative alkaline phosphatase levels in three of seven patients with radiological bone cysts, and three other patients required little IV calcium supplementation to a total of <1 g in the first 12 post-operative days. In contrast, Heath et al. (1979) [10] showed that six patients with PHPT and radiological evidence of bone involvement, who were treated pre-operatively with 2 μg/day of $1,25(OH)_2D$ for 1 week, were as likely to develop hungry bone disease as patients with PHPT and radiological evidence of bone involvement who did not receive active vitamin D preparations pre-operatively (two of six vs. one of six, respectively).

11.2.12 Prognosis

Regarding prognosis of patients with hungry bone syndrome, there is great variability in the time duration that the syndrome can last. In some case reports, the need for replacement of calcium and active vitamin D can last for up to 1 year post-operatively [43, 51, 63, 64].

11.3 Proposed Mechanisms in Graves' Disease

Patients with Graves' disease have much higher rates of symptomatic hypocalcemia after total thyroidectomy (TT) than patients undergoing TT for other diagnoses [70–76]. Factors contributing to this increased rate of hypocalcemia after surgery include (1) *increased bone hunger* secondary to *thyrotoxic osteodystrophy*, (2) increased release of calcitonin during gland manipulation during surgery, and (3) the increased inflammation and friability of the gland making the procedure technically more demanding and therefore placing the parathyroid glands (PTGs) at increased risk for injury [70, 74, 77].

As total thyroidectomy (TT) is the operation of choice for the surgical management of Graves' disease, it is critical that the risk of developing symptomatic hypocalcemia is minimized [72, 76, 78, 79]. Some authors have proposed the use of calcium pre-operatively for Graves' patients; however, none have reported on how this practice influences patient outcome [74]. Given the multifactorial etiology of hypocalcemia after TT for Graves' disease, pre-operative calcium supplementation allows for replenishment of whole-body calcium stores, which may be depleted secondary to the increased bone metabolism as a result of thyrotoxic osteodystrophy. With this contributing factor addressed in the pre-operative period through calcium supplementation, Graves' patients undergoing TT are found to experience rates of symptomatic hypocalcemia equivalent to patients undergoing TT for other disease processes. The observed equivalence of PTH levels between the study cohorts further supports the non-parathyroid mediated causes for increased hypocalcemia rates historically described in Graves' patients undergoing total thyroidectomy [70, 74, 75].

As previously mentioned, patients with Graves' disease have multiple proposed mechanisms which contribute to decreased serum calcium after TT separate from parathyroid function. Thyroid hormone has a direct effect on osteoclasts, which stimulates bone turnover. This, in turn, can lead to increased serum alkaline phosphatase, serum osteocalcin, urinary calcium, and urinary deoxy-pyridinoline [74, 77]. This *continued bone destruction* and subsequent loss of calcium via the urine results in depletion of whole-body stores of calcium. Previous authors have also demonstrated concomitant vitamin D deficiency to place patients at increased risk for symptomatic hypocalcemia or tetany after TT for Graves' disease, but this was not necessarily a deficiency caused by the Graves' disease [80]. Given the influence *vitamin D* has on the absorption of calcium, underlying deficiency would understandably result in exacerbation of hypocalcemia, as well as make calcium replacement more difficult without also addressing the vitamin D deficiency.

It has also been postulated that during manipulation of the gland at time of surgery, *calcitonin* is released in an abnormal fashion [78]. While measurements of alkaline phosphatase, osteocalcin, calcitonin, or urinary measures of calcium and deoxy-pyridinoline were not measured in the scope of this study, the similar post-operative PTH levels favor these alternative explanations.

Lastly, additional cause of transient hypocalcemia after thyroidectomy is transient ischemia due to *hypothermia*, or *excessive release of endothelia-1*. Hypothermia of the PTGs, which results from intra-operative irrigation of the wound, can cause transient ischemia. Endothelia-1, the vaso-constricting peptide, is present in high concentrations in both the parathyroid and thyroid glands. Intra-operative manipulation of the thyroid or parathyroid gland can induce release of endothelia-1 and cause transient ischemia of the remaining parathyroid tissue and subsequent hypocalcemia [81].

11.4 Summary

Hungry bone syndrome (HBS) is a relatively uncommon but serious complication of parathyroidectomy for HPT associated with high bone turnover. The hallmark of HBS is profound and persistent hypocalcemia that persists beyond 4 days post-operatively. It presents with hypomagnesemia, hypophosphatemia, and normal PTH level. Symptomatic patients or those with profound hypocalcemia less than 7.6 mg/dL will need emergent intravenous (IV) calcium treatment.

There are no clear guidelines for the management of the HBS, but treatment is aimed at replenishing the severe calcium deficit and at restoring normal bone turnover with the use of high doses of calcium and active metabolites or analogues of vitamin D. Adequate correction of magnesium deficiency and normalization of bone turnover are required for resolution of the hypocalcemia, which may last for several months (up to 1 year in some reported cases) after successful surgery. Adequate pre-operative treatment with bisphosphonates may reduce the severity and duration of post-operative hypocalcemia. However, data are lacking to elucidate the long-term effects on bone mineral density if utilized in this patient population.

In patients with PHPT and vitamin D deficiency, vitamin D supplementation merits consideration. Thus far, it appears that vitamin D supplementation will help to improve bone mineral density, bone resorption markers, and reduce PTH levels before parathyroidectomy without causing adverse effects. Further prospective studies are needed to optimize pre- and post-operative treatment strategies in patients with HPT and skeletal manifestations at high risk for HBS.

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Post-thyroidectomy Hypocalcemia: Incidence and Risk Factors

12

12.1 Introduction

Post-thyroidectomy hypocalcemia is a common complication with significant short- and long-term morbidity. Parathyroid secretory reserve is abundant; thus, significant injury must occur before post-surgical hypocalcemia develops. It is estimated that one normal gland is adequate for the preservation of calcium homeostasis. Still however, hypocalcemia is a common complication following thyroidectomy. The incidence of post-operative hypocalcemia varies widely in the literature, and the factors associated with hypocalcemia, after thyroid surgery, are still not well established [1].

Hypocalcemia, secondary to hypoparathyroidism, may present clinically with muscle cramps, perioral and peripheral paresthesias, carpo-pedal spasm, and/or confusion. Rarely, patients present with more severe symptoms, such as seizures (tetany), laryngospasm, bronchospasm, or cardiac rhythm abnormalities. The symptoms can be presented acutely after surgery or can occur later; if symptoms remain 6 months after surgery, the post-operative hypocalcemia is considered as permanent.

Symptomatic patients often require extended hospitalizations and the need for biochemical tests following thyroid surgery, leading to increased healthcare costs [1]. Depending on the extent of damage of parathyroid glands (PTGs), hypocalcemia may be *transient*, resolving within a few months, or *permanent*, requiring lifelong oral calcium and vitamin D supplementation.

Particularly with ambulatory thyroid surgery, which allows for early discharge of patients, post-operative hypocalcemia is an important consideration. In fact, some surgeons advocate indiscriminate post-operative calcium supplementation for patients undergoing total thyroidectomy, though this approach has been contested [2]. The interest in outpatient and short-stay thyroid surgery makes it especially helpful for surgeons to be able to identify patients at risk of developing hypocalcemia [3, 4]. Therefore, accurate and standardized outcomes data following thyroidectomy are essential [5, 6].

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12.2 General Incidence

Transient hypocalcemia is one of the most common postoperative complications following thyroid surgery in clinical practice [7, 8]. Unfortunately, although hypocalcemia is well documented in the thyroid surgery literature, there are significant limitations to the results of previous studies. Perhaps most noteworthy, the reported hypocalcemia incidence rates range widely; studies report that anywhere from 0.3% to 66.2% of patients develop hypocalcemia after thyroid surgery. However, others reported that the incidence of post-thyroidectomy hypocalcemia ranges from 3.1% to 100% depending on the definition used [9, 10]. The frequency of *transient* hypocalcemia after thyroid surgery has been reported to vary between 6.9% and 49% and that of *permanent* hypocalcemia between 0.4% and 33% [1, 11–16].

In a large study by Baldassarre et al. (2012) [16], a total of 119,567 thyroidectomy patients were identified in the Nationwide In-patient Sample (NIS) database from 1998 to 2008 (Healthcare Cost and Utilization Project [HCUP]). Post-operative hypocalcemia occurred in 5.5% (n = 6605) of all thyroidectomy patients before discharge. Roughly half (49.3%) the patients were diagnosed with a neoplasm of the thyroid gland, classified as either malignant (61.6%) or benign (38.4%). In 2014, Edafe et al. reported that the incidence of post-thyroidectomy hypocalcemia in their study of 238 patients who underwent total or completion thyroidectomy was 29.0%; a rate which is comparable with the 24.9% rates reported by The British Association of Endocrine and Thyroid Surgeons (BAETS). However, the rate of long-term post-thyroidectomy hypocalcemia (5.5%) in their study was lower than that reported by BAETS (12.1%) [17].

In 2017, Wang et al. [18] reported an incidence of post-thyroidectomy hypocalcemia of 27.3% (76/278). They identified eight significant risk factors, namely, age (p = 0.049), gender (p = 0.015), lateral lymph node (LN) dissection (p = 0.017), operation type ($p < 0.001$), pre-operative PTH level (p = 0.035), operation time (p = 0.001), parathyroid auto-transplantation (p = 0.002), and applying carbon nanoparticle suspension (CNs) (p = 0.007). However, pathology, central lymph node dissection, parathyroid inadvertent dissection, number of identified parathyroid glands, and preoperative serum calcium levels were not significantly correlated with the presence of postoperative hypocalcemia ($p > 0.05$) in their series. Moreover, multivariate analyses showed that age ($p = 0.038$), lateral LN dissection ($p = 0.050$), operation type ($p < 0.001$), and applying CNs ($p = 0.036$) were independent predictors for post-thyroidectomy hypocalcemia.

Part of the variation in incidence of post-thyroidectomy hypocalcemia is likely related to the fact that reports differ in the thyroid *surgery procedure* assessed. Some studies, for example, include patients who underwent not only total thyroidectomy (TT), but also less extensive procedures with relatively low risk of hypocalcemia, such as thyroid lobectomy [19]. Such reporting can underestimate the incidence of hypocalcemia and may lead to misinterpretation.

Much of the variability among results may also be attributed to the numerous clinical *definitions of hypocalcemia* used at different institutions. For instance, some authors consider hypocalcemia to be the clinical presentation of symptoms, whereas

others document hypocalcemia on the basis of serum thresholds alone [20, 21]. The British Association of Endocrine and Thyroid Surgeons (BAETS) registry defines post-thyroidectomy hypocalcemia as corrected calcium less than 2.10 mmol/L on first post-operative day (reference range 2.20–2.60 mmol/L) [17]. Permanent hypocalcemia is defined as the need for calcium and/or vitamin D supplements to maintain normo-calcemia at 6 months or more after the date of surgery [17]. The authors of one recent study (2010) [22] showed that their thyroidectomy patient cohort had a post-operative hypocalcemia rate ranging from 0% to 46%, depending on 10 different definitions of hypocalcemia adopted by previous studies. The discrepancies that result from these definitions clearly hinder the clinical relevance of thyroidectomy outcome studies.

12.3 Risk Factors/Predictors of Post-thyroidectomy Hypocalcemia

Post-operative hypoparathyroidism remains a clinical challenge for thyroid surgeons because of its frequency and the limited number of established preoperative predictors. Without reliable parameters, the relative risk of thyroidectomy cannot be properly assessed for informed consent, and outcomes research lacks a standard benchmark for comparison. Numerous small studies have attempted to identify predictors of post-operative hypocalcemia [23, 24], but if the results of such studies are to influence the surgical management of patients at other institutions, a standard definition of hypocalcemia is essential. Alternatively, a population-based study of hypocalcemia can address the limitations of series reports.

The incidence of hypocalcemia may be affected by a number of risk factors. More *extensive thyroidectomy procedures*, for instance, result in a greater incidence of hypocalcemia, though the exact mechanism behind the association is unclear [23]. Other potentially predictive variables of post-operative hypocalcemia, such as *iatrogenic parathyroidectomy*, were *not* demonstrated to have an effect on patient outcomes [25]. Some experts posit that a surgeon's skill and experience affect the occurrence of post-thyroidectomy hypocalcemia [3, 26]. However, one study reported that patients operated on by surgical trainees had complications that were comparable to patients operated on by consultant surgeons [24].

In general, the mechanism of hypocalcemia after thyroidectomy is *not* precisely disclosed, although is accepted to be *multifactorial*; factors like surgical technique, parathyroid iatrogenic removal or damage (injury, edema, infarction, ischemia), extent of thyroidectomy, hyperthyroidism, malignancy, patient gender, perioperative serum calcium drop, presence of thyroiditis, diabetes mellitus (DM), number of identified parathyroid glands (PTGs) during surgery can be considered as etiological factors [27–29]. Most studies underline the significance of expertise and surgeon's experience. Additional mechanisms, such as vitamin D deficiency, an acute increase in calcitonin serum levels (because of gland handling during surgery), or a "hungry bone syndrome" (HBS) are believed to contribute to this process [3, 30–33]. Etiological considerations include post-operative alkalosis-induced

hypocalcemia resulting from hyperventilation triggered by post-operative pain, and dilution hypocalcemia [34].

Given that most studies exploring parameters associated with complications after thyroid surgery have small sample sizes and include limited procedures, risk factors are still largely debatable. A few studies [35–39] have conducted population-based analyses of thyroidectomy outcomes.

12.3.1 Pre-operative Serum Level of Calcium

Several studies identified low pre-operative level of serum calcium as a risk factor for the development of transient hypocalcemia [12, 39–43]. Some studies have shown that patients who received vitamin D and calcium suffered less from hypocalcemia [44, 45].

In the recent study by Del Rio et al. (2019) [46] no difference was identified between mean pre-operative serum calcium level in the post-thyroidectomy hypocalcemia group and in the normo-calcemic group. There was, however, a significant difference in serum calcium level drop; mean *peri-operative variation in serum calcium levels* (difference between pre-operative level and 24-h post-operative level) being significantly higher in patients who developed early post-operative hypocalcemia ($p < 0.001$). These findings clearly show that although pre-operative level of serum calcium may not have an influence on development of post-thyroidectomy hypocalcemia, yet, peri-operative level variation plays a decisive role in this process. This mechanism is confirmed by other studies in which a larger decrease in post-operative calcium from pre-operative levels was associated with transient hypocalcemia [40, 42, 47–49].

12.3.2 Pre-operative Serum Level Vitamin D

Vitamin D level may be an important pre-operative risk factor in predicting post-operative hypocalcemia. Recently, Danan and Shonka (2017) [50] demonstrated that vitamin D level is a significant predictor of post-operative hypocalcemia in patients in whom ≥3 PTGs were identified. Moreover, the severity of hypocalcemia seems to be remarkably higher in those with lower than normal pre-operative vitamin D levels [51, 52]. On the other hand, some authors found that vitamin D does *not* play a significant role in the occurrence of post-operative hypocalcemia [53, 54].

12.3.3 Parathyroid Hormone (PTH) Level

Serum iPTH levels taken *before*, *during*, and *after* thyroidectomy have been evaluated in different studies as a predictive factor and reliable marker for the development of mild to severe post-surgical hypocalcemia and post-surgical hypoparathyroidism [55, 56]. In addition, a low level of *intra-operative* PTH (at any

time after the resection of the thyroid gland to 10 min after the skin's closure) was related with *transient* hypocalcemia [42, 57–59].

The decrease of the *post-operative* iPTH value compared with the pre-operative value has been proven as a predicting factor of transient and permanent hypocalcemia [40]. In a recent retrospective study by AbdelHamid and Moussa (2020) [41], low post-operative PTH levels were a significant risk factor for developing post-thyroidectomy hypocalcemia on univariate analysis ($p = 0.021$). It had mean values of 35.9 and 14.23 pg/mL in the normocalcemic and hypocalcemic groups, respectively. Likewise, Islam et al. (2014) [60] have reported that post-operative PTH levels can be used as a reliable predictor of post-operative hypocalcemia. Approximately 60% of cases whose PTH level was less than 23 ng/L developed early post-operative hypocalcemia.

Different values of iPTH defined as threshold taken at different latency times, which can be as early as 5 min after thyroidectomy (intra-operative iPTH), in the first post-surgical hour (peri-operative iPTH) or at 24 h post-surgical (post-operative iPTH), have been reported. Regarding levels of intra-operative iPTH, values less than 9.5 pg/mL—less than 18 pg/mL have predicted hypocalcemia post-operatively, but the most accepted threshold is <10 pg/mL with a sensitivity of 72–97.5%, specificity of 80–99%, positive predictive value (PPV) of 53–90%, and a negative predictive value (NPV) of 80–99% [42].

Conversely, Del Rio et al. (2005) [61] reported no significant correlation between post-operative PTH levels and the development of post-operative hypocalcemia. Moreover, in a meta-analysis including 115 observational studies, the iPTH taken before surgery had no predictive value by itself in the multivariate analysis [40].

12.3.4 Post-operative Level of Serum Phosphorus (P) and Magnesium (Mg)

Parathyroid hormone (PTH) helps regulate the body's level of calcium (Ca) and phosphorus (P). It stimulates bone to slowly release Ca and P into blood. PTH stimulates the kidneys to increase re-absorption of Ca, while simultaneously signaling the kidneys to excrete P. This process balances Ca and P levels in the blood by creation of an inverse relationship [62–65]. Temporary hypo-parathyroidism also leads to a reduction in renal reabsorption of magnesium (Mg) and expansion of the extracellular volume increases Mg excretion [66].

Homeostasis of magnesium (Mg) ions is directly related to Ca levels. An abrupt fall in Ca concentration leads to increase of the production and release of PTH and exacerbates the secondary clinical manifestations, because of hypocalcemia. Phosphorus concentration is inversely related to calcium and is regulated by Ca, PTH, and vitamin D [67].

Recently (2016), Sakr et al. [68] reported that serum Mg level in hypo-calcemic patients at 24 h post-operative seems to have a significant role in predicting the development of *permanent* hypocalcemia. In other words, patients with combined low Ca and Mg levels 24 h post-operatively are likely to have permanent

hypocalcemia, and serum calcium level tends to return to normal levels before 6 months post-operatively in hypo-calcemic patients with normal 24 h Mg level. Several authors reported that low post-operative Mg [49, 65] and high post-operative phosphate [58, 69] levels are factors associated with higher rates of post-thyroidectomy hypocalcemia.

12.3.5 Gender

According to literature, women seemed to be more prone to develop post-thyroidectomy hypocalcemia than men [12, 16, 18, 27, 37, 40, 70, 71]. Female gender was reported to be an *independent* predictor of post-operative hypocalcemia [16]. Recently, Del Rio et al. (2019) [46] reported that female patients experienced post-thyroidectomy hypocalcemia in 42% (701/1669) of cases, which was significantly more than the 21.4% (94/439) incidence detected in men ($p < 0.001$). There was *no* significant difference in rates of post-thyroidectomy hypocalcemia between pre-menopausal women and post-menopausal women, as confirmed by other studies [33].

Many studies tried to find an explanation to the female predisposition to post-thyroidectomy hypocalcemia, but the specific mechanisms underlying this gender difference can only be assumed. The association between post-operative hypocalcemia and female gender may be due to women being more prone to calcium and vitamin D deficiency than men. This gender disparity may be also related to effects of sex steroids on PTH secretion, genetic variation among cell-signaling pathways, or anatomical differences that can cause more frequent iatrogenic damages because of a more diminutive operative field [33]. In addition, it has been reported that intra-thyroidal PTGs were more frequent in women resulting in higher rates of parathyroid injury and hypocalcemia [33].

On the other hand, several other studies showed that gender has *no* significant effect on the incidence of post-thyroidectomy hypocalcemia [72–75].

12.3.6 Age

There are conflicting data in the literature about the effect of age in the development of post-operative hypocalcemia [28, 76, 77]. A systematic review performed by Edafe et al. (2014) observed no significant difference in mean age between patients who had transient hypocalcemia and those who did not [27]. Del Rio et al. [46] also reported no significant intergroup difference with regard to patient age. They even divided patients in four age groups, but no significant differences were noticed between groups.

On the other hand, some studies found transient hypocalcemia to be associated with advanced age, whereas others reported an association with younger age. Baldassarre et al. (2012) [16] reported that although patients between the ages of 30 years and 44 years had similar rates of hypocalcemia when compared with

younger patients, individuals aged 45 years to 84 years had significantly lower likelihoods of developing hypocalcemia. Older age seemed to have a protective effect against post-thyroidectomy hypocalcemia. Each 1-year increase in age was associated with a 1.0% decreased risk of post-operative hypocalcemia [16]. However, patients 85 years or older had an incidence of post-operative hypocalcemia that was statistically indistinguishable from that of the youngest group of patients [16].

Although the inverse association between hypocalcemia and advancing age has also been reported by other authors [28, 71], yet there is some conflict found in the literature. A previous study showed that patients 65 years and older, after adjusting for other risk factors, experienced similar rates of hypocalcemia and recurrent laryngeal nerve (RLN) injury compared with younger patients [77]. In fact, older patients in the study had higher rates of total complications, consistent with a recent series [52]. It was previously demonstrated that younger patients may be more likely to undergo bilateral surgery for malignancy, which would expectedly result in an association between young age and hypocalcemia [76]. However, the data reported by Baldassarre et al. [16] revealed an increased risk of hypocalcemia among younger patients irrespective of malignancy.

12.3.7 Ethnicity

Baldassarre et al. [16] reported, albeit without explanation, that when compared with white patients, Hispanic and Asian or Pacific Islander patients were more likely and black patients were less likely ($p = 0.003$) to develop post-thyroidectomy hypocalcemia. The effect of ethnicity on post-operative hypocalcemia has not been demonstrated elsewhere in the literature.

12.3.8 Operative Procedure (Extent of Surgery)

Injury of the parathyroid glands (PTGs) and/or damage of their blood supply during thyroidectomy, incidental parathyroidectomy, and failed auto-transplantation are independent risk factors for the development of post-thyroidectomy hypocalcemia [72]. Dissection carried around the PTGs and efforts to isolate the recurrent laryngeal nerve (RLN) in this region can lead to venous congestion and edema. In addition, ligating of thyroid veins is among the causes of venous stasis. Venous stasis and edema slow down parathyroid function and may cause a temporary hypoparathyroidism [29].

The surgical technique and the extent of thyroidectomy are related to parathyroid injury, edema, infarction, ischemia, or incidental parathyroidectomy. The extent of thyroidectomy has a significant impact on the occurrence of post-operative hypocalcemia [12, 18, 27, 28, 73, 78, 79]. Several studies reported that hypocalcemia is encountered significantly more often after *total thyroidectomy* (TT) than after unilateral thyroid lobectomy [3, 46, 70]. In 2012, Baldassarre et al. [16] reported that patients undergoing TT had a post-operative hypocalcemia incidence

of 9.0%, compared with only 1.9% following unilateral thyroid lobectomy. One international study [37] and another reporting on outcomes throughout Maryland, USA [38], similarly reported that approximately one-tenth of TT patients (10%) resulted in hypocalcemia. Similarly, Nawrot et al. [80] have demonstrated that hypoparathyroidism was more frequently seen after TT (20.2%) than near-TT (6.7%) or subtotal thyroidectomy (4.1%). Increased thyroid specimen weight is another predictor of transient hypocalcemia [81, 82]. Moreover, the rate of hypocalcemia after a *re-operation* has been reported to be higher than the rate after the first surgery [83, 84]. However, González-Botas and Piedrahita [85] as well as Merchavy et al. [86] have reported that post-operative hypocalcemia was less common in patients with completion thyroidectomy than in patients who underwent total thyroidectomy.

Patients treated by thyroidectomy with *concomitant neck dissection* were more likely to develop hypocalcemia than patients who underwent TT alone [16, 45]. Baldassarre et al. (2012) reported an incidence of post-operative hypocalcemia in 14.4% of patients following thyroidectomy plus unilateral neck dissection, 23.4% following thyroidectomy plus bilateral neck dissection, 9.6% following complete substernal thyroidectomy, 3.4% following partial substernal thyroidectomy, and 3.4% following isthmectomy [16]. They reported that the type of operative procedure was independently associated with hypocalcemia. Of all risk factors, thyroidectomy plus bilateral neck dissection was most likely to result in post-operative hypocalcemia [16].

Shen et al. (2010) [87] have demonstrated that the incidence of hypoparathyroidism was statistically significant between patients who underwent thyroidectomy with or without neck lymph node dissection. Similarly, we found that patients with lateral lymph node dissected showed a higher incidence of hypocalcemia and hypoparathyroidism than those without receiving lateral lymph node dissection ($p = 0.017$; $p = 0.038$). Actually, parathyroid blood vessels are thin, fragile, and terminal; parathyroid blood supply is easily affected or disrupted, which may result in the high occurrence of hypocalcemia after lateral lymph node dissection [88].

12.3.9 Carbon Nanoparticle Suspension (CNs) Injection

Injection of CNs is applied for helping identify LNs during LN dissection, including breast cancer and gastrointestinal cancer [89–91]. The CNs comprises nano-sized carbon particles with an average diameter of 150 nm. The cell gap between capillary endothelial cells is 20–50 nm, and the capillary lymphatic endothelial cell gap is 120–500 nm with a hypoplasia of the basement membrane. Therefore, CNs is unable to enter the blood vessels when it is injected into the thyroid tissue, and it will rapidly enter lymphatic vessels or the lymphatic capillaries through macrophage phagocytosis and be retained in the lymph nodes. The thyroid and

lymph in their drainage areas are stained black in surgery [92]. However, the PTGs do *not* stain black, and hence, the black-stained thyroid and lymph nodes can be identified and are distinguished clearly. Wang et al. (2017) [18] administered one injection of 0.1 mL CNs with a fine needle in the lower one-third of the ventral surface of each thyroid lobe, and the injection depth was roughly within the upper third of the glands. The suspension does not enter the blood circulation and has no toxic side effects on the human body [92]. They reported that applying CNs was an independent predictor of post-thyroidectomy hypocalcemia. Furthermore, recent studies have shown that CNs injection can aid in identifying the PTGs, which may provide a new strategy for identification and protection during parathyroid surgery [93–96].

12.3.10 Identification of All Parathyroid Glands

The importance of identification of all four PTGs during thyroid surgery is one of the most controversial factors debated in the literature. Some authors recommend routine physical identification and preservation of as many of PTGs as possible [97]. Other series questioned this strategy [27, 98–101]. Del Rio et al. [46] reported in 2019, that among their patients they noticed an increasing rate of post-thyroidectomy hypocalcemia when a higher number of PTG have been identified during surgery, but statistical analysis did not show significant results ($p = 0.63$). To avoid potential injury of the PTGs, every surgeon must be thoroughly aware of their anatomical complexity that contributes to the difficulty of their identification and possible injury. Strict adherence to capsular dissection seems to be the optimum method for safe preservation of the PTGs without necessitating their systemic identification. Distal ligation of all terminal branches of the superior and inferior thyroid arteries, close to the thyroid capsule, enables reliable separation of all tissues carrying PTG away from the thyroid surface. Continued dissection in this tissue, with the aim to identify all PTGs, may increase the risk of their mechanical injury or devascularization.

12.3.11 Parathyroid Auto-transplantation

Selective *auto-transplantation* of one or more PTGs was related with transient hypocalcemia independently of the extent of thyroidectomy and neck dissection [7, 42, 81, 102–104]. Wang et al. (2017) [18] reported that parathyroid auto-transplantation is a risk factor for developing post-operative hypoparathyroidism. Many studies have demonstrated that parathyroid auto-transplantation plays an important role in avoiding permanent hypoparathyroidism and should be a routine surgery [1]. After auto-transplantation, the grafted parathyroid requires time to regain its function [105].

12.3.12 Thyroid Cancer

A higher incidence of post-operative hypocalcemia among thyroid cancer patients has been reported by several studies [16, 29, 38, 41, 76, 106–109]. Some authors believe that malignancy tends to be treated with a more aggressive approach to thyroid surgery, thereby leading to incidental parathyroidectomy and hypocalcemia [52]. Indeed, neck dissection, which is indicated for thyroid cancer patients with lymph node (LN) metastases, was the strongest risk factor for post-operative hypocalcemia in the study of Baldassarre et al. [16]. Nonetheless, malignancy emerged as an *independent predictor* of post-operative hypocalcemia.

The altered anatomy of patients with thyroid cancer could increase the likelihood of accidental parathyroid tissue removal or jeopardy of its blood supply during surgery. In total thyroidectomy for carcinoma, the posterior capsule is usually removed with the thyroid gland hence the parathyroid glands are at a high risk of injury, which results in higher rates of post-operative hypocalcemia [109].

However, in the recent study by Del Rio et al. (2019) [46], post-thyroidectomy hypocalcemia developed in 36.5% of patients with pre-operative malignant or suspected malignant (Thyr 3, Thyr 4, Thyr 5) diagnosis, and in 38.5% of patients that underwent surgery for benign pathology. Surgery for malignant pathology, as has been described also in other studies [15], was not found as a significant factor for the development of post-thyroidectomy hypocalcemia.

12.3.13 Graves' Disease/Hyperthyroidism

Grave's disease is related to transient hypocalcemia and the presence of hyperthyroidism is a well-established *independent* risk factor for the development of post-operative hypocalcemia [29, 32, 41]. Increased bone turnover and challenging operations owing to increased vascularity of thyroid gland could be possible explanations [110–112]. In the study by Del Rio et al. (2019) [46], thyroid hyperfunction did *not* appear to be a significant factor in the development of post-thyroidectomy hypocalcemia as reported also by other studies in literature [8, 113].

12.3.14 Hungry Bone Syndrome (HBS)

The "hungry bone syndrome" (HBS) is another cause of post-operative hypocalcemia and can be seen after successful parathyroidectomy in patients with severe hyper-parathyroid bone disease pre-operatively or in cases of severe hyperthyroidism. Low serum calcium levels result from re-mineralization of the bone when the stimulus for high bone turnover (e.g., high PTH or thyroid hormone levels) is removed.

Independent risk factors for the development of HBS are high pre-operative alkaline phosphatase level, blood urea nitrogen (BUN), age, and parathyroid adenoma size [114]. It can typically be distinguished from post-surgical hypoparathyroidism by the serum phosphorus, which is low in the hungry bone syndrome, because of skeletal avidity for phosphate and high in post-surgical hypoparathyroidism, as well as the serum PTH, which becomes appropriately elevated in the hungry bone syndrome.

12.3.15 Diabetes Mellitus (DM)

A few articles in literature investigated the effect diabetes mellitus (DM) has on hypocalcemia following thyroidectomy. Some authors prospectively explored factors affecting recovery of parathyroid function after thyroidectomy and found DM to be a statistically significant factor [111, 113]. The mechanism by which diabetes can cause this effect is unclear; however, it is hypothesized that the small vessel disease and the impact on angiogenesis may leave the parathyroid glands more vulnerable to hypoxia in these patients. This hypothesis is *not* confirmed by Del Rio et al. [46], no significant difference ($p = 0.399$) was found between diabetic and non-diabetic patients regarding development of post-thyroidectomy hypocalcemia.

12.3.16 Type of Hospital/Surgeon's Experience

Post-operative hypocalcemia was reported to more likely occur at *non-teaching* hospitals ($p = 0.008$) and by low-volume surgeons [16, 38]. The presence of the PTG in the histopathological specimen (unintended removal of the PTG) and the surgeon's experience were recognized as important risk factors for permanent post-thyroidectomy hypocalcemia [105, 115].

12.3.17 Summary of Risk Factors According to Definition of Hypocalcemia

Predictors of in-patient post-operative hypocalcemia after thyroidectomy among multicenter patient cohorts are summarized in Table 12.1.

12.3.18 Summary of Risk Factors Reported in the Literature

The main factors that are related to post-thyroidectomy hypocalcemia, according to different studies, are summarized in Table 12.2.

Table 12.1 Risk factors of post-thyroidectomy hypocalcemia according to definition

Authors (years of study)	*N*	Hypocalcemia incidence—%	Definition	Independent risk factors
Rosato et al. [35] (1995–2000)	14,934	14.0	Symptomatic	– Thyroid cancer
Hundahl et al. [36] (1996)	5354	12.4	Study protocol	– Na
Bergenfelz et al. [37] (2004–2006)	3660	9.9	Required vitamin D at 1–6 w after surgery	– Female gender – ND – Previous thyroidectomy – Resected PTGs – Low pre-operative serum Ca
Gourin et al. [38] (1990–2009)	21,270	10.0	ICD-9	– Thyroid cancer – TT, ND – Low-volume surgeons
Baldassarri et al. [16] (1998–2008)	119,567	9.0	ICD-9	– Female gender – Younger age – Ethnicity – Extent of surgery – Thyroid cancer – Non-teaching hospital
Edafe et al. [40] (2008–2011)	238	29.0	BAETS [17]	– Low pre-operative Ca – PTG transplantation
Wang et al. [18] (2012–2014)	278	27.3	ATA [116]	– Age
			Serum Ca <2.0 mmol/L (first 48 h post-surgery)	– Gender – Lateral LN dissection – Operation type – Preoperative PTH level – Operation time – PTG autotransplantation – Applying CNs
Del Rio et al. [46] (2004–2016)	2101	37.7	Serum Ca < 8 mg/dL (first post-operative day)	– Female gender – Extent of surgery – Peri-operative change in serum Ca
AbdelHamid and Moussa [41] (2017–2019)	200	18.0%	Serum Ca < 8 mg/dL (first post-operative day)	– Thyroid cancer – Toxic goiter – Extent of surgery – Low pre-operative serum Ca

ND neck dissection, *PTG* parathyroid gland, *NA* not available, *ICD-9* International Classification of Diseases, *BAETS* British Association of Endocrine and Thyroid Surgeons, *ATA* American Thyroid Association, *CNs* Carbon nanoparticle suspension

Table 12.2 Factors associated with post-thyroidectomy hypocalcemia

Risk factors	References
Patient-related factors	
– Female gender	[12, 16, 18, 27, 33, 37, 40, 52, 70, 71, 82, 116, 117]
– Older age	[51, 52, 56, 118]
– Ethnicity	[16]
Clinical and surgical factors	
– Graves' disease	[29, 32, 41, 42, 70, 116, 119–122]
– Malignancy	[16, 29, 38, 41, 42, 76, 106–109, 123, 124]
– Larger goiter	[61, 82]
– Long operative time	[42, 81, 82]
– Few identified PTGs	[103]
– PTG auto-transplantation	[7, 18, 42, 81, 102–105]
– Injection of CNs	[18, 92]
– Surgeon's experience	[16, 38, 105, 115]
– Diabetes mellitus	[111, 113]
Biochemical factors	
– Lower pre-operative Ca	[1, 12, 39–43, 82, 103, 125–127]
– Lower post-operative Ca	[42, 58, 123, 126–141]
– Larger drop in post-operative Ca	[42, 61, 123, 128, 129, 131–133, 137–154]
– Higher pre-operative PTH	[127, 155, 156]
– Lower intra-operative PTH	[41, 42, 56–59, 119, 123, 134, 136, 137, 140–144]
– Larger drop in post-operative PTH	[57, 58, 123, 127, 141, 143, 145, 149, 156–158]
– Low peri-operative calcium and PTH	[42, 58, 137, 159, 160]
– Low pre-operative vitamin D	[11, 50–52, 129, 161]
– Low post-operative mg	[49, 65, 156]
– High post-operative phosphate level	[58, 69, 148]
– High pre-operative alkaline phosphatase	[51, 52, 82, 162]

PTGs parathyroid glands, *CNs* carbon nanoparticle suspension, *Ca* Calcium, *PTH* parathyroid hormone, *Mg* Magnesium

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Post-thyroidectomy Hypocalcemia: Clinical Presentation

13

13.1 Symptoms of Hypocalcemia

Patients with post-surgical hypocalcemia usually present with paresthesia, cramps, or tetany, but the disorder may also manifest acutely with seizures, bronchospasm, laryngospasm, or cardiac rhythm disturbances [1].

Tetany, a state of spontaneous tonic muscular contraction, is the typical clinical sign of severe hypocalcemia. Tingling paresthesia in the fingers and around the mouth indicate *overt tetany*; carpo-pedal spasm is the classic muscular component of tetany.

The typical "*main d'accoucheur*" posture is characterized by thumb adduction, flexion of metacarpo-phalangeal joints, extension of inter-phalangeal joints, and flexion of wrists. In pedal spasm, there is big toe extension and flexion of metatarso-phalangeal joints of the lateral four toes. These automatic muscle contractions are painful. All muscles can participate in tetany, but the most dangerous is the spasm of laryngeal muscles.

Symptoms of hypocalcemia are summarized in Table 13.1. They include muscular, dermatological, neuro-psychological manifestations.

Table 13.1 Symptoms of hypocalcemia

Structures involved	Symptoms
Muscular	– Muscle twitches
	– Muscle aches or cramps
Dermatological	– Hair loss
	– Dry skin
	– Brittle nails
Neuro-psychological	– Anxiety
	– Depression
	– Headache
	– Memory loss
	– Weakness and fatigue
	– Tingling in the lips, fingers or toes

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13.2 Signs of Hypocalcemia

Signs of hypocalcemia are summarized in Table 13.2. Focal or generalized seizures can be seen in patients with hypocalcemia. Other clinical presentations are pseudo-tumor cerebri, papilledema, confusion, lassitude, and organic brain syndrome. Basal ganglia are often calcified in patients with long-lasting hypocalcemia and this can be related to movement disorders.

Other manifestations of hypocalcemia include cardiac effects (delayed repolarization, prolongation of QT, refractory congestive heart failure), ophthalmological effects (cataract), and dermatological effects (dry skin and brittle nails).

13.3 Recovery from Hypocalcemia

In most cases, parathyroid dysfunction after thyroidectomy resolves within a few weeks or 1 month after surgery [2]. Post-operative hypoparathyroidism is considered *permanent* if parathyroid gland function has not recovered within 6 months after surgery [1, 3, 4]. *Transient* post-operative hypoparathyroidism after neck surgery is rather usual, often termed "*stunning*" of the glands; "chronic partial post-operative hypoparathyroidism" is less common, whereas "chronic complete post-operative hypoparathyroidism" is rare.

Table 13.2 Signs of hypocalcemia (post-surgical)

Structures involved	Physical signs
Neuro-muscular	– Paresthesia (mouth and extremities)
	– Muscle spasms
	– Seizures
	– ***Chvostek*** sign
	– Trousseau sign—Main d'accoucheur
	– Tetany (clinical or latent)
	– Laryngeal spasm (stridor)
	– Bronchospasm
	– Coma
	– Pseudo-tumor cerebri
	– Papilledema
Cardiovascular	– Arrhythmia
	– Hypotension
	– Refractory congestive heart failure (CHF)
Ophthalmological	– Cataract
	– Papilledema
Dermatological	– Dry skin (xeroderma)
	– Brittle nails
	– Hair loss
	– Surgical skin scar

Recovery of PTG function is considered when PTH levels are above 10 pg/mL and the patients did not require daily calcitriol and calcium supplementation to avoid symptoms of hypocalcemia [5]. Post-operative calcium values <8 mg/dL are considered as "*biochemical hypocalcaemia,*" while the patients presenting paresthesia in the extremities and around the mouth, with positive Chvostek's and Trousseau's signs, are considered as "*symptomatic hypocalcaemia*" [6]. In another study, post-operative hypocalcemia was defined as a documented post-surgical serum calcium level of <7.6 mg/dL, with or without symptoms, or post-operative serum calcium level of 4.0–8.4 mg/dL with neuro-muscular symptoms 2 days after surgery. The study showed that a PTH level of ≤15 pg/mL or post-operative serum calcium of ≤7.6 mg/dL on the day after surgery was related to increased risk of post-operative hypocalcemia [7].

Most patients with parathyroid dysfunction after thyroidectomy return to normal function within a few weeks or 1 month after surgery (total thyroidectomy) [2, 8]. When PTH levels recover to at least 10 pg/mL and hypocalcemic symptoms are absent, the patient is considered euparathyroid [9]. According to additional reports, recovery is considered when the patient does not require any more therapeutic calcium or calcitriol supplementation to avoid symptoms of hypocalcemia [10, 11].

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Post-thyroidectomy Hypocalcemia: Prevention

14

14.1 Introduction

The true prevalence of post-thyroidectomy hypocalcemia is probably underestimated for many reasons: (1) lack of clear definitions of hypocalcemia, (2) variability of laboratory ranges for normo-calcemia and reference values, (3) timing of blood sampling in the post-operative period, and (4) short or incomplete follow-up.

Post-operative hypocalcemia should clearly be considered in discussions concerning the appropriate extent of thyroid surgery. Particularly with more extensive resections, surgeons may take preventive methods and corrective measures to reduce the incidence of post-thyroidectomy hypocalcemia and improve long-term outcomes. These include (1) modification of operative technique, (2) selective calcium and vitamin D supplementation post-operatively, (3) routine calcium and vitamin D supplementation post-operatively for all patients, (4) pre-operative supplementation with calcium for patients with Graves' disease, (5) intravenous calcium injection intra-operatively, (6) administration of iPTH (teriparatide) post-operatively, and (7) parathyroid gland auto-transplantation.

14.2 Modification of Operative Technique

Given the proximity of the parathyroid glands (PTGs) to the thyroid capsule, and the shared blood supply via the inferior thyroid artery (ITA), damage of PTGs contributes to symptomatic hypocalcemia after TT for any diagnosis. The literature reports a wide range of transient hypocalcemia after total thyroidectomy (6–72%) for all diagnoses [1–7]. Other factors noted to increase the risk of transient and/or permanent hypoparathyroidism after thyroid surgery include the extent of thyroid resection, recurrent goiter, Graves' disease, hospital volume, and female gender [6].

A well-known complication of bilateral thyroid surgery is the compromise of the PTGs resulting in transient symptomatic hypocalcemia or potentially, even

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permanent hypo-parathyroidism [1–4]. This complication has plagued thyroid surgeons, and led to modifications to the procedure, including *subtotal thyroidectomy* to minimize disruption to the PTGs, and *abandonment of central ligation* of the ITA, adopted by Thomusch et al. [8], who found that central ligation of the ITA results in higher rates of hypo-parathyroidism due to the compromise of blood supply to the PTGs.

As the blood supply to the PTGs had become better understood, total thyroidectomy (TT) is now routinely performed with division of the vascular supply as it directly enters the capsule of the gland, that is, ligating the secondary and tertiary branches of the ITA and not the main trunk.

In the American Thyroid Association (ATA) guidelines for the management of hyperthyroidism, TT, radioactive iodine ablation (RAI), and anti-thyroid drugs (ATDs) are listed as the "*three effective and relatively safe initial treatment options*" for patients diagnosed with *Graves' disease* [9]. Despite this recommendation, a recent survey of the membership of three major international endocrinology organizations demonstrated that surgery as first-line therapy is used only 0.7% of the time worldwide, and for only 0.9% of cases in the USA [10]. However, there were selective instances when TT was the preferred first-line treatment; patients with severe ophthalmopathy (18.5%) and for women wanting to conceive in the near future (20.3%). For patients who do not achieve remission after 12–18 months of ATDs, TT has also proven to be more cost effective in the definitive management of Graves' than either life-long ATDs or RAI [11]. The data presented in the growing literature demonstrates that TT for Graves' disease does not pose any greater risk of hypoparathyroidism than TT for benign causes [5, 12–15]. With a failure rate of RAI between 10% and 38%, the documented cost effectiveness of TT as definitive management, and the severe, life-threatening side-effects from ATDs, it is surprising that surgical management of Graves' disease has not become more widely adopted [9, 12, 16–19].

Another caveat to the ATA guidelines is that near-total or TT should be performed by a *high-volume surgeon* to ensure optimal outcomes and minimize risk of permanent complications [9]. This recommendation is based on several studies showing superior patient outcomes for both benign and malignant thyroid conditions when thyroid surgery is performed by a high-volume thyroid surgeon [20–22].

14.3 Selective Calcium and Vitamin D Supplementation Post-operatively

In addition to surgical technique modifications, there are a variety of clinical practices to try to prevent symptomatic hypocalcemia, including selective calcium and vitamin D supplementation based on post-operative parathyroid hormone (PTH) levels [3, 10, 23–25].

Oltmann et al. [26] reported that a standard practice within their institution includes the measurement of serum calcium and PTH levels on all patients in the immediate post-operative period. They proposed a protocol (Table 14.1) for selective

Table 14.1 Protocol for calcium and calcitriol supplementation based on post-operative PTH level

	PTH			
Treatment	<2 pg/mL	2–10 pg/mL	10–20 pg/mL	>20 pg/mL
Calcitriol	0.5 μg twice/day	0.25 μg twice/day	None	None
$CaCO_3$	1–1.5 g tds	1–1.5 g tds	1–1.5 g tds	Scheduled Ca at attending discretion
	2 g every 30 min as needed for symptoms	2 g every 30 min as needed for symptoms	2 g every 30 min as needed for symptoms	2 g every 30 min as needed for symptoms

post-operative supplementation with calcium carbonate (CC) and vitamin D (Calcitriol) according to the level of PTH post-operatively and documented significant reduction in the rate of post-operative hypocalcemia.

14.4 Routine Calcium and Vitamin D Supplementation Post-operatively for All Patients

Another proposed protocol by several authors to reduce the rate of post-thyroidectomy hypocalcemia was the *routine* post-operative calcium and vitamin D supplementation for *all* patients subjected to thyroidectomy, without evaluation of PTH levels in the post-operative period [3, 10, 23–25].

14.5 Pre-operative Calcium Supplementation for Patients with Graves' Disease

Patients with Graves' disease have much higher rates of symptomatic hypocalcemia after TT than patients undergoing TT for other diagnoses [1, 3, 5, 9, 12, 27, 28]. Factors contributing to this increased rate of post-operative hypocalcemia include increased bone hunger secondary to thyrotoxic osteodystrophy, increased release of calcitonin during gland manipulation during surgery, and the increased friability of the gland, making the procedure technically more demanding and placing the PTGs at increased risk of injury [1, 28, 29].

As TT is the operation of choice for the surgical management of Graves' disease, it is critical that the risk of developing symptomatic hypocalcemia is minimized [9, 12, 30, 31]. Some authors have proposed the use of *calcium in the pre-operative period for Graves' patients* [28]. The study hypothesis was that pre-treatment of Graves' patients with calcium supplementation before TT decreases the frequency of symptomatic post-operative hypocalcemia.

Oltmann et al. [26] compared the results of 45 patients with Graves' disease who underwent TT and were pre-treated with calcium carbonate for 2 weeks prior to surgery, and 38 patients with Graves' disease who underwent TT and were not given calcium carbonate prior to surgery. Forty patients undergoing TT only for a

diagnosis other than Graves' disease were also identified as procedure controls. These patients were not given calcium carbonate prior to surgery either. They concluded that counseling patients to taking 1 g of calcium carbonate three times a day (for 2 weeks prior to surgery) is a simple intervention to add to the pre-operative preparation for the Graves' patient. This regimen would decrease the incidence and severity of hypocalcemia experienced by Graves' patients after TT [26].

Given the multifactorial etiology of hypocalcemia after TT for Graves' disease, pre-operative calcium supplementation allows for the replenishment of whole-body calcium stores, which may be depleted secondary to the increased bone metabolism as a result of thyrotoxic osteodystrophy. With this contributing factor addressed in the pre-operative period through calcium supplementation, Graves' patients undergoing TT are found to experience rates of symptomatic hypocalcemia similar to patients undergoing TT for other diseases [1, 5, 28].

As previously mentioned, patients with Graves' disease have multiple proposed mechanisms that contribute to hypocalcemia after TT separate from parathyroid function. *Thyroid hormone* has a direct effect on osteoclasts, which stimulates bone turnover. This, in turn, can lead to increased serum alkaline phosphatase, serum osteocalcin, urinary calcium, and urinary deoxy-pyridinoline [28, 29]. This continued bone destruction and subsequent loss of calcium in urine results in depletion of whole-body stores of calcium. Several authors have also demonstrated concomitant vitamin D deficiency to place patients at increased risk for symptomatic hypocalcemia or tetany after total thyroidectomy for Graves' disease, but this was not necessarily a deficiency caused by Graves' disease [32]. Given the influence vitamin D has on the absorption of calcium, underlying deficiency would understandably result in exacerbation of hypocalcemia, and make calcium replacement more difficult without also addressing the vitamin D deficiency. Lastly, it has also been postulated that during manipulation of the gland at the time of surgery, *calcitonin* is released in an abnormal fashion [30].

In conclusion, transient hypocalcemia is a common issue after total thyroidectomy due to direct injury to the PTGs. As patients with Graves' disease have also struggled with hyperthyroidism prior to surgery with resultant high bone turnover, they have a potential second etiology to contribute to and/or exacerbate hypocalcemia in the post-operative period independent of parathyroid function. Pre-operative supplementation of such patients with 1 g of CC three times a day (for 2 weeks) reduces the incidence and severity of hypocalcemia experienced by Graves' patients after total thyroidectomy [26].

14.6 Intravenous Calcium Injection Intra-operatively

Several authors studied the value intra-operative intravenous (IV) calcium gluconate injection or infusion in decreasing the incidence of post-thyroidectomy hypocalcemia. The results reported by several authors are summarized in Table 14.2.

Although Bellantone et al. [33] and Roh et al. [34] reported no significant difference between patients who received intra-operative IV calcium gluconate and those

Table 14.2 Intra-operative calcium injection

Study (Year) [Ref]	Intervention		No intervention		*p*-Value
	N	Hypocalcemia *N* (%)	*N*	Hypocalcemia *N* (%)	
Bellantone et al. (2002) [33]	26	9 (34.6)	27	11 (24.4)	0.78
Uruno et al. (2006) [35]	243	5 (2.1)	304	26 (8.6)	0.001*
Roh et al. (2009) [34]	49	18 (36.7)	99	44 (44.4)	0.38
Hafez et al. (2014) [36]	20	8 (40)	20	13 (65)	0.023*
Sakr et al. (2017) [37]	50	19 (38)	50	31 (62)	0.016*

Ref reference; * Statistically significant

who did not, Uruno and colleagues [35], Hafez et al.[36], and more recently, in 2017, Sakr et al. [37] reported a significant reduction in post-operative hypocalcemia with IV injection of calcium intra-operatively.

Sakr et al. reported that hypocalcemia occurred for up to 3 days after surgery [37]. Similarly, Wu et al. [38] reported that no patient developed hypocalcemia after the third post-operative day. The critical period for serum calcium monitoring was 24–72 h after surgery. However, Pisaniello et al. [39] reported that hypocalcemia can occur from 2 to 5 days after surgery, while Sanabria et al. [40] found that hypocalcemia can occur from the immediate post-operative period up to 5 days after surgery.

In 2001, Tredici et al. [41] proposed an assessment of the drop in calcium levels post-operatively compared to the immediate pre-operative levels as a useful and simple predictor of hypocalcemia in patients undergoing TT. Adoption of 1.1 mg/dL (a 12% decrease from the pre-operative level) can be used as the "cut-off" for determining whether or not to start prophylactic calcium replacement. Graff et al. [42] reported that specificity to predict hypocalcemia can be achieved by combining the early intact PTH findings with a serum calcium measurement taken 6 h post-operatively. The combination of the two measurements is the safest method for assessing risk and justifying the discharge of patients with favorable laboratory results on the day of surgery.

In 2006, Uruno et al. [35] reported that, in patients receiving prophylactic intra-operative calcium, symptoms of hypocalcemia, numbness, and tetany were significantly reduced, with the prevalence of tetany dropping from 8.6% to 2.1%. Moreover, several authors reported that serum calcium levels in the first post-operative day were significantly higher in patients who received intra-operative calcium than those who did not [35–37].

14.7 Administration of iPTH Post-operatively

Some studies indicate that iPTH (teriparatide) levels measured shortly after thyroidectomy have a high predictive value; iPTH levels below the normal range (10–64 pg/mL) at 4 and 6 h after the operation may correctly predict post-operative hypocalcemia [43, 44]. Grodski et al. [45] have concluded that iPTH levels below 10 pg/mL,

at 4 h after TT, had a good precision to predict hypocalcemia (serum albumin-adjusted calcium level < 8 mg/dL) 24 h after surgery, with a positive predictive value of 90%, sensitivity of 94%, specificity of 100%, and an overall accuracy of 98%.

Palermo et al. [46] conducted a prospective phase II randomized open-label trial (Teriparatide for Hypocalcemia in Post-surgical Subjects: THYPOS Trial) to evaluate whether teriparatide can prevent postsurgical hypocalcemia and shorten the hospitalization in subjects at high risk of hypocalcemia following thyroid surgery. The study included 26 subjects (6 males, 20 females) with iPTH <10 pg/mL 4 h after thyroidectomy. Subjects were randomized to receive 20 mcg of teriparatide SC every 12 h until discharge (treatment group) or to follow standard clinical care (control group). Overall, the incidence of hypocalcemia was 3/13 in the treatment group and 11/13 in the control group ($p = 0.006$). Treated patients had a lower risk of hypocalcemia than controls (relative risk, 0.26). The median duration of hospitalization was 2 days in treated subjects and 3 days in controls ($p = 0.012$). A month after discharge, 10/13 subjects in the treatment group had stopped calcium carbonate supplements as compared to 5/13 in the control group ($p = 0.04$). In addition, there was a significant difference between discharge and 1-month visit in the treatment group (*p value* for interaction time group = 0.04). Palermo et al. [46] hypothesized that by rapidly counteracting the iPTH post-surgical fall with teriparatide, the stress on parathyroid glands is reduced as calcium homeostasis is exogenously maintained. They concluded that teriparatide may prevent post-surgical hypocalcemia, shorten the duration of hospitalization, and reduce the need for calcium and vitamin D supplementation after discharge in high-risk subjects after thyroid surgery. However, larger and more robust randomized placebo-controlled trials are needed in order to confirm these findings.

14.8 Parathyroid Auto-transplantation

If incidental excision or devascularization of the PTGs is noted during thyroidectomy, *parathyroid auto-transplantation* may reduce the occurrence of permanent post-operative hypocalcemia [47–49]. Another study confirmed that post-thyroidectomy parathyroid auto-transplantation plays an important role in preventing permanent hypoparathyroidism and should be a routine surgery [1].

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Parathyroid Transplantation

15

15.1 Introduction

Post-surgical hypocalcemia due to hypoparathyroidism is the most frequent and occasionally the most serious complication of total thyroidectomy (TT) [1]. Inadvertent compromise of parathyroid blood supply or unintentional excision of parathyroid glands (PTGs) is the usual cause [2]. Parathyroid auto-transplantation provides a solution to intra-operative parathyroid compromise. Despite common utilization, the impact of auto-transplantation on parathyroid function remains incompletely understood.

Symptoms of post-operative hypocalcemia usually present in the first 24–72 h after surgery [3]. These include circumoral or peripheral paresthesia, tetany, carpopedal spasm, laryngospasm, and ECG changes progressing from long QT interval to VT arrest [4]. In addition, post-thyroidectomy hypocalcemia leads to greater healthcare costs due to the need for extra-biochemical testing, electrolyte supplementation, and increased length of hospital stays [5].

In the longer term, undiagnosed hypoparathyroidism can lead to multiple systemic sequelae such as chronic renal impairment, reduced bone remodeling, increased psychiatric complaints, and basal ganglia calcification [6]. This causes significant morbidity and reduced quality of life. A recent population study by Hadker et al. showed that 75% of sufferers of chronic hypoparathyroidism experienced symptoms despite treatment; 79% required hospital admissions, and 85% reported inability to perform household tasks [7].

The recognition of the disease burden associated with permanent hypoparathyroidism has led to the emergence of parathyroid auto-transplantation to reduce the prevalence of this complication in at-risk patients.

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15.2 History of Parathyroid Gland Transplantation

Many surgeons who have left their mark on the development of surgery as a science have been intrigued by the PTGs. The first transplantation of the parathyroids was performed by Schift and Horsley in 1885 as reported by Niederle, Roka et al. [8], and von Eiselsberg [9]. In 1892, von Eiselsberg [9] performed a large number of auto-transplantations of the PTGs in the peritoneum and the posterior wall of the sheath of the rectum abdominal muscle of ***cats***. He thereby showed that tetany was absent and new vessels had formed in the transplants. Furthermore, tetany occurred after these transplants were removed.

Halstead [10] in Baltimore attempted "iso-auto-transplantation of the parathyroid glands" in *dogs* in 1909. He transplanted the tissues of the glands under the abdominal skin or into the parenchyma of the thyroid gland. Halstead and several other researchers called this situation "*loan of insufficiency*." Parathyroid auto-transplantation was first described and performed in *humans* during a thyroidectomy by Lahey [11] in 1926. Later on, in 1936, Shambangh [12] pointed out that the above-mentioned "loan" was not necessary for successful transplantation of these glands. The procedure was largely forgotten for 50 years until Wells et al. reported the first patient series that confirmed functional auto-grafts clinically, physiologically, and histologically. Since then, parathyroid gland transplantation, using of a range of different techniques, has been a common procedure for the treatment of hypoparathyroidism.

15.3 Burden of Disease and Defining Parathyroid Failure

Part of the difficulty in defining the role of parathyroid auto-transplantation relates to the variability in the incidence and presentation of hypo-parathyroid disease. Reported incidences of transient and permanent hypocalcemia are highly variable, ranging from 10% to 61% [13, 14] and 1% to 32% [15–18], respectively. In a more recent meta-analysis, the estimated incidence of transient and permanent hypocalcemia was 19–38% and 0–3%, respectively [19]. National registries and large multicenter studies, however, consistently demonstrate higher rates of permanent hypocalcemia ranging from 6.4% to 9% [1, 20].

The Fifth National Audit Report from the British Association of Endocrine and Thyroid Surgeons demonstrates a rate of 6.5% in 2017 [21], down from 12.1% in 2012 [22]. The variable rates of hypoparathyroidism and concomitant hypocalcemia in the literature partly relate to inconsistent definitions of hypoparathyroidism and hypocalcemia, and the division between transient and permanent conditions [23]. A recent paper by Mehanna et al. described that the reported rate of post-operative hypocalcemia for the same cohort of patients varied 46-fold depending on the definitions used [24].

Lorente-Poch et al. [25] attempted to address the diagnostic confusion by defining three distinct syndromes of parathyroid failure post-TT. This consisted of (1) "post-operative hypocalcemia": a serum calcium of <2 mmol/L or <8 mg/dL within

24 h after surgery requiring calcium/vitamin D replacement therapy at the time of hospital discharge; (2) "protracted hypoparathyroidism": a subnormal iPTH concentration <13 pg/mL and/or need for calcium/vitamin D replacement at 4 to 6 weeks; and (3) "permanent hypoparathyroidism": subnormal iPTH concentration <13 pg/mL and/or need for calcium/vitamin D replacement 1 year after TT.

Implementation of standardized definitions for hypocalcemia would greatly improve the quality of literature and improve our understanding of the role of parathyroid auto-transplantation in preventing hypoparathyroidism after thyroid surgery.

15.4 Risk Factors and Prevention of Hypoparathyroidism

The earliest thyroid operations were performed in the mid-1800s. However, at this early juncture, procedures had such poor outcomes that *Samuel Gross* wrote in 1866 "if a surgeon should be so adventurous or foolhardy as to undertake thyroidectomy, every step he takes will be environed with difficulties" [26]. Nevertheless, by the end of the 1800s, Professor *Theodore Kocher* had reported 900 thyroid procedures with a mortality of merely 1% and minimal morbidity. However, Kocher's case mix included only 18 TTs, as he had found that his post-thyroidectomy patients did poorly, developing a condition he termed "*cachexia strumipriva*," in actuality, hypoparathyroidism. This led Professor Kocher to abandon TT in favor of subtotal procedures [27].

Since then and particularly in the last 30 years, improvements in surgical techniques such as the advent of capsular dissection [26], careful handling of the parathyroid blood supply, loupe magnification [28], and avoiding truncal ligation of the inferior thyroid artery (ITA) have rendered TT safer, allowing modern surgeons to harness the benefits of TT over subtotal thyroidectomy (STT) such as reduced recurrence for benign disease and increased survival for malignancy. Consequently, TT has become a preferred operation [26, 29–31] for many benign and malignant thyroid pathologies. In 2015, Antakia et al. [32] underwent an extensive systematic review and meta-analysis to evaluate the effect of surgical procedures on post-operative hypocalcemia. They found that less extensive surgeries, such as STT, are associated with lower risk of transient hypocalcemia but felt that this did not influence the argument about the extent of thyroidectomy as there was no impact in terms of permanent hypocalcemia.

Recently, Edafe et al. [19] undertook a systematic review of predictors for post-thyroidectomy hypocalcemia and found female gender, pre-operative calcium, peri-operative PTH levels, surgery for recurrent goiter or Grave's disease, re-operation for bleeding, inadvertent PTG excision, and parathyroid auto-transplantation are the predictors of *transient hypocalcemia*. Predictors of *permanent hypocalcemia* included a calcium level <1.88 mmol/L 7.54 mg/dL at 24 h after surgery, identification of <2 PTGs at surgery, re-operation for bleeding, Graves' disease, and heavier thyroid specimens. They noted that no study included in the review found parathyroid auto-transplantation to be a predictor of permanent hypocalcemia.

Any factor that compromises PTG function is a potential risk factor of post-operative hypoparathyroidism [2, 4, 14, 33]. Hence, the extent of surgery and inadvertent excision of PTGs are repeatedly demonstrated to be important factors for the development of post-operative hypoparathyroidism [19, 20, 34, 35]. The incidence of incidental parathyroidectomy during thyroidectomy can be as high as 17.7% [35]. Selective parathyroid auto-transplantation with functional grafted parathyroid tissue theoretically should negate the other factors causing dysfunction. However, it has also been shown that the number of PTGs remaining in-situ is a critical factor in the prevention of permanent hypoparathyroidism [36]. Therefore, the success of parathyroid auto-transplantation relies on the recognition of compromised PTGs while maintaining the function of PTGs left in place.

15.4.1 Identifying Devascularized Glands

Parathyroid glands are usually identified by experienced surgeons through subjective *visual assessment* and detailed knowledge of anatomy [37]. With appropriate training, endocrine surgeons have been shown to develop satisfactory skills for the visual identification of viable PTGs [38]. Sung et al. [39] reported that if at least one PTG was deemed to have a normal appearance at the time of closure, then the development of hypocalcemia requiring treatment is uncommon. However, it has also been demonstrated that even with meticulous dissection, anatomically intact glands may not be physiologically viable due to thrombosis of the delicate parathyroid vascular pedicle, or parathyroid capsule edema [40]. This is recently reinforced by Lang et al. [41], who found that PTGs' dusky discoloration was associated with transient hypoparathyroidism and that an apparently normal gland with seemingly intact vascularity does not always imply that the gland is functional.

The most straightforward indication for parathyroid auto-transplantation is when PTGs are inadvertently removed with the thyroid specimen or when glands are obviously devascularized. Novel *fluorescence techniques* are currently under evaluation to improve parathyroid identification during thyroidectomy. The PTGs exhibit significantly higher fluorescence intensity than surrounding tissues and this has been suggested as a tool for identification of parathyroid tissue [42, 43]. However, fluorescence has only the benefit of improving gland localization, but does not indicate that the gland remains viable after dissection. For this reason, some studies advocate a "*knife test*" of questionable glands checking for capillary bleeding [44]; this has the added benefit of avoiding venous congestion in the gland, yet there is some concern that this may compromise viable glands.

Routine frozen-section of potential parathyroid tissue is used in some centers to confirm parathyroid tissue prior to transplantation [45]. However, Lo and Lam [46] determined that this was unnecessary for experienced surgeons as they felt unquestionable macroscopic appearance negated the need for frozen sections, which risked reducing the amount of parathyroid tissue available for transplantation. There has also been an initial report regarding the use of *Doppler ultrasound* (US); however, clinically this is not feasible intra-operatively [47].

Perhaps the most useful assessment of parathyroid function intra-operatively is the use of *parathyroid hormone immunoassay*. Barczyński et al. [48] demonstrated that taking a PTH level 10–20 min after TT prior to closure and utilizing a level <10 ng/L as an indicator for parathyroid auto-transplantation resulted in a lower incidence of transient hypocalcemia and reduced the risk of permanent hypoparathyroidism. This was also cost effective, calculated to cost $35, and time effective, with results available within 8–10 min. Utilizing parathyroid-level biochemistry and visual assessment of incidentally removed or discolored compromised glands as a guide to parathyroid auto-transplant may reduce the incidence of transient hypoparathyroidism while mitigating the risk of permanent hypothyroidism.

15.5 Parathyroid Transplantation: Modes of Application

In general, parathyroid transplantation can be considered in three distinct modes of application [49]:

1. *Fresh parathyroid tissue auto-transplantation* during thyroidectomy in order to reduce the risk of permanent hypoparathyroidism.
2. *Cryo-preserved parathyroid tissue auto-transplantation* in patients with permanent hypocalcemia.
3. *Parathyroid allo-transplantation* in patients with permanent hypoparathyroidism when cryopreserved parathyroid tissue is not available for grafting.

15.5.1 Fresh Parathyroid Tissue Auto-Transplantation

In 1975, Wells et al. reported on a successful parathyroid auto-transplantation in a large cohort of patients undergoing parathyroidectomy with a transplant success rate of 93% [50]. This study opened the way for further interest in re-implantation as an effective method for the preservation of parathyroid function not only in parathyroid surgery, but also in thyroid surgery, and especially in patients undergoing TT. Parathyroid auto-transplantation soon became a widely accepted technique in head and neck surgical oncology and endocrine surgery as an effective way to reduce the risk of permanent postoperative hypocalcemia [45].

15.5.1.1 Techniques

There are various techniques for auto-transplantation; these include (1) thin section *slicing*, (2) *mincing,* and (3) injection of a *suspension* of parathyroid tissue [45, 50–52]. The most widely used technique for parathyroid auto-transplantation is described by Wells et al. [50]. In this approach, parathyroid tissue is placed in a saline solution at 4 °C or in a tissue culture medium as soon as possible after excision. After cooling for 30 min, the glands are sufficiently firm to be sliced into 1-mm *slices* or 1-mm cubes. Generally, 10–20 pieces are inserted into individual muscle pockets. The incision is closed with a non-absorbable suture or clip to assist subsequent identification (Fig. 15.1).

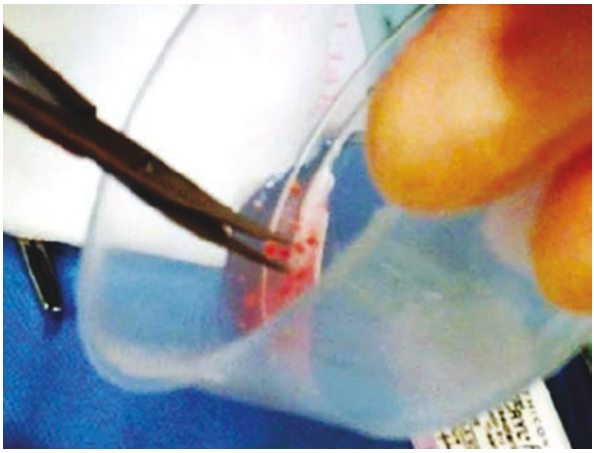

Fig. 15.1 Slicing technique for fresh auto-transplantation

Another common technique involves injection of a *suspension* of parathyroid tissue in buffered saline into the *sternocleidomastoid (SCM) muscle*. A 1–2 mL of sterile physiological saline solution is used and the de-vascularized PTG is carefully minced using fine scissors. The small fragments of tissue are drawn into a syringe and the suspension is injected into the right SCM muscle at its midpoint. Gauger et al. [51] reported that an injection of a parathyroid tissue suspension in saline was as effective as sectioning or mincing of PTG for auto-transplantation in patients undergoing thyroid surgery [51]. This technique should be avoided when there may be a need for subsequent excision of part of the graft, as injected parathyroid tissue is diffuse and difficult to localize for re-excision. When surgery is undertaken for Multiple Endocrine Neoplasia Types 1 and 2, or renal failure patients with secondary and tertiary HPT this approach should be *avoided*. On the other hand, the relative ease of this technique makes it generally the *procedure of choice* for parathyroid auto-transplantation during thyroidectomy.

Most patients after parathyroid auto-transplantation require temporary oral calcium and vitamin D supplementation and close biochemical monitoring of serum calcium for 2 to 4 weeks following surgery. Using such an approach markedly decreases the incidence of permanent post-surgical hypo-parathyroidism [52, 53]. In the majority of published series, proof of successful parathyroid auto-transplantation during thyroid surgery has been recognized based on the maintenance of normocalcemia without the need for life-long calcium supplementation after experiencing a short period of post-operative hypocalcemia [37, 54]. In more recent papers, this was also confirmed by PTH serum level measurements in peripheral blood [48, 51].

15.5.1.2 Sites for Auto-transplant

There are many different potential sites for re-implantation of parathyroid tissue including (1) *muscles* (SCM, brachio-radialis, pectoralis major, or deltoid) [55] and, more recently, (2) *subcutaneous (SC) tissue* (of the abdominal wall, lower-third of sternum, or forearm) [56].

The most common site in TT is the *SCM muscle*, which usually already lies exposed in the operative field [47, 57, 58]. As PTGs are expected to be functionally normal in the vast majority of cases of thyroid surgery, this is a safe and easily accessible area. However, it is not possible to biochemically prove graft hyperfunction when implanted into the neck. If there is a future need for removal of the graft, then re-operative surgery requires repeat cervical exploration.

If PTG auto-transplantation is indicated for abnormal or hyperplastic parathyroid tissue, then the preferred graft location is usually in the *brachio-radialis muscle* of the non-dominant forearm [59]. Venous sampling from the forearm containing the graft allows for checking of graft function or dysfunction. A gradient of 1.5 or greater in PTH measurement between the grafted and non-grafted arms has been generally accepted as proof of graft hyperfunction [60]. Additionally, if removal of the graft is indicated, the potential difficulties and risks associated with redo cervical surgery are alleviated. Although rare, auto-transplanted parathyroid tissue has been shown to result in primary HPT even after the grafting of normal parathyroid tissue in TT [61]. Using the brachio-radialis muscle has been successfully used by Lo and Tam to demonstrate parathyroid graft function after auto-transplantation for TT [60].

More recently, Cavallaro et al. [56] showed parathyroid auto-transplantation into *forearm SC tissue* to be a safe and effective procedure when used for normal functioning PTGs inadvertently removed during TT. This had previously been documented to be effective in parathyroid hyperplasia [62]. In a study of 25 cases, they demonstrated recovery of re-implanted glands in 96% of cases at 3 months. This technique is faster and less invasive than intra-muscular techniques, requiring only 2-mm skin excisions. Forearm implantation provides an effective alternative to the traditional technique of re-implantation into the SCM muscle, and has the added benefit of easier monitoring of graft function and subsequent removal if graft dysfunction ensues. However, it is more time-consuming due to the need for secondary incisions at a distant site. For this reason, the SCM muscle with its ease and proximity is the preferred site for auto-transplantation of parathyroid tissue during thyroidectomy.

15.5.1.3 Selective Versus Routine Parathyroid Auto-Transplantation

Indications of parathyroid auto-transplantation during thyroid surgery are (1) an inadvertent removal of PTGs, (2) finding PTGs in the surgical specimen soon after excision, (3) no anatomical capacity for preservation of the parathyroid in-situ, and (4) devascularization of the PTGs. In such cases, the parathyroid gland should be re-implanted, most commonly into the SCM muscle [53].

Parathyroid auto-transplantation has been demonstrated to be effective, clinically and biochemically, with a functional graft survival rate of 93% [50]. However, the clinical utility of parathyroid auto-transplantation following thyroid surgery is more difficult to evaluate, because it is a rare event for all four PTGs to be removed or devascularized during thyroidectomy. Indeed, Song et al. reported that even one remaining functional gland in-situ provides a safeguard against permanent hypoparathyroidism; although the incidence of transient hypocalcemia correlates with the number of PTGs damaged or removed.

The question that arises is whether parathyroid auto-transplantation should be performed when only *one or two PTGs* have been removed accidentally or are suspected to be devascularized. In other words, is there any additional benefit of PTG re-implantation in the likely presence of at least one functional in-situ PTG? Delbridge 92,003) [26] suggested that "the viability of in-situ vascularized parathyroid remains unpredictable with late ischemia always a possibility". While unnecessary in most cases, the routine auto-transplantation of at least one PTG during every TT provides insurance in cases where late ischemia of the remaining glands actually occurs [26]. Zedenius et al. [44] demonstrated this, showing that *routine auto-transplantation* of one PTG during TT eliminated permanent hypoparathyroidism in a study of 100 consecutive total thyroidectomies.

Conversely, Lo and Lam [15] examined a policy of routine parathyroid auto-transplantation compared to selective auto-transplantation and found no significant difference in the rates of permanent hypoparathyroidism, 0% versus 1.8%, but reported a significantly higher rate of transient hypocalcemia, 23% versus 13%. This is reinforced by Barczynski et al. [48], who used IOPTH assay to guide parathyroid auto-transplantation and found that *selective auto-transplantation* yielded a lower incidence of transient hypocalcemia when compared to routine auto-transplantation, 11.2% versus 22.4%. Both approaches yielded a 100% success rate in preventing permanent hypoparathyroidism. Thus, routine auto-transplantation, although still highly effective in preventing permanent hypoparathyroidism, likely increases transient parathyroid dysfunction, which extends hospital stays, causing discomfort and potentially life-threatening complications, and could be avoided if a normal well-vascularized gland had remained in-situ.

15.5.1.4 IOPTH during Thyroidectomy for Selective Parathyroid Auto-Transplantation

An intra-operative assessment of parathyroid function was reported to be useful in the identification of PTGs with a degree of impaired vascularity, the method which has the potential to facilitate the decision to perform auto-transplantation [44]. In a randomized controlled trial of 340 patients undergoing TT, Barczyński et al. found that IOPTH offered clinically important information during thyroid surgery, allowing for correct identification of patients with increased risk of post-operative hypocalcemia. Selective IOPTH-based parathyroid auto-transplantation in patients with serum PTH levels <10 ng/L, at 10 to 20 min after TT, abolished the risk of permanent hypoparathyroidism, and this concept turned out to be as effective as elective parathyroid auto-transplantation of at least one PTG without IOPTH monitoring. In addition, selective IOPTH-based parathyroid re-implantation markedly reduced the prevalence of transient post-operative hypocalcemia and the overall doses of calcium slats used for supplementation in this study arm were lower when compared to elective parathyroid auto-transplantation without IOPTH monitoring [48].

15.5.1.5 Results of Fresh Parathyroid Auto-Transplantation

Successful parathyroid auto-transplantation during thyroid surgery has been recognized based on the maintenance of normocalcemia without the need for life-long

calcium supplementation after experiencing a short-term period of post-operative hypocalcemia [37, 54]. More recently, it was also confirmed by PTH serum level measurements in peripheral blood [48, 51].

Although some studies appear to demonstrate lower rates of permanent hypoparathyroidism after parathyroid auto-transplantation compared to controls, most of these were under-powered and failed to demonstrate statistically significant differences. On the other hand, some scholars have argued that parathyroid auto-transplantation places potentially viable PTGs at risk, and have cautioned against routine auto-transplantation. Lorente-Poch and colleagues [36] measured the PTGs' remaining in-situ score (*PGRIS*) and found it is inversely related to the rate of permanent hypoparathyroidism. However, this score included both auto-transplanted and removed glands, thereby not directly testing function of the grafted PTG. A further study by the same authors found that the rates of permanent hypoparathyroidism were similar whether the glands are incidentally resected or auto-transplanted. In a larger population study [63], parathyroid auto-transplantation significantly increased the risk of transient hypoparathyroidism ($p < 0.0001$), while it showed a non-statistically significant trend toward minimizing the risk of permanent hyperparathyroidism.

Parathyroid auto-transplantation has repeatedly been found to be a risk factor for transient hypo-calcemia [14, 15, 19, 63–65]. Edafe et al. [19] conducted a systematic review and meta-analyses of predictors of post-operative hypocalcemia and found that patients undergoing parathyroid auto-transplantation had double the risk of transient hypocalcemia. However, these studies instituted selective auto-transplantation only in cases when the blood supply to a gland was deemed to be questionable, which in turn were compared against controls in which auto-transplantation had not been indicated. Therefore, on the basis of this evidence, it cannot be answered if PTG auto-transplantation is an independent risk factor. Additionally, Testini et al. [58] found that parathyroid auto-transplantation reduced the incidence of transient hypocalcemia when they compared age, gender, and surgical indication matched controls with one devascularized gland to patients undergoing parathyroid auto-transplantation for having one devascularized gland. Therefore, despite the strong correlation between auto-transplantation and transient hypocalcemia, these results may be partially confounded by the indication for auto-transplantation being parathyroid devascularization.

Two studies have demonstrated a statistically significant decrease in permanent hypoparathyroidism after parathyroid auto-transplantation. Ahmed et al. [66] demonstrated a 3.09% incidence of permanent hypocalcemia in patients with no parathyroid auto-transplantation and a 0.34% incidence in patients following auto-transplantation ($p = 0.0417$). The patients in this study were initially randomly assorted but favorable results in the auto-transplantation group led to a policy of routine auto-transplantation; this demonstrates a bias toward the use of parathyroid grafting. Wei et al. [67] examined the role of selective auto-transplantation of inferior PTGs in patients undergoing TT and central neck dissection. They found that permanent hypoparathyroidism was lower after parathyroid auto-transplantation compared with preservation in-situ, 0.9% and 3.8%, respectively ($p = 0.003$). The

Table 15.1 Impact of auto-transplantation on hypocalcemia comparing selective auto-transplantation to preservation in-situ with no auto-transplantation

	Impact on transient hypocalcemia			Impact on permanent hypocalcemia		
Authors	Impact	Auto-Tx	No auto-Tx	Impact	Auto-Tx	No auto-Tx
Testini [58]	↓	17.7%	45.7%	–	0%	2.5%
Lo [65]	↑	21.4%	8.1%	–	0%	2.9%
Kidak [64]	↑	55.7%	26.2%	–	11.5%	3.3%
Weil [67]	–	26.5%	25.0%	↓	0.9%	3.8%
Ahmed [68]	–	16.8%	23.7%	↓	0.3%	2.9%
Pallazo [14]	↑	13.3%	9.8%	–	0.58%	0.98%

Auto-Tx Auto-transplantation

authors also noted that auto-transplantation may allow for a more comprehensive central neck dissection. This may illustrate that parathyroid auto-transplantation is more effective in cases where central neck dissection is required as these have been demonstrated to have an increased risk of post-operative hypocalcemia [32]. Additionally, a large retrospective cohort study of 1196 patients demonstrated that using a selective policy of auto-transplantation maintains a rate of permanent hypoparathyroidism at <1% [14]. However, no significant difference was found between patients undergoing parathyroid transplantation or controls.

Overall parathyroid auto-transplantation is associated with transient hypoparathyroidism, but a reduction in the rates of permanent hypoparathyroidism. Although the number of patients benefitted will be low, as only one functioning gland in-situ may be enough for prevention, the morbidity related to permanent hypocalcemia is so significant that this small potential benefit is more advantageous than leaving devascularized or jeopardized glands in place where their ongoing function is unpredictable. Despite a lack of clear empirical evidence, parathyroid auto-transplantation is an effective procedure that can safeguard against permanent hypoparathyroidism (Table 15.1).

15.5.2 Cryo-Preserved Parathyroid Tissue Auto-Transplantation

The possibility of cryo-preserving animal parathyroid cells preserving their morphology was demonstrated by Blumenthal and Walsh [68]. Since that first experience, many authors have explored the possibility of stimulating "in-vitro" and auto-transplanting parathyroid tissue that had been cryo-preserved for various periods of time. However, it was Brennan et al. (1979) who for the first time showed that "in vitro" PTH suppression in the presence of high calcium concentrations in cryo-preserved human parathyroid cells could be a good indicator of cell vitality and functionality before auto-transplantation [69].

Two main aspects regarding cryo-preservation of parathyroid tissue were considered, namely, preservation of cell function and structure after various periods of cryo-preservation, and finding whether there is a maximum period of cryo-preservation after which histological and functional characteristics begin to deteriorate.

Direct re-implantation of PTGs that are damaged or inadvertently removed minimizes the risk of *graft non-viability* and *non-functionality*. However, immediate auto-transplantation may not be necessary in all patients undergoing thyroidectomy because in most subjects who experience hypocalcemia post-operatively, this state is transient. Hence, cryo-preservation of parathyroid tissue, the concept that was developed by Wells et al. in 1975, to cope with a problem of *permanent* hypoparathyroidism, can be an alternative [50]. *Permanent* hypoparathyroidism is defined as "persistent hypocalcemia requiring calcium and vitamin D supplementation six months after surgery" [70].

The accidental onset of permanent hypoparathyroidism can be agonizing for both the patient and the clinician. For the patient, its negative impact includes a reduced quality of life, expensive life-long medication supplementation, frequent laboratory testing, and the potential for frequent hospital admissions. In addition, the persistent absence of parathyroid hormone (PTH) has long-term systemic effects on the body, such as the development of osteoporosis (due to the decreased function of osteocytes), premature cataracts, cardiac dysfunction, and neurological dysfunction [70, 71].

Cryo-preservation permits parathyroid tissue to be stored for potential subsequent auto-transplantation in a delayed manner after the diagnosis of permanent hypothyroidism is confirmed, thereby avoiding the risk of needlessly implanting parathyroid tissue during initial surgery [72, 73]. The physician is able to determine more accurately if there is any residual parathyroid tissue left behind with a potential for regaining functioning or whether delayed auto-transplantation is needed [74]. However, parathyroid tissue cryo-preservation entails the potential risk of transplant failure or malfunction, which is difficult to predict [72].

15.5.2.1 Indications of Cryo-Preservation

The development of hypoparathyroidism is related to the type of operation performed. The risk is nominal during a minimally invasive parathyroidectomy for a single adenoma, but is greatest after subtotal or total parathyroidectomy, total thyroidectomy (TT), nodal dissection for large and extensive thyroid cancers, and re-operative neck operations [70].

Initial Neck Operations

The obvious indication for auto-transplantation of cryopreserved parathyroid tissue is permanent iatrogenic *post-surgical hypoparathyroidism*. The risk is particularly low in patients with sporadic primary hyperparathyroidism (PHPT), most of whom have a single parathyroid adenoma. Nonetheless, certain patients have a higher risk of developing permanent hypoparathyroidism after their initial neck surgery (Table 15.1). Patients at the highest risk are those with multigland parathyroid hyperplasia, especially those with familial PHPT [75]. Such patients may undergo either a subtotal (3.5-gland) parathyroidectomy or a total parathyroidectomy with an immediate auto-transplant. Both procedures can result in aparathyroidism, so cryopreservation of parathyroid tissue is recommended at the time of initial surgery [75]. In addition, it has been reported that the use of intra-operative parathyroid

hormone (IOPTH) monitoring during parathyroid surgery can accurately predict patients at risk of developing postoperative hypocalcemia. A drop of >80% of IOPTH at 10 min is a significant factor for postoperative hypocalcemia [76]. Therefore, cryopreservation of parathyroid tissue should be considered during parathyroid surgery when the IOPTH drops >80%.

Patients with end-stage renal disease are at high risk of developing secondary hyperparathyroidism (SHPT) and tertiary (THPT) hyperparathyroidism (THPT). Such patients have persistent stimulation of the PTGs secondary to abnormalities in the metabolism of calcium, phosphorus, and vitamin D, resulting in multigland parathyroid hyperplasia. The choice of operation for such patients can be problematic. They have an inherently high risk of disease recurrence if subtotal parathyroidectomy is performed but a high risk of permanent hypoparathyroidism if total parathyroidectomy and immediate auto-transplant are performed [77]. Moreover, such patients may require multiple operations; to prevent aparathyroidism as a consequence of the initial or subsequent operations, cryo-preservation of parathyroid tissue is recommended [69].

The prevalence of permanent hypoparathyroidism after thyroidectomy in a virgin neck is below 1–2% if only the operation is performed by an experienced thyroid surgeon [73]. Although rare, it renders the patient permanently aparathyroid with significant consequences on health and quality of life. The risk of permanent hypoparathyroidism is considered minimal for thyroidectomy alone, but increases with a more radical extent of surgery. In particular, routine *central neck dissection* during surgery for thyroid cancer increases the risk of permanent hypoparathyroidism, which occurs in up to 14% of cases [78]. Hence, the concept of prophylactic central neck dissection for papillary thyroid cancer (PTC) remains controversial. An immediate intra-operative auto-transplant is preferred during a neck dissection for thyroid cancer, yet cryo-preservation of parathyroid tissue fragments is also warranted given the multiple operations that may be required in the future. Subsequent operations increase the risk of permanent aparathyroidism, a detrimental outcome that cryo-preservation of parathyroid tissue may prevent.

Re-Do Neck Operations

Despite the fact that an immediate intra-operative auto-transplantation of fresh parathyroid tissue is the method of choice during a neck operation for thyroid cancer, the cryo-preservation of parathyroid tissue may be rewarding for high-risk patients with more risk for recurrent disease, which makes them more likely to undergo revision neck operations in the future. Any redo neck surgery, particularly in the central neck, involves an increased risk of permanent hypoparathyroidism, approaching 30% in some series, which can be potentially preventable by re-implantation of cryo-preserved parathyroid tissue [72, 73]. During a redo neck operation, an identification and in-situ preservation of the functioning of the remaining PTGs is much more difficult as the dissection is undertaken in the scar tissues. In addition, parathyroids left in-situ during primary surgery might have been injured as a result of inadequate blood supply preservation. Hence, during a revision central neck dissection, inadvertent removal of or injury to any remaining functional gland may lead to permanent hypoparathyroidism.

In general, it is widely accepted for a redo central neck dissection that any PTG encountered should be considered the last functional parathyroid tissue and should be re-implanted immediately soon after unintentional removal. However, a few small pieces of parathyroid tissue can be secured for cryopreservation and possible re-implantation in the future if any further neck revisions lead to permanent hypoparathyroidism later on [73].

Other common reasons for parathyroid re-operations include *persistent* HPT (hypercalcemia <6 months after initial surgery) and *recurrent* HPT (hypercalcemia >6 months after initial surgery). Operative success for re-do parathyroid surgery is <90% and is fraught with an 18% rate of causing permanent hypoparathyroidism [79]. Immediate auto-transplantation of parathyroid tissue to prevent hypoparathyroidism impedes determination of surgical outcome, which is unpredictable during re-do parathyroid surgery [80]. Accurately assessing the number of PTGs previously resected, or viability of the remaining PTGs, is difficult. Cryopreservation of parathyroid tissue, rather than an immediate auto-transplant, allows the surgeon to appropriately predict surgical outcome, functionality of any remaining parathyroid tissue, and the need for a delayed parathyroid auto-transplant.

Operative failure and disease recurrence are infrequent in patients with sporadic PHPT; re-operations are more commonly needed in those with SHPT and THPT [77]. Up to 15% of patients with SHPT and THPT tend to have more than four PTGs [81], increasing the risk of operative failure. Cryo-preservation of their parathyroid tissue is especially important, because the long-term renal effect of prolonged SHPT and THPT predisposes patients to transient hypocalcemia from bone hunger. Before any parathyroid auto-transplant, it is critical to differentiate transient from permanent hypoparathyroidism. Similarly, patients with thyroid cancer who require repeating operations are at risk of hypoparathyroidism, because their remaining PTG function cannot be properly assessed. Moreover, if PTGs are immediately auto-transplanted into the neck muscles during the initial thyroid surgery, the function of those glands cannot be properly evaluated [80]. During re-operations for thyroid cancer, a portion of any inadvertently removed or devascularized PTGs should be sent for cryo-preservation before any immediate auto-transplant. Patients who develop aparathyroidism during subsequent operations might later benefit from a delayed auto-transplant of the cryo-preserved parathyroid remnant.

Indications of cryo-preservation of parathyroid tissue in initial and re-do neck operations are summarized in Table 15.2.

Table 15.2 Indications of parathyroid cryo-preservation

Initial neck operations	Re-do neck operations
1. Multigland parathyroid hyperplasia	1. Parathyroidectomy after thyroidectomy
– Familial primary hyperparathyroidism (PHPT)	2. Persistent hyperparathyroidism
– Secondary hyperparathyroidism (SHPT)	3. Recurrent hyperparathyroidism
– Tertiary hyperparathyroidism (THPT)	4. Redo central neck dissection for thyroid cancer
2. Total thyroidectomy with central neck dissection	5. Any re-do neck surgery, particularly in the central neck

15.5.2.2 Cryo-Preservation Technique

Parathyroid Tissue Preparation

Intra-operative preparation of parathyroid tissue is relatively uniform. Parathyroid tissue removed during thyroid surgery is fragmented into 30–40 small pieces of 1 mm × 1 mm × 1 mm (Fig. 15.2). The pieces are then placed into a sterile vial containing ice-chilled saline. The vial is then transported to the laboratory. The supernatant is decanted; about 10 (8–12) tissue fragments are transferred into each sterile freezing vial to be resuspended in the freezing media (Fig. 15.3).

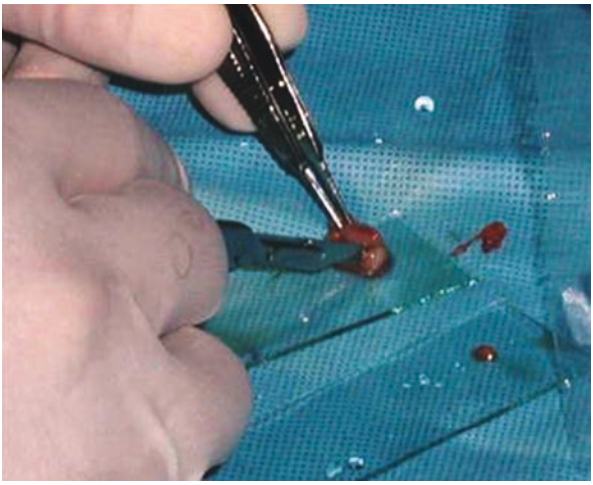

Fig. 15.2 Fragmentation of parathyroid tissue into 30–40 small pieces in preparation for cryo-preservation and grafting

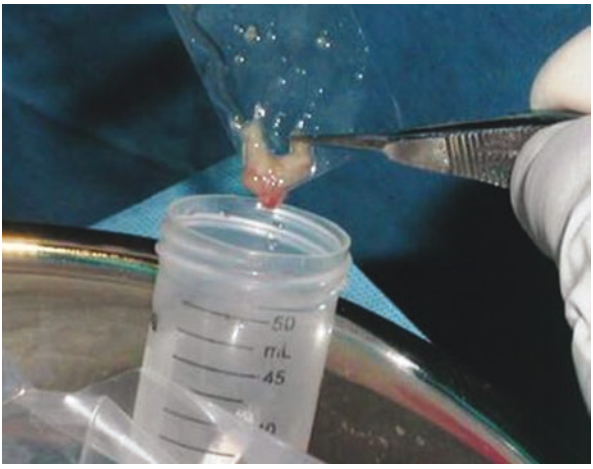

Fig. 15.3 Transportation of the parathyroid pieces to the laboratory in a sterile vial to be resuspended in the freezing media

Freezing Media

The use of a standardized cryo-preservation method (process) is vital to preserving graft functionality. A crucial component is the freezing medium used during the freezing process. Several media have been proposed in the literature since the initial report by Wells et al. in 1977 [82]. The typical freezing medium contains Roswell Park Memorial Institute (RPMI) 1640 solution [69, 71, 74, 75, 80, 82–84]. Most institutions use an 80% RPMI 1640 solution [71, 80, 82], but some use either a 60% RPMI solution 1640 [83] or no RPMI 1640 solution [85].

In addition, some authors recommend supplementing the RPMI 1640 solution with 2 mM of glutamine [69, 79] and 5 μg/mL of penicillin streptomycin [69] or 50 μg/mL of gentamicin [79]. Dimethyl sulfoxide (DMSO) in a 10% concentration is added as a cytoplasmic stabilizer.

Other reported concentrations of DMSO range from 7.5% to 20% [69, 86]. The last component of the storage medium is either a 10–30% autologous serum [69, 71, 79, 80, 83] or a 10–20% fetal bovine serum [74, 79]. When the RPMI 1640 solution is excluded, a 90% fetal bovine serum is used [85].

Freezing Process

The goal of the freezing process is to preserve cellular function by maintaining cellular integrity through the temperature change. To accomplish that goal, the vials are cooled slowly, before being transferred into long-term storage [79]. A cooling technique developed at the Mayo Clinic entails placing the vials in an ice chest filled with dry ice prechilled to −55 °C to −60 °C for 1 h to allow cooling by −1 °C per min [11]. Other authors recommend placing the vials in a −60 °C ethyl alcohol bath [80] or in either a −70 °C [83] or a −80 °C [85] freezer overnight. The vials can also be placed in a programmable freezer and cooled by −1 °C per min until a temperature of −80 °C is reached [69]. Once the vials are cooled, they are transferred into a liquid nitrogen freezer and stored at any of several recommended temperatures: −170 °C [69, 83], −180 °C [74, 85], −190 °C [80], or −196 °C [71, 79].

15.5.2.3 Auto-Transplantation Technique

Thawing and Washing

The vials containing the parathyroid tissue designated for delayed auto-transplantation are removed from the liquid nitrogen freezer and placed in a warm water bath. The vials are shaken at 37 °C [79, 85] to 42 °C [80] until the parathyroid tissue fragments are thawed. The fragments are washed in RPMI 1640 solution at 37 °C three times [79, 80]. Other authors recommend rinsing the fragments five times in 1 mL of RPMI 1640 solution with a 20% autologous serum [71]. The RPMI wash is performed to rinse the dimethyl sulfoxide, which is toxic to cells at room temperature. Once the parathyroid tissue pieces are thawed and washed at body temperature a few times, they are ready for grafting [80].

Re-implantation

The patient's non-dominant forearm is chosen for the parathyroid tissue reimplantation under local anesthesia. A longitudinal incision is made on the forearm.

Dissection is continued until a flexor muscle, preferably the brachioradialis muscle, is exposed. Bluntly, pockets are created in the brachioradialis muscle. One to three parathyroid graft fragments are transplanted into separate muscle pockets [82]. To maximize the chances of graft function, a total of 20 to 40 fragments are auto-transplanted [71, 80]. Caution must be exercised not to cause any hematoma within the intra-muscular pockets, which may compromise the vitality of the transplants and compromise graft function [80].

15.5.2.4 Functionality Assessment and Outcomes

Post-transplant success is determined by the functionality of the cryo-preserved parathyroid tissue graft. Functionality is determined not only clinically but also biochemically (by sampling blood from the grafted and non-grafted antecubital veins, to determine the PTH level at both sites). The parathyroid graft is reported as fully functional, partially functional, or non-functional. In renal patients, the functionality of the parathyroid graft is determined by their PTH levels, independent of calcium and vitamin D supplementation (since most renal patients require supplementation) [86] (Table 15.3).

Fully Functional Graft

Clinically, the graft is considered "fully functional" when the patient remains eucalcemic and asymptomatic—after all the calcium and vitamin D

Table 15.3 Definitions of parathyroid graft functionality

Graft function	Criteria
Fully functional	*Asymptomatic non-renal patients*
	– Off calcium and vitamin D supplementation
	– Eucalcemic with normal PTH levels and/or grafted-to-nongrafted arm, PTH ratio > 1.5 [79]
	Renal patients
	– PTH levels of 51 to 300 pg/mL with normal or decreased calcium levels [86]
Partially functional	*Symptomatic non-renal patients*
	– On calcium supplementation, with or without vitamin D supplementation
	– Hypocalcemic with normal PTH levels and/or grafted-to-nongrafted arm, PTH ratio > 1.5 [79]
	Renal patients
	– PTH levels of 21 to 50 pg/mL with normal or decreased calcium levels [86]
Non-functional	*Symptomatic non-renal patients*
	– On calcium supplementation, with or without vitamin D supplementation
	– Hypocalcemic with low PTH levels and/or grafted-to-nongrafted arm, PTH ratio < 1.5 [79]
	Renal patients
	– PTH levels <20 pg/mL with normal or decreased calcium levels [86]

supplementation has been discontinued. Complete independence from exogenous supplementation is considered the best evidence of graft function [80]. A graft is also considered fully functional when the PTH ratio between the grafted and non-grafted arms is greater than 1.5, after all the calcium and vitamin D supplementation has been discontinued [79]. Saxe et al. (1982) recommended a PTH ratio of greater than 2 [80].

Partially Functional Graft

The cryo-preserved parathyroid graft is considered "partially functional" when the patient continues to require calcium supplementation, with or without vitamin D supplementation, with a PTH ratio of greater than 1.5 [79].

Non-functional Graft

The cryo-preserved parathyroid graft is considered "non-functional" when the patient is hypocalcemic and requires calcium supplementation, with or without vitamin D supplementation, with a PTH ratio of less than 1.5 [79].

15.5.2.5 Effects of Cryo-Preservation—Cell Viability and Cell Function

Herrera et al. published their experience in 1992 and showed that parathyroid cell morphology and functional activity were maintained, regardless of the duration of cryopreservation, up to a period of 24 months [79]. Agarwal et al. [87] cryo-preserved 630 specimens following parathyroid surgery and reported a 100% success rate as measured by an increase in circulating PTH from 9 delayed parathyroid transplantation procedures using stored parathyroid tissue. However, two of the patients remained on high-dose calcium at the conclusion of their study. They did *not* offer parathyroid cryo-preservation for routine thyroidectomy patients. On the other hand, a large multicenter trial in France cryopreserved 1376 parathyroid tissue samples. Of these, only 22 were auto-grafted into 20 patients, of which only 10% were fully functional and another 10% retained partial function with patients requiring ongoing calcium and vitamin D supplementation [88].

The potential benefits of cryo-preservation are limited by the reduced functionality of cryopreserved grafts, as compared with immediately auto-transplanted grafts [79, 83, 87, 89]. In general, cryo-preserved parathyroid tissue grafts turn out to be functional in less than 70% of patients, whereas the fresh auto-grafts retain functionality in above 90% of patients [71, 83].

The cryo-preservation process may induce cellular necrosis and impair cellular viability and, ultimately, cellular function. A question is raised; does cell viability determine cell function? Earlier studies found no difference in cell viability and secretory capacity between fresh and cryo-preserved parathyroid tissue grafts [75, 90]. Yet other studies demonstrated that, even though the percentage of viable cells did not necessarily differ between fresh and cryo-preserved tissue, cryo-preservation decreased the total number of live cells by >70% [74]. That effect on live cell yield was the same whether the parathyroid tissue was frozen as tissue fragments or as dispersed cells [74].

Recently, other authors reported that the cryo-preservation process decreased total cell viability and functionality [83], both of which were associated with increased storage time [85]. Both viability and function were drastically reduced with a storage time of 22 months [83, 85]. It is recommended that cryo-preserved parathyroid tissue be used within 18 months, and preferably as soon as possible, as longer storage significantly reduces the delayed auto-transplantation functionality rate [73]. In addition, to counterbalance the effects of cellular necrosis, some authors routinely perform histological examination of the cryo-preserved tissue and auto-transplant parathyroid tissue according to the percentage of necrotic cells [71].

15.5.2.6 Conclusion

The devastating effect of permanent aparathyroidism has been, for the most part, ameliorated by PTG cryo-preservation and delayed auto-transplantation. Cryo-preservation is an extremely valuable tool that is exceedingly useful in parathyroid surgery. An immediate auto-transplant is preferred during thyroid surgery, yet cryo-preservation of a portion of the parathyroid tissue can also greatly help patients at high risk of undergoing further surgery. Cryo-preservation allows the clinician to make appropriate decisions regarding the status of the remaining PTGs. Such enhanced decision-making is important because most patients undergoing parathyroid and thyroid surgery experience only transient hypocalcemia. Differentiating between transient and permanent hypocalcemia is critical, especially after a parathyroidectomy when hypocalcemia may result from bone hunger, rather than from insufficiency of PTH. Cryo-preservation facilitates appropriate surgical and clinical decisions, prevents unnecessary immediate parathyroid auto-transplants, and offers a chance to cure aparathyroidism [73].

Cryo-preservation is a useful and potentially beneficial procedure in only a very small number of select cases of permanent hypocalcemia. The benefit of retaining parathyroid tissue for cryo-preservation following the majority of cases of thyroidectomy remains doubtful, given that rates of permanent hypoparathyroidism are below 1% when selective immediate parathyroid auto-transplantation is used [14]. The cost-effectiveness of maintaining an institutional bank of cryo-preserved parathyroid tissue should also be considered.

15.5.3 Parathyroid Allo-Transplantation

Most studies continue to focus on the prevention of parathyroid dysfunction by careful preservation in-situ and using selective parathyroid auto-transplantation when necessary. Yet the disease burden of post-operative hypocalcemia remains high, with many studies reporting a low level of permanent hypocalcemia despite the use of auto-transplantation. Considering the relative success of parathyroid auto-transplantation and the innate characteristic of parathyroid tissue to be transplanted [91], it is worth considering *allo-transplantation* in the treatment of *chronic* hypoparathyroidism.

15.5.3.1 Allo-Transplantation of Parathyroid Tissue

Unfortunately, to date, allo-transplantation has had variable results usually due to *rejection* by allo-immunization or inflammatory responses, causing fibrosis and compromising graft survival [86, 92]. The risks involved in *immuno-suppression* both from medication side-effects and the risk of infection are generally not considered to outweigh the benefit of long-term treatment for hypoparathyroidism. Yet, Agha et al. argue in a recent case study that this needs to be considered on an individual basis after demonstrating successful allo-transplantation in a 30-year-old with post-operative permanent hypocalcemia who had failed medical therapy [93].

From the very beginning it was clear that major histocompatibility complex (MHC) class I and II antigens are expressed on parathyroid tissue limiting the ability of direct grafting. In the initial animal studies, immuno-suppression used after parathyroid tissue allo-transplantation reduced the risk of graft rejection to <17% compared to 100% in animals left without immuno-suppression [94]. In 1975, Wells et al. published the outcomes of parathyroid allograft transplanted within family members who had previously received a kidney transplant and during a 30-month follow-up the graft remained functional [50]. In the subsequent years, many of such transplantations with varying success rates were reported in the literature [72, 95]. However, taking into consideration the side-effects of life-long immunosuppression, this treatment is hardly acceptable for a relatively indolent disease like iatrogenic permanent hypoparathyroidism. Almost a half of a parathyroid tissue is composed of non-endocrine and highly immunogenic cells. Human leucocyte antigen (HLA) class I antigens are poorly expressed on parathyroid cells, and are not involved in the induction of the process of host versus graft rejection. Hence, a successful and long-term functioning parathyroid allograft is possible when the transplant is free of antigen-presenting cells strongly expressing HLA class II antigens. Thus, allo-transplantation of cultured parathyroid cells, but not parathyroid tissue, allows for the elimination of lymphocytes, macrophages, granulocytes, which represent the so-called "*passenger cells*," and endothelial cells presenting HLA class II antigens, responsible to much extent for graft rejection.

15.5.3.2 Allo-Transplantation of Cultured Parathyroid Cells

Nowadays, allo-transplantation of *cultured parathyroid cells* without immunosuppression (developed by Woźniewicz et al. [1996]) [96] is an alternative to calcium and vitamin D3 supplementation in the treatment of permanent hypoparathyroidism in select patients. However, it took many years to establish the protocol of cultured parathyroid cell allo-transplantation.

The world's first successful cultured parathyroid cells allo-transplantation in humans without immunosuppression for permanent hypoparathyroidism was undertaken by Tołłoczko et al. in Warsaw, Poland, in 1990 [97]. In 1995, this group reported a series of 18 patients who were treated with cultured, hormonally active, living, and ABO-matched parathyroid cells for post-thyroidectomy parathyroid insufficiency. Explants had been taken from two operated patients with secondary hyperparathyroidism. Hormonal activity of the transplanted parathyroid cells under the fascia of the brachioradialis muscle had been confirmed by clinical, biochemical

tests and the level of PTH in blood serum from the vein of the non-grafted arm. Hormonal activity of the graft was variable but lasted up to 14 months [97].

In 2007, Nawrot et al. presented encouraging clinical outcomes of parathyroid cell allo-transplantation for surgical hypoparathyroidism in a series of 85 patients and described a modified technique for preparing the parathyroid grafts using in-vitro *breeding* [98]. The method allowed for obtaining a new parathyroid cell population with a limited expression of immunogenic antigens. As a result of 6 weeks of breeding and freezing, the parathyroid cells markedly decreased their normal HLA class I antigen presenting cell expression and were free of HLA class II positive cells. In this study, cells grown using that procedure were allo-transplanted without immuno-suppression. Sixty patients underwent one allo-transplantation, while 25 patients had a repeat grafting. The cellular allografts remained functional for the mean of 6.35 ± 13.08 months. In 64 patients (55.1%), the allografts remained functional for more than 2 months [98]. This study protocol served as a basis for the development of a clinical protocol of allo-transplantation of cultured parathyroid cells which had been finalized in 2015 and this procedure is nowadays reimbursed in Poland by the National Health Fund. In the years 1990–2016, a total number of 316 parathyroid allo-transplantations and redo allo-transplantations were performed in Warsaw, Poland [49]. Objective improvement, defined as "an increase in serum PTH level and normalization of serum calcium level allowing for decreased substitution with oral calcium and vitamin D3," was observed in 55.1% of patients. In addition, 34.5% grafts remained functioning within 1–6 months, 10.2% within 6–12 months, 6.2% within 12–24 months, and 1.9% within 24–127 months. A remarkable improvement in patient quality of life and return to normal professional and social functioning was observed in the majority of patients with permanent hypoparathyroidism who had properly functioning graft following allo-transplantation [49].

In case of immediately non-functioning graft or function withdrawal, there is still an option of redo allo-transplantation as this method is minimally invasive and free of any adverse effects. Hence, in the twenty-first century, cultured parathyroid cell allo-transplantation without immunosuppression, although still not widely available, is an alternative to substitute the treatment for permanent post-operative hypoparathyroidism in select patients.

In 1983, the idea about the need to encapsulate parathyroid tissue to prevent rejection and increase the transplant vital period arose for the first time [99]. This concept assumed pre-transplant immobilization of cells or tissue into microspheres, which creates a mechanical barrier to immunoglobulins, complement components, and immuno-competent cells of the recipient, and, at the same time, does not hinder transport of nutrients and products of cellular secretion. However, most of these *microcapsules* provoke the development of a non-specific inflammatory response with subsequent peri-capsular fibrosis and imminent failure of graft functionality.

Further research in this area is aimed at developing mechanisms for improvement in graft survival. It was hypothesized that the combination of cultured parathyroid cells and micro-encapsulation could make parathyroid allo-transplantation an even more successful procedure in the management of permanent symptomatic

hypoparathyroidism [95, 100]. Many animal experiments with long-term follow-up have shown that the concept of micro-encapsulation is effective. However, it remains unclear if the microcapsules prevent immunization itself or rather protect the tissues by separation from the immune response. Nevertheless, Cabané et al. (2009) [100] reported also in humans that using such a combined technique allows for maintaining the functionality of the graft for at least 20 months without the requirement of endo-venous calcium supplementation.

The method of micro- and macro-encapsulation of transplanted tissue is based on the principle of creating a mechanical barrier for antibodies and white blood cells, but it allows the nutrition and hormones to diffuse [101]. In 2008, Tretyak et al. [102] demonstrated that grafts of pancreatic islet cells and thyroid cells into the blood stream may preserve viability and long-term functioning without the use of immunosuppression; they concluded that bloodstream is one of the immunologically privileged sites [102].

More recently, in 2016, Khryshchanovich et al. [103] reported their results of allo-transplantation of macro-encapsulated parathyroid cells in a 39-year-old woman (recipient), who had undergone total thyroidectomy for Hashimoto thyroiditis at the age of 23 years. At 3 months post-transplantation, the patient was symptom free, had no hypocalcemia on lowered doses of oral substitution therapy, and did not need intravenous (IV) calcium after allo-transplantation. Moreover, Doppler ultrasound showed a fixed graft with no stenosis or thrombosis of the deep femoral artery. These preliminary results suggest the possibility of using macro-encapsulated parathyroid allograft as an alternative treatment of severe hypoparathyroidism.

In their study, Khryshchanovich et al. [103] reported that parathyroid tissue was obtained from a 27-year-old man with parathyroid hyperplasia secondary to renal failure. Isolation of parathyroid donor tissue and cell culturing were performed under sterile conditions. Gland samples were delivered to laboratory in a transport medium based on Dulbecco's modified eagle medium, containing 10% adult bovine serum and antibiotics (Gentamycin 100 μg/mL and penicillin 100 U/mL). Storage time of the biomaterial to cell seeding was not more than 5 h at a temperature of 4 °C. Isolation of the cell biomass was carried out by mechanical grinding of tissue fragments to the size of 0.1–2 mm^3 and enzymatic treatment with collagenase type II (1%), trypsin (0.25%), and DNase (0.01%). The time of incubation with enzymes was 18 h at 4 °C, followed by 10 min at 37 °C, and then cryopreservation. The duration of cryopreservation before transplantation was 30 days. The concentration of PTH in the culture fluid after thawing was 1385 pg/mL. To determine cell phenotype, an immuno-cytochemical study of culture smears was performed using monoclonal antibodies to human PTH. Subsequent culturing confirmed sterility of the graft.

The macro-capsule was designed as a cylindrical tube 15–20 mm in length and 3–4 mm in diameter from a microporous, 157-μm thick, polyvinylidine difluoride artificial membrane with a pore diameter of 0.55–1.37 μm and a porosity of 28.2%. Then, approximately (20–30) × 10^6 parathyroid cells were injected to the lumen of the capsule.

Under spinal anesthesia, the encapsulated graft was implanted into the lumen of the deep femoral artery, followed by plastic repair of the arteriotomy using an auto-venous patch. Artery patency was confirmed by palpation at the end of the operation and by Doppler sonography in the post-operative period.

In conclusion, parathyroid allo-transplantation is a potential option for the treatment of long-term hypoparathyroidism; however, it does not negate the importance of in-situ preservation and parathyroid auto-transplantation in total thyroidectomy. Khryshchanovich et al. [103] believed that transplantation of macro-encapsulated (cryo-preserved) parathyroid cells may become the method of choice in the treatment of severe forms of hypoparathyroidism. Along with the low trauma of the surgical intervention and the possibility of its performance in most surgical hospitals, an additional advantage is the possibility of repeated transplantation in the case of a decrease in parathyroid graft function. Further investigations about the porosity, biocompatibility, and stability of the micro-porous membranes are definitely still required.

15.6 A Novel Device for Parathyroid Auto-Transplantation

Secondary hyperparathyroidism (SHPT) is a frequent complication of end-stage renal disease (ESRD) causing metabolic bone diseases, severe atherosclerosis, and undesirable cardiovascular events [104]. Although advances in the medical treatment of SHPT have reduced the need for surgery, parathyroidectomy is still required for 10–30% of the patients with more than 10 years of hemodialysis [105]. The best surgical approach for the treatment of SHPT is still controversial. Either subtotal parathyroidectomy or total parathyroidectomy could be performed with or without auto-transplantation [106]. Auto-transplantation of parathyroid grafts into the sternocleidomastoid (SCM) muscle has been widely used; however, early in 1979, Wells Jr. et al. demonstrated that the forearm muscle can be more advantageous [107]. Subcutaneous injection or transplantation of parathyroid tissue in the forearm has also been reported to be effective in patients of chronic renal failure (CRF) [62]. However, parathyroid tissues should be sliced into a suitable size for immediate injection. To shorten the preparation time, Zhang et al. [108] recently (2018) reported the successful use of a novel stainless steel squeezing device that has been designed by Jianping Huang and given a Chinese utility model patent (ZL 2016 20280921.2).

In their prospective study, Zhang et al. [108] studied six patients who have been on hemodialysis for 5 years and have received unsatisfactory medical treatment with calcitriol and vitamin D for 6 months for reducing iPTH. Patients underwent endoscopic parathyroidectomy and auto-transplantation by the same surgical team. With the patient in the supine position and the neck extended, a 10-mm incision was made in the intersection point of the median thoracic line and the two nipples. A metal rod with blunt round end was used to create a straight-line tunnel toward the sternal notch. Two 5-mm incisions were made in the intersection point of the bilateral midclavicular line and the second rib. Two 5-mm metal rods were also used to create straight line tunnels.

After blunt dissection, three trocars were inserted through each tunnel. Carbon dioxide gas was injected with a pressure of 8 mmHg. A 30-degree 10-mm endoscope was inserted through the 10-mm middle trocar. An ultrasonic scalpel and a pair of grasping forceps were inserted through the two 5-mm trocar.

The sub-platysmal space was dissected to create a working space from the suprasternal fossa to the thyroid cartilage level and laterally to the medial edge of the SCM muscles. A longitudinal incision of the linea-alba cervicalis was made, and the bilateral infrahyoid muscle groups were transected to expose the thyroid gland. The posterior surface of the thyroid was explored to find the parathyroid glands (PTGs).

The removed PTGs were carefully examined in order to select a non-nodular area rich in stromal fat cells for immediate graft implant. The selected parathyroid fragment was gently diced into small pieces measuring approximately 2.0 mm^3. The novel device is a metal sleeve that could easily be put into a syringe. The metal sleeve is composed of two parts: the outer part is a hollow tube with multiple holes and the inner part is a solid core.

Parathyroid fragments were roughly diced, put into the metal sleeve, and squeezed in a syringe. The parathyroid tissue after squeezing was mixed with normal saline and injected into the brachioradialis muscle in the forearm without the formation of an arterio-venous (A-V) fistula for hemodialysis. Compared to implantation in forearm muscles, considerable time was saved by using this novel device. A pathological examination revealed that at least 80% of the parathyroid cells remained active.

All six patients underwent endoscopic parathyroidectomy successfully without any complications. The preparation time of parathyroid fragments for auto-transplantation was less by 10 min in each of the six patients as compared to the conventional methods. Using the squeezing device had saved much time while keeping parathyroid tissues active for further injective transplantation. The clinical symptoms and the biochemical index of SHPT were significantly improved. Pruritis and bone pain disappeared within 6 months. By the third post-operative day, the serum calcium level dropped to within the normal range in all patients. Recurrence of graft-dependent HPT was not observed in any of the patients during a 6-month follow-up. However, more data is definitely needed for statistical comparison [108].

15.7 Summary

The most common complication of total thyroidectomy is parathyroid insufficiency. Parathyroid identification and preservation in-situ with good vascular supply is the mainstay of safe thyroid surgery. However, if the PTGs are damaged, incidentally removed, or their blood supply is jeopardized, auto-transplantation should be undertaken to preserve their function. Parathyroid transplantation can be considered in three distinct modes of application: (1) fresh parathyroid tissue auto-transplantation during thyroidectomy to reduce the risk of permanent hypoparathyroidism; (2) cryo-preserved parathyroid tissue auto-transplantation in patients with permanent hypocalcemia; and (3) parathyroid allo-transplantation in patients with permanent

hypoparathyroidism when cryo-preserved parathyroid tissue is not available for grafting. Allo-transplantation of cultured parathyroid cells without immunosuppression should be taken into consideration in select patients as an alternative to treatment with calcium and vitamin D3 for permanent hypoparathyroidism. Application of a novel squeezing device is an economic, effective, and safe way in endoscopic parathyroidectomy and auto-transplantation for patients with SHPT.

Functional viability of PTGs may best be assessed by visual inspection and the use of IOPTH. An approach of *selective* auto-transplantation of devascularized glands provides an effective means of restoring parathyroid function and is protective against permanent hypoparathyroidism. Some centers use *routine* auto-transplantation to reduce the risk of permanent hypoparathyroidism. Novel fluorescence techniques to aid in parathyroid detection during thyroid surgery are under evaluation. Transplantation of macro-encapsulated parathyroid cells may become the method of choice in the treatment of severe forms of hypoparathyroidism.

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Parathyroid Cancer

16

16.1 Introduction

Parathyroid carcinoma is a rare endocrine malignancy derived from the parenchymal cells of the parathyroid glands (PTGs). It accounts for 1–5% of all cases of primary hyperparathyroidism (PHPT) and presents a clinical challenge in diagnosis, management, and adjuvant therapy [1–5]. It is usually associated with more profound clinical and laboratory manifestations than its more common benign counterparts, presenting with symptoms of hypercalcemia, renal failure, nephrolithiasis, osteoporosis, cardiac or neuro-cognitive dysfunction, and dramatic elevations in serum calcium or parathyroid hormone (PTH) or presentation with hypercalcemic crisis. Unlike other malignancies, most patients die because of metabolic complications of parathormone (PTH)-related hypercalcemia rather than tumor invasion and spread [6–10].

The first case of metastatic parathyroid carcinoma causing manifestations of Recklinghausen's disease was reported in 1933 by Sainton and Millot [11], although the very first description of this malignant neoplasm was probably made by De Quervain in 1904 [12].

Generally, pre-operative imaging modalities are *unhelpful* in distinguishing between benign and malignant parathyroid disease. In many cases, diagnosis of parathyroid carcinoma is suspected intra-operatively. Definitive post-operative diagnosis may also be challenging since the histology of parathyroid tumors may be equivocal or misleading [13, 14]. Malignancy is often confirmed on a clinical basis only when local or distant metastases occurs [1, 15].

Recent advances in the molecular pathogenesis of the disease will lead to the development of more reliable diagnostic markers [16–25]. Given the rarity of parathyroid carcinoma, controversies exist regarding the management, staging, follow-up, and opportunities for large-scale studies. Currently, surgery remains the most effective therapy for parathyroid carcinoma since the ultimate prognosis depends upon complete successful excision at initial operation [1, 8, 9, 26–28].

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16.2 Epidemiology

Parathyroid cancer accounts for approximately 1% of cases of PTH-dependent hypercalcemia. It accounts for <100 cases per year in the United States. Fewer than 1000 cases have been reported in the entire English-language literature [15]. A meta-analysis [29] including 20,225 cases of PHPT revealed only 0.74% of parathyroid carcinoma. The largest series collected by the National Cancer Data Base reported 286 cases in a 10-year period, accounting for 0.005% of all cancer with no predominance with respect to *race* or *geographic* regions [2]. However, the incidence appears to be higher (approximately 5%) in the Japanese and Italian series [1, 3–5]. It remains unknown if this discrepancy is related to genetic, geographic, environmental, epidemiological reasons, or to varying pathological criteria for its diagnosis.

Unlike benign parathyroid disease, in which females predominate over males by 3–4:1, men and women are usually equally affected by parathyroid carcinoma [6, 10, 15, 30–33]. Age at diagnosis is approximately a decade earlier as compared to benign PHPT (in the mid-40s or 50s) [6, 10, 15, 30–33], although patients as young as 8 years have been reported in the literature [34].

16.3 Etiology/Risk Factors

The etiology of parathyroid carcinoma is largely unknown. Several *risk factors* have been reported including neck irradiation, chronic stimulation from long-standing hypocalcemia, and familial HPT [7, 15, 35–38]. Prior *neck irradiation* has been documented in some cases, with a reported latency of more than 20 years [39, 40]. However, its role is less evident than in the development of benign parathyroid disease [31, 38–42]. *End-stage renal disease with secondary HPT* has been reported in a subset of patients with parathyroid carcinoma [43], with an average latency of 6 years following the start of hemodialysis. The clinical course in such patients is more indolent because of the tendency of renal insufficiency to lower serum Ca levels [43, 44]. It is noteworthy that the prevalence of parathyroid carcinoma remained constant despite the increased number of hemodialyzed patients in recent years, suggesting an uncertain pathogenetic role of renal failure [2, 8, 9].

Although parathyroid carcinoma is usually a sporadic tumor, it has also been reported in associations with hereditary variants of HPT [45–50], especially in *hyperparathyroidism-jaw tumor syndrome* (HPT-JT), which is an autosomal dominant disease with incomplete penetrance and variable expression. It is characterized by multiple parathyroid tumors, with a significantly increased prevalence of carcinomas and atypical adenomas (10–25% of cases), ossifying fibromas of mandible (Fig. 16.1) and/or maxilla (5–30% of cases), uterine tumors in about 60% of cases (leyomiomas, endometrial hyperplasia, adenomyosis, adenosarcomas, and adenofibromas), and a variety of renal lesions in 5–15% of cases (hamartomas, polycystic disease, Wilms' tumor, and adenocarcinoma) [16, 51, 52].

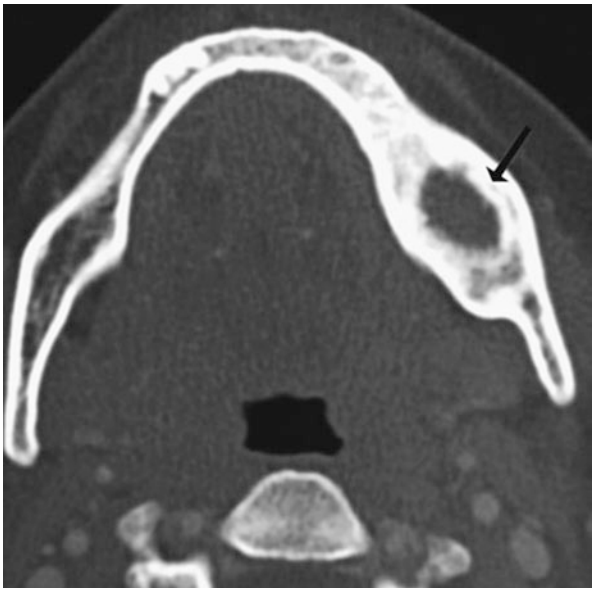

Fig. 16.1 CT scan showing ossifying fibroma of the left ramus of the mandible in a young patient with HPT-JT (arrow)

16.4 Pathogenesis

Hyperparathyroidism—jaw tumor syndrome (HPT-JT) is caused by mutations in the tumor suppressor gene HRPT2 (CDC73), located on chromosome 1q25–31, which encodes parafibromin, a nuclear protein with anti-proliferative properties [16, 37, 53, 54] involved in the cell ycle control, with a role in the transcription elongation, in the RNA processing pathways, and in the histone methylation [55–64]. Parafibromin participates in transcription regulation by interacting with the polymerase II-associated factor 1 transcription elongation complex [57]; it may inhibit cell proliferation by inducing cell cycle arrest by blocking the cyclin D1 expression [60, 65].

In HPT-JT patients, inactivating mutations lead to abnormal hemizygosity; loss of heterozygosity after chromosomal deletions or further inactivating mutations in the remaining copy of the gene cause a biallelic HRPT2 inactivation, with subsequent premature codon stop and/or production of a truncate, inactive, or easily degradable parafibromin [16, 66].

Parafibromin inactivation has been confirmed by immunohistochemical and functional studies, which showed that HRPT2 mutations result in the loss of parafibromin expression [25, 51, 59, 67, 68] or abnormal sub-cellular localization [62, 63], and subsequent abolition of its anti-proliferative activity [60]. The loss of parafibromin expression could be a pivotal step in parathyroid oncogenetic process; in fact, it is considered the distinctive feature in *all* affected PTGs in HPT-JT patients and in nearly one-third of sporadic parathyroid carcinoma cases [21, 25, 51, 52, 68] suggesting also a diagnostic role for this protein. They are rare in sporadic parathyroid adenomas [17–19, 26, 69–72]. This finding supports the hypothesis that a

subset of patients with apparently sporadic parathyroid carcinomas may have the HPT-JT syndrome or a variant with altered penetrance of the mutation [6, 13, 19, 37, 69, 73]. Thus, every patient with sporadic parathyroid carcinoma should be tested for germ-line HRPT2 mutations.

A few cases of parathyroid carcinoma occurring in an *MEN-1* setting have been described in the literature [74, 75]. Somatic mutations of the MEN-1 gene have also been rarely reported in parathyroid carcinoma [55, 76], suggesting a limited role for Menin in the pathogenesis of parathyroid malignancies. Only one case of parathyroid carcinoma has been observed in patients with MEN-2A and none in MEN-2B [77].

Many other tumor suppressor genes and oncogenes have been related to parathyroid cancer, especially those that have a role in the control of the cell cycle as retinoblastoma (Rb), breast carcinoma susceptibility (BRCA2), p53, and cyclin D1/parathyroid adenomatosis gene 1 (PRAD1) genes [6, 10, 15]. P53 is another important cell cycle regulator, which has been considered as a candidate for malignant parathyroid tumors, but the frequency of abnormal p53 expression in parathyroid carcinomas is low [10].

Some studies reported an over-expression of the oncogene cyclin D1 in only 20–40% of patients with parathyroid adenoma and in up to 91% of those with parathyroid carcinoma. Still, however, it is unclear if this feature is causative or only an association [10, 37].

16.5 Clinical Presentation

The majority of parathyroid cancers have little tendency to local invasion and clinical manifestations from tumor burden occur late [10, 78–80]. Because these are functioning tumors, the most frequent symptoms and signs are related to HPT and hypercalcemia [10, 79, 80], and so are the main causes of death [1, 6, 7]. Generally, manifestations of HPT in parathyroid cancer are indistinguishable from those in patients with benign disease, although they are usually more severe [10, 30]. Hypercalcemia may result in fatigue, malaise, weakness, weight loss, anemia, depression [6, 15, 33, 37, 78], lethargy, confusion, and coma [33]. Hyper-calcemic crisis, although rare (about 10%), is more commonly associated with parathyroid carcinoma than with benign tumors [6, 7, 10, 13, 47].

The classic target organs, such as the kidneys and the skeleton, are mostly affected at the time of presentation, unlike in benign disease, in which the kidneys and the bones are involved in 20% and 5%, respectively [8–10]. In parathyroid cancer, polyuria, polydipsia, renal colic, nephrolithiasis, nephrocalcinosis, and impaired renal function occur in up to 80% of cases. Bone impairment includes diffuse osteopenia, pathological fractures, and bone aches that occur in approximately 90% of cases [10, 81–83]. Radiological findings such as sub-periosteal resorption, "salt and pepper" skull, and osteitis fibrosa cystica are seen in more than 40% of patients (Fig. 16.2). Gastrointestinal symptoms such as nausea, vomiting, abdominal pain,

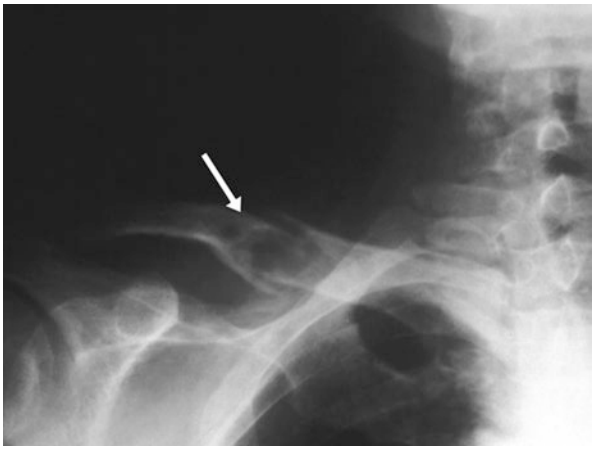

Fig. 16.2 Plain X-ray of the right clavicle showing a pathological fracture of a lytic bone lesion (Brown's tumor) (white arrow)

Table 16.1 Clinical features of parathyroid carcinoma

Organ/system	Clinical features
Renal	Polyuria, polydipsia, stones, nephrocalcinosis, renal failure
Skeleton	Bone aches, sub-periosteal resorption, salt and pepper skull, osteitis fibrosa cystica, osteopenia, pathological fractures
Neuromuscular	Fatigue, myalgia, headache, muscle weakness, pruritis, mental disturbance, RLN palsy
Rheumatological	Joint pains, gout, chondrocalcinosis, calcific tendonitis
Gastrointestinal	Anorexia, nausea, vomiting, constipation, peptic ulcer, pancreatitis
Cardiovascular	Arrhythmias, reduced QT-interval
Cornea	Calcification, band keratopathy

peptic ulcer, recurrent severe pancreatitis, and constipation occur with greater frequency in patients with malignant disease than in those with benign PHPT.

Non-functioning carcinomas are extremely rare (2% of all parathyroid malignancies) and usually show only signs and symptoms of local growth and invasion, including neck mass, hoarseness of voice, and dysphagia [84]. As opposed to functional parathyroid cancer, patients with non-functional tumors eventually die from invasion of vital organs and systemic spread rather than hypercalcemia [33, 84]. Clinical features of PTG carcinoma are shown in Table 16.1.

Physical examination in patients with parathyroid carcinoma is generally unrevealing, but the presence of a paralyzed vocal cord and a palpable cervical lymph node (LN) may predict the presence of a parathyroid malignancy. In fact, a paralyzed vocal cord in a patient with HPT not previously subjected to neck surgery may predict a parathyroid carcinoma on the side of paralysis. Palpable cervical LNs are found in less than 5% of patients with benign parathyroid lesions, as compared to 15–70% of patients with parathyroid carcinoma [1–5, 8–10, 80, 85–88]; however, these findings have become less frequent in the recent years because the diagnosis is possibly performed earlier [2, 33].

16.6 Diagnosis

Diagnosis of parathyroid carcinoma may be suspected pre- or intra-operatively but, in most cases, it is made post-operatively by histological examination. In some equivocal cases, even pathology may be inconclusive, and the diagnosis is confirmed only by the clinical course at a prolonged follow-up by the occurrence of metastases [1, 6, 7, 13, 14].

16.6.1 Pre-operative Diagnosis

Pre-operatively parathyroid cancer can only be suspected by means of clinical, laboratory, and radiological examinations [7–10]. However, these features may be frequently absent and so pre-operative confirmation is very difficult and may even be impossible. Only the presence of local invasion or distant metastases can definitively confirm the diagnosis, but these are rare at initial presentation [1, 6, 15, 30, 33, 89].

16.6.1.1 Clinical Features

Clinical suspicion should rise if the patient is an adult male or female [6, 7, 10, 15, 30–33], with a palpable neck mass, renal and/or skeletal disease from HPT, peptic ulcers, pancreatitis, or RLN palsy [6, 10, 14, 32, 76, 90–93]. The average age of patients is nearly 40–50 years, one decade younger than those with benign disease [6, 10, 15, 30, 33]. Contrary to benign disease, where most patients are asymptomatic, parathyroid cancer patients usually show clinical features of end-organ disease and more frequent renal and/or bone involvement [6, 10, 15, 30, 31, 33, 93].

16.6.1.2 Laboratory Studies

The biochemical abnormalities observed in benign PHPT are usually over-expressed in parathyroid carcinoma. Patients with parathyroid carcinoma have PTH levels 3–10 times above normal values and Ca levels above 3.5 mmol/L; sometimes they show hypercalcemic crisis [6, 7, 36]. On the other hand, serum PTH and calcium levels are usually only mildly raised in benign disease [6, 8, 9, 15]; however, no predictive cutoff values have been indicated [94].

Different PTH molecules (other than the usual intact human 1–84 PTH) may be produced by parathyroid carcinoma, especially N-terminal fragments that can be selectively identified by modern laboratory techniques, although the diagnostic value of this finding needs to be further assessed [95, 96]. Paraneoplastic production of α- and β-subunits of human chorionic gonadotropin (HCGT) has also been detected in these patients [96, 97].

16.6.1.3 Fine-Needle Aspiration Cytology (FNAC)

Benign and malignant disease cannot be effectively differentiated on cytology, and so fine-needle aspiration cytology (FNAC) of a suspected parathyroid carcinoma is *not* recommended. In addition, a case with cutaneous spread of parathyroid

carcinoma after FNAC leading to higher chances of recurrence was reported in 2000 by Spinelli et al. [98]. Furthermore, false negative and false positive results may be caused by sampling errors and by degenerative changes following FNA that closely mimic parathyroid carcinoma at final pathology. However, FNAC may be useful in distinguishing thyroid from parathyroid tissue or in identifying metastatic parathyroid carcinoma [99–101].

16.6.1.4 Imaging Techniques

Various imaging modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and Sestamibi scintigraphy (MIBI) can be used to investigate parathyroid carcinoma. They are rarely diagnostic but are effective in assessing the size and localizing the PTGs. Imaging studies are *optional* at initial presentation, but *mandatory* in case of recurrent or metastatic disease before surgery [102, 103]. Ultrasonography (US) and Technetium-99m (^{99m}Tc) Sestamibi are the first line imaging studies [101–106].

Ultrasonography (US)

There have been a few studies on the contribution of ultrasound (US) in the diagnosis of parathyroid carcinoma (compared with parathyroid adenoma). Generally, parathyroid carcinoma appears on US as a large hypoechoic soft tissue mass with poorly defined margins and, possibly, signs of local invasion; LN metastases can be also accurately detected [78]. A study (2011), by Sidhu et al., of 69 cases of parathyroid lesions >15 mm in size, of which eight (11.6%) were carcinomas, and the rest adenomas, examined the useful differentiating sonographic features [107]. It was found that the presence of invasiveness or calcification of the lesion had a 100% positive predictive value (PPV) for carcinoma. Conversely, those features with a high negative predictive value (NPV) were (1) the absence of suspicious vascularity [radial vascularity without clear feeding vessels] (NPV 98%), (2) the absence of a thick capsule (NPV 97%), and (3) the homogeneity of contents (NPV 100%). The presence/absence of necrotic/cystic change is sufficiently common in benign disease—that it only has a limited role as a discriminator. *Features favoring parathyroid carcinoma* were (1) heterogeneity of contents, (2) lobulated morphology, and (3) large size (often >3 cm). On the other hand, *features favoring parathyroid adenoma* were (1) homogeneity of contents, (2) regular morphology, and (3) smaller size.

More recently, Nam et al. [108] compared the US features of parathyroid carcinoma ($n = 7$) and parathyroid adenoma ($n = 32$) in patients with PHPT. Compared to parathyroid adenomas, parathyroid carcinomas were significantly larger (3.5 vs. 1.9 cm; $p = 0.0133$) and exhibited higher incidences of heterogeneous echotexture ($p = 0.0002$), irregular shape ($p < 0.0001$), non-circumscribed margin ($p < 0.0001$), intra-nodular calcifications ($p = 0.014$), and local invasion ($p = 0.0004$).

In a similar comparative study, Liu et al. [109] compared the sonographic features of 21 patients with parathyroid carcinoma and 64 consecutive patients with benign parathyroid lesions, whose diagnoses were confirmed at surgery. On US imaging, parathyroid carcinoma exhibited significantly higher incidences of larger size and higher depth/width (D/W) ratio, heterogeneous echotexture, irregular

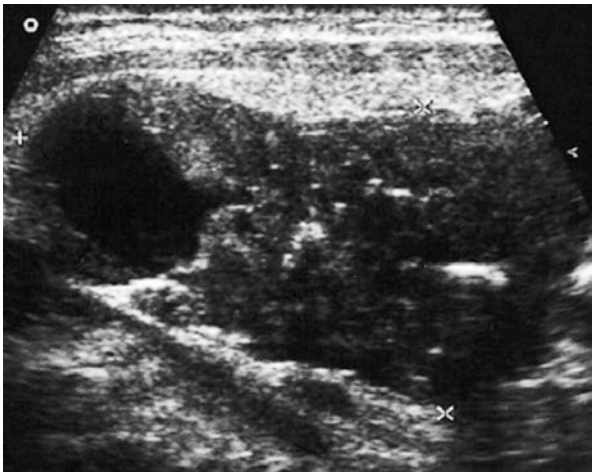

Fig. 16.3 Ultrasound of parathyroid carcinoma showing a tumor with cystic degeneration and calcifications

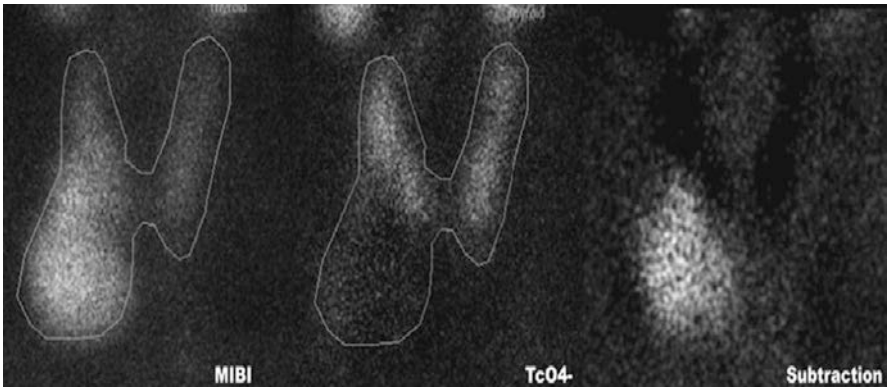

Fig. 16.4 Sestamibi scan (MIBI, Technetium, and subtraction images) showing a large right inferior parathyroid lesion that histologically proved to be parathyroid carcinoma

shape, non-circumscribed margin, intra-nodular calcifications, indistinct border, cystic change, and the presence of suspicious LNs compared to benign parathyroid lesions (Fig. 16.3).

Sestamibi Scintigraphy (MIBI)/SPECT

Sestamibi scintigraphy (MIBI) is a radio-pharmaceutical scan with a high affinity for the mitochondria of parathyroid tissue. It may localize abnormal parathyroid tissue with a high sensitivity of 85% and specificity of 95%, particularly with the adoption of the dual subtraction technique (Fig. 16.4) [101–105].

Specifically, parathyroid scintigraphy by ^{99mTc}Sestamibi Single Photon Emission Computed Tomography (SPECT) is considered a conventional analysis to detect abnormal parathyroid glands. For qualitative analysis of ^{99mTc}Sestamibi SPECT, lesions with no demonstrable uptake and those with diffuse heterogeneous or

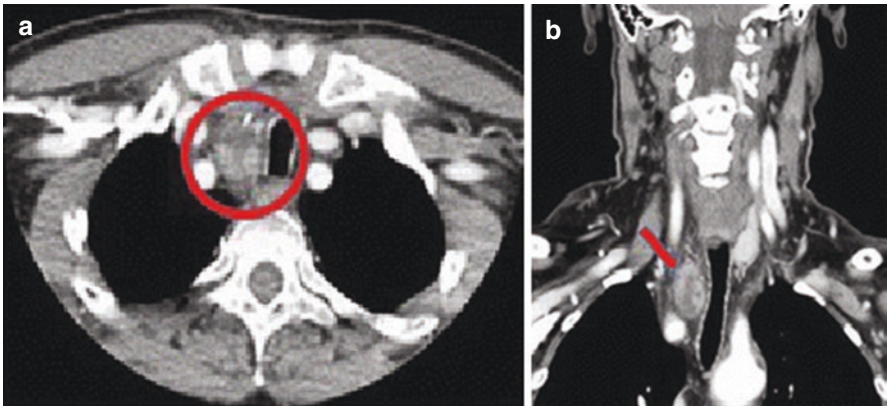

Fig. 16.5 Contrast CT scan (**a**) Transverse view demonstrating parathyroid gland with possible tracheal invasion (red circle); (**b**) Coronal view suggesting possible tracheal involvement by parathyroid mass (red arrow)

minimal patchy uptake are considered negative, whereas lesions with scattered patchy uptake, partially focal uptake, or any other focal uptake are regarded as positive [110].

Contrast Computed Tomography (CT) Scan

Contrast CT scan is useful in providing some details on the localization of the lesion and revealing invasion of surrounding structures and enlarged LNs. It is more sensitive in detecting recurrent and metastatic parathyroid carcinoma, especially at mediastinal, pulmonary, hepatic, and bone sites [103]. Occasionally imaging findings may suggest tumor invasion and raise a suspicion of parathyroid malignancy as well (Fig. 16.5). Invasion of surrounding structures at the time of operation also points toward a diagnosis of parathyroid carcinoma [111].

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) with gadolinium and fat suppression gives the best details on the soft tissues of the neck; it is the investigation of choice for localizing an ectopic gland in the mediastinum and for the characterization of metastatic lesions at specific sites such as liver and bone. During assessment of recurrence, MRI also avoids the artifacts produced by surgical clips that make CT interpretation difficult [15, 78, 106]. However, US, CT, and MRI, although sensitive, have a limited specificity, because they are *not* able to differentiate between recurrence and non-neoplastic masses (e.g., LNs, scar tissue), while MIBI scan is more sensitive and specific in detecting the sites of recurrent and metastatic disease [102, 103].

Positron Emission Tomography (PET) Scan

Very few reports exist on the use of fluoro-deoxyglucose positron emission tomography *(FDG-PET)* in parathyroid carcinoma. Primary parathyroid carcinoma, and recurrent and metastatic lesions have a mild increase in metabolic activity; however,

it should be remembered that also lytic bone lesions appear hyper-metabolic at FDG-PET scan and can be mistaken as bone metastases [112]. The classical nuclear bone scans also show increased bone turnover consistent with metabolic bone disease both in Brown's tumors and metastatic lesions; in these cases, a whole-body MIBI scan helps differentiate Brown's tumors from metastatic bone disease [112].

Selective Venous Catheterization with PTH Measurements

In case of *recurrent* disease, if non-invasive imaging is inconclusive in identifying the lesion, selective venous catheterization with PTH measurements has been recommended, or, as an alternative, at least two concordant non-invasive localization studies should be performed before embarking on surgery in order to avoid negative re-explorations [102, 103].

16.6.2 Intra-operative Diagnosis

Parathyroid carcinoma may be intra-operatively suspected if glands are particularly large (>3 cm if solid), lobulated, firm to stonyhard, whitish-gray, surrounded by a dense, fibrous, grayish-white capsule, with tenacious adhesion to adjacent structures, or if local LN involvement, though rare, is found [76, 87, 113, 114]. However, the surgical gross appearance of parathyroid cancer may sometimes be indistinguishable from benign disease as it may simulate degenerative changes in parathyroid adenomas [14, 115].

Intra-operative frozen-section may sometimes suggest the diagnosis (e.g., dense fibrosis, nuclear monotony), but it is usually of little value in distinguishing benign from malignant disease. In addition, it may cause artifactual dislodgement that can cause false positive results at definite post-operative histology [13].

16.6.3 Post-operative Diagnosis

16.6.3.1 Gross Appearance

Grossly, the malignant PTG is usually large, typically with a weight between 2 and 10 g, firm, solid, whitish-gray, and adherent to the adjacent structures (Fig. 16.6).

16.6.3.2 Histopathological Pathognomonic Criteria

Parathyroid carcinoma may demonstrate a uniform appearance in a nodular or trabecular pattern. The most used histopathological criteria for parathyroid carcinoma, established by Schantz and Castleman in 1973 [87], include the presence of uniform sheets of chief cells arranged in a lobular pattern (Fig. 16.7) separated by dense, thick fibrous trabeculae that extend into and divide the gland (Fig. 16.8); atypical mitotic figures within tumor cells (Fig. 16.9), invasion of peri-glandular soft tissue (Fig. 16.10), and vascular or capsular invasion (Fig. 16.11).

Epithelial cells of parathyroid carcinoma are larger than normal cells; mitotic activity is present in 80% of carcinomas (60% of adenomas) [116]. However, a high

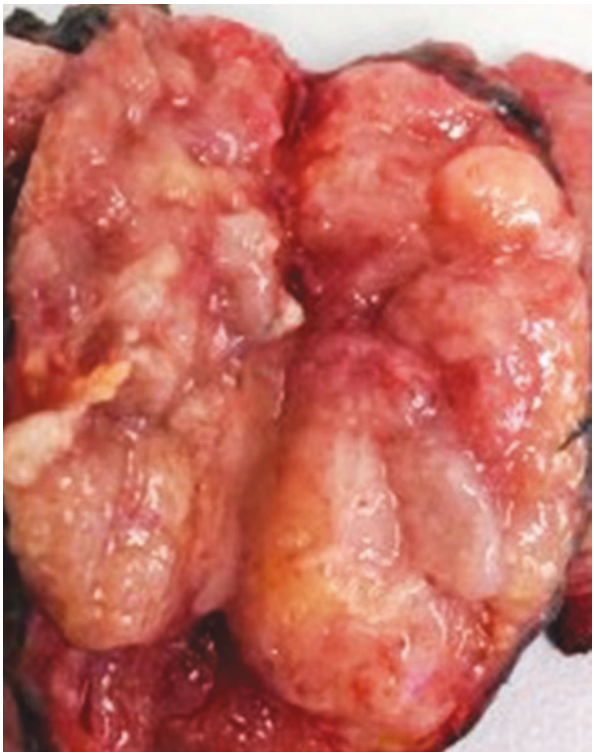

Fig. 16.6 Surgical specimen: parathyroid carcinoma; necrosis and degenerative changes seen in the sectioned specimen

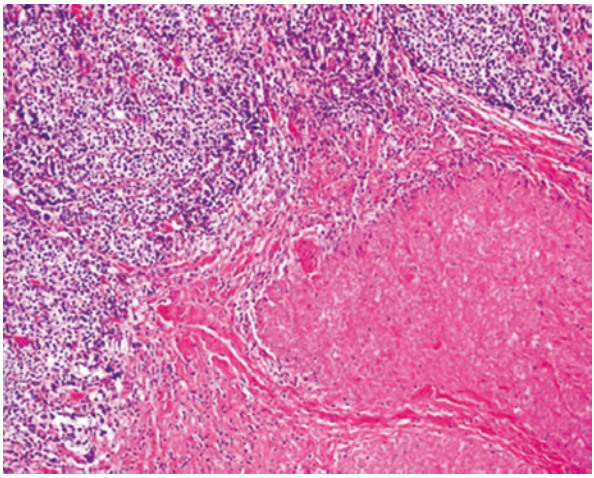

Fig. 16.7 Histological section of parathyroid carcinoma showing solid (sheet-like) proliferation of monotonous cells with solid growth pattern, focal tumor necrosis, and fibrous bands within the tumor (H&E, 100×)

mitotic rate (>5 per 50 high-power fields) and atypical mitoses indicate an increased risk of malignant behavior [117]. Giant cells and/or focal necrosis may also be present [14, 36, 118, 119]. Dense fibrous trabeculae and trabecular growth pattern have also been found in parathyroid adenomas, especially, in the presence of

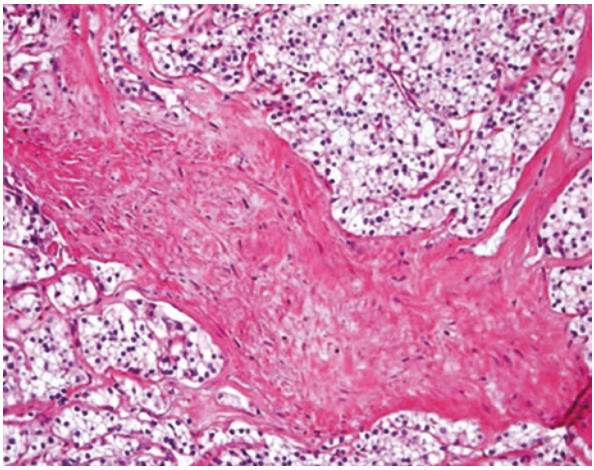

Fig. 16.8 Histological section of parathyroid carcinoma showing neoplastic clear cells separated by broad bands of fibrous tissue (H&E 200×)

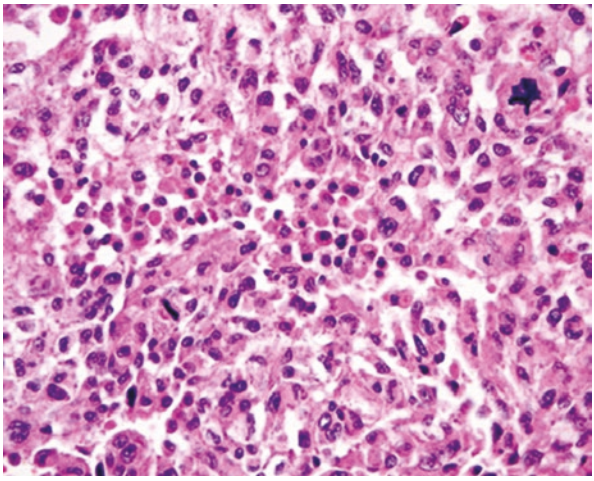

Fig. 16.9 Histological section of parathyroid carcinoma showing high mitotic activity with atypical figures (H&E, 400×)

degenerative changes [13], which have been reported to be caused also by preoperative FNA [105, 106].

True *capsular invasion* is evident only in a limited portion of early cases [75, 85] and should be distinguished from entrapment of tumor cells within the capsule, which may be particularly prominent in adenomas that have undergone cystic regressive transformation. *Vascular invasion* is evident even in fewer cases [75, 85] and should be diagnosed only in cases of vessels resident within the tumor capsule or in the surrounding soft tissues.

Adopting current histopathological criteria [117], only capsular and adjacent tissue invasion (60% of cases), vascular invasion (10–15%), and peri-neural space invasion (rarely present) [75, 85, 120] appear to correlate best with tumor recurrence and metastatic course, and can be considered pathognomonic of malignancy.

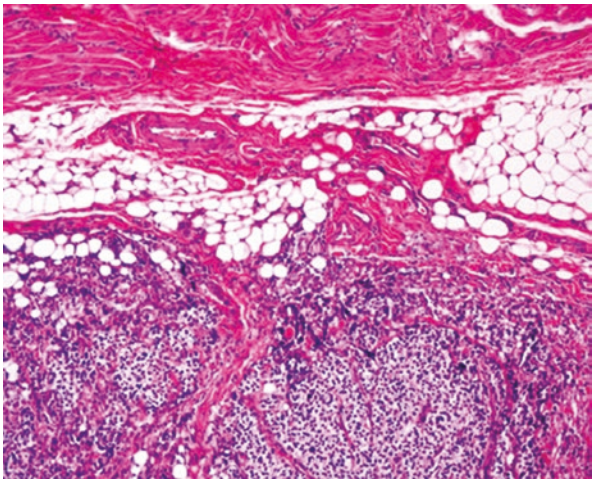

Fig. 16.10 Histological section of parathyroid carcinoma showing the neoplasm invading the peri-glandular soft tissue (H&E, 100×)

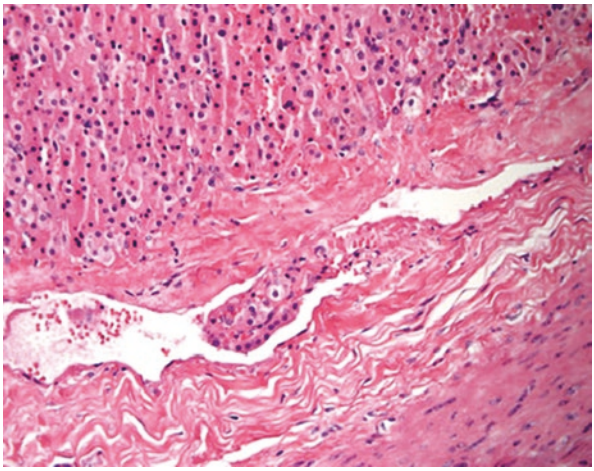

Fig. 16.11 Histological section of parathyroid carcinoma showing vascular invasion in the tumor capsule (H&E, 200×)

True parathyroid carcinoma should be distinguished from parathyromatosis and atypical parathyroid adenoma. *Parathyromatosis*, defined as "miliary seeding of benign parathyroid tissue into surrounding muscle and soft tissue," can occur from embryonic rests of parathyroid tissue or, more frequently, from iatrogenic spillage of parathyroid tissue following intra-operative capsular rupture or incomplete excision of a parathyroid benign lesion [121, 122]. *Parathyromatosis* may appear as small, white plaques of disease, or may not be visible until the final pathological analysis of a specimen is completed. It typically presents as recurrent disease with mild calcium elevations in patients who have had prior parathyroid surgery (particularly subtotal resections for secondary hyperparathyroidism) and can be confused with parathyroid carcinoma [123]. Differentiation of parathyromatosis from the recurrence of a previously excised and possibly under-diagnosed carcinoma is

difficult since both may be associated with extensive infiltration of soft tissues and fibrosis. The presence of vascular and perineural space invasion are helpful features to distinguish recurrent parathyroid carcinoma from parathyromatosis.

Atypical parathyroid adenoma is an equivocal lesion that shares only some of the features of carcinomas (fibrosis, mitoses, eventual capsular invasive growth of the surrounding tissue and vascular invasion) [124]. The behavior of atypical adenomas may not differ from that of adenomas of usual type [125], although late recurrences and metastasis have also been reported, thus requiring a prolonged follow-up [13, 33, 78, 115]. In fact, histology alone will not diagnose all cases [109], since a proportion of parathyroid tumors, which do not meet the histopathological criteria of carcinoma, may recur or rarely metastasize [16, 59]. In contrast, only a subset of tumors diagnosed histologically as "malignant" will show the development of recurrent disease or distant metastases [59, 126].

16.6.3.3 Electron Microscopy

Electron microscopy of parathyroid cancer tissue reveals nuclear and mitochondrial alterations, and evidence of increased secretory activity, but does *not* appear to be of value in distinguishing benign from malignant tumors [89, 127–130]. Nuclear diameter appears to be greater and the chromatin is clumped and dispersed through the karyoplasmas in parathyroid carcinoma, but this index is *not* very useful in the individual case [87, 89, 127–130].

16.6.3.4 Flow Cytometry

Measurement of nuclear DNA content by flow cytometry may be of some value; the mean nuclear DNA content is greater and an aneuploid DNA pattern is more common in parathyroid carcinoma than in adenoma, but is *not* of great value in differentiating between the two conditions [26–28, 131–134].

16.6.3.5 Immunohistochemistry (IHC)

Immunohistochemistry (IHC) staining can assist in the differentiation of parathyroid carcinoma from benign parathyroid disease. Immunohistochemistry of the cell cycle marker *Ki67* has been studied; a count >5% may suggest carcinoma [127, 135], but the overlap of values in equivocal cases has limited the role of this approach [136]. Immunohistochemical staining of the retinoblastoma protein (*Rb protein)* has been suggested to differentiate benign from malignant parathyroid tumors, since it has been reported to be commonly *absent* in parathyroid carcinomas while present in adenomas [137], although controversial results have also been reported [138].

An additional approach has involved the use of *antibodies to p27*, which encodes a cyclin-dependent kinase inhibitor. Carcinomas have a threefold decrease in p27 expression as compared to parathyroid adenomas [139]; however, these findings are difficult to be used in individual cases because their predictive value in reaching a definite diagnosis is often inadequate.

More recently, immunohistochemical evaluation of *parafibromin* (the product of the HRPT2 gene) has become the most commonly used marker for the diagnosis of parathyroid malignancy. Loss of parafibromin may suggest definitive diagnosis with a sensitivity of 68–96% and a specificity of 99% [21, 25]; however, this protein is

also absent in adenomas in patients with HPT-JT [17, 51, 52, 59, 67, 68]. Furthermore, normal parafibromin expression has been reported in 80% of metastatic unequivocal parathyroid carcinomas in a series of patients with chronic renal failure [140]. This finding suggests that genetic events other than HRPT2 mutations may be of significance in the genesis of different subsets of parathyroid malignancies [23, 24, 140]. Recently, also the adenomatous polyposis coli *(APC)* and the protein gene product 9.5 (*PGP9.5*, encoded by ubiquitin carboxyl-terminal esterase L1) have shown a promising role in the diagnosis of parathyroid carcinoma. Loss of APC expression and increased expression of PGP9.5 may be strongly predictive of parathyroid malignancy, especially when associated with the loss of parafibromin expression [22, 141].

In general, a panel of IHC analysis is considered more accurate than any single marker in diagnosing parathyroid carcinoma. Immunohistochemical positivity to loss of expression of parafibromin, retinoblastoma protein (Rb), p27, Bcl-2a, mdm-2, and APC, combined with positivity for galectin-3, over-expression of p53, and increased Ki67 proliferation index (>5%) have been implied to confirm malignancy in parathyroid tumors. Parafibromin, galectin-3, and bcl-2 are the most helpful ancillary biomarkers.

16.6.3.6 Genetics

The first hereditary syndrome linked to parathyroid carcinoma was the HPT-JT syndrome, derived from inactivating mutations in the gene *CDC73* (previously known as *HRPT2*) [16]. These mutations can occur in over 75% of confirmed (by recurrence or metastases) parathyroid carcinoma, and more importantly, only very rarely (less than 1% of the time) are found in benign parathyroid disease [142]. It has been recommended that all patients with parathyroid carcinoma should be considered for germline testing for *HRPT2*. The *HRPT2* gene is a tumor suppressor that codes for a protein called parafibromin. Since parafibromin expression can be detected via immunohistochemistry (IHC), it can be used to test for parafibromin expression and identify patients with *HRPT2* mutations [142], which have been linked not only to the presence of parathyroid carcinoma, but also to the risk of disease recurrence [76].

As parathyroid carcinoma is a very rare disease, genetic and epigenetic studies may hold the most promise for future developments. Gene alterations between benign parathyroid adenomas and parathyroid carcinomas have been identified [143]. Large-scale epigenetic studies have demonstrated repression of miRNAs in parathyroid carcinoma tissue relative to normal parathyroid glands as well, arguing that further studies on the epigenetic deregulation of parathyroid tumors may provide new strategies for treatment [144].

16.7 Staging

Parathyroid cancer is typically described as localized, metastatic, or recurrent.

- *Localized*: Cancer is only located in the PTG and has not spread to nearby tissues or organs.
- *Metastatic:* Cancer has spread to lymph nodes (LNs) in the head and neck or to other parts of the body, such as the lungs, liver, or bone.

– *Recurrent:* The most common site of recurrence is in the neck. If the cancer does recur, another round of tests and scans will be required to determine the extent of the recurrence.

16.7.1 Staging: New AJCC

In early 2017, the newest edition of the American Joint Committee on Cancer (AJCC) guidelines introduced a staging system for parathyroid carcinoma [145]. Acknowledging that adequate identification of significant prognostic factors has been challenging due to mostly retrospective and single-institution studies, the panel showed a demonstrable difference in cancer-specific survival between patients with disease localized to the neck and those with distant metastatic disease. The proposed registry data collection variables for parathyroid carcinoma included age at diagnosis, gender, race, size of the primary tumor, location of the tumor, presence of invasion into the surrounding structures, distant metastatic disease, number of lymph nodes (LNs) removed, number of positive LNs, highest pre-operative calcium, highest pre-operative PTH, presence of lympho-vascular invasion, histological grade (high grade or low grade), weight of the primary tumor, mitotic rate, and time to recurrence.

As may be seen in Table 16.2, the TNM definitions for parathyroid carcinoma include atypical parathyroid neoplasm (Tis), a common pathological result that may confound treatment strategies. T1 tumors are localized to the parathyroid gland with extension limited to the soft tissue, while T2–T4 tumors directly invade the thyroid gland (T2), surrounding structures such as recurrent laryngeal nerve (RLN), esophagus, or trachea (T3), or major blood vessels/spine (T4). Lymph node disease is quantified by the absence (N0) or presence of disease in the central (N1a) or lateral (N1b) cervical LNs. Likewise, distant metastatic disease is described by the absence of disease outside of the neck (M0) versus evidence of disease not confined to the neck (M1).

Table 16.2 TNM classification of parathyroid carcinoma [145]

TNM		Description
T	*Tis*	Atypical parathyroid neoplasm
	T1	Tumor is localized to the PTG with extension limited to the soft tissue
	T2	Tumor directly invading the thyroid gland
	T3	Tumor invading surrounding structures (e.g., RLN, trachea, esophagus)
	T4	Tumor invading major blood vessels or spine
N	*N0*	Absence of tumor
	N1a	Presence of disease in the central cervical LNs
	N1b	Presence of disease in the lateral cervical LNs
M	*M0*	Absence of metastatic disease outside the neck
	M1	Presence of metastatic disease outside the neck

16.8 Prognosis

Although parathyroid carcinoma usually has a slow, indolent but progressive course because of the rather low malignant potential, its prognosis is quite variable. In fact, more than 80% of cases are described as "well differentiated" by pathologists [2].

The National Cancer Data Base of patients with parathyroid carcinoma [2] reported a cumulative 5-year and 10-year survival of 86% and 49%, respectively. Other series reported a 5-year *survival* ranging from 40% to 90% [146]. *Mortality* usually results from complications of hypercalcemia such as renal failure, cardiac arrhythmias, or pancreatitis, rather than the tumor burden itself [1, 4, 6–10, 80, 101, 103].

The tumor tends to invade the surrounding structures and to spread to regional LNs. In spite of radical excision, local recurrence ranges from 30% to 80% [15], usually in the first 3 years post-operatively [1, 10, 51], though recurrences as late as 20 years have been reported by several authors [10, 28]. Young age and pre-operative high calcium levels have been reported as risk factors for early recurrence [1]. Once the disease has recurred, the chances of cure are remote. However, aggressive resection of residual disease and metastasectomy may improve the survival [1–10]. Tumor cells also disseminate hematogenously, and distant metastases occur in lungs (40%), liver (10%), and bones, although very few patients (<5%) have the involvement of regional LNs or distant sites (<2%) at initial presentation. The presence of vascular invasion is probably the single most important predictor of distant recurrence and metastasis [6, 10].

The most important factor affecting prognosis of parathyroid cancer is the completeness of tumor resection [8, 9, 27]. Patients undergoing complete en-bloc resection have survival rates as high as 90% at 5 years and 67% at 10 years [146]. Negative prognostic factors include LN metastases at the time of diagnosis, distant metastases, and incomplete excision [31]; moreover, patients treated initially with simple parathyroidectomy have a worse prognosis, although in some series, tumor size and LN involvement were not prognostic predictive factors [2].

There is no agreed prognostic staging system for parathyroid cancer. A TNM staging system has been proposed by Shaha [147]. Recently, Talat and Schulte have proposed, in a meta-analysis of 330 cases, a simpler prognostic staging system recognizing low-risk (according to capsular and soft tissue invasion) and high-risk patterns (according to vascular invasion and/or LN or distant metastases or invasion of vital organs), similarly to other neuroendocrine tumors [32]. This categorization may identify a 3.5-fold increased risk for recurrence and 4.9-fold for death in high-risk patients [32].

Aneuploidy has been reported by several researchers to be associated with a poorer prognosis [26–28, 124, 130, 148]; higher proliferation rates (Ki67) within parathyroid carcinomas can predict a more aggressive behavior [2, 140, 148].

16.9 Treatment

16.9.1 Surgical Treatment

16.9.1.1 En-Bloc Resection

The single most effective treatment of parathyroid carcinoma documented in the literature is surgery [6, 7, 31, 33, 76, 113, 148], with the gold standard being "en-bloc" resection of the primary lesion at the time of initial operation [6, 7, 31, 37, 76, 149, 150]. This approach entails parathyroidectomy with the excision of the adjacent ipsilateral thyroid lobe in continuity with the tumor. Any capsular rupture of the tumor and neoplastic spillage should be accurately avoided, since seeding leads to recurrence [1, 7, 31, 37, 76, 78, 151]. Pre-operative status of vocal cord mobility is important [15] and if intra-operatively, the RLN is unequivocally not infiltrated, it should be preserved, otherwise its sacrifice is necessary [7, 15, 30, 33, 37, 78, 102]. Intra-operative assay of quick PTH may confirm the complete removal of all hyperfunctioning parathyroid tissue and may possibly help determine the extent of surgery [37]; in fact, it may predict the persistence of the disease suggesting wider excision or prolonged exploration, but does not prevent late recurrences [152].

Effective surgery is usually followed by severe hypocalcemia due to "hungry bone syndrome," requiring adequate calcium and vitamin D replacement and close monitoring of calcium and PTH levels.

16.9.1.2 More Extended Procedures

More extended procedures have also been proposed, consisting of tumor excision in addition to surrounding soft tissues, ipsilateral hemi-thyroidectomy, skeletonization of trachea, and excision of the strap muscles and of the RLN [76]. However, this approach has been criticized for the possibility of over-treatment of a parathyroid adenoma misdiagnosed as carcinoma [15]. Occasionally, more invasive tumors may necessitate tracheal resections, or may involve portions of the esophagus, blood vessels, or bone [153].

16.9.1.3 Lymph Node Dissection

Therapeutic cervical LN dissection is usually recommended in the case of unequivocal evident nodal metastases [7, 15, 76, 78, 151]; mediastinal dissection, along with, central compartment dissection, may be required for the extension of soft tissue disease through the thoracic inlet [33].

The role of *prophylactic* nodal dissection is still controversial. Many authors reported that nodal metastases are exceedingly rare [1, 26–28, 30, 76] and that prophylactic neck dissection does *not* improve prognosis but may increase morbidity (RLN palsy and post-operative hypocalcemia) [27, 76, 148]. Recently, other authors have suggested a systematic clearance of the *central* compartment (level VI) with prophylactic removal of all soft tissues and central lymph nodes [3, 32, 33, 151]. With this approach, nodal metastases were found in up to 41% of patients and may

be the source of local recurrence [150]. Tumors larger than 3 cm had a greater incidence of lymph node metastases, and larger studies may help identify select populations that would benefit from prophylactic CND in addition to *en bloc* tumor removal [154]. Prophylactic *lateral* compartment clearance in the absence of demonstrable involvement is *not* recommended, given that jugular LN metastases seem to be uncommon and this procedure does not yield therapeutic benefits [85, 150].

16.9.1.4 When Diagnosis Is Made Post-operatively

When the diagnosis of parathyroid cancer is made in the early post-operative period on the basis of histology, as usually occurs, the management plan becomes more complex and the benefits of further radical operations remain controversial. If the serum calcium and PTH levels are normal, most authors tend to follow the patient without attempts at immediate re-operations, given that the first surgery could have been curative [5, 30, 155]. Further explorations of the neck have been proposed in case of persistent hypercalcemia [6, 7, 10], following adequate pre-operative imaging study to localize the disease as accurately as possible [102, 103].

16.9.1.5 Recurrent Disease

Parathyroid hormone level should be checked annually to check for recurrence. In spite of all efforts, most patients experience disease recurrence after initial surgery [7, 10, 102]. Reoperation, in these cases, can be considered a good palliation [1, 6, 10, 27, 31, 37, 103, 151]. Appropriate localizing studies should be performed in all patients before the surgery is repeated and, if non-invasive imaging approaches are negative, selective venous sampling for PTH measurement may be a useful tool [67, 102]. Recurrences in the neck and mediastinum, including regional LNs and all involved structures, should be excised with margins as wide as possible [6, 7, 10]. Multiple re-operations may be required, since they offer a valuable palliative option, although surgical morbidity should be considered [102, 103].

16.9.1.6 Distant Metastases

Approximately one-third of patients with parathyroid carcinoma have metastatic lesions at presentation and the most common site of metastasis is the lung, followed by the liver and bone [102, 156, 157]. Whenever diagnosis of the metastatic lesion is confirmed, its resection is recommended [5, 15, 103, 158]. This may include pulmonary resections, hepatectomies, bone resection, or craniotomies [157, 159, 160]. Although resection is rarely curative, yet it may result in a period of normo-calcemia from months to years. Thus, metastasectomy is justified as it results in a reduction in severe hypercalcemia and has been associated with improved survival, probably because mortality in advanced metastatic parathyroid carcinoma is related mainly to severe hypercalcemia rather than a mass effect. Even incomplete resections can control calcium levels or facilitate medical control of hypercalcemia [6, 101, 103, 159].

16.9.2 Medical and Adjuvant Treatments

Although surgery remains the mainstay of management, the availability of new drugs such as calcimimetics has opened new perspectives for the treatment of intractable hyper-calcemia [155, 158]. Whenever possible, severe hypercalcemia should be corrected before surgical treatment, which should be performed as an "elective" procedure [33]. Furthermore, treatment of hypercalcemia is particularly important in patients with recurrent or metastatic parathyroid cancer or those who are not suitable for surgical treatment.

16.9.2.1 Fluid Volume Restoration and Diuretics

Patients with severe hypercalcemia are significantly dehydrated because of nephrogenic diabetes insipidus and associated nausea and vomiting; an aggressive *hydration* with 200–300 mL/h of normal saline intravenously (IV) is necessary as initial treatment. *Loop diuretics*, such as furosemide, are given to increase renal calcium excretion.

16.9.2.2 Bisphosphonates

Bisphosphonates, such as *clodronate, etidronate, pamidronate, and zolendronate* (inhibit osteoclast-mediated bone resorption by incorporation into the bone matrix) are effective, but they lose efficacy over time [7, 10, 26, 33, 37, 78, 148, 161]. Bisphosphonates are poorly absorbed when given orally; therefore, IV administration is required. *Pamidronate*, infused in doses of 30–90 mg/day over 2 to 4 h, is effective in lowering serum calcium levels in patients affected by parathyroid cancer, at least transiently; responses last for 1 to 3 weeks and the treatment can be repeated [26, 78, 148, 161]. *Zolendronate* (*Zometa*) has been reported to be more effective and can be infused more quickly at a dose of 4 mg IV over 15 min [8, 78, 162, 163]. Patients should be adequately rehydrated prior to administration of Zometa and should have serum creatinine assessed prior to each treatment. Dose adjustments of Zometa are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <4.5 mg/dL).

Potential complications of bisphosphonates include avascular necrosis of the jaw and acute renal failure following rapid IV administration in patients with impaired renal function [164]. Moreover, the effectiveness of these drugs decreases over time [78].

16.9.2.3 Mithramycin (Plicamycin)

When patients are unresponsive to IV bisphosphonates, IV mithramycin (an antibiotic found to have calcium-lowering properties by inhibiting bone resorption) at a dose of 25 μg/kg over 4 to 8 h has been indicated as a second-line drug for life-threatening hypercalcemia. It may be repeated at daily intervals for up to 7 days until the serum calcium returns into an acceptable range [10]. However, this drug is also toxic to the liver, kidney, and bone marrow, and is *not* very effective, since complete normalization of the calcium values is rarely achieved [7, 10, 15].

16.9.2.4 Calcitonin

Calcitonin inhibits osteoclastic bone resorption and facilitates renal excretion of calcium. It is administered through subcutaneous (SC) or intra-muscular (IM) access at a dose of 3–6 IU/kg and has a rapid onset of action (12–24 h). However, the serum calcium levels show only a modest reduction and rapidly return to pre-treatment values within 48 h in most patients with parathyroid carcinoma [165–169]. It has been effective in a single patient when used at a dose of 200–600 Medical Research Council units/day in combination with glucocorticoids (300 mg hydrocortisone) [170] and in occasional patients when used alone [171].

16.9.2.5 Corticosteroids

Corticosteroids may be used to lower the serum calcium levels, increasing the urinary excretion of calcium and decreasing intestinal calcium absorption. However, they have a slow onset of action and may cause side-effects such as immunosuppression, hyperglycemia, and cushingoid symptoms. The *combination* of calcitonin and hydrocortisone may be useful when patients are afflicted by renal failure [78].

16.9.2.6 Amifostine and Gallium Nitrate (Ganite)

Amifostine, a chemoprotective agent that acts by inhibiting PTH secretion, is effective in controlling hypercalcemia, but its use is limited because of severe toxicity [10]. Gallium nitrate is also effective in inhibiting bone resorption by preventing the dissolution of hydroxyapatite crystals [172]. Gallium nitrate lowered serum calcium in two patients with parathyroid carcinoma [173] and was later reported to be effective in four of five patients [174]. It is administered as a continuous 5-day infusion at a dose of 200 mg/m^2·day. However, it is extremely nephrotoxic causing elevation of serum creatinine that is potentiated by volume depletion and the concomitant use of potentially nephrotoxic drugs. It remains unclear whether gallium nitrate will prove useful in the management of chronic hypercalcemia due to parathyroid cancer.

16.9.2.7 Calcinomimetic: Cinacalcet

Most parts of the treatments of hypercalcemia have been replaced by more recent agents. Cinacalcet, a potent long-acting second-generation Calcimimetic drug, is approved by the US FDA for the treatment of hypercalcemia in patients with parathyroid carcinoma. It acts as an allosteric modulator of calcium-sensing receptors (CASR) that are responsible for the regulation of PTH secretion. Cinacalcet binds to the calcium receptors on the surface of parathyroid cells and increases the receptor sensitivity to extra-cellular calcium and subsequently effectively reduces the serum PTH and Ca levels [7, 8, 15, 33, 78, 175, 176]. Cinacalcet is administrated orally, and the initial dose is 30 mg twice-daily, but can be increased every 2 to 4 weeks, based on drug tolerance and serum calcium levels [78]; nausea and vomiting are the most common adverse events. A dose of 30–60 mg once daily is well tolerated.

Cinacalcet has been investigated in a multicenter study including 29 patients with inoperable parathyroid carcinoma [177]. The primary endpoint of the study was the proportion of patients experiencing a ≥1 mg/dL reduction in serum calcium from the baseline at the end of the titration phase. The dose of cinacalcet in this study was

titrated from 30 mg twice daily up to 90 mg four times daily and the duration of treatment ranged from 1 to 1051 days (mean 328 ± 306 days). Cinacalcet effectively reduced hypercalcemia in about two-thirds of patients. In the responders (18 of 29 patients), serum calcium levels decreased from 15.0 ± 0.5 to 11.2 ± 0.3 mg/dL ($p < 0.001$), with the greatest responses seen in patients with the highest levels of serum calcium at study entry. Interestingly, the PTH levels were only slightly reduced. PTH levels reached a nadir 4 h after drug administration, but the decline was not pronounced, nor was it sustained. Although hypotheses abound, the reason for the discrepancy in calcium and PTH response to cinacalcet remains unclear at this time. The most common adverse events were, as mentioned before, were nausea and vomiting, which led to treatment withdrawal in 23 patients. There are no data suggesting that cinacalcet alters the course of the parathyroid cancer itself. Therefore, Cinacalcet cannot replace surgical intervention in case of resectable disease, but it is an important option in patients with widely metastatic disease or with renal insufficiency to alleviate the complications of hypercalcemia [6, 15, 33, 175, 176, 178].

16.9.2.8 Octreotide

Finally, indium-labeled octreotide, the somatostatin analog, has been reported to inhibit PTH secretion [179] and provide palliative effects in metastatic neuroendocrine tumors; the radio-metabolic treatment might represent a therapeutical option in patients with metastatic carcinoma in the future [179].

16.9.2.9 WR-2721

WR-2721[5-,2-(3-aminopropyl) amino] ethylphosphorothoric acid is a hypocalcemic agent that acts by inhibiting PTH secretion and bone resorption. It has been shown to lower PTH levels and serum calcium levels in parathyroid carcinoma; however, severe toxicities limit its use [180].

16.9.2.10 Anti-parathyroid Immunotherapy

In the recent years, anti-parathyroid immunotherapy has also been reported to be a useful treatment in patients with refractory hypercalcemia from metastatic disease [7]. A rapid decline in PTH and serum calcium levels, improvement in clinical conditions, and a reduction in the size of lung metastases, without relevant adverse effects, have been reported after immunization by a mixture of human and bovine PTH peptides [181]. However, this approach has not been further developed.

16.9.2.11 Dendritic Cell Immunotherapy

Dendritic cell immunotherapy has also been used to induce a T-cell immune response [182, 183]. It has been shown to be effective in a few patients with a short follow-up. Recently, a monoclonal antibody to PTH has also been used for the treatment of parathyroid carcinoma [184].

16.9.2.12 Denosumab

Denosumab (anti-receptor activator of nuclear factor-kappa B ligand antibody – anti-RANKL), a novel agent, is a fully human monoclonal antibody that inhibits

osteoclastic-medicated bone resorption by binding to osteoblast-produced RANKL. When RANKL binding to the osteoclast receptor RANK is reduced, bone resorption and turnover decrease. It has successfully been used in a patient with parathyroid carcinoma. Denosumab (60 mg SC every 6 months) significantly reduced vertebral, non-vertebral, and hip fracture risk compared with placebo, and had an excellent safety profile through 3 years of use. Unlike bisphosphonate, denosumab does not require dose adjustment for renal impairment, which is common in patients with marked hypercalcemia [185–188].

16.9.2.13 Radiotherapy

Concerning radiotherapy (and chemotherapy) in parathyroid cancer, all data are derived from case reports [80, 165, 189] as no controlled trials have been carried out because of the rarity of the disease. Generally, radiotherapy is *not* considered an effective treatment, whether as a single technique or adjuvant to surgery [31]. A single case of 10-year apparent cure in a patient with neoplastic invasion of trachea has been reported [80]. Recently, the Mayo Clinic and MD Anderson Cancer Center groups in the USA have proposed a possible role for radiotherapy as adjuvant treatment following surgery; lower recurrence and longer disease-free with adjuvant radiotherapy, independently from the type of operation and the disease stage, have been reported in the literature [75, 85, 190]. Unfortunately, these conclusions were conducted on very small series, and need to be confirmed by further studies. In the Surveillance, Epidemiology, and End Results (SEER) study, 9.8% of patients with parathyroid carcinoma received radiation therapy and it was *not* associated with an improved survival rate. Nonetheless, several case series reported reduced recurrence in patients submitted to radiation therapy [161, 191, 192].

16.9.2.14 Chemotherapy

Chemotherapy is usually used for patients with inoperable disease or those unsuitable for surgery, and there is no standard treatment protocol. The results of chemotherapy in the treatment of parathyroid carcinoma are generally disappointing. Several regimens have been attempted (nitrogen mustard, vincristine, cyclophosphamide, and actinomycin D, and Adriamycin alone or in combination with Cyclophosphamide and 5-Fluorouracil), but none of them has proved to be effective [80, 102, 104]. Currently, there is no conclusive evidence supporting chemotherapy for the management of patients with parathyroid carcinoma [160].

The side-effects of chemotherapy depend on the individual chemotherapeutic agent used and the dose given, but they may include fatigue, risk of infection, nausea and vomiting, hair loss, loss of appetite, and diarrhea. These side-effects usually resolve after the treatment is completed.

16.9.2.15 Embolization

There are a few reports in the literature of successful radiofrequency embolization or trans-arterial catheter embolization of distant metastatic disease, but the number of patients in these studies is limited [193, 194].

16.9.3 Ablative Therapy

Ethanol ablation guided by ultrasound with percutaneous injection of 98% ethanol into the tumor has been reported Stratigis et al. [195] to reduce PTH and serum calcium levels. It has minimal side-effects, but should be reserved to palliative cases, due to potential tumor seeding along needle tracks and risk of local nerve and tissue injuries [195].

16.9.4 New Developments/Future Treatment

Advanced techniques such as whole-exome sequencing have been employed in an attempt to identify genetic abnormalities in PC [196]. These studies have reinforced the importance of *CDC73*, but additionally, recurrent germline and somatic mutations in prune homolog 2 (*PRUNE2*) were found in a significant percentage of PC samples [196]. Likewise, amplification of *CCND1*, a gene that encodes cyclin D1, may be implicated in the molecular pathogenesis of PC as it was found to be significantly more prevalent in cases of PC than benign parathyroid adenomas [197]. A complete genomic analysis of both primary and recurrent tumor samples is available for one patient, and this demonstrated a loss of PIK3CA activation during tumor evolution, and offered insights into several potential new diagnostic or therapeutic targets first identified as somatic mutations [198]. In order to practically apply this information, large-scale studies with PC patients will be necessary. Because PC is a rare disease, advances in treatment for PC are difficult to develop and study.

16.9.5 Surveillance/Follow-Up

After an initial surgical resection, the patients should be followed up carefully at regular intervals with laboratory testing for both calcium and PTH levels, as well as neck ultrasounds. Long-term survival is possible, and routine surveillance can help identify early recurrence of disease [199, 200].

For patients with known germline mutations of *HRPT2*, routine surveillance with annual calcium, PTH, and 25-OH vitamin D levels, as well as periodic neck ultrasound (to assess for the rare, but reported detection of non-functioning parathyroid carcinoma), are suggested. Given the development of jaw tumors, a dental panorex image every 5 years is also recommended [27]. In patients with diagnosed parathyroid carcinoma, lifelong surveillance is recommended [148, 201].

Follow-up recommendations for patients with atypical parathyroid adenomas remain less clear, as the behavior of this heterogeneous group of tumors is less well defined. In general, those with atypical parathyroid adenomas are often treated more like patients with a malignant diagnosis, in order to eliminate missing aggressive or recurrent disease. These patients should be followed up closely to identify signs of recurrence. Since most tumors produce PTH and lead to hypercalcemia, routine laboratory testing is a simple way to follow up these patients.

16.10 Summary

Parathyroid carcinoma remains a rare entity, making widely applicable studies about prognosis, treatment, or recurrence difficult. Pre-operative diagnosis remains challenging, mandating surgeons maintain a high index of suspicion for possible malignancy during parathyroid operations. Parathyroid carcinoma should be suspected with markedly elevated serum calcium levels (>14 mg/dL or >3.5 mmol/L). Fine needle aspiration cytology (FNAC) should be avoided if there is a suspicion of parathyroid carcinoma. Adequate surgical resection with *en-bloc* resection of all tumor and involved structures is the best initial treatment necessary for optimal outcomes, and is best performed by high-volume parathyroid surgeons. Few adjuvant therapies currently exist for the treatment of recurrent or metastatic parathyroid carcinoma, and further studies and innovations are needed to improve options and outcomes. Patients with parathyroid carcinoma should have lifelong surveillance. Management of refractory parathyroid carcinoma often focuses on optimizing the treatment of hypercalcemia. In the coming years, early recognition, appropriate initial surgical treatment, and close surveillance should be emphasized as further research works to identify unique adjuvant therapies for parathyroid carcinoma.

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Intra-operative Tools in Parathyroidectomy

17

17.1 Background

Surgery is the definitive treatment of primary hyperparathyroidism (PHPT) [1]. *Pathologically*, PHPT is caused by single-gland disease [2] in 80–85% of cases, and by multi-gland disease [3, 4] in the rest of cases. *Anatomically*, variations in the number and location of the parathyroid glands (PTGs) reach up to approximately 25% for super-numerary and 43% for ectopic glands [5, 6]. Such PTGs may also be pathological [7, 8]. *Surgically*, the advantageous minimally invasive parathyroidectomy (MIP), which allows exposure of the diseased gland only, has currently replaced the time-honored bilateral neck exploration (BNE), which allowed the surgeon to visually inspect all PTGs.

Intra-operative identification of PTG(s) is not easy since they may morphologically mimic fat, lymph nodes (LNs), or thyroid nodules; hence, surgeon expertise is invaluable. For these reasons, parathyroid surgery has been heavily reliant on imaging, aiming at pre-operatively localizing the diseased PTG(s) and achieving cure through the MIP approach whenever possible. Unfortunately, however, none of the currently available imaging modalities has 100% localization accuracy. Both combined ultrasound (US) and Sestamibi/single-photon emission computed tomography (MIBI/SPECT), the two most commonly used modalities, have a localization accuracy rate of nearly 91% for *single gland disease* (SGD), but a significantly lower rate for *multiple gland disease* (MGD), smaller pathologies, and coexistent nodular thyroid disease [1, 9]. Many tools have thus been proposed to aid intra-operative identification of PTGs to facilitate optimal parathyroid surgery. Another merit of some of these adjuncts is to aid intra-operative identification of PTGs to prevent their inadvertent removal during thyroidectomy.

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17.2 Methylene Blue (MB)

Methylene blue (MB) is a cationic thiazine dye, which accumulates rapidly preferentially in parathyroid tissue, staining it and aiding its identification during surgery. The mechanism of preferential parathyroid MB staining is thought to be due to its retention in the mitochondria of oxyphil cells, based on the observation of oxyphil predominance in the stained compared to the unstained areas of a partially MB-stained adenoma case, reported by Lavelle in 1980 [10].

Methylene blue is given in a dose ranging between 1.75 and 7.5 mg/kg, via 100–500 mL intravenous (IV) infusion volume, before or at skin incision or during surgery [11–13]. Methylene blue may be given by a "surgeon-performed ultrasound-guided needle dye injection." The advantage of the surgeon performing the US needle injection is to help increase the accuracy and consistency of the placement of the dye, and reduce the time and costs associated with using a US technician or radiologist. Intra-operatively, a 25-gauge needle is inserted in the center of the targeted tumor under ultrasound (US) guidance in a parallel or perpendicular fashion in relation to the transducer, depending on the anatomical structures in the surrounding area. Once the tip of the needle is seen in the center of the tumor, 0.1 mL of 1% MB dye is injected slowly. A blush of fluid is confirmed visually on the US monitor. The needle is then removed from the mass and the patient. After the injection, the blue color helps guide the direction of dissection and the extent of the excision.

A prospective longitudinal cohort study was conducted by Pedrasa et al. [14]. Intra-operative infusion of MB was used to dye and facilitate identification of PTGs when there was discordance between pre-operative information provided by the ultrasound and technetium ^{99m}Tc-MIBI. The study included 43 patients with PHPT. In 37 cases, the adenoma was visualized in dark blue, clearly evident from the surrounding tissues (Fig. 17.1). In six patients (14%), the adenoma was not

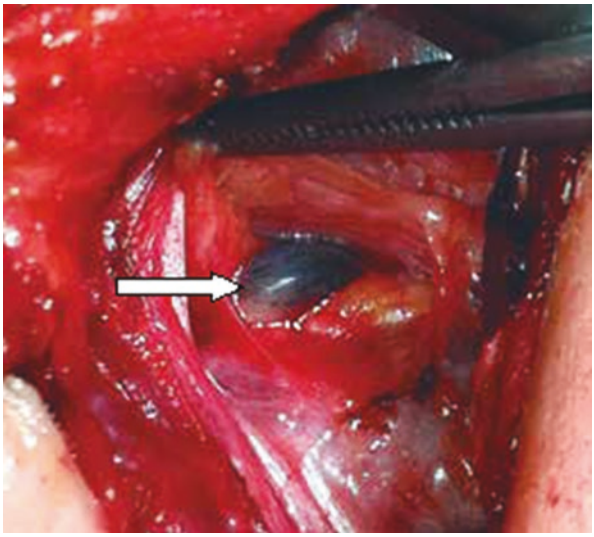

Fig. 17.1 The pathological gland was identified as an oval-shape lesion, intensely purplish blue or blackish in color (arrow), with clear contrast with thyroid tissue and the surrounding connective tissues

detected due to mediastinal, para-esophageal, or intra-thyroidal location; they were found in the same operation, but were not stained due to the increase in surgical time. No false positive case was found and no neurotoxic side-effects were recorded. All patients returned to normocalcemia. Pedrasa et al. [14] concluded that IV infusion of MB is a useful technique for the intra-operative identification of parathyroid adenomas and complements the information provided by other routine diagnostic techniques, without intending to replace them. It is a safe and easily applied technique; with the use of an adjusted dose, no complications are observed including neurotoxicity.

In their study of 35 patients with PHPT who underwent MB-guided surgery, Kuriloff et al. [15] reported staining of 89% of adenomas as "dark blue to purple," and 100% of hyperplastic glands "to a lesser degree," while 41% of normal glands showed "a pale, greenish-grey hue." They also noted occasional varying degree of staining of the surrounding non-parathyroid tissue; however, it was not to the degree to result in confusion with parathyroid tissue [14].

Although some authors reported 100% staining in SGD and MGD, others reported false negative rates of 17% and 33% in SGD and MGD, respectively [16, 17]. Patel et al. [18], in their systematic review, calculated a median false positive staining rate of 59% for normal PTGs and 14.4% for thyroid glands, in addition to frequent false positive staining of lymph nodes. *Adverse reactions* have also been documented in the form of transient neurotoxicity (5.2%), thrombophlebitis (8%), and transient pain at infusion site (33%) [18]. Neurotoxicity occurred only with concurrent use of selective serotonin reuptake inhibitors (SSRIs), as MB can increase central serotonin in these patients owing to its structural similarity to monoamine oxidase inhibitors. Even the lowest possible dose of MB does not obviate the risk of neurotoxicity [19]. Due to dye interference with photometry, MB can result in a spurious fall in oxygen saturation (pseudo-hypoxia). Other reactions included fever, headaches, nausea, pseudo-hypoxia, and hemolytic anemia in glucose-6-phosphate deficiency (G-6-PD) patients. It is therefore contraindicated in patients taking SSRIs, in G-6-PD patients, as well as in pregnancy.

A single retrospective study of 147 and 205 PHPT patients who underwent surgery with and without MB reported that operating time was significantly shorter when MB was used; however, the cure rate was not significantly affected [20].

Given the lack of data to demonstrate any role of MB in improving PHPT surgical cure rate, in addition to its well-documented potential toxicity, its routine use in PHPT surgery is *not* supported.

17.3 Frozen-Section (FS)

Three main diagnostic pathological methods are available to identify parathyroid tissue during operative exploration; namely, frozen-section (FS), scrape cytology, and reflected-light microscopy. In parathyroidectomy, frozen-section (FS) has two roles; first, confirmation of "parathyroid tissue" excised and, second, defining the pathological lesion of the PTGs, whether adenoma, hyperplasia, or

carcinoma [21]. If surgery is to be guided by FS, the pathology team should be notified in advance about the clinical details, date, and approximate time of specimen reception. Immediately after excision, the specimen is sent fresh (unfixed) to the laboratory where excess fat is dissected off, and the specimen is grossly described in terms of weight, dimensions, and color. A tissue block is then taken from a transverse cross-section including the vascular pole if possible. After FS reporting, the tissue is fixed in formalin and embedded in paraffin for subsequent examination [22].

Pathological identification of "parathyroid tissue" is usually possible depending on the demonstration of parathyroid chief and oxyphil cells, although this could occasionally be difficult if the parathyroid acini show enlargement and luminal material resembling colloid-filled thyroid follicles. Distinction between adenoma and hyperplasia may sometimes be impossible based on the pathological examination of a single gland because the distinction requires information on the gross appearance of other PTGs; in the latter case, the PTG is frequently reported as "hyper-cellular."

In their retrospective study of 97 FS-guided minimally invasive parathyroidectomies, Furderer et al. (2017) reported that FS correctly changed the operative strategy in 12 cases, contributing to their 100% cure rate [23]. Other authors, however, reported false results and pitfalls of FS. Back in 1998, Westra et al. had retrospectively reviewed 455 cases and reported false negative results in 13, and deferred examination in additional seven cases, making FS not useful or even potentially misleading in 20 (4.4%) of cases [24]. Such FS inaccuracy in detecting parathyroid tissue may be attributed to frozen tissue artifacts, sampling errors, and the inability to distinguish between PTGs and cellular thyroid nodules. There are no studies in the litrature that compared surgical cure rates of PHPT with versus without the use of frozen-section. In the study by Fuderer et al. [23], the mean added time for a single FS examination was 24.2 ± 8.6 min.

The routine use of frozen-section in PHPT surgery is not recommended because of (1) its frequent potentially misleading pitfalls, (2) lack of data to demonstrate its added value in PHPT surgical cure rates, (3) its added cost and time, and (4) the availability of more accurate adjuncts to intra-operatively identify parathyroid pathology.

Recently, El-Bolkainy et al. [25] published the results of their comparative study of frozen-section, scrape cytology, and reflected-light microscopy, used singly or in combination, on 30 tissue samples (10 parathyroid tissues and 20 non-parathyroid tissues) obtained from nine patients. Modifications were made on a monocular microscope to allow transmitted-light, reflected-light, and digital photography. The three diagnostic methods were used in a sequential order starting with cytology, then reflected-light microscopy, and finally frozen section. This ensured that diagnosis of cytology and reflected-light microscopy was not influenced by frozen-section diagnosis.

The *cytomorphological features* of parathyroid tissue were characterized by small cells with scanty cytoplasm, occurring separately or in clusters (Fig. 17.2a) and rarely in a follicular pattern (Fig. 17.2b). Conversely, thyroid tissue showed a

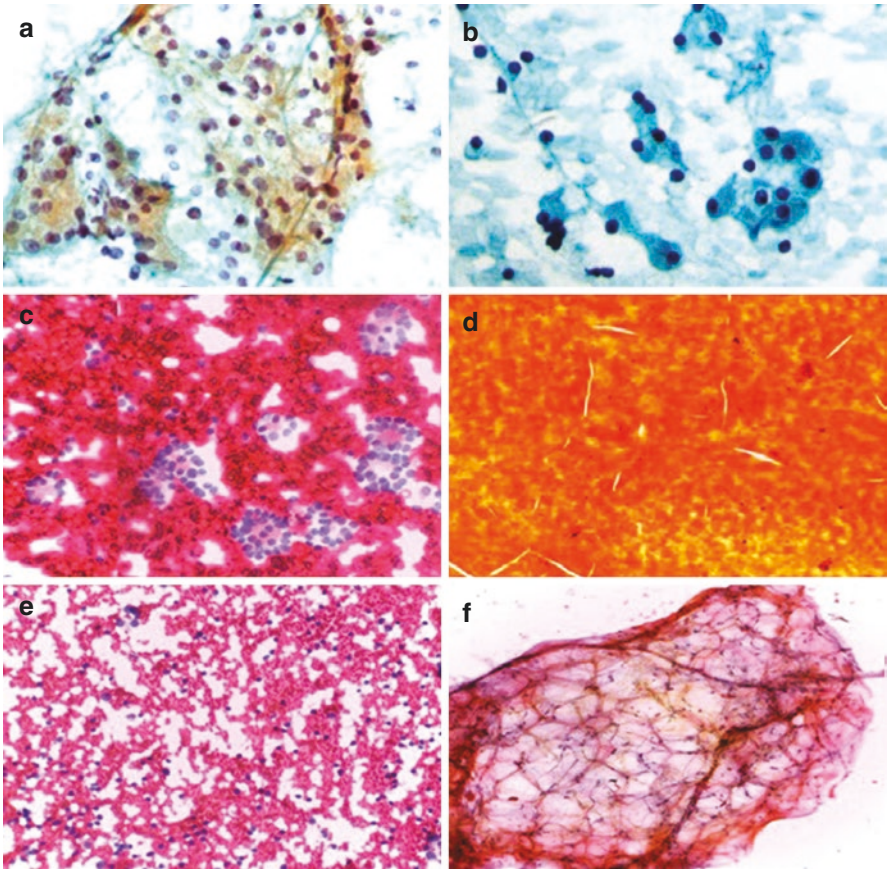

Fig. 17.2 Cytomorphology, H&E×200. (**a**) Parathyroid smear showing small round and oval cells in clusters related to blood vessels. (**b**) Most cells have cytoplasm, but few have naked or large nuclei; chromatin is fine and dispersed, with unusual follicular pattern. (**c**) Thyroid hyperplasia with numerous follicular patterns. (**d**) Thyroid hyperplasia with background rich in colloid with crack artifacts and few histiocytes. (**e**) Lymph node smears showing dispersed lymphocytes with indistinct cytoplasm and clumped chromatin. (**f**) Fatty tissue smear, showing large cells with cytoplasmic vacuoles and eccentric nuclei with associated blood vessels

follicular pattern (Fig. 17.2c), as well as a background rich in colloid and histiocytes (Fig. 17.2d). In lymph node samples, dissociated lymphocytes with indistinct cytoplasm were a diagnostic feature (Fig. 17.2e). Soft-tissue fat typically appeared as large cells with eccentric nuclei and large cytoplasmic vacuoles (Fig. 17.2f).

Reflected-light pictures of tissue samples demonstrated that parathyroid tissue appeared as small cells with a solid pattern, lacking follicular or nodular features, but with few fat cells, especially in normal PTGs (Fig. 17.3a). Thyroid tissue showed a prominent follicular pattern (Fig. 17.3b), whereas lymph nodes were identified by

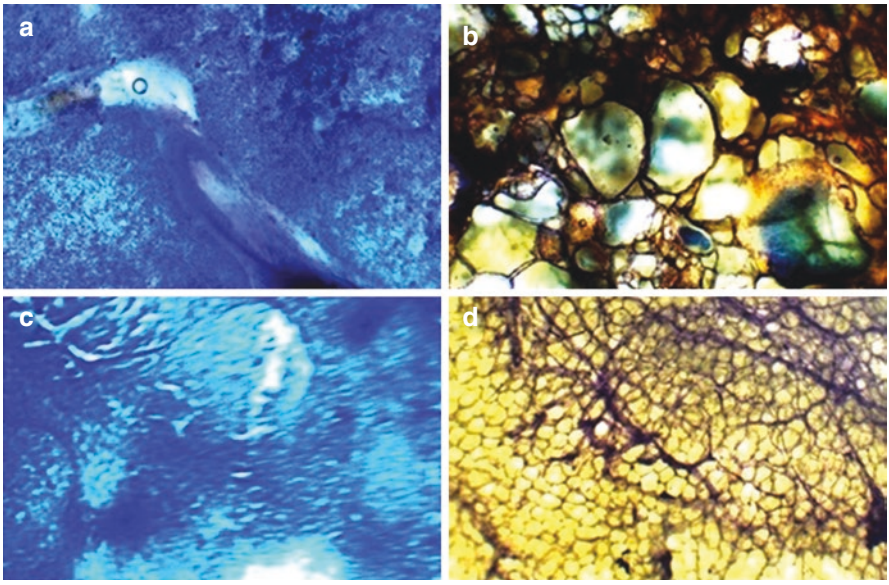

Fig. 17.3 Reflected-light histo-morphology, toluidine blue stain, ×40. (**a**) Normal parathyroid tissue showing small cells related to blood vessels. (**b**) Thyroid tissue showing numerous follicles. (**c**) Lymph node tissue with multiple germinal centers. (**d**) Adipose tissue with diagnostic natural yellow color of fat

the presence of germinal centers (Fig. 17.3c) and fatty tissue showed the natural yellow color of fat (Fig. 17.3d).

With FS, fat cells were commonly observed in normal PTGs (Fig. 17.4a). The histomorphology of adenoma and hyperplasia is basically similar with the presence of chief, oxyphil, and clear cells (Fig. 17.4b). A focal nodular pattern was observed in hyperplastic glands (Fig. 17.4c). In thyroid tissue, a prominent follicular pattern with colloid is diagnostic (Fig. 17.4d). Lymph nodes were identified by the presence of germinal centers (Fig. 17.4e) and adipose tissue by the characteristic fat cells (Fig. 17.4f).

When used alone, the diagnostic accuracy was 96.6% for FS, 86.6% for cytology, and 80% for reflected-light microscopy. The combined use of cytology with reflected-light microscopy increased the diagnostic accuracy to 93.3%, with good concordance with the accuracy of FS combined with cytology (κ ratio 0.651). Regarding the time factor, cytological and reflected-light studies were completed in 4 min, but frozen section took 20 min. El-Bolkainy et al. [25] concluded that in specialized centers, FS combined with cytology is the preferred method for intra-operative diagnosis of parathyroid tissue. Conversely, in developing countries, where FS equipment may not be available, a combination of reflected-light microscopy and cytology is a good, inexpensive, rapid, and effective alternative. However, proper training is needed for these methods to ensure an accurate diagnosis [26].

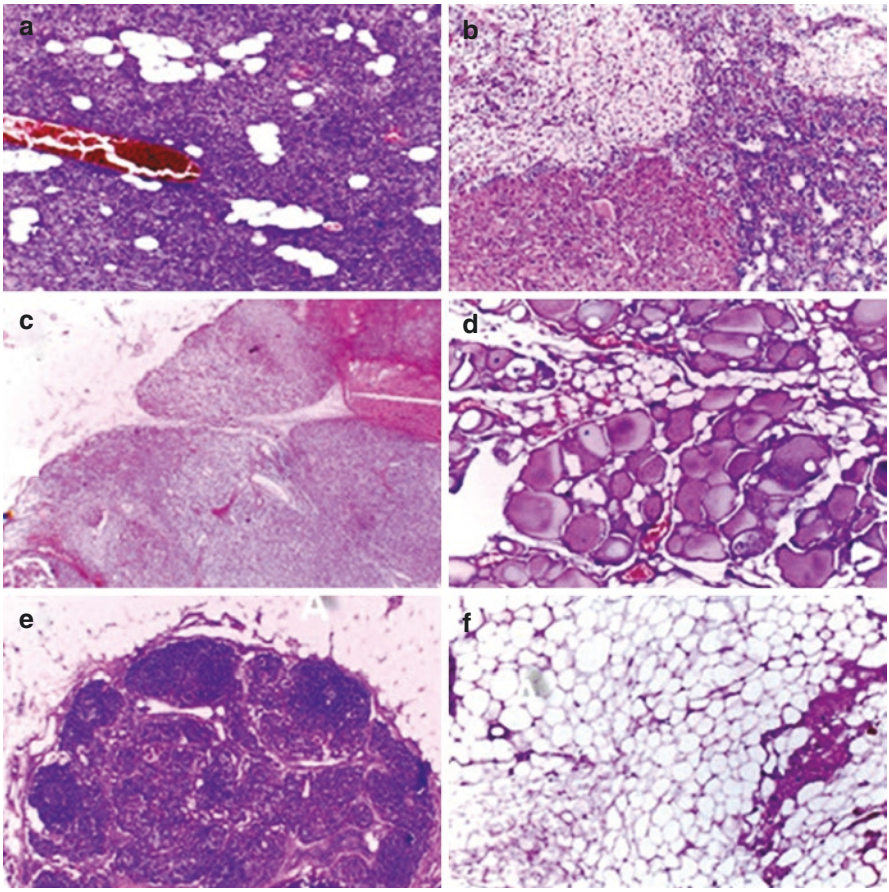

Fig. 17.4 Frozen-section histopathology, H&E×100. (**a**) Normal parathyroid gland, small size (<5 mm) showing vascular stroma with few scattered fat cells. (**b**) Parathyroid adenoma with three cell types, namely, chief cells (right field), oxyphil cells (left field), and clear cells (upper field), arranged in a vascular and trabecular pattern. (**c**) Secondary parathyroid hyperplasia with a focal nodular pattern. (**d**) Thyroid tissue showing numerous follicles filled with colloid. (**e**) Lymph node with prominent germinal centers. (**f**) Fibroadipose tissue, characterized by fat cells with large cytoplasmic vacuoles and fibrovascular septa

17.4 Gamma Probe

Radio-guided surgery involves using a radiation detection probe to intra-operatively detect a pre- or intra-operatively administrated radio-nucleotide. The technique consists of intravenous (IV) injection of 10–20 miCu ^{99m}Tc-MIBI, one to 3 h before surgery. Regional neck radioactivity is subsequently measured in the operating room (OR) using a hand-held gamma probe, which provides readable counts and acoustic signals (Fig. 17.5).

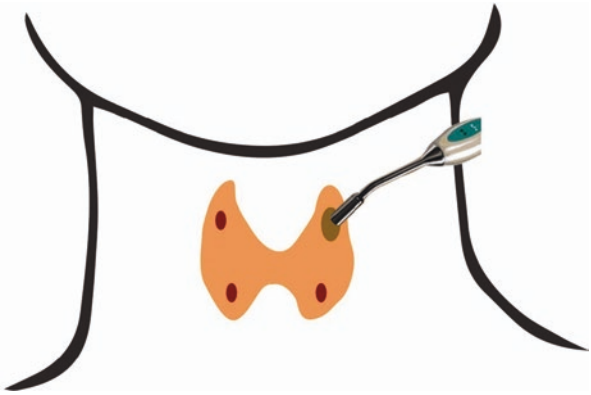

Fig. 17.5 Radioactivity is measured in the operating room using a hand-held gamma probe, which provides readable counts and acoustic signals

Radioactivity measurement protocols vary among practices, with all surgeons measuring radioactivity over the thyroid isthmus before skin incision to obtain "background radioactivity." Some surgeons then measure radioactivity in four neck quadrants to place the incision over the area of maximum radioactivity [27], while others place the incision guided by pre-operative scans and use the gamma probe to guide subsequent dissection [28]. The radioactivity count, while the PTG is in-situ, is termed "in-vivo count" and is expressed as a percentage of background. The area with maximum radioactivity count corresponds to the pathological PTG [29]. After excision, the tissue is placed on the probe to obtain the "ex-vivo count," which, if greater than 20% of background radioactivity, is confirmatory of parathyroid adenoma rather than parathyroid hyperplasia or non-parathyroid tissue. This is known as the "20% rule" as popularized by Normans et al. in 1999 [30]; however, it was subsequently questioned by Chen et al. [31] and Friedman et al. [32], who found that ex-vivo counts of hyperplastic glands, although significantly lower than adenomatous, are always greater than 20%. They highlighted the efficacy of gamma probe in guiding surgery for MGD as well as SGD, refuting the role of the "20% rule" in differentiating adenoma from hyperplasia. In a retrospective analysis of 1656 initial radio-guided parathyroidectomies for PHPT, Tobin and colleagues (2016) reported that a "50% *ex-vivo* count of the first excised gland" was the best threshold to differentiate SGD and MGD, with a reported positive predictive value for MGD of 42.1% and an overall accuracy of 72.8% [33].

The issue of using radio-guidance in parathyroid surgery has always been controversial with regard to its efficacy, and time and cost effectiveness. Several studies reported cure rates of 97–100% after radio-guided surgery for PHPT [34–37]. However, these studies included highly selected patient cohorts with SGD localized pre-operatively by ^{99m}Tc-MIBI scan, which would therefore be expected to be found intra-operatively by gamma probe detection. Goldstien et al. compared 20 PHPT patients who had minimally invasive radio-guided parathyroidectomy (MIRP) with a matched cohort who had a conventional surgical approach, and found a significantly reduced operative time, operating recovery, and total hospital charges in the MIRP group. It could be argued, however, that the shorter operative time and

possible use of local anesthesia, which subsequently reduced recovery time, hospital stay, and charges are the merits of MIP approach in general rather than radio-guidance per se, as this has been demonstrated in other studies, which did not use radio-guidance [37, 38]. In their non-randomized prospective study, Burkey et al. did not find a significant difference in cure rates, operative time, or cost between PHPT patients operated with and without radio-guidance [39]. On the other hand, several reports showed usefulness in search of ectopic adenomas [40–42] and in re-operative neck surgery [43, 44].

In their evaluation of 252 patients with PHPT, Chen et al. reported 92% sensitivity and 83% accuracy of gamma probe localization [28]. Others, however, reported an up to 30% rate of false positive results, mostly attributable to thyroid sources [45]. A major concern on radio-guided surgery is that most literature evaluated its utility in patients having lesion(s) pre-operatively known to concentrate the tracer (MIBI +ve), while its role in MIBI -ve cases is less established. The latter issue has been investigated by Chen et al. in a 769 PHPT case series, who found that the in-vivo count of MIBI -ve patients was significantly higher than the background and that the ex-vivo counts of both MIBI -ve and MIBI +ve parathyroid were greater than 20%, although the mean ex-vivo count of MIBI +ve patients was significantly higher than that of MIBI -ve patients [46].

In general, the use of gamma probe in PHPT surgery is considered a complementary tool to other adjuncts to facilitate localization of PTG pathology. However, given the lack of randomized controlled trials to compare surgical outcomes with and without radio-guidance in the absence of confounding effects of other adjuncts, there is no high-level evidence to support its routine use in PHPT surgery.

17.5 Intra-operative 3-D Mapping Using F-Spect

Technetium-99m Sestamibi (^{99m}Tc-MIBI) scan is considered the procedure of choice for the localization of parathyroid adenomas with improved accuracy using single photon emission computed tomography (SPECT) [47]. SPECT/CT has contributed to the localization of parathyroid adenomas by providing an anatomical context to scintigraphic images and correcting for attenuation effects [48]. Intra-operative localization using gamma probes has been proposed especially in minimally invasive surgery. This concept was the basis for the development of hand-held imaging devices [49, 50]. Free-hand single photon emission computed tomography (f-SPECT) was introduced lately as a three-dimensional (3-D) imaging and navigation technique designed for use in the operating room (OR) [51].

The technique is based on the use of a gamma probe, the position and orientation of which is stereotactically monitored while scanning an area of interest [51]. “Scanning” here means moving the gamma probe freely with the hand pointing at the body of the patient from different directions, that is, “painting” the surface of the patient with the gamma probe. Each count rate acquired at a certain position can be seen as a one-pixel projection acquired by a one-pixel gamma camera (the gamma probe). A set of these one-pixel projections can be reconstructed into a 3-D image

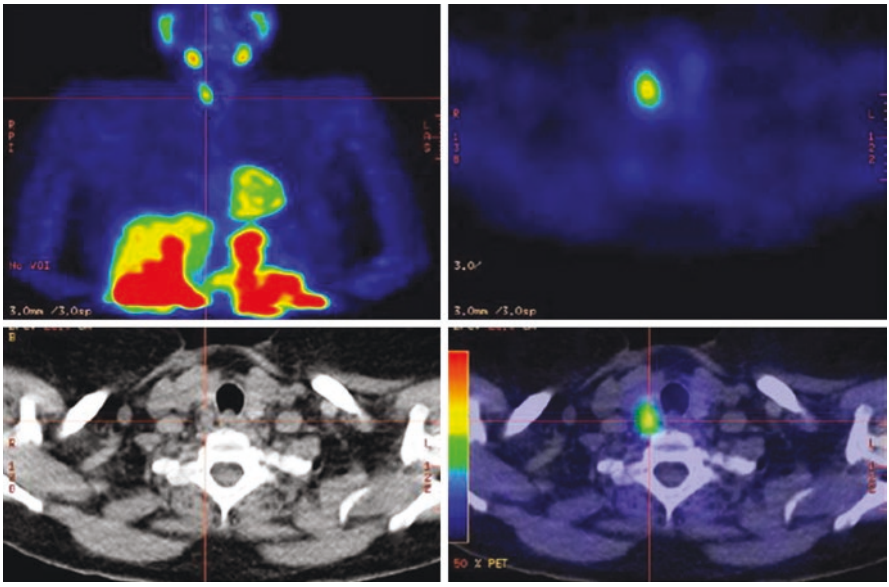

Fig. 17.6 Single photon emission computed tomography (SPECT)/CT showing a right parathyroid adenoma

as in SPECT using also the information on its position and orientation. For visualization, the reconstructed images are then superimposed on a conventional video of the body surface, which is simultaneously recorded.

The superimposition succeeds using augmented reality means, where virtual data (here, SPECT/CT or f-SPECT images) are overlaid on the live video of an optical video camera. The use of intra-operative 3-D imaging for navigated extirpation of parathyroid adenomas might change the operation time and potentially the morbidity related to exploratory search of these adenomas using just the gamma probe (Fig. 17.6). The possibility of controlling parathyroidectomy may also reduce the need for reoperation.

17.6 Intra-operative Parathyroid Hormone (IOPTH)

Three physiological facts constitute the basis of IOPTH monitoring; first, PTH short half-life; second, being exclusively secreted from the chief cells of the PTG; and third, suppression of the normally functioning glands by the excess PTH in PHPT patients.

Generally, PTH level is measured in blood samples taken from a peripheral venous line: either pre-incision or pre-excision (baseline level), and then every 5 min (up to 20 min) after excision. The percentage drop in PTH level correlates with the adequacy of PTG resection, and consequently predicts cure. A drop in the PTH level of more than 50% at 10 min after PTG excision relative to the highest baseline level has been reported to be 97.3% accurate in the prediction of operative

success, the so-called "*Miami criterion*" proposed by Irvin in 1993 [52]. Several criteria have subsequently been proposed with the main differences being the point of reference of initial level (i.e., pre-incision vs. pre-excision vs. highest) and final PTH concentration (i.e., drop ≥50% vs. drop to normal vs. drop ≥50% and to normal) and its timing (i.e., 10 vs. 15 vs. 20 min).

Two analyses from Mayo Clinic Experience of 1361 PHPT patients with initial surgery and 228 patients with re-operative surgery reported IOPTH monitoring accuracy of 98% and 97%, respectively, in the prediction of cure [53, 54]. In a comparative study of 254 patients with PHPT, sensitivity, positive predictive value, and accuracy of IOPTH monitoring exceeded that of radio-guided surgery [28]. However, false results are not uncommon; in one study of 125 PHPT patients, false positives (IOPTH dropped despite the presence of an additional pathology) and false negatives (IOPTH did not drop despite eradication of pathology) were reported in 5% and 4% of the cases, respectively. False positive results have been more frequently observed in patients with parathyroid cancer, double adenoma, concomitant thyroid surgery, and renal impairment. False negative results may occur due to excessive manipulation of the adenoma causing a pre-excision spike resulting in post-excision IOPTH not falling adequately despite eradication of the causative pathology [55].

Several studies compared IOPTH-guided versus non-IOPTH-guided parathyroidectomy and reported either significant or non-significant improvement in the cure rate in the former group. The impact of the use of IOPTH on operative time and cost has been more controversial, depending on the way they have been analyzed. A shorter operative time has been reported in IOPTH-guided MIP compared to non-IOPTH-guided bilateral neck exploration (BNE), a finding probably related to dissection and manipulation being less in MIP [56]. However, longer operative time has been reported in IOPTH-guided MIP compared to non-IOPTH-guided MIP, expectedly related to the time required for sample transportation and preparation, and essay performance [57]. Similarly, studies which included only patients with well-localized parathyroid pathology, in which case IOPTH monitoring is known to contribute the least, have concluded non-cost effectiveness of its use in view on the only modest increase in the cure rate [58, 59]. However, studies which took into account operation time and hospital stay cost have demonstrated cost effectiveness in the IOPTH-guided group [55, 60, 61].

Both the PHPT diagnosis and surgical outcome are defined on a biochemical basis, and IOPTH is the only tool capable of intra-operatively assessing the adequacy of parathyroid resection on the same—biochemical—basis. Several comparative studies have demonstrated its impact on the cure rate; therefore, the use of IOPTH is recommended in PHPT surgery, particularly if image-guided minimally invasive parathyroidectomy is planned.

17.7 Intra-operative Ultrasound (IOUS)

Ultrasound (US) neck scan is a widely available, cheap, and safe imaging tool that has been commonly used for pre-operative parathyroid localization. Its sensitivity ranges between 27% and 89% due to operator factor (experience), patient/disease

factors such as lower performance with associated thyroid pathology, multigland disease, and retrosternal lesions. Although its role as a pre-operative scan has been extensively investigated, only a few studies evaluated its performance and possible impact as an intra-operative adjunct in parathyroid surgery.

Intra-operative ultrasound can be performed by a head and neck radiologist or by a trained head and neck surgeon, as one report of 42 initial parathyroidectomies demonstrated similar surgeon/radiologist results [62]. In the era of BNE, IOUS was performed after raising the platysmal flaps, while in the current MIP era, it is performed after patient positioning to help optimally place the skin incision [62].

Surgeon-performed ultrasound is a highly sensitive pre-operative localization study for patients with primary hyperparathyroidism [63]. Occasionally, repeating the ultrasound in the operating room after the patient has received general anesthesia and has been optimally positioned can help identify parathyroid adenomas that were not visible in the office (Fig. 17.7). The necessary amount of pressure with the transducer can be obtained under anesthesia. Applying pressure with the transducer on the neck can distinguish the relationship of parathyroid adenomas to the thyroid gland and can produce real-time information to target the dissection. Similar to IOUS of the thyroid, repeating the examination can re-familiarize the surgeon with the patient's unique anatomy to identifying the relationship of enlarged parathyroid adenomas to the thyroid gland, tubercle of Zuckerkandl, vasculature, thymus, and sternothyroid muscle.

In 1986, Norton et al. reported a significantly higher sensitivity of IOUS compared to pre-operative US (POUS) in their series of 25 persistent/recurrent PHPT, although the use of IOUS did not impact the cure rate [64]. Moreover, in their study of 74 re-operative PHPT surgeries, Powell et al. reported that IOUS assisted the surgeon in parathyroid adenoma (PA) localization in 58 cases [65].

In the event that no abnormal parathyroid gland is found during exploration, IOUS can be performed to scrutinize the remainder of the neck, especially regions historically known to harbor ectopic glands. For example, IOUS can re-identify thyroid nodules and their laterality, prompting the consideration of an intra-thyroidal parathyroid adenoma if the intra-operative findings warrant this possibility (Fig. 17.8).

Perhaps the most valuable use of IOUS in parathyroid operations is in the setting of the challenging re-operative parathyroidectomy. Cervical ultrasound is 55–69% successful in identifying the offensive gland in patients with persistent or recurrent disease [66, 67]. If the patient's offending gland was identified on POUS, performing IOUS can facilitate targeted dissection in the scarred, re-operative field.

In their series of 22 PHPT patients with discordant pre-operative MIBI/US undergoing initial MIP, Al-Almi et al. reported that IOUS results correlated with operative and histology findings in all cases, and therefore helped in achieving successful MIP in all cases [68]. In the latter study, IOUS correctly detected PAs in nine unusual locations (retro-sternal, retro-carotid, retro-esophageal), as well as in additional eight PAs pre-operatively obscured by thyroid pathology. Appropriate exposure and muscle relaxation may allow more proper placement of the US probe to

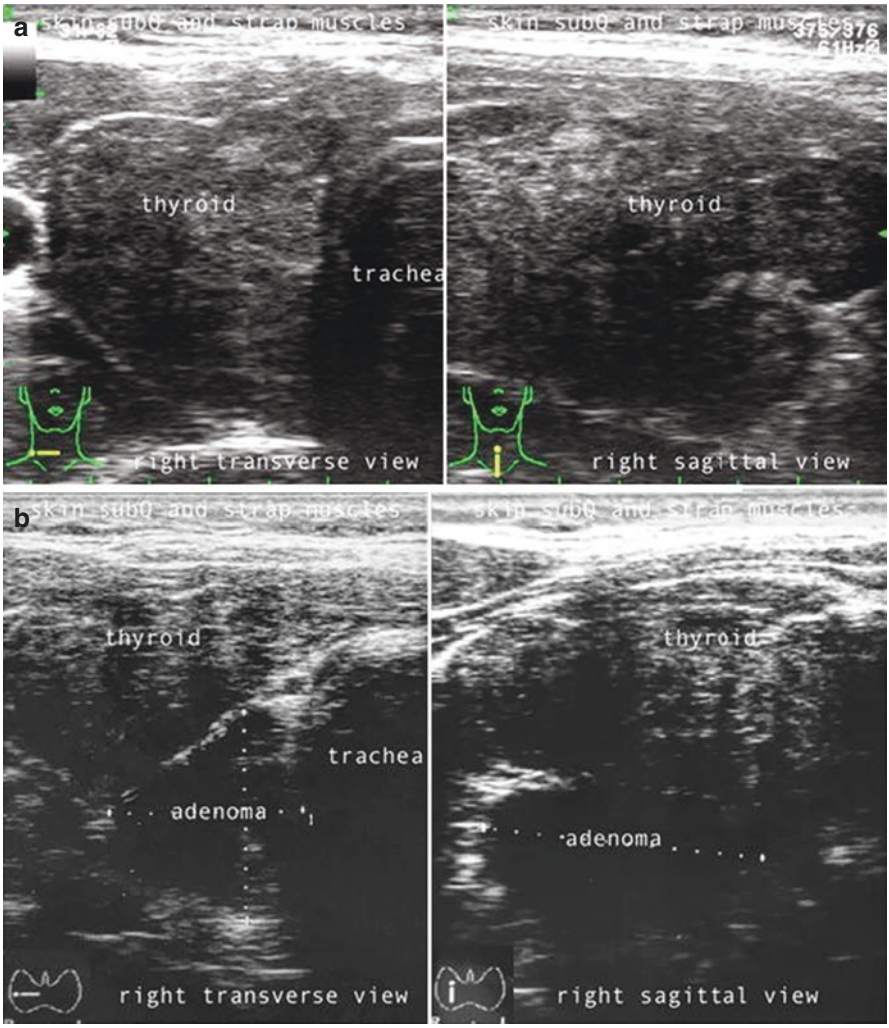

Fig. 17.7 Parathyroid adenoma identified on intra-operative ultrasound: (**a**) During ultrasound in the office setting, no parathyroid adenomas were identified in the neck (in a patient with negative nuclear scan). (**b**) In the operating room with the patient under anesthesia and the neck hyperextended, gentle pressure with the transducer identified a parathyroid adenoma posterior to the right thyroid lobe

detect retro-carotid and retro-esophageal PAs. Performance of IOUS adds little cost and time, but requires the cooperation of an expert sonographer to perform it on time.

Surgeon-performed ultrasound (SP-US) provides the surgeon with direct and dynamic information about the location of the targeted tumor in relation to other identifiable anatomical landmarks as coordinates. Similar to thyroid operations, IOUS can influence where to make the incision during parathyroid explorations.

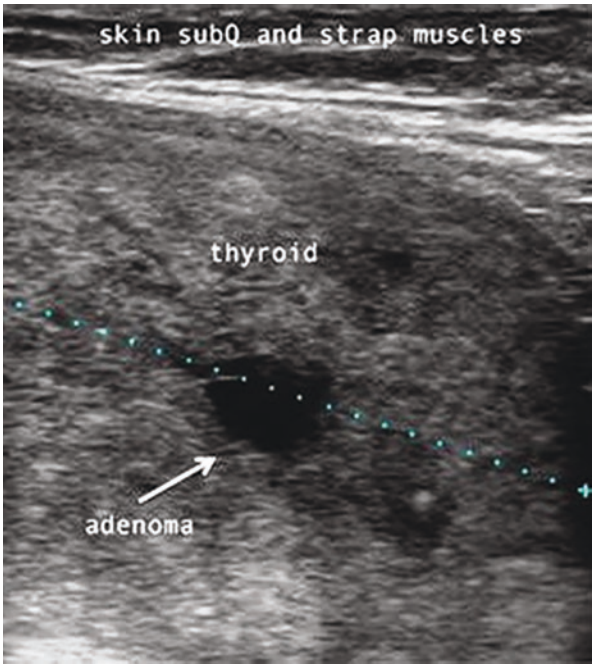

Fig. 17.8 IOUS (right sagittal view) showing intra-thyroidal parathyroid adenoma: During parathyroid exploration, operative findings and intra-operative PTH levels indicated persistent disease. A hypoechoic lesion in the right thyroid lobe was identified during IOUS. A right thyroid lobectomy was performed, which resulted in an appropriate decline in the intra-operative PTH level. Frozen-section examination and final pathology confirmed intra-thyroidal parathyroid adenoma

Surgeons who plan to perform a focal (single-gland) parathyroid exploration can use IOUS to guide the placement of the incision [69]. Surgeons who plan to perform a comprehensive (four-gland) parathyroid exploration can use IOUS to make an incision that is centered over the thyroid or equidistant from the suspected location of all four parathyroid glands. For both operative approaches, IOUS helps minimize the size of the incision. However, even with an US performed in the operating room prior to incision, localizing certain tumors can still be confounded by the disorientation of dissecting in scar tissue, especially for small tumors. Hook-needle guidance, systemic radioactivity uptake/gamma probe guidance, and US-guided injection of radioisotope, charcoal, and dye have all been described as solutions to localization, each with advantages and disadvantages [70–76].

To our knowledge, there are no prospective randomized studies that compare PHPT surgical cure rates with versus without IOUS. Despite the scarcity of the studies, however, it appears that, in a good sonographer's hand, IOUS may be of value in resolving the discordance of pre-operative scans and in guiding re-operative PHPT surgeries. In addition, it may shorten the operative time either by minimizing dissections during BNE or by facilitating the performance of MIP. In conclusion, IOUS, with the patient under general anesthesia and the neck hyper-extended, facilitates incision planning, shapes intra-operative expectations, and improves operative success in parathyroid surgery, especially in re-operations [77].

17.8 Intra-operative Fluorescence

Fluorescence diagnosis (FD) using the photo-sensitizer (PS) aminolevulinic acid (ALA) has been described for identifying PTGs during bilateral neck exploration (BNE) for hyperparathyroidism (HPT) in an experimental setting [78]. When PTGs are atypically located, this method may be helpful in detect the glands intra-operatively. Hence, the technique may reduce high morbidity rates, long exploration time, and persistent hypercalcemia.

The principle of FD, formerly known as *photodynamic diagnosis*, is based on the almost specific accumulation of administered photosensitizers in malignant cells. After intravenous, oral, or topical application, the drug predominantly concentrates in tumors and remains inactive until exposed to light of a specific wavelength. When light is delivered to the cancer site, either directly or indirectly through a fiber optic device, it causes fluorescence of the PS. While earlier generations of PSs, such as porfimer sodium, were already fluorescent at the time of application (*exogenous PS*), the PS "ALA" requires endogenous metabolism before it acquires fluorescence capabilities (*endogenous PS*). Administration of ALA, either systemically or locally, overloads the last step in the haem biosynthesis pathway of tumor cells due to missing negative feedback mechanisms or reduced enzymatic activities. This results in an increased accumulation of ALA's metabolite PpIX, which is a fluorescent agent when stimulated by the light of a defined wavelength within its absorption spectrum. One main emission wavelength is within the visible light spectrum at 635 nm (red light). The positive, red fluorescence of PpIX is even detectable in macroscopically invisible tumor foci and can indicate lesions, which would be missed when illuminated with conventional white light only. Although theoretically available for several decades, fluorescence techniques became more attractive for clinical use when more effective generations of PSs such as ALA were clinically implemented and tested. They were intended to reduce common side-effects of PSs such as skin sensitivity, nausea, vomiting, and transiently elevated liver transaminase levels.

Aminolevulinic acid (ALA)-induced PpIX photosensitization showed several advantages; (1) ALA, PpIX, and other intermediates are rapidly eliminated from the human organism, thus minimizing the risk of skin photo-toxicity, (2) ALA can be applied locally, providing an acceptable and convenient route of administration for patients, and (3) the fluorescence ratio between tumor and surrounding healthy tissue is superior to that of other PSs [79]. With this technique, parathyroid gland surgery to correct PHPT is successful in approximately, 80–97% of initial explorations [79–83].

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Parathyroidectomy

18

18.1 Background

Successful parathyroidectomy requires an understanding of the embryology and anatomy of the parathyroid glands (PTGs), which arise from the dorsal endoderm of the third and fourth branchial pouches. The majority of people have four PTGs parathyroid glands; two superior and two inferior.

The inferior PTGs arise from the third branchial pouch and initially migrate with the thymus until they separate to take their final position, usually at the level of the inferior pole of each lobe of the thyroid gland. The superior PTGs arise from the fourth branchial pouch and follow migration of the ultimobranchial bodies to take their final position, usually along the posterior part of the middle third of each thyroid lobe [1]. The superior PTGs have less anatomical variation than the inferior PTGs.

Grossly, the PTGs have a distinct, encapsulated, smooth surface that differs from the thyroid gland, which is has a more lobular surface, and lymph nodes, which are more pitted in appearance. Color of the PTGs varies from yellow to light brown to tan. The yellow color may be confused with surrounding adipose tissue.

Most parathyroidectomies are performed for *primary hyperparathyroidism* (PHPT), the most common cause of which is parathyroid adenoma (Fig. 18.1), accounting for 75–90% of cases. Most parathyroid adenomas are sporadic and involve all PTGs equally. While most authors believe that double parathyroid adenomas do occur, it is unclear how prevalent they are. Four-gland *hyperplasia* can be asymmetric with some glands being very large and others appearing closer to normal in size, shape, and appearance. In 2012, In the cohort of 3000 patients who underwent bilateral operations, the number of PTGs excised were one in about 75%, two in 17%, three in 5% and three and a half in about 3% [2]. *Cancer* of the parathyroid glands is rare and accounts for less than 1% of PHPT patients.

While PHPT occurs when PTH level is inappropriately elevated in relation to the serum calcium level, *secondary hyperparathyroidism* (SHPT) occurs when PTH is

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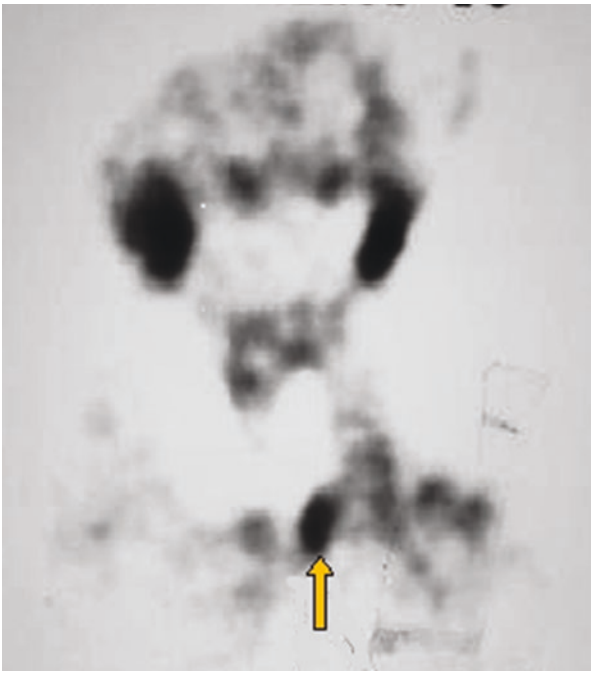

Fig. 18.1 The single left lower adenoma localized pre-operatively by ^{99m}Tc Sestamibi scan (yellow arrow)

elevated as the result of another cause, most commonly vitamin D deficiency and renal failure.

Tertiary hyperparathyroidism (THPT) occurs when glands affected by SHPT become autonomous and are no longer controlled by the normal feedback mechanisms. An example would be a patient with SHPT due to chronic renal failure who undergoes a renal transplant that corrects the renal failure, but who continues to have inappropriate release of PTH.

18.2 Indications

Historically, patients with PHPT presented with symptoms related to the effects of PTH on the bone and kidneys. However, with the advent of routine blood screening tests, most patients today are asymptomatic or present with minimal or non-specific symptoms such as fatigue, musculoskeletal pains and aches, depression, decreased memory, constipation, and abdominal discomfort. Currently, only 10–20% has renal stones, and very few have osteitis fibrosis [3].

Diagnosis of PHPT requires an increased serum total calcium level with an increased intact PTH level or, at least, an inappropriately high normal PTH level. Patients with an elevated intact PTH level and a calcium concentration in the normal range often have secondary HPT, usually resulting from insufficient calcium or vitamin D intake, reduced intestinal calcium absorption, vitamin D malabsorption, or renal hypercalciuria.

Depending on the cause of secondary HPT, surgery may or may not be an appropriate treatment option. Vitamin D levels should be checked preoperatively to rule out vitamin D deficiency, which can cause elevation of PTH. Some patients may present with a high PTH, low vitamin D, and calcium within the high normal range. Often in this case, once the low vitamin D is corrected, the patient will develop elevated calcium, and if PTH remains elevated, now fit the classic presentation for PHPT [4]. A 24-h urine calcium and creatinine test should also be administered to rule out familial hypocalciuric hypercalcemia (FHH).

A new clinical entity called "normo-calcemic PHPT" has been introduced, referring to normal calcium level and persistently elevated PTH level with exclusion of secondary HPT causes [5–7]. Some of these patients may also benefit from surgery.

The National Institutes of Health (NIH) consensus introduced guidelines in 1990 for recommending surgery in asymptomatic patients [8–10]. These guidelines were then amended in 2002 and later again in 2008 [11] and include the following:

- Serum calcium level > 1.0 mg/dL above the upper limit of normal.
- Creatinine clearance <30% of normal.
- Marked bone density reduction with a T-score < 2.5 at any site.
- Age < 50 years (if left untreated, many of these patients eventually develop complications of PHPT).
- A patient who requests surgery or a patient for whom surveillance and follow-up are difficult or impossible.

Although not included in the criteria, there is some conflicting evidence suggesting that PHPT contributes to cardiovascular disease [12–14]. Some authors believe that the cardiovascular risks, as well as other non-specific symptoms, can improve in patients with PHPT who do not meet the above criteria [11, 13].

18.3 Contraindications

Parathyroid surgery is contraindicated in patients with *familial hypocalciuric hypercalcemia (FHH)*. Patients with this disorder can present with elevated calcium and PTH levels mimicking PHPT. However, FHH is not treated surgically. In patients with FHH, 24-h urine calcium excretion is lower than expected in comparison with the serum calcium level. The ratio of 24-h urinary calcium to creatinine clearance is usually <0.01 in these patients, whereas it is typically >0.01 in patients with PHPT [15, 16]. In addition, FHH patients typically have normal or mildly elevated PTH levels. Calcium excretion over 24 h is <100 mg in 75% of FHH patients but usually >200 mg in patients with PHPT [17].

Some medications such as Thiazide diuretics and lithium excess can cause elevated PTH and serum calcium levels, mimicking PHPT. These medications should thus be considered during history-taking before proceeding with surgery.

Negative localization studies are not a contra-indication for surgery. If the patient clearly meets the criteria of PHPT based on blood and urine tests, then they should

be referred to an experienced surgeon for consultation regardless of the localization tests.

18.4 Pre-procedural Care

18.4.1 Pre-procedural Planning

If patients are receiving anti-coagulants, these agents should be discontinued before surgery, and medical status should be optimized before surgery as indicated. Pre-operative parathyroid localization studies should also be planned and carried out.

18.4.2 Pre-operative Parathyroid Localization

When parathyroid localization studies were first introduced, many surgeons maintained that the only localization necessary was "locating an experienced parathyroid surgeon" [18]. At that time, a comprehensive four-gland bilateral exploration was the standard of care.

The technique of four-gland bilateral exploration is still fundamental to parathyroid surgery and remains the gold standard by which all other more limited operations are measured. However, the development of preoperative parathyroid localization studies has allowed more focused exploration of the neck for PHPT, and such studies are now the standard of care in cases of re-exploration for persistent or recurrent HPT [19–22].

Technetium (^{99m}Tc) Sestamibi was first discovered to have persistent uptake in parathyroid tissue during myocardial perfusion studies. Because it is cleared faster from thyroid tissue than parathyroid tissue, it facilitates identification of abnormal parathyroid tissue on delayed imaging. This technique allows identification of parathyroid adenomas whether in normal or ectopic locations; however, the presence of thyroid nodules may reduce its accuracy [22]. On the other hand, accuracy of ^{99m}Tc Sestamibi scanning can be improved by combining it with single-photon emission computed tomography (SPECT) [23, 24], which is believed by some authors to be the best study for evaluating patients with HPT and concomitant nodular goiter [25, 26].

Although *ultrasonography* is non-invasive and the least expensive localization study of the parathyroid glands [10], it is operator-dependent and yields variable results. The use of a 7.5–10 MHz transducer is essential [27]. Compared with the thyroid, abnormal parathyroid glands are usually hypoechoic because of the uniform hyper-cellularity of the lesions, and approximately 15–20% is isoechoic or has a cystic component. Nearly 90% of cases demonstrate a hyper-vascular pattern [27].

Ultrasonography often misses retro-esophageal or mediastinal adenomas due to the shadowing effect of the laryngeal-tracheal complex and the sternum. It identifies

95% of adenomas weighing more than 1000 mg but less than 50% of adenomas weighing less than 200 mg [11]. Nowadays, many preoperative ultrasounds are done by the surgeons themselves.

Currently, both ultrasonography and ^{99m}Tc Sestamibi scan (with or without SPECT) are commonly performed pre-operatively during the evaluation of patients with PHPT [22, 28, 29].

Computed tomography (CT) scan and *magnetic resonance imaging* (MRI) can also be helpful in localizing abnormal PTGs. CT scan is useful in localizing ectopic mediastinal glands, and has been reported to locate abnormal parathyroid glands in patients with PHPT and negative ^{99m}Tc Sestamibi scan thus allowing a focused neck exploration in approximately 66% of such patients [30].

18.4.3 Equipment

In addition to the basic equipment necessary to perform the operation itself, materials and devices for preoperative localization and intra-operative guidance studies such as intra-operative parathyroid hormone (IOPTH) assay may be required.

If four-gland parathyroid exploration is going to be performed, no special intra-operative equipment is needed. However, if more targeted parathyroid surgery is going to be performed, additional equipment may be required, such as a gamma probe for radio-guided PTG identification and removal. Other intra-operative equipments that are used by some surgeons although not essential include tissue-sealing devices (e.g., LigaSure), ultrasonic dissectors, and special endotracheal tubes for intra-operative laryngeal nerve monitoring.

18.4.4 Anesthesia

Surgery for PTHP can be performed under either local or general anesthesia [31]. Patients with localized scans who are at high risk of general anesthesia may be better off under local anesthesia with sedation. However, preoperative imaging does not always correlate with intra-operative findings and the surgeon should always be prepared to perform a four-gland exploration. In such patients, conversion to general anesthesia is carried out.

In a survey of surgeons by Greene et al. [18], 90% of respondents preferred general anesthesia with intubation for parathyroid surgery [18]. Half of those who preferred local anesthesia used only local anesthetic infiltration with monitored sedation, and the other half used both local anesthetic infiltration and cervical nerve blocks with monitored sedation [18].

Local anesthesia eliminates the risk of intubation, shortens recovery time, allows same-day discharge, and reduces cost [32]. However, many patients are also currently being discharged home the same day after targeted one-gland, unilateral parathyroid operation, or even bilateral parathyroid surgery [18].

18.4.5 Positioning

The patient is positioned with the neck extended to improve access to the lower neck. Arms are positioned along the sides to allow the surgeon and an assistant to stand on either side of the patient and operate comfortably. If intra-operative PTH levels will be checked, an accessible intravascular site (either venous or arterial) should be available. Using the reverse Trendelenburg position or simply elevating the back of the bed decreases venous congestion and helps minimize venous bleeding during the operation.

18.5 Technique

18.5.1 Approach Considerations

Historically, the traditional standard approach was a comprehensive four-gland parathyroid exploration. With the introduction of Sestamibi scan in the 1990s, surgeons started to prefer unilateral and targeted surgery, which allow for smaller incisions, regional anesthesia, reduced operative time, and same-day hospital discharge, in addition to reduced risk of recurrent laryngeal nerve (RLN) injury and postoperative hypocalcemia [22]. Some experienced surgeons, however, advocate the return of bilateral parathyroid surgery, though they still use ^{99m}Tc Sestamibi scintigraphy before operation and a gamma probe or PTH assays during the operation [2, 33, 34].

Intra-operative PTH assay is often done to predict surgical cure in patients with PHPT [35, 36]. Whether measured *pre-incision* or *pre-excision*, if PTH level does not decrease by 50% and fall into the normal range, the surgeon should continue with four-gland exploration, or, at least, continue exploring until additional abnormal PTGs are identified and removed and PTH level is in the normal range and 50% or more below the starting value [32, 37]. In patients with diffuse four-gland hyperplasia, PTH levels should decrease further with each gland excision. After 3.5 glands have been excised, PTH level should be in the normal range and at least 50% below the starting level [38].

Making a patient hypoparathyroid is often worse than having the patient mildly hyper-parathyroid. This is where surgical experience and judgment becomes critical.

In 1998, Norman et al. advocated radio-guided PTG identification and removal [2, 39]. In this technique, patients receive an injection of ^{99m}Tc Sestamibi in the morning 2 h before surgery. A hand-held gamma probe is used to confirm which gland(s) are concentrating ^{99m}Tc Sestamibi. The abnormal gland or glands are excised, and the tissue is assessed against background radiation levels with the probe. Parathyroid adenomas should exceed background activity by at least 20% (on average, approximately 60%) [40].

Some surgeons perform intra-operative RLN monitoring. This may be particularly helpful in recurrent cases. However, it is certainly not possible in operations using local anesthesia with sedation or laryngeal mask airway anesthesia.

18.5.2 Steps of the Procedure

A low cervical *Kocher incision*, usually 2–4 cm long, is made two finger-breadths above the suprasternal notch. Similar to conventional thyroidectomy, dissection continues through the platysmal muscle, and the sub-platysmal flaps are raised. If a unilateral abnormality has been localized, then the thyroid lobe is mobilized first on that side.

Dissection continues along the thyroid capsule, and the thyroid lobe is rotated anteriorly and medially. If a preoperative localization study suggested either a superior or inferior gland, the corresponding area is examined first. However, the standard parathyroid ^{99m}Tc Sestamibi scans may be misleading.

The location of the *superior* PTG is sought on the posterior and lateral aspect of the thyroid gland. The middle thyroid veins are ligated, and the gland is rotated. The superior gland should be located deep to the plane of the RLN and superior to the intersection of the RLN and the inferior thyroid artery (ITA). The superior PTG is often found within 1 cm of the cricothyroid cartilage articulation. Dissection of the fibro-areolar tissue in this area facilitates finding both normal and abnormal PTGs.

If there is a covering layer of fascia just superficial to the PTG, it should be divided to clearly identify the PTG. Most normal PTGs are light brown in color, which distinguishes them from the surrounding yellowish fat.

The clefts within the thyroid gland are carefully examined to confirm that the PTG is not within a cleft and to make sure that the PTG has not been accidentally caught by the retractor or retracted with the thyroid. If the superior gland is still not found, exploration proceeds to the common ectopic locations.

Although identification of the RLN is not always necessary, it is important if the PTG cannot be found. The superior PTG is posterior to the plane of the RLN and can often be found in the tracheo-esophageal groove, in the posterior mediastinum, or adjacent or posterior to the esophagus. If additional exposure is needed, the superior thyroid artery (STA) can be ligated as it enters the superior aspect of the thyroid, and the thyroid gland can be further rotated antero-medially. It is sometimes also helpful to divide the sterno-thyroid muscle.

The search for the *inferior* PTG begins at the inferior and posterior aspect of the thyroid lobe and should include the thyrothymic ligament and the superior aspect of the thymus. The inferior PTG is typically anterior to the plane of the RLN and is often found just medial and anterior to the intersection of the RLN and ITA. With gentle retraction, the ectopic inferior gland can usually be pulled up into the neck and removed.

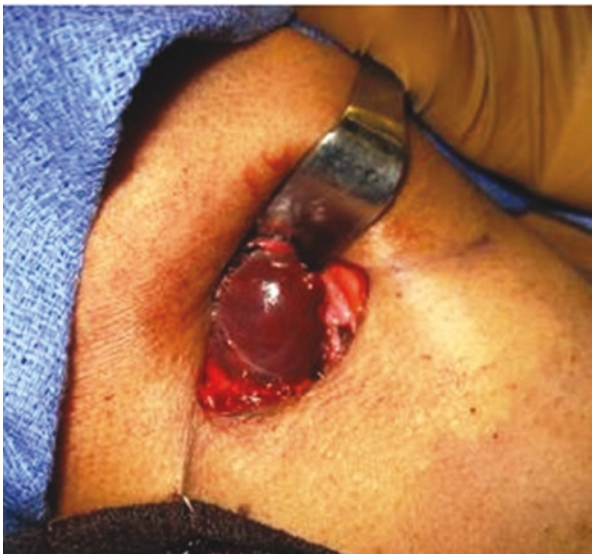

Fig. 18.2 Direct approach to ectopic parathyroid adenoma, localized pre-operatively by Sestamibi scan, inferior to the right submandibular gland

If a normal PTG is inadvertently devascularized during the dissection, it should be set aside in saline for later reimplantation. The gland should be cut into 1 mm cubes and placed in 1 or more small pockets that are made within the sternocleidomastoid (SCM) muscle. The area should be marked with non-absorbable suture and with staple clips to facilitate imaging and intra-operative identification should the patient becomes hyper-parathyroid again in the future.

If a localization scan indicates a *single parathyroid adenoma*, the procedure may be ended after the IOPTH assay yields a level within the normal range and at least 50% lower than the pre-operative level. Success rate with this method is above 95% and is comparable with that of traditional bilateral parathyroid surgery [10, 32].

If the patient has *four-gland hyperplasia* or *secondary HPT*, then either 3.5 glands are excised or four glands are excised with auto-transplantation subsequently performed.

Alternatively, if there is a well-localized parathyroid adenoma on pre-operative scanning, a small (2.0–2.5 cm) incision may be made directly over the location of the gland (Fig. 18.2). Dissection is proceeded between the strap muscles and SCM muscle and then directly toward the abnormal PTG. If PTH does not drop sufficiently after the removal of the gland, the incision must.

Currently, most surgeons practice limited exploration for parathyroidectomy, using ^{99m}Tc Sestamibi scans and (US with IOPTH assays [18]. Others achieved excellent results with a radio-guided approach that uses a gamma probe during surgery done within 2 h of obtaining a ^{99m}Tc Sestamibi [33]. However, less than 1% of surgeons adopt this approach [18].

Parathyroid *carcinoma* accounts for less than 1% of PHPT cases. To provide the best chance of survival, a wide local excision should be done in the initial procedure. The parathyroid tumor should be removed en-bloc with the adjacent tissue and

the surrounding lymph nodes (LNs). There is no indication for prophylactic lateral neck dissection [41, 42].

18.6 Methods of Parathyroidectomy

18.6.1 Bilateral Neck Exploration (BNE)

Bilateral exploration was the traditional surgical approach to parathyroid surgery and may be referred to as *open* parathyroidectomy, *standard* or *conventional* parathyroidectomy, or *four-gland exploration*. This approach has proven over time to be highly successful with cure rates of 95% or greater when performed by an experienced surgeon.

Pre-operative localization and special intra-operative techniques (such as OPPTH assay or radio-guidance) are *not* required, but may be used to guide the surgeon.

Traditionally, a BNE was performed through a 5–7 in. *incision*. However, most surgeons can now perform this operation via a much smaller 1.5–2 in. curved incision in a cervical crease in the lower part of the neck (Fig. 18.3). Muscles are separated to expose the thyroid gland, which is retracted to expose the parathyroids. Temporary post-operative hypocalcemia may occur in as many as 25% of patients [43], and may cause numbness and tingling in lips, fingers, and toes. This can be treated with calcium and vitamin D supplements and symptoms usually resolve within 15–30 min.

18.6.2 Minimally Invasive Parathyroidectomy (MIP) (Non-endoscopic)

Most surgeons favor a minimally invasive parathyroidectomy (MIP). The frequency of multi-glandular disease is however still a matter of debate, ranging from 5% in small series up to 30% in large series of parathyroidectomy, probably due to referral bias [2, 44, 45].

This technique may also be referred to as *focused parathyroidectomy, directed parathyroidectomy,* or *targeted parathyroidectomy*. There are many different ways to perform a focused parathyroidectomy and these include *image-guided,*

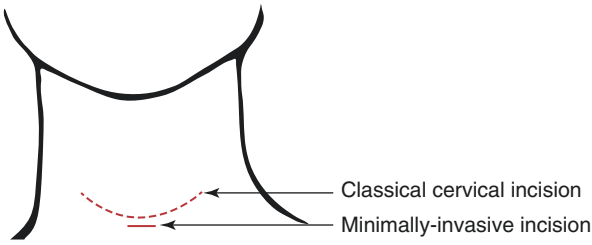

Fig. 18.3 Traditional incision for *open* parathyroidectomy (*standard* or *conventional* parathyroidectomy, or *four-gland exploration*) and minimally-invasive incision (medial approach)

radio-guided, and video-assisted techniques. Since the surgeon will not attempt to look at all four parathyroid glands in the operating room, it is crucial to perform pre-operative localizing tests. A patient may be considered for focused parathyroidectomy if a pre-operative localization reveals one or two abnormal glands (on the same side of the neck). Many surgeons also use IOPTH monitoring to confirm that there is no other hyperactive parathyroid tissue. Other adjuncts such as radioguidance or video-assistance may also be used.

Focused parathyroidectomy is typically performed through a smaller incision than the BNE, usually 1/2 or 1¼ in. long and can be performed through either a medial or lateral approach (Fig. 18.3). For the *medial approach* the incision is typically 3/4 to 1½ in. in size and is placed in the center of the neck. Muscles are separated along the midline and the thyroid is exposed and retracted medially. For the *lateral approach*, a 1/2 to 1¼ in. incision is made on the side of the neck over the muscle. Muscles are separated to expose the carotid artery and the edge of the thyroid gland. The thyroid is retracted medially and the carotid artery is retracted laterally to expose the space where the PTGs lie. In either method, once the abnormal gland is removed, many surgeons use the IOPTH test to confirm that all abnormal tissue has been removed. The cure rate of focused parathyroidectomy is similar to BNE, being approximately 95–98% [2, 31, 46]. A Mayo Clinic cohort analysis of 1361 patients showed equally cure rates for MIP and conventional bilateral parathyroidectomy (97%) [47].

There are several potential *advantages* of focused parathyroidectomy over a BNE including: smaller incision size, improved cosmetic result, shorter operative time, creation of less scar tissue, and fewer problems with post-operative hypocalcemia.

The incidence of symptomatic hypocalcemia has been reported to be reduced from 25% in BNE to 7% or less with focused parathyroidectomy [2]. Moreover, the majority of patients can be discharged the same day. Peel et al. [45] could discharge 101 of 154 patients the same day after performing a unilateral MIP. Reasons for an overnight hospital in their series were distance and availability of home care.

18.6.3 Minimally-Invasive Radio-Guided Parathyroidectomy (MIRP)

It is a type of *focused* parathyroidectomy and involves injecting a small dose of ^{99m}Tc Sestamibi 2–3 h before surgery. The surgeon then uses a hand-held gamma probe in the operating room to help place the incision directly over the abnormal PTG and identify the hyperactive gland during surgery. The gamma probe also confirms that the tissue that has been removed is indeed parathyroid tissue.

Recently, Mehrabibahar et al. [48] evaluated 87 patients with previous neck US and MIBI scan, performing radio-guided surgery. One mCi MIBI was injected in the operating room before starting surgery. MIRP was successfully performed in 86 of 87 patients.

The gamma probe was particularly useful in detection of an ectopic parathyroid adenoma in the upper mediastinum. The mean operation time was 24 min and the mean hospital stay was 1.5 days. Radiation exposure was 20 times lower, than using the conventional 20 mCi 99mTc-MIBI. Neither IOPTH monitoring nor frozen section tissue samples were used. Mean follow-up of 6 months showed no complications or recurrences.

The *benefits* of the intra-operative gamma probe have been debated. The greatest benefit appears to be in potentially reducing operative time when it is a reoperation, finding an ectopic PTG, and identifying the times the Sestamibi Scan incorrectly identifies a thyroid nodule as a PTG. The major *disadvantages* of this technique include increased cost and additional radiation exposure. Although this technique can be useful, many surgeons feel that experience and a thorough knowledge of parathyroid anatomy make it unnecessary.

18.6.4 Video-Assisted Parathyroidectomy (VAP)

It is a type of *focused* parathyroidectomy and also known as *minimally invasive video-assisted parathyroidectomy* (MIVAP) and *endoscopic parathyroidectomy*. Several techniques of VAP have been described using approaches from the middle or the side of the neck.

18.6.4.1 Advantages and Disadvantages

Compared to MIP, a large retrospective case-controlled study demonstrated that MIVAP is equally safe and effective. However, pain and cosmetic outcomes were in favor of MIVAP [49]. The main benefit of the VAP is that it provides greater magnification and may allow the surgeon to do the operation through a smaller incision.

Disadvantages include a longer operating time, the need for additional equipment, and the inability to reach certain areas of the neck. The safety and cure rate seem equal to other forms of focused parathyroidectomy [50, 51].

18.6.4.2 Contraindications

Contra-indications of MIVAP are broadly classified into absolute and relative and are summarized in Table 18.1 [52].

Table 18.1 Contraindications to minimally invasive video-assisted parathyroidectomy (MIVAP)

Absolute	Relative
– Thyroid volume > 30 mL	– Lack of pre-operative localization
– Adenomas >4 cm	– Four-gland disease (hyperplasia)
– Previous neck surgery	– Suspicion of a parathyroid carcinoma[a]

[a]Bakkar et al. (2016) [52] consider a parathyroid lesion clinically suspicious of a carcinoma a relative contraindication. Surgeons with adequate proficiency in performing minimally invasive video-assisted thyroidectomy (MIVAT) could perform an en bloc parathyroidectomy and thyroid lobectomy via the same access without the need to convert to a standard cervicotomy

18.6.4.3 Patient's Position

The patient is placed supine on the operating table with the arms tucked at the sides. The neck should be midline and only slightly extended. Extending the neck as in conventional surgery reduces the working space. The lack of neck extension offers an additional advantage; it minimizes the degree of potential post-operative neck discomfort.

18.6.4.4 Anesthesia

Local-regional anesthesia and general anesthesia with endotracheal intubation are both viable options. In general, the procedure is performed under general anesthesia with local anesthesia being reserved for the rare situation in which the patients' comorbidities favor avoiding general anesthesia [52].

18.6.4.5 Parathyroid Hormone Level Measurement

Prior to commencing the procedure, a basal serum parathyroid hormone (PTH) measurement is obtained in the theater.

18.6.4.6 Site Preparation

The skin is prepped from the level of the lower lip to the level of the nipples.

18.6.4.7 Position of the Surgical Team

The surgical team consists of three surgeons. The operator always stands on the patient's right side regardless of the location of the pathology. The first assistant stands on the patient's left side and is in charge of holding the camera. The second assistant stands at the head of the operating table above the patient's head, holding the retractors.

18.6.4.8 Instruments

The set of instruments used in MIVAP could be assembled from different sets of instruments used in General Surgery and Otorhinolaryngology. No energy devices are required. However, ultrasonic shears can be used if the need for a concomitant thyroid lobectomy emerges.

18.6.4.9 Steps of the Procedure

A 1.5 cm transverse incision is made in a neck crease, two finger breadths above the sternal notch. The incision should never be higher than the cricoid cartilage. The incision is deepened through the subcutaneous (SC) fat and platysma using electrocautery. Subplatysmal flaps are *not* raised. The cervical linea Alba is then exposed by lateral retraction using small retractors. It is then incised vertically using electrocautery to expose the thyroid gland, which is then bluntly dissected from the overlying strap muscles by gentle traction and the use of a tiny spatula. Once the thyroid gland has been completely dissected free from the strap muscles, the small retractors are replaced by two larger ones that are used to maintain the working space

throughout the procedure. The thyroid lobe is placed under the medial retractor and the lateral one is used to retract the strap muscles laterally.

A 5-mm 30° camera is then introduced and preparation of the working space is completed using two spatulas. Typically, the camera is held at a 90° angle on the field with its 30° tips looking upward. The abnormal PTG is identified. Grossly, an adenomatous PTG is large and tan or beefy red. Once identified, excision should not be attempted until the RLN is identified and preserved. The abnormal PTG is then grasped from the adipose tissue attached to it using a special grasper. Care must be taken not to grasp it directly from its capsule due to the potential risk of capsule rupture and subsequent parathyromatosis. The gland is then bluntly dissected from its surroundings using a spatula to expose its vascular pedicle, which is then controlled using small metallic clips and subsequently divided, and the PTG is removed. An appropriate drop in serum PTH levels should be confirmed by obtaining an intra-operative measurement 5 min following pedicle ligation.

Finally, the surgical site is carefully inspected for adequate hemostasis. No drains are placed. The muscles are re-approximated with a single figure-of-eight suture using 3-0 Vicryl. The SC tissue is approximated by two simple interrupted sutures using 4-0 Vicryl and the skin is closed with glue.

18.6.4.10 Special Situations

At times, the need for a bilateral exploration and/or performing a concomitant thyroid lobectomy or even a total thyroidectomy emerges. Double adenomas, intrathyroidal parathyroid lesions, and those suspicious of carcinomas are all rare, but well recognized entities [53–55]. They are considered a limitation to most minimally invasive parathyroid surgeries such as MIP, and the video-assisted lateral approach [56]. However, MIVAP in experienced hands allows for both conducting a full neck exploration and for performing a concomitant thyroid surgery without the need to convert to a standard cervicotomy [57, 58]. This is attributed to its central and direct access, in addition to adequacy of the working space, which is identical to that created for minimally invasive video-assisted thyroidectomy (MIVAT) [59], allowing four-gland disease management [60].

18.6.4.11 Outcome

Bakkar et al. [52] reported that, with growing experience, the mean operative time became 31 ± 20.4 min, with a mean incision length of 17 mm. None of the patients in their series developed vocal fold palsy nor experienced post-operative bleeding requiring revision surgery. The mean visual analogue scale (VAS) score for the patients was 2, and all patients were cured following the first operation. One patient required a concomitant thyroid lobectomy due to features suspicious of a parathyroid carcinoma, and exploration was required in two patients because of the normality of the glands on the side suggested by imaging studies. In none of these three patients was conversion to standard cervicotomy required.

18.7 Complications

Bleeding and infection are potential complications, but should be rare in parathyroidectomy. As with thyroid surgery, there is a risk of injury to the recurrent and superior laryngeal nerves. In difficult cases, where the abnormal PTG is not found easily, it is important to identify the recurrent laryngeal nerve (RLN), to protect it from injury and to have it available as a landmark during dissection. Bleeding and infection are extremely rare complications in MIP, as is damage to the RLN [51, 52].

Failure to cure the hyperparathyroidism (HPT), persistent or recurrent hypercalcemia, and post-operative hypocalcemia are also potential adverse results of parathyroidectomy.

In a prospective randomized controlled trial ($n = 91$), unilateral minimally invasive parathyroidectomy (MIP) yielded the same cure rates and histology as the bilateral neck dissection (BNE). However, patients in the BNE had a higher incidence of early symptomatic hypocalcemia (28% vs. 49%) [53, 54].

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