Stephen Z. Fadem
Editor

Staying Healthy with Kidney Disease

A Complete Guide for Patients

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Preface

It was the beginning of my medical school training, the summer of 1969. In addition to classes, I volunteered as an aide at the Children's Hospital. Each day for several weeks we cared for Floyd, an adorable 4-year-old child with Bright's Disease, now called end-stage kidney disease, and known to all as a terminal condition. Floyd was wasted, weak, and frail. But when we came on the ward, he was so happy to see us that his smile went from ear to ear. Each day, however, he grew weaker, dying of a disease that had a therapy, but sadly not for him. Floyd was not eligible for dialysis – he was too young to qualify and had no insurance. He grew pale and feeble despite regular blood transfusions. At the end of his life, his arms and legs were like toothpicks. He died in the arms of his anguished mother and grief-stricken father. I will never be able to forget the excruciating pain and anguish I shared with his parents, both mentally and physically; I felt powerless. It was at that moment that I resolved I would devote my career to helping kidney patients.

Around the time Floyd died, a group of Brooklyn dialysis patients convened to start a newsletter. The National Association of Patients on Hemodialysis was born to network patients from around the country, help share the burgeoning knowledge about this new lifesaving therapy, and make them aware of the need for legislation that would enable patients with end-stage kidney disease to receive treatment through Medicare. I remember distinctly two members of this group, Bill Litchfield and Peter Lundin. Bill was a petroleum engineer who did dialysis at home. When he traveled, he used the portable Redy Machine our dialysis unit had purchased. I would help Bill load up his car for his trips to the oil fields in Louisiana. Bill taught me that having kidney disease was an inconvenience but need not control one's life. Then there was Peter, the first dialysis patient to ever be accepted into medical school. He later became a nephrologist. Peter and I worked on a website for patient education. He also taught me that there is no reason why patients with kidney disease cannot live a full life. It was Peter who introduced me to NAPH (National Association of Patients on Hemodialysis), which was later renamed the AAKP (American Association of Kidney Patients). Their mission resounded with me, and I have since become chairman of their Medical Advisory Board where I have authored over 30 articles for their patient journal.

Finally, there was Cora, my office assistant. When I started practicing nephrology, she showed me the chart of a female with a GFR of 21 mL/min/1.73 m^2 who had polycystic kidney disease. I gave her instructions to find a room for that person immediately; she replied back that she was, in fact, that person. I then telephoned the smartest person I knew and asked for advice. Bill Mitch said to put her on a restricted protein diet with keto-analogs. She was able to remain off peritoneal dialysis (PD) for 12 years, and even after starting PD continued to work in the office. Cora was the most compliant patient one could have; she taught me that awareness and motivation were both necessary for success.

After finishing a four-volume textbook series on nephrology, my head was full of facts. I wanted to get the message out to patients that having kidney disease also has options for success. The management of kidney disease is divided into two parts – one which we can control and the other which we cannot control. This book is about the former, what we can control. The kidneys integrate with every other organ in the body, so it is impossible to separate caring for your kidneys from caring for your heart, keeping your muscles strong, or eating well. All cells burn fuel and require oxygen, so it is impossible to talk about the kidneys and skip over some key essentials of metabolism. Every effort was made to make this knowledge understandable and easy to follow.

A book like this is a team effort, and I would like to acknowledge the mentorship of Bill Mitch and Richard Glassock. Bill has a sixth sense for understanding how to prevent kidney disease, and his research and observations have shaped many of our patient's lives. Richard is one of the most distinguished physicians in the country and has shaped the field of nephrology for over 50 years. Misha Nguyen is devoted to fitness, and her dedication to health and well-being has given her the passion to make invaluable contributions to this book. In addition to being a certified master trainer, she has a Master of Science degree in healthcare administration and is also the consummate grammarian. This combination, plus an amazing work ethic, made it possible for me to assure that this work is readable, understandable, and meets the requirements of good English usage. Linda Moore and Kamyar Kalantar-Zadeh are both leaders in the field of nutrition. They have greatly contributed to our understanding the role proper eating plays in the well-being of kidney patients. I would also like to acknowledge our associate editor, Hannah Campeanu of Springer Nature. Her guidance and advice has been invaluable in helping to transform this project into a book that is clear and comprehensible.

My lovely wife Joyce has been my friend, life partner, and support for nearly a half century. My children and inquisitive grandchildren keep me young and ageless. It is amazing how the youth of today are so knowledgeable. When I spoke with my 13-year-old grandson about mitochondria, he told me they already studied it in school, and he wanted to know about the role kidneys play in anemia.

This book is dedicated to patients. Your resilience and bravery inspire and motivate me every day. I constantly try to learn so I can better care for you. If this book can help bring your knowledge of this highly complex subject to a higher level, as well as motivate, encourage, and excite you that there are actionable things that can make a positive difference in your life, the many hours I spent behind a giant computer screen is worth all the while.

Houston, TX, USA Stephen Z. Fadem

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Chapter 1
Introduction to Kidney Disease

Stephen Z. Fadem

Introduction

Perhaps you or a family member has just been told you have kidney disease. Maybe you are interested in kidney disease because you are diabetic or have high blood pressure. In either case, do not feel isolated – you are not alone. Exactly what do we mean by kidney disease? This umbrella term may be broadly used to define any disorder that affects the kidneys. But, more specifically, we will be referring to chronic kidney disease (CKD). CKD is a common, progressive disorder characterized by declining kidney function. It has multiple causes but the ultimate same result - the slow deterioration in kidney function. Kidney disease is common in the United States, affecting 15% of all US adults. For most people it will not progress, but approximately 112,000 patients start dialysis each year. Although there are around 550,000 patients on dialysis and another 230,000 are living with a kidney transplant, the progression of CKD to these final stages is relatively rare. The disease progression varies according to race but is four times as common in African Americans than Caucasians. In the United States, the patients who require dialysis each year ranges from over 280 per million in New England to over 430 per million in Texas (Source USRDS.org 2020). The rate of kidney disease progression has been decreasing because of advancements in care.

Although most patients with kidney disease may never progress to the stage where they will require dialysis, they will still have other risks and therefore must remain vigilant and cautious. Patients with kidney disease are nearly twice as likely to have heart disease. Kidney disease is also associated with hypertension, diabetes,

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and more rapid aging. Each of these problems will be addressed in a chapter in this book.

This book is intended as a guide, as well as a starting point for a discussion with your own doctor and caregiver. The research in kidney disease and its associated problems is expanding rapidly. This book will put you in touch with resources that can help you stay updated on the science and management of chronic kidney disease. It will present the information that you need to know to stay healthy. But many of you will want to dig deeper and understand the mechanisms associated with kidney disease. It will also present illustrated stories and highlight additional information for you.

How Do the Kidneys Work, and What Happens When They Do Not Work?

The kidneys are organs located in your back, just in front of your ribs (See Fig. 1.1).

The aorta is the large blood vessel branching off the heart like a giant tree trunk. As it ascends, major arteries travel to deliver blood to the heart and brain. It descends to supply blood to the rest of the body. Arteries are blood vessels that carry the blood away from the heart while veins are the blood vessels that return the blood to the heart. The heart pumps blood through the aorta and through the renal arteries to the left and the right kidney (See Fig. 1.2).

Inside the kidneys, the arteries continue to branch, becoming smaller and smaller. Soon they become tiny arteries known as arterioles which then turn to capillaries (See Fig. 1.3).

The arterioles act like resistors, making sure that the blood flow and pressure that flows into the capillaries is not too high. The afferent arteriole brings blood into the filter.

The Glomerulus

The delicate capillaries that control filtration are part of the glomerulus – a saccular system that holds back blood and proteins, but let body fluids, waste products, and important minerals pass through. The fluid that does pass through is filtered across the capillary and its adjacent basement membrane, and then collected in a capsular sac called Bowman's capsule (Fig. 1.4).

The membrane has projections known as foot processes to increase the surface area needed for effective filtration. For this reason the cells that make up this membrane are known as podocytes. It is the podocytes that make filtration possible. The capillary also has an internal cell known as the endothelial cells. These manage the health of the capillary.

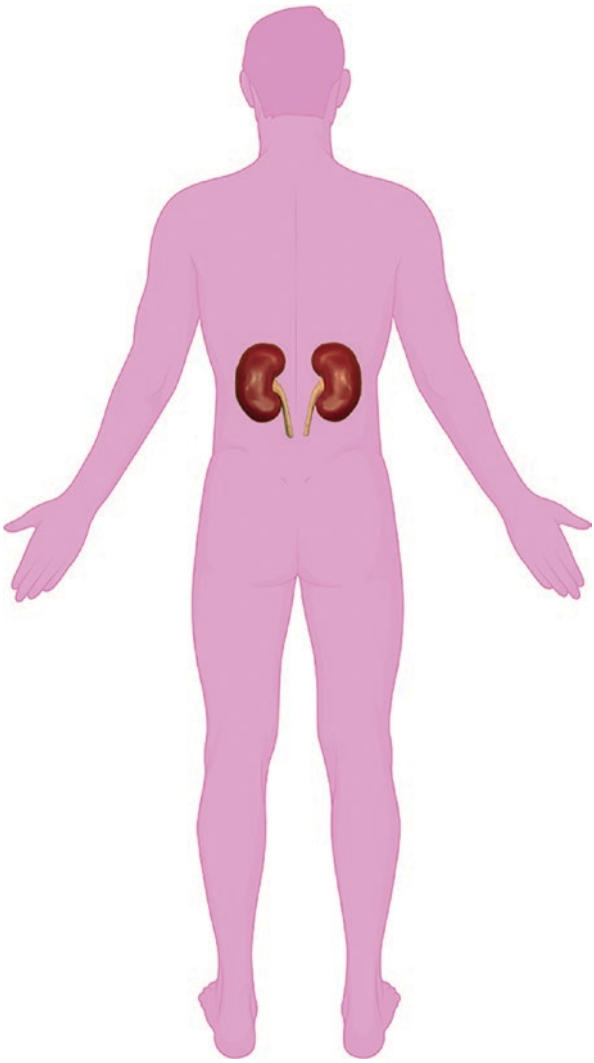

Fig. 1.1 Location of the kidneys. (Made with Adobe Photoshop and Biorender (Biorender.com))

The mesangium is the area that is in between the capillaries. It is made of cells, structured bundles of tissues that serve as a scaffold for the glomerulus, and matrix proteins. It is the "housekeeping" area of the glomerulus, and helps remove substances that can harm the filter. As the result, the mesangium is highly reactive to both environmental and internal stimuli. Its response to stimuli plays a key role in kidney damage and disease.

The capillaries then convert back to another arteriole that leaves the filter – the efferent arteriole. They carry the filtered blood back to the general circulation. The fluid that is filtered leaves the capsule and enters the earliest (proximal) part of a long tubule known as the nephron.

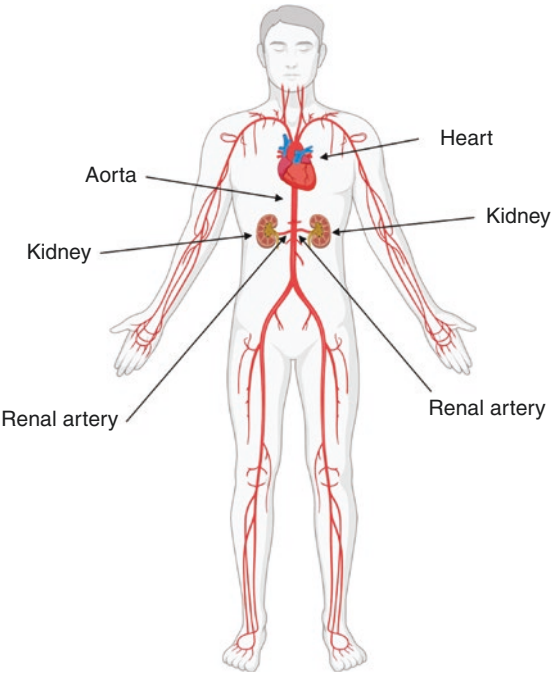

Fig. 1.2 Showing how blood is pumped to the heart through the aorta and the renal arteries to the kidney. (Made with Biorender (biorender.com) and Adobe Photoshop)

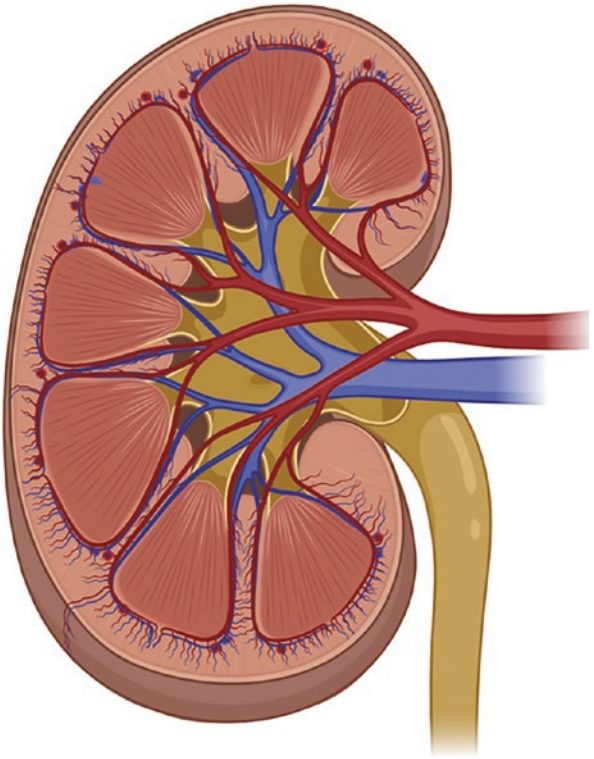

Fig. 1.3 The renal circulation showing how the blood vessels inside the kidney continue to branch - made with Biorender (Biorender.com)

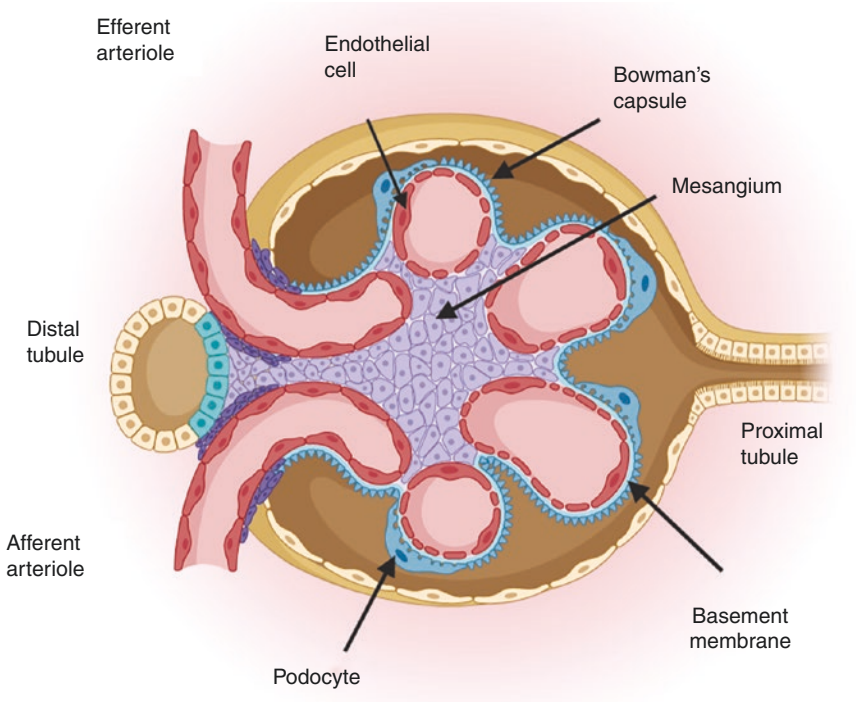

Fig. 1.4 The glomerulus – made with Biorender (Biorender.com)

The Nephron

If the tubular structures were simply conduits, we would just lose fluid and minerals along with waste products and would quickly become dehydrated. But this is not what happens; the tubule curves on itself and actively participates in recycling fluids and minerals. Some of the fluid is ultimately eliminated as urine, most of the filtered fluid is recycled by the tubules. This marvelous system of glomerulus and tubules is called the nephron. There are around one million nephrons in each kidney.

The nephron is the main working part of the kidney. It contains the glomerulus, and a long and winding tubule. After filtration takes place the fluid enters a long winding tubule that has several distinct parts, a proximal tubule where a great deal of the work of reclaiming many minerals and substances takes place. The tubule transcends downward, and then upward again. This is the Loop of Henle, and it plays a key role in forming the high concentrations of sodium the kidney required to regulate volume. In the distal tubule, "fine tuning" of mineral balance occurs. The collecting duct makes the final determination of how much water is lost or conserved (Fig. 1.5).

The kidneys have several jobs (See Table 1.1): they filter waste products from the blood; get rid of excess acid; help balance minerals like sodium, potassium, calcium

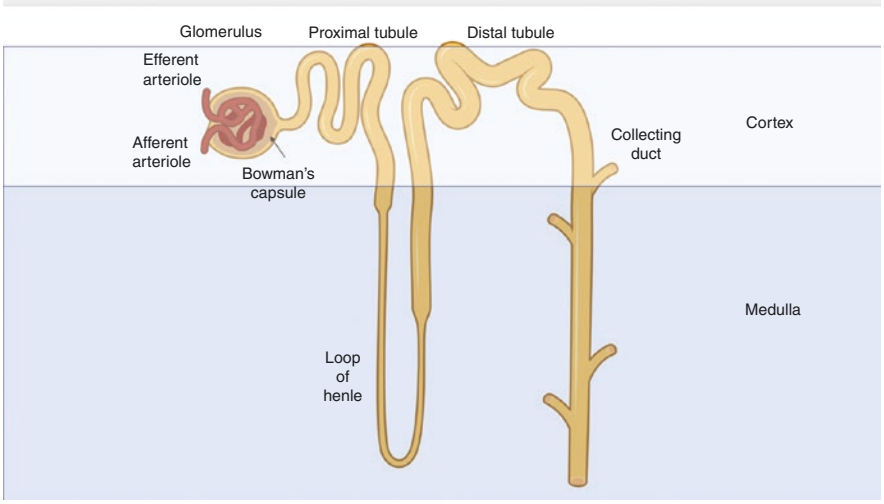

Fig. 1.5 The nephron. (Made with Biorender.com and Microsoft Power Point)

Table 1.1 The jobs of the kidney, and what happens when the kidneys are failing

Job	In health	Failure
Filter wastes	The kidney eliminates urea and other waste products	These products accumulate. They have a toxic effect
Filters some medications	Many medications are eliminated by the kidney	These medications accumulate and can be toxic. Their dosage should be adjusted, or they should be avoided
Make erythropoietin	The kidneys make the hormone that stimulates bone marrow cells to produce red blood cells	Anemia (low red blood cell count) occurs. The red blood cells carry oxygen to tissues and are important components of body function
Activate vitamin D	Vitamin D absorbs calcium from the GI tract and helps form healthy bone	The vitamin D levels fall. This may affect bone, the GI tract, and stimulate the parathyroid hormone (PTH) glands in the neck
Secrete acids	Foods contain acids that are eliminated by the kidney	Acid accumulation requires buffering by bone to neutralize the acids. Acids weaken cells and promote aging
Secrete potassium	Potassium balance is partly controlled by the kidney	The accumulation of potassium causes muscle dysfunction and death
Excrete phosphorus	The kidneys filter and reabsorb phosphorus	The accumulation of phosphorus signals a type of hardening of the arteries known as vascular calcification. It also stimulates small glands in the neck to enlarge and secrete a hormone, the parathyroid hormone (PTH). PTH weakens bones
Balance sodium	The balance of sodium by kidney tubules regulates blood pressure and body volume	In severe kidney disease the body is unable to get rid of fluids; this fluid overload can lead to high blood pressure and heart failure
Concentrate/ Dilute urine	The kidneys make it possible for us to go for extended periods without drinking. They concentrate the urine. They also keep fluids in balance by diluting urine when we drink too much water	The kidneys cannot concentrate the urine, and when they are failing, dehydration may occur

and phosphorus; help control and regulate volume, water, and blood pressure; and make a hormone known as erythropoietin that is necessary for controlling anemia. When they do not work properly these jobs cannot be accomplished, and we become ill.

How Can We Measure Kidney Function?

The most common method to measure kidney function is to draw a serum creatinine blood level. Creatinine is a breakdown product of creatine, a molecule that helps muscles receive energy. Muscle tissues are in a constant state of being repaired and replaced, and thus the breakdown product, creatinine. Since creatinine stays in a steady state and is eliminated by the kidney without any further metabolism, it is an excellent index of kidney function. If the kidney function worsens, the serum creatinine level will rise. Creatinine is easily measured, and the results from the laboratory are standardized. This means that whether you go to the hospital, a neighborhood laboratory, or a clinic, the serum creatinine should be analyzed the same way. Several years ago, scientists developed mathematical formulas that estimated the glomerular filtration rate.

In a previous section we talked about the glomerulus, the filter that rids the body of wastes. The rate of filtration gives us an idea of how the kidney is working. When you see your laboratory results, the serum creatinine will be measured in milligrams (mg) per 100 cubic centimeters (cc), also called decaliters (dL), and abbreviated 100 mg/dL. The estimated glomerular filtration rate (eGFR) is calculated in cc per minute. Since we are of different sizes, this is adjusted to the standard size of 1.73 square meters (1.73 m^2). A 60-year-old African American woman with a serum creatinine of 1.00 mg/dL will have an eGFR or 69 cc/min/1.73 m^2.

eGFR - Table 1.2 lists some of the current ways to evaluate the kidney. (Chap. 14 further discusses the eGFR and other calculators.)

Reversible Kidney Tests and False Positives

The diagnosis of chronic kidney disease (CKD) is not made on a single laboratory value, but instead on reviewing laboratory values over 3 months. It can also be made by imaging studies. The reason is that often times the laboratory value is falsely positive, or that the kidney disease has reversed itself. Several factors are associated with reversible kidney disease. Table 1.3 highlights some of the reasons. The glomerular filtration rate (GFR) is measured by using the creatinine. Creatinine is a muscle breakdown product of creatine, a molecule that helps muscles contract. A picture is included of both creatine and creatinine's chemical structure. The creatinine level is measured or analyzed in a laboratory using a method that was first discovered in 1886. The assay method for measuring the serum creatinine can vary

Table 1.2 Measures and markers of kidney disease

Estimated GFR (eGFR)	These are formulae to estimate the GFR. They are based on the data from clinical trials. They may be referred to as the MDRD GFR or the CKD-EPI GFR. The more recent formulae use the age, gender, serum creatinine, and often another marker of kidney function, the serum cystatin C. The newer calculators do not require a race coefficient
Cystatin C	A low molecular weight molecule that can be used to calculate the eGFR (http://mdrd.com). It does not rely on muscle mass or race
Creatinine clearance	A24-hour collection of urine multiplied by the volume of the urine collected and divided by the serum creatinine. It is expressed in cc/min. 24-hour urines are difficult to collect (https://www.ncbi.nlm.nih.gov/books/NBK544228/)
Cockcroft Gault Equation	A calculation that uses the patient's weight, age and sex, along with the serum creatinine. It is used extensively by the pharmaceutical industry. (http://touchcalc.com/calculators/cgsi)
Measured GFR	The gold standard using radioactive isotopes like ^{125}Iothalamate. It is cumbersome and expensive but highly accurate [1]
Urine albumin/creatinine	This ratio is a simple yet accurate way to estimate the amount of urine that is leaking through the filter. Small amounts (microalbuminuria) can indicate either early kidney damage or systemic vascular damage. Quantities over 300 mg of albumin/gram of protein indicate significant glomerular disease. The nephrotic syndrome is characterized by greater than 3.5 g of protein loss and indicated damage to the filtration barrier
Urinalysis	Examination of the urine is routine and gives the doctor many indicators of kidney disease. Testing includes an evaluation for concentration, the presence of protein or sugar, and the presence of crystals that may cause kidney stones, abnormal cells, or urine casts that can indicate diseases like acute kidney injury or glomerulonephritis
Renal ultrasound	This is an imaging study that includes determining kidney disease, the thickness of the cortex or filtering section of the kidney, as well as the presence of blockage, cysts, or masses. A Doppler study can determine kidney blood flow
Kidney biopsy	A needle biopsy of the kidney can give the doctor information about what disease is causing damage to the kidney. It is most widely used to determine the type of glomerulonephritis when there are available options for therapy

up to 19%. We now have newer methods to measure the creatinine, but even so the results can vary. Sometimes the laboratory methodology is inaccurate - this would be called an analytic variation. Variation has been minimized since 2006 by using calibration methods that are traceable to the National Institute of Standards reference creatinine.

What is biological variation? That is the difference in serum creatinine that is based on features that are relative to the individual. Creatinine is broken down from creatine, a component of muscle that helps it use energy.

Usually, it exists in a steady state in the body, but this can depend on many factors, even the diet. Creatine is present in animal tissues such as meat, fish, and poultry. It is an essential part of muscle. When cooked, it can convert to creatinine. As will soon become apparent, kidney disease can be classified into various stages. Measuring the serum creatinine too soon after eating can falsely raise the value, particularly when kidney disease is in the later stages [2].

Table 1.3 Common causes of false positive tests or reversible kidney disease

1. Variations
(a) Analytical variation
(b) Biological variation
1. Muscle mass
2. Animal protein consumption
3. Medications
2. Hemodynamics
(a) Hypertension
(b) Dehydration
(c) Exercise intensity
(d) Diabetes
(e) Diuretics
(f) Heart failure
(g) Renin- angiotensin blockade
(h) Non-steroidal anti-inflammatory drugs (NSAIDS)
(i) Acute febrile illness
(j) COVID-19
(k) Obesity
3. Acute kidney injury
(a) Rhabdomyolysis
(b) Radioiodinated contrast agent
(c) Hospitalization for an acute illness
(d) Nephrotoxins
(e) Pneumonia or sepsis
(f) Anabolic steroids
(g) Worsening underlying disease
(h) Urinary tract infection
(i) Urinary tract obstruction
4. Kidney stones

The serum creatinine is not just dependent on meat consumption, but on muscle mass. It can be higher in bodybuilders, but also lower with the muscle breakdown that accompanies age and kidney disease. Certain medications can interfere with creatinine secretion by the kidney tubule. The best known is the commonly used antibiotic, trimethoprim (Bactrim). Another medication used to treat irregular heart rhythms, dronedarone (Multaq) can also interfere with the tubular secretion of serum creatinine and artificially lower the eGFR.

Kidney function is constantly fluctuating in order to adapt to the environment. This dynamic interaction can alter the kidney function. Being too dehydrated, exercising intensely, the taking of medications like diuretics or nonsteroidal anti-inflammatory drugs (NSAIDS), or having a fever, can temporarily affect kidney function without really causing disease. The kidneys are also very responsive to changes in heart function. 20% of the cardiac output of blood is constantly being pumped through the kidneys. Uncontrolled heart failure can also affect the kidney function.

The body has developed an emergency system to maintain our blood pressure. This is known as the renin-angiotensin system (RAS). If this system does not work

properly, it can cause kidney damage and high blood pressure. Thus, medications to block RAS are commonly used to treat hypertension and kidney disease. However, RAS blockade may also transiently affect the eGFR.

Acute kidney injury and kidney stones are capable to altering kidney function, but most of the time, the kidneys improve back to a baseline.

Understanding these common causes for why the laboratory values vary can help you alleviate the stress associated with having your kidney function tested. In many cases we can "reverse the reversible."

How Is Kidney Disease Classified?

Table 1.4 simplifies the task of sharing with others what degree of kidney disease you may have. In the late 1990s, kidney function measurement was confusing; there was no standard system. Furthermore, the terminology added to the muddle. Doctors talking about renal disease, nephrology problems, kidney disease, early renal insufficiency, end-stage renal disease, pre ESRD, or chronic renal failure confused patients, as well as each other. A classification was thus established and has since been updated (Source: KDIGO.com). Today, we speak of 5 classes of kidney disease. We divide stage 3 into two groups: Stage 3a and Stage 3b. Since 2009, kidney function is measured by a mathematical equation known as the CKD-EPI eGFR. For reference to this and other equations, you can assess the website http://ckd-epi.com. Patients are considered to have kidney disease if the measurements recur over 3 months. This is because many reversible factors can interfere with the serum creatinine measurement.

Table 1.4 Classification of kidney disease

Stage	Level of function	eGFR cc/min/1.73 m^2	Comment
1	Normal or high	90 and above	Kidney disease may occur with normal function. Focus on treating underlying disease and managing lifestyle
2	Mildly decrease	60–89	Early changes of CKD are occurring. Continue treating underlying disease, managing lifestyle, and early complications
3a	Mild to moderate decrease	45–59	Treat underlying disease. Avoid harmful medications. Manage lifestyle and diet. Risk of heart disease rising
3b	Moderate to severe decrease	30–44	Treat underlying disease and avoid harmful medications. Manage lifestyle and diet. Consider renal replacement modalities such as dialysis or a kidney transplant
4	Severe decrease	15–29	Measures to preserve kidney function. Modalities decision and preparation for renal replacement therapy (RRT)
5	Kidney failure	<15	Measures to preserve kidney function. Prepare for or start RRT

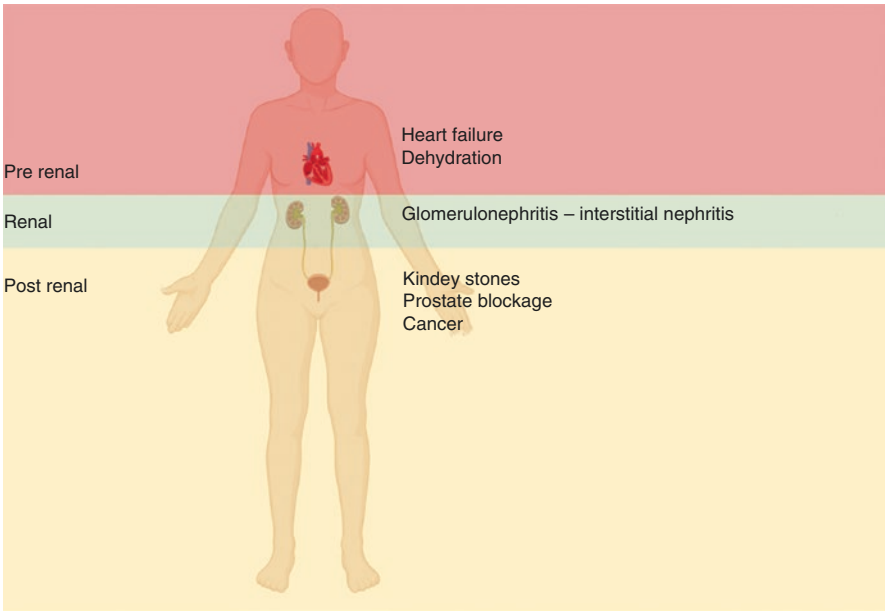

Fig. 1.6 The different types of kidney disease. (Made with Biorender.com and Adobe PowerPoint)

What Are the Different Types of Chronic Kidney Disease?

Kidney disease may be the result of factors reducing the flow to the kidney, intrinsic kidney problems, or kidney outflow. This is described as pre-renal, renal, and post-renal, and is described in Fig. 1.6.

Patients with heart failure or dehydration will have a decreased blood supply to the kidney, which will affect glomerular filtration. The kidney tests may be abnormal. Generally, prerenal causes of kidney disease reverse with treatment of the underlying condition. In patients with true renal causes of disease, there is inflammation or damage that interferes with kidney function. This will generally require therapy. Post renal causes are secondary to impairment of the kidney outflow. Blockage of the urinary tract will interfere with how the kidney functions. Kidney stones or urinary obstruction because of cancer or an enlarged prostate can cause this type of kidney disease.

Intrinsic kidney disease refers to disorders that primarily effect the kidney. This category is not dependent upon extrarenal "prerenal" or "post renal" factors. Intrinsic diseases can have primary causes or be related to systemic diseases like diabetes, hypertension, or lupus. Table 1.5 highlights several causes of primary and secondary causes of intrinsic kidney disease. In many cases, intrinsic kidney diseases also have manifestations in other organs. The most common causes of kidney disease are either related to systemic hypertension, diabetes mellitus, or genetic disorders such as polycystic kidney disease or Alport Syndrome. Intrinsic kidney

Table 1.5 Primary and secondary causes of kidney disease and intrinsic kidney disease

Primary causes	**Comment**
Glomerulonephritis	There are many types of glomerulonephritis (GN). GN is characterized by inflammation or deposits that affect the glomerulus or filtering part of this kidney. It is usually caused by inflammatory cells that attack either the capillary wall, the podocytes or filtering cells, or the mesangial matrix that is also present in the filter. It can also be the result of immune complexes that deposit and disrupt the integrity of the filter, leading to a leakage of protein into the urine. Generally, a kidney biopsy is necessary for diagnosis
Autosomal dominant polycystic kidney disease	This is a genetic disorder where some of the nephrons create cysts. These cysts continue to grow and block normal tissue. The disease is usually autosomal dominant, meaning if it is expressed on a gene, it will cause disease in the offspring
Crystalline nephropathies	The presence of crystals in the urine can cause kidney stones if they become supersaturated, particularly when the patient is dehydrated
Medullary sponge kidney	Medullary sponge kidney is a birth defect affecting 1/500 in the population. It is benign but may be associated with kidney stone formation. In medullary sponge kidneys, tiny cysts form in the medulla or inner part of the kidney, giving it a sponge-like appearance on imaging studies
Secondary causes	
Hypertension	Hypertension is a disease that is associated with high blood pressure. It affects around one fifth of the population. It is common in patients with kidney disease, and management of hypertension is a cornerstone of CKD therapy
Diabetes	Type 2 diabetes is one of the most common causes of CKD. It is a slowly progressive disease characterized by hyperglycemia or high blood sugar. Cardiovascular disease commonly accompanies diabetes
Autoimmune disorders	Systemic lupus erythematosus is the classic autoimmune disorder and is characterized by antibodies attacking the glomerular filter.
Monoclonal Gammopathies	These are a class of diseases characterized by specialized cells producing too much of an antibody. That antibody can attack kidney cells as well as other cells in the body. This class includes amyloidosis, a medical disease characterized by abnormal deposits of a protein-like material in organs. It must be distinguished from multiple myeloma, which is a blood cancer related to plasma cells
Vasculitis	When antibodies directly attack the blood vessels, they can disrupt the integrity of the glomerulus, which is essentially a bag of blood vessels. Sometimes this is so severe that cytokines – tiny immune hormones designed to fight viruses and bacteria – break through the filter and attack its outer wall. Vasculitis can be a very serious disease that results in kidney failure
Acute infectious glomerulonephritis	Sometimes an infection will induce antibodies that will acutely attack the glomerulus
Glomerulonephritis related to malignancy	Cancers can induce an antibody response. These antibodies can lead to deposits in the kidney and result in glomerulonephritis

Table 1.5 (continued)

HIV	HIV causes several types of glomerulonephritis that vary in severity. A type of HIV nephropathy, collapsing GN, has also been seen in COVID-19. HIV and COVID-19 nephropathy are more common in patients with a genetic variant known as APOL1. Nephropathy is a general term for any disorder that is related to the kidney
Thrombotic microangiopathies	This is characterized by a consumption of blood clotting elements with both abnormal clotting and bleeding occurring at the same time. It can be related to medical therapies such as Avastin that attack the lining of blood vessel walls known as the endothelium. It can also be associated with pregnancy or with bacterial diarrhea, as well as a clotting disorder known as thrombotic thrombocytopenic purpura
Drug induced TIN	Drug-induced interstitial nephritis is the most common cause of TIN, and a major cause of acute kidney injury
Secondary TIN	In addition to drugs, TIN can be related to heavy metals such as lead, or immune disorders like sarcoidosis
Alport syndrome	A genetic disorder of collagen that causes kidney damage, hearing loss, and eye disorders
Fabry's disease	An inherited disorder that results in the buildup of a fatty metabolite. The accumulation of metabolites damage the kidneys, the heart, the gastrointestinal system, ears, skin, and brain
CAKUT	Congenital abnormalities of the kidney and urinary tract. They cause up to 50% of serious cases of kidney disease in children

disease may either be related to inflammation of the vascular – vasculitis, the glomerulus – glomerulonephritis, or the structures supporting the kidney, or interstitium – interstitial nephritis.

Acute Kidney Injury

Kidney diseases can be chronic or acute. Chronic kidney disease, also known as chronic kidney failure, describes the gradual loss of kidney function. The term acute renal failure has been replaced by acute kidney injury, and generally refers to an injury to the kidney associated with trauma, surgery, a toxin, or some sudden event. It can be reversible but sometimes results in permanent kidney damage. Acute kidney injury makes the likelihood for developing chronic kidney disease more likely. Also, the presence of chronic kidney disease can predispose one to develop acute kidney injury. Acute kidney injury occurs when the serum creatinine is over 1.5–1.9 its baseline or the serum creatinine increases greater than 0.3 mg/dl. It can also be classified by a urine decrease below 0.5 ml/kg/h for 6–12 h. Several agents and events are associated with acute damage to the kidney. Contrast agents that contain iodine are used for heart catheterizations. They can cause a transient acute kidney injury. On a more serious note, trauma, seizures, hyperthermia, or a severe virus can lead to muscle breakdown that acutely damages the kidneys. Hospitalization for any major illness or surgery can result in acute injury for many reasons – the most

common being an underlying illness, hemodynamic change ranging from hemorrhage to dehydration, medications, or alterations in blood pressure. Many drugs used to treat malignancies can acutely damage the kidneys. The most common of these include cisplatin and ifosfamide.

How Can I Prevent Complications, Delay Disease Progression, and Live a Good Quality of Life?

Regardless of cause, once the cycle of chronic kidney disease occurs, progression is inexorable. However, the disease can be slowed. Awareness of the factors that promote its progression is a step toward developing a focused plan to ameliorate progression. The progression of kidney disease is related to ongoing inflammatory processes that were instigated by an underlying cause. Breaking the cycle of inflammation starts with treating the underlying disease, reducing oxidative stress, and controlling the inflammatory response. It also entails confronting the complications that result from kidney damage. Once kidney disease has been diagnosed, efforts must be made to slow its progression. Disease progression is associated with age, cigarette smoking, presence of diabetes, degree of illness, and blood pressure. Men fare worse than women with respect to disease progression; in around 60% of the patients, the disease does worsen. The patients who improve generally discontinue medications that are dangerous and initiate therapy that is beneficial [2].

Avoiding toxic medications, controlling blood pressure and diabetes, the use of RAS blockade, and the use of a class of medications known as sodium-glucose transport (SGLT2) inhibitors 2 have been extensively studied, and either slow progressive kidney disease or help ameliorate some of its complications. There are several dietary strategies that can help retard the progression of kidney disease. Lifestyle changes that include increasing physical exercise and stopping the use of tobacco can also help slow kidney disease. These and other strategies are discussed in this book.

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Chapter 2
Aging: Challenges and Interventions

Stephen Z. Fadem

In the early 1830s, Charles Darwin, the British naturalist famous for his theories on animal survival, meticulously observed nature in the isolated Galapagos Islands. While in the Galapagos, he studied the giant tortoises that lived there (See Fig. 2.1). There is a remarkable irony that surrounds the timing of his visit. While Darwin was visiting the Galapagos, Jonathan, a giant tortoise was born on another remote island, the Aldabra atoll. But what is amazing is that Jonathan is still alive today; he is the oldest living land animal and an inspiration to all.

Fig. 2.1 A giant tortoise. Giant tortoises are not limited to the Galapagos. They can live to be well over 100 years old. (Photo by Stephen Fadem)

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Jonathan can teach us a lesson, not just for our lives but for our kidneys. Darwin deduced that the primary determinants of survival included essentially staying out of harm's way, avoiding "predators". So long as a tortoise can avoid harm and not fall prey to predators or disease, it can stay alive. With kidneys, avoiding harm can also slow aging, as diseases that are known to damage the kidney accelerate the aging process. If inflammation is a process known to accelerate the aging process, should we be thinking of it the same way as an animal thinks of a predator? There was once a study looking at 1203 healthy living kidney donors of all ages. In the 18–29-year-old group, the prevalence of kidneys that were damaged was only 3.7%. However, in those 70–77 years of age, the incidence of damaged kidneys was 73% [1]. In another study, 75-year-olds have 48% fewer nephrons than the 18–29 year-old group [2].

All cells experience wear and tear and must have mechanisms to repair themselves. As cells age, the biochemical reactions that drive cellular repair break down and no longer function well. The inability to engage in self repair is part of the process of senescence. Ultimately, a cell that cannot repair itself will die. Aging and consequently senescence are linked to disease progression in chronic kidney disease. The mechanisms are somewhat complex, and in many instances have not been completely unraveled. Inflammation plays a major role in causing the aging cell to die. Inflammation worsens when cellular repair mechanisms do not function properly.

Inflammation is how our body defends against bacteria, viruses, parasites, and cancer. There is an innate immune system that is reactionary, responding to any perceived insult to the body. It responds with fever, a decreased appetite and weakness. However, it is meanwhile initiating a highly complex chain of events that result in the creation of an antibody to the virus or bacterium. This includes engulfing the organism in a cell appropriately named the macrophage. Macrophage means "big eater". The process by which a cell eats offending organisms or particles it deems as foreign is termed phagocytosis. The process of cellular digestion of a distinct piece of the viral or bacterial wall is called phagocytosis. Once digested, cells in the immune system label portions of the organism as an antigen. The antigen is then presented to specialized cells that learn to make antibodies to it. If the organism attacks again, the body is ready. Specialized cells attacks the invader. White cells are attracted to the organism and destroy it through a process known as oxidation. Although oxidation is beneficial when used to destroy offending organisms, the same process can also destroy the body's own cells and is part of the inflammatory process. Inflammation is a byproduct of many diseases. Left alone, inflammation and secondary oxidation leads to cell senescence. The result is scar tissue and permanent damage to the kidneys.

Tiny energy-producing organs within cells, known as mitochondria, also break down with aging, reducing the energy required for all critical cellular processes. These little organs are found inside of most cells and are termed organelles. Their function is to break down sugar or fat to carbon. The end result is combining carbon and hydrogen with oxygen to form carbon dioxide and water. The energy process

Table 2.1 Factors that affect aging in the kidney

1.	Eating healthy and not too much
2.	Avoid excess sugar and keep disease under control if diabetic
3.	Control hypertension
4.	Manage metabolic acidosis early
5.	Consider angiotensin II blockade for hypertension
6.	Restrict dietary sodium
7.	Avoid smoking cigarettes
8.	Maximize intake of fruits and vegetables
9.	Moderate exercise
10.	Reduce inflammation and oxidative stress

involves the flow of electrons, and any mismatch results in free electrons that can damage other tissues through oxidation. This is known as oxidative stress.

Glomerular sclerosis, tubular atrophy, interstitial fibrosis, and vascular narrowing are each terms that describe the pathology that results in permanent kidney damage. A major aim is to discover factors that can both slow down the aging process, prevent senescence, and reduce the pathological response to inflammation and other factors that may affect aging. Paying attention to those factors we can control is key to our staying healthy. The reason is that each factor sets up an inflammatory and oxidative response that both compromise the ability to generate energy and stimulate the formation of scarred and damaged kidney. For a more detailed discussion of inflammation refer to the Appendix. See Table 2.1.

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Chapter 3
The Kidney and Cardiovascular Disease

Stephen Z. Fadem

In chronic kidney disease and its major causes, hypertension and diabetes, cardiovascular disease is a major complication. It is essential to control risks for cardiovascular disease as it is an independent determinant of mortality in CKD.

The Heart, Lungs, and Kidneys Work Together

Each cell in the body requires oxygen and nutrition to survive. In addition, it must be able to repair and rid itself of broken internal fragments. When we think of how oxygen gets to a cell from our atmosphere, we are reminded of a fine-tuned orchestra – each musical instrument performs its specific duty, and what seems like an isolated event is actually part of a unified process. Oxygen from the lungs passes into red blood cells where it is attracted to the iron in hemoglobin. The heart then pumps the oxygenated blood back through the pulmonary vein into the left atrium and ventricle. Then it is pumped through the aorta to progressively smaller and smaller blood vessels. At the capillary level, the oxygen is released into the cell where it engages in biochemical reactions that produce energy.

Energy is created through the splitting of carbon-containing molecules down to a single carbon. As in chemistry and electricity, this requires the movement of electrons. The end result is that oxygen accepts these electrons and combines with hydrogen to produce water; carbon dioxideis created as a byproduct. The veins then ferry this CO_2 back through the right side of the heart where the lungs exhale it into the environment. The carbon dioxide the we exhale enters the atmosphere [1].

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In order for all these processes to occur, the orchestra of the body must be perfectly tuned and playing perfectly. If off key, the system breaks down. Sometimes, the kidney is a troublemaker; if damaged, it can ruin the symphony.

Mineral Metabolism and the Kidney

At the simplest level, the kidney must excrete phosphorus and be able to make vitamin D. When the kidneys start to fail, they lose the ability to rid the body of phosphorus. As a result, bone cells releases a protein to compensate. Although this hormone, known as fibroblast growth factor 23 (FGF23), increases the kidney's excretion of phosphorus, it also causes heart damage. After a while the phosphorus levels rise, and the elevation in the blood levels of phosphorus stimulate glands in the neck to make and release a hormone to release calcium from bone. An important point to remember is that the hormones released by the body try to keep the system in balance. When the serum phosphorus levels in the blood become too high, the body tries to compensate by stimulating the release of calcium from the bone. The calcium that is released may combine with excess phosphorus resulting in a hardening of the outer layer of blood vessels, causing them to become stiff [2].

How Does This Affect the Heart?

The heart must work harder to pump blood through stiff arteries, and this causes the heart muscles to enlarge, outstripping the blood supply it requires to support its ability to pump. This is termed left ventricular hypertrophy and may lead to heart failure.Heart failure is characterized by shortness of breath as the heart struggles to provide sufficient oxygen. If the heart cannot meet its demands, fluid can build up in the lungs and rest of the body.

When the heart muscles work harder, they endure wear and tear, creating fragments that must be disposed of and recycled. Factors responsible for cellular repair may not be sufficient to rid the heart muscle cells of these waste fragments. The fragments can induce the development of fibrosis (scarring) or cell death. Not only does this cell death weaken the heart leading to heart failure, but also interferes with how the heart beats.

The heart beats because electrical signals are sent from nodes throughout heart muscle and tell each muscle cell exactly when to beat. Since cells that have become fibrotic cannot conduct the electrical signals,the fibrotic tissue blocks the propagation of heart signals and sometimes other areas of the heart decide to beat on their own – the result is an arrhythmia known as ventricular fibrillation. It is fatal and a common cause of death in advanced heart and kidney disease [3].

Atherosclerosis

Atherosclerosis, a type of hardening of the arteries, occurs because of dietary factors. Animal-based foods are broken down into fatty acids and fats that are not always metabolized. The fat in the body is stored in fat cells; but in response to high loads of fat, these cells also stimulate the production of inflammatory cells.

Macrophages are part of the inflammatory cell family. These "big eaters" are giant cells that gobble up foreign bodies and protect us from disease, but they cannot distinguish the fat-protein combination of lipoproteins from last night's roast beef from other foreign bodies. Unfortunately, as macrophages internalize the excess lipoproteins they ingest, they die. When the cells die, they attract calcium. The combination of dead cells plus calcium form streaks when we are younger, but hard atherosclerotic plaques as we age. These plaques narrow the arteries and may give rise to symptoms such as angina. They can also completely occlude blood flow and lead to the death of tissues in virtually any body organ. This type of tissue death is known as an infarction. This is a major cause for stroke as well as myocardial infarction, or death of heart tissue. Atherosclerosis or hardening of the arteries commonly occurs with kidney disease, diabetes, and hypertension [4].

CKD is an independent risk factor for heart disease. A large clinical trial was performed to determine if this risk could be lowered. The Study of Heart and Renal Protection (SHARP) clinical trial was able to demonstrate a 17% reduction in major atherosclerotic events [5, 6]. This involves the use of a class of medications known as statins. Although statin therapy is an option to reduce atherosclerosis in CKD, users must be aware of it side effects. Statins block the production of mevalonic acid, a precursor to Coenzyme Q10. CoQ10 is part of a chain of molecules that act inside the mitochondria to turn electrons into energy. If the electrons do not move along the chain, they back up, may leak, and could "become radical." In this context, the term radical refers to the observation that they attack adjacent structures in the mitochondria and damage it. This is known as oxidative stress. CoQ10 is thus an important factor, and substances that block it can cause oxidative stress. Some vitamins like E also block Q10, so it is ill-advised to continue vitamin E with statins. There is evidence that taking Coenzyme Q10 suppresses oxidative stress [7].

Heart Failure

Not only is the heart muscle weakened because of scarring but because of the inability of the kidney to eliminate fluid properly. As discussed in the previous chapters, the nephrons handle water and sodium balance. As the kidneys fail, these nephrons die. Thus, their ability to excrete sodium lessens. The accumulation of sodium results in fluid retention. This can often be managedwith drugs known as diuretics, specifically formulated to increase the excretion of sodium. A build up of fluid puts

extra work on the heart. Muscles require more energy to relax than contract. Thus, an early sign of heart disease is an impairment in how the ventricle fills back up with blood after it contracts to pump the blood through the aorta. This is known as diastolic dysfunction.

As the left ventricle weakens, the heart cannot pump the excess fluids throughout the body. This can result in the accumulation of fluid in the lungs. This may lead to heart failure, and it may be characterized by shortness of breath with exertion, when lying down and even at rest. In the early stages of kidney disease, this is generally manageable.

To conclude this chapter, heart disease is common in patients with CKD. It is associated with atherosclerosis, a cause of heart of attacks, cardiac fibrosis that potentiates heart failure and rhythm disturbances, as well as calcification that can force the heart to pump harder and weaken.

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Chapter 4
Diabetes and Kidney Disease

Stephen Z. Fadem

Diabetes is the leading cause of kidney disease. There are two main types of diabetes: type 1 and type 2. Type 1 occurs in younger individuals and is characterized by a loss of the cells in the pancreas that make insulin. Type 2 occurs during adulthood. It is characterized by a resistance to insulin, although the insulin-producing cells still work until the end stages of disease. 90% of all diabetics are type 2. Both types are associated with an elevated blood sugar, and in both cases the disease progresses slowly over a 10–15-year period.

Diabetic kidney disease (diabetic nephropathy) can be delayed in the early stages. During this period, the glomerular filter is enlarged, and some protein may be leaking across the glomerulus. You will recall that the glomerular filter separates red blood cells and proteins from waste products. In the early stages, the leakage of the protein albumin across the filter is known as microalbuminuria. Kidney function is well-preserved in this stage, and the kidney may be hyperfiltering. Hyperfiltering is when sugar builds up pressure inside blood vessels and attracts excess water that must pass through the kidney's filter. After several years, the cells and matrix inside the kidney become seriously damaged. Protein leakage worsens and kidney function declines. Diabetes results in several adverse consequences that lead to the replacement of kidney tissue by scar tissue. These will be discussed in Chap. 6.

Unfortunately, the same factors that damage the kidney cause wear and tear on blood vessels leading to progressive cardiovascular disease – heart attacks, strokes, peripheral vascular disease, and heart failure. Diabetes also damages the eyes and the nerves. Tightly controlling diabetes can prevent the microalbuminuria, and there is hope that hyperfiltration can also be controlled.

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Strategies to Slow the Progression of Diabetic Kidney Disease

Fortunately, we can often prevent disease progression; modifiable factors being diabetes and blood pressure control, the reduction in urine protein excretion, control of hyperlipidemia and uric acid. Lifestyle modifications include stopping cigarette use, exercise, weight reduction, and adopting healthy eating habits.

Intensive Blood Sugar Control Intensive control of diabetes can reduce the relative risk for kidney disease by 20%. Diabetes control can be measured by a value known as the HbA1C, a value that relates to blood sugar. The higher the HbA1C, the worse the diabetes is controlled. But a reduction in the HbA1C to less than 6.0% will result in a higher risk of mortality when compared with keeping the HbA1C in the 7.0–7.9% range. Too low of a HbA1C is associated with increased hypoglycemia, a factor in falls, morbidity, and injuries. Over-rigorous control of diabetes has not been shown to improve survival [1–3].

Blood Pressure Control A large review in 2015 looked at 40 clinical trials of patients with diabetes. High blood pressure is more common in diabetics and increases the risks for developing chronic kidney disease, as well as cardiovascular disease, heart failure, and stroke. Lowering the blood pressure in persons whose BP is over 140 mm Hg reduces the risk for mortality. It can also lower the chance to develop worsening heart, kidney, and eye disease [4].

Renin Angiotensin System (RAS) Blockade - Angiotensin Receptor Blockers (ARBS) and Angiotensin Converting Enzyme Inhibitors (ACEi)

These drug classes have been the major forces in slowing the progression of diabetic nephropathy. Angiotensin II is a hormone that constricts the efferent arteriole and can therefore increase pressure across the glomerular filter, damaging it. These medications can block angiotensin II, which has numerous other negative effects on the kidney. The drugs are also excellent antihypertensive agents. They both reduce the urine albumin levels, but it is not recommended that the drugs be used simultaneously. RAS blockade also slows the leakage of protein across the glomerular membrane. This leakage results in protein in the urine or proteinuria. Proteinuria is particularly harmful to the kidneys, and RAS blockade can reduce proteinuria.

RAS blockage can lead to an elevated serum potassium level. Patients with diabetes who are on ACE or ARB therapy should avoid medications that can increase the serum potassium, particularly NSAIDS. They should have their serum levels monitored and watch the potassium in their diet. There are medications that can lower the serum potassium, and they may be necessary. They include sodium zirconium cyclosilicate, patiromer, and sodium polystyrene sulfonate.

Medications Showing Promise: Finerenone, GLP1 Receptor Agonists, SGLT2 Inhibitors, Bardoxolone

When new medications are developed and when drugs are repurposed, the doctor and patient must be mindful of adverse effects of these medications as well as the strength of evidence.

Metformin

Metformin is a medication that was originally developed for type 2 diabetes and is commonly used alone or in combination with other medications. It can make the body more sensitive to insulin, which can be beneficial in slowing kidney damage. Metformin may delay the deterioration associated with aging in animal models. Insulin sensitivity also slows the aging process. Many of the factors that are associated with the aging kidney are indistinguishable with those that result in renal function deterioration, particularly with diabetes. It appears that metformin can help turn on some of the mechanisms that slow aging and extend the life of cells.

Metformin not only inhibits hyperglycemia but inhibits transforming growth factor ß1 (TGFß1). This is a particularly dangerous factor that induces inflammatory changes in patients with kidney disease. Meformin can also inhibit a critical signaling pathway that induces cellular repair through autophagy. Autophagy means to devour one's own body tissues as a result of starvation and certain metabolic diseases. The self-ingestion of damaged intracellular organelles is essential for cellular maintenance. Metformin may protect the kidneys from stone formation, help metabolize fatty acids that are related to obesity, and help reduce oxidative stress.

Metformin controls the blood sugar levels and can cause levels to fall too low. It can also cause gastrointestinal effects, and in rare cases can cause metabolic acidosis. It is not recommended when the kidney function has declined to below 40 mL/min/1.73 m^2.

Finerenone

Spironolactone is a diuretic (water pill) that, unlike many other water pills, blocks aldosterone. Aldosterone helps rid the body of potassium but retains salt. Since aldosterone blockade leads to high potassium levels, the effect of this drug in protecting the kidney is limited by elevations in the serum potassium level. Finerenone is a new formulation that does not raise the serum potassium to the same extent but still blocks aldosterone. A large clinical trial has demonstrated that finerenone lowers the risk of CKD progression and cardiovascular events in patients with eGFR ranges from 25 to 60 ml/min/1.73 m^2 [5].

SGLT2 Inhibitors

Sodium glucose transporter 2 (SGLT2) inhibitors (calagliflozin, empagliflozin, and dapagliflozin) were developed to reduce glucose reabsorption and lower serum glucose levels. In addition to being successful in controlling type 2 diabetes, they have been demonstrated to have a protective effect on the kidney and cardiovascular system. The blood vessel flowing into the glomerular filter is known as the afferent arteriole. When it is dilated, it allows a higher pressure to cross the delicate filter. This process is known as hyperfiltration, and it plays a major role in damaging the glomerular filter. However, when the arteriolar diameter is reduced to an appropriate diameter, the pressure is lowered and the filter protected. The SGLT2 inhibitors help decrease afferent arteriolar pressure. Clinical trials demonstrate that SGLT2 inhibitors significantly lower the risk of developing end-stage kidney disease, lower the risk of cardiovascular death, myocardial infarction, stroke, and hospitalization for heart failure [6]. Patients were studied with eGFR levels >30 ml/min/1.73 m^2 and less than 90 ml/min/1.73 m^2 [7, 8]. It appears that the SGLT2 inhibitors reduce the risk of end-stage kidney disease or death from cardiovascular causes regardless of whether diabetes is present [9].

Glucagon-Like Protein-1 (GLP1) Receptor Agonists

GLP-1 is a protein that is secreted from cells in the intestines after eating glucose. It responds to the glucose in the intestines. It stimulates insulin and lowers the glucose just eaten. It may also help improve kidney function by causing the afferent arteriole entering the glomerulus to contract and protect the delicate filter. Its benefits have been demonstrated in clinical trials [10].

Bardoxolone

Earlier in this book, we discussed the radical oxygen molecules, also called reactive oxygen species that cause oxidative stress. Most of what we do to protect the kidney is to defend against oxidative stress, and the body has a system to protect against it. A protective molecule is kept in check by a protein cleverly known as KEAP (Kelch-like ECH-associated Protein. The medication bardoxolone, as well as cinnamon and cruciferous vegetables like broccoli, will cause the protective molecule to be released (See Fig. 4.1). Once released, it moves into the nucleus of the cell. Once in the nucleus, it signals genes to release antioxidant molecules that will counter the reactive species. These reactive species play a role in inducing kidney fibrosis, and it is possible that drugs like bardoxalone can reduce kidney scarring, extending the life of the kidney. Unfortunately, bardoxolone can promote water and sodium retention in some patients and may have a higher level of toxicity in persons with

Fig. 4.1 Broccoli – a great way to "KEAP" healthy. (Photograph by Stephen Fadem)

underlying heart disease. An early trial in diabetic nephropathy patients had to be terminated. The protocols have been revised, however, and the drug is being studied in patients with chronic kidney disease and with polycystic kidney disease [11].

Endothelin Receptor Antagonists

Endothelin was first discovered in 1987 as a molecule that constricts the blood vessel wall. Like nitric oxide, it is related to vascular tone, and has been implicated in a variety of pathological processes, including aging and inflammation [12]. Medications that can modulate the action of endothelin have been studied as possible therapy for patients with diabetic kidney disease, hypertension, as well as other types of kidney disease. Clinical trials are needed to demonstrate that this novel strategy is safe and effective for treating renal disease [13].

Potassium Management Specific to Diabetes

Potassium is a positively charged mineral that is essential for body function. Its presence inside and outside of the cells creates a difference in charges that helps stabilize the cellular membrane. Having too much or too little affects body functions; it is essential for muscle function and movement. Too little potassium can increase the risk of hypertension, coronary artery disease, or stroke. It can worsen diabetes and aggravate kidney stone formation. It can be associated with one's diet, with the overuse of laxatives or diuretics, and with inflammatory bowel disease (See Fig. 4.2).

Diabetic patients are often on ACE inhibitors or ARB therapy, as these medications have been demonstrated in clinical trials to help preserve kidney function.

Fig. 4.2 Some well-known foods high in potassium. (Photograph by Stephen Fadem)

With reduced kidney function, the potassium secreted by the kidneys declines, leading to elevated levels. This is known as hyperkalemia. It is also associated with the aldosterone blockers that may be used in diabetes. In particular, a rise in potassium can be seen with the use of non steroidal anti-inflammatory drugs commonly used to treat arthritis. An elevated serum potassium can be secondary to trauma that has caused severe muscle injury.

As kidney function declines, the ability to eliminate the acids associated with many types of food decreases. These acids can accumulate in the body and must be neutralized. This was discussed in Chap. 1. There is also a type of metabolic acidosis that occurs in diabetes patients with CKD. It happens when the accompanying hyperkalemia blocks the production of ammonia, a compound used by the kidney to trap and rid the body of acids. The potassium levels may also be high in these patients because of a deficiency in aldosterone. This is known as type 4 renal tubular acidosis. It can be treated with bicarbonate tablets. The same clinical picture of hyperkalemia and acidosis can also be seen when the urinary tract is obstructed, so this must be excluded.

Symptoms of hyperkalemia include cramps, weakness, and even trouble walking or paralysis. These signs can indicate a medical injury, or hyperkalemia can result in an erratic heart function that can lead to ventricular tachycardia, ventricular fibrillation, and death.

Nutrition Management to Control the Blood Sugar

Since the body handles food differently in diabetic patients, dietary control is the cornerstone of treatment in not just diabetes but its complications, kidney disease, hypertension, and atherosclerotic disease. Each of these disorders can be managed through nutritional adjustments. Diabetic patients who can maintain their body mass index, restrict their caloric intake, and reduce the use of sugars and starches are at an advantage.

Prevention and management of diabetes include incorporating plant-based diets. Such diets emphasize legumes, whole grains, fruits, vegetables, beans, nuts, and

seeds. The diabetic diet should include non-starchy vegetables, such as broccoli, cauliflower, spinach, and carrots. Fish is an ideal source of protein. Most or all animal products are discouraged. Look for "100% whole grain" or "100% whole wheat" bread. Sugars should be avoided.

Ceylon cinnamon may also help control blood sugars. Cinnamon contains antioxidant properties and can also improve insulin control. It is an easy and delicious measure than can help us stay healthy (See Fig. 4.3).

Fig. 4.3 Ceylon cinnamon – A healthy alternative to Chinese cinnamon. (Photograph by Stephen Fadem)

Ceylon cinnamon, *Cinnamomum verum,* is native to Sri Lanka, and is much safer than Chinese or cassia cinnamon. While *C. verum* contains only trace coumarin, Chinese cinnamon contains 7–18 mg/tsp. In large quantities, coumarin can be toxic to the liver.

Substituting sweeteners such as allulose and erythritol can control satiety and maintain the quality of life when dieting.

Smoking Cessation

Cigarette Smoking is associated with progressive diabetic kidney disease. This was shown back in 1993, which demonstrated that diabetes related kidney disease progresses in only 11% of nonsmokers, in 33% of those who quit smoking cigarettes, and in 53% of those who continue to smoke [14]. Other more recent studies have confirmed these findings [15]. Smoking is also associated with hypertension, heart and vascular disease, amputations, lung disease, and several forms of cancer.

Exercise

A sedentary lifestyle that increases intra-abdominal obesity puts burdens on the cells in the pancreas that make insulin. Several studies have demonstrated that exercising three times a week will improve blood sugar. The combination of diet and exercise will not only help control blood sugar but can also help preserve kidney function [16] (See Fig. 4.4).

Fig. 4.4 Exercise may help control diabetes. (Photograph by Michelle L. Nguyen)

Reducing Diabetic Complications

As discussed in Chap. 6, diabetic kidney disease is caused by hyperglycemia, inflammation, and oxidative stress. These same factors also cause aging and deterioration of other organs. In particular, diabetes damages the eyes, blood vessels, and nerves. Diabetes induces ocular damage through the stimulation of new blood vessels inside the eye. These blood vessels are weak and can easily rupture. In particular, diabetes damages the retina, the sensor of visual stimuli. It is a major cause of blindness but can often be treated in early stages. Therefore, patients with diabetes are encouraged to see their eye doctors regularly.

Diabetes can also damage the blood vessels. It not only interferes with their relaxation, resulting in increased vascular resistance and hypertension, but is also associated with vascular calcification in the outer vessel walls that result in stiffness weakening the heart, as well as atherosclerotic plaque formation in the inner blood vessel wall that weaken the heart. These atherosclerotic changes can cause severe narrowing that can occlude blood vessels. This can lead to gangrene in the limbs and make the diabetic patient more prone to infections. Gangrene can be so severe that it can result in the loss of a limb. Since many of the foot and leg problems associated with diabetes start with early ulcers and non healing wounds, active inspection by health care providers can detect early and potentially treatable changes.

To further complicate this disease, the hyperglycemia damages the nerves that send sensations and signals to the brain from all over the body. Damage to the nerves in the stomach can delay its emptying. The bladder also has nerves that tell us when our bladders are full and it is time to void. These nerves can be damaged in diabetes, leading to over distended bladders. To avoid this complication, many patients have learned to void on time intervals and not await the sensation of fullness.

Since sensory nerves are also damaged, diabetic patients may not be aware of a wound on the foot or lower extremity that is not healing and may be getting infected. It is easy to bump into an object and sustain an injury without knowing it. Bathing can be problematic if the shower or bath is too hot, as the patient cannot sense hot temperatures. Trimming toenails and walking barefoot can result in injuries that may start as minor lacerations, but can become seriously infected. The poor circulation impedes antibiotic delivery and also blocks oxygen and nutrient delivery making it nearly impossible to fight the infection. Thus, caution is always advised when persons with diabetes are bathing, ambulating, or even having their toenails clipped.

Table 4.1 is a simple checklist highlighting the optimal management of diabetic kidney disease (See Table 4.1).

Table 4.2 shows several of the conditions related to diabetic kidney disease, their consequences and management. There is considerable overlap between diabetic kidney disease and other causes of CKD (See Table 4.2).

Table 4.1 Optimal management of diabetic kidney disease

Evaluate the eGFR
Renal ultrasound and urinalysis
Assess urine albumin/creatinine ratio
Converting enzyme inhibition or angiotensin receptor blockade
Keep the blood pressure controlled
Control metabolic acidosis
Optimize HgbA1C control with diet and medications
Check eyes for retinopathy
Evaluate feet for ulcers
Caution when bathing to avoid excessive water temperatures
Avoid trimming one's own toenails
Nutritional management associated with general kidney disease management
See a nephrologist
Avoid toxic medications such as NSAIDS

Table 4.2 Highlights of diabetes care

Condition	Event	Therapy
Hyperglycemia	Hyperglycemia promotes inflammation and free radicals This damages the glomerulus and surrounding tissues	Diabetes control with diet and medications
Hyperfiltration	This overworks the glomular filter and damages it	Controlling blood pressure and diabetes
Autoregulation	The filter system has a feedback system to regulate and protect its delicate membranes from hyperfiltration. When this mechanism fails, kidney function can worsen	Controlling the blood pressure. Salt restriction
Inflammation	Related to injury from blood pressure and hyperglycemia	Control underlying disorders. Diet and exercise control. Avoid other causes of inflammation like smoking
Atheroslcerosis	When animal fats are metabolized, they are devoured by inflammatory cells known as macrophages. The macrophages enlarge and die, attracting calcium deposits. This is known as atherosclerosis	This can be controlled with diet and statin medications in CKD patients. Patients on dialysis do not need statins
Vascular calcification	Phosphorus turns on the genes that make bone. When this happens inside blood vessels they create a bone-like substance and becomes stiff. This is predominant in diabetes and CKD. It makes the heart's job of pumping blood difficult and can lead to heart failure	Control with diet, phosphorus binders
Acidosis	Damages cells and weakens muscles. In diabetes, it can be associated with an elevated potassium levels. ACE or ARB therapy, control of blood pressure and diabetes, along with lifestyle modification are the mainstays of therapy, so attention to potassium is important	Can be controlled with medication and or diet
Hypertension	Common in diabetes. Damages the kidneys	In most patients ACE or ARB therapy helps control the blood pressure as well as protect the glomerular filter. Sodium restriction can help control hypertension

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Chapter 5
Hypertension and Kidney Disease

Stephen Z. Fadem

Hypertension, or high blood pressure, is one of the most common diseases on the planet. It is estimated that 1.39 billion people (31.1% of adults) worldwide have hypertension. It is a global burden, the prevalence being higher in lower and middle-income countries than higher-income countries. In developing countries, 1 in 3 adults are hypertensive [1].

Sodium intake, alcohol use, the lack of physical activity, and obesity all contribute to hypertension [2]. The heart beats with a high force against blood vessels. This can cause wear and tear on the blood vessel wall; there is evidence to support that intensive blood pressure control will protect the heart. Keeping the blood pressure under control will decrease not just this wear and tear of blood vessels, but also damage to target organs. Blood pressure is best controlled with sodium restriction, either through diet or diuretics (water pills), along with dilating the blood vessels and reducing their resistance through several classes of medications. Most CKD patients require blood pressure-lowering therapy, particularly those with proteinuria.

CKD Causes Hypertension, Not the Other Way Around

Historically, we have been taught that hypertension was a major cause of kidney disease. Yet, when the genes associated with kidney disease were compared with the genes associated with hypertension, it was the early genetic damage to the kidneys - the CKD - that caused hypertension, not the other way around [3]. We now

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know of 179 unique kidney gene variants that can cause an elevated blood pressure [4]. If it is kidney disease that causes hypertension, it is logical to pay more attention to the subclinical abnormalities that drive kidney disease when evaluating patients with early hypertension.

Treating Blood Pressure Prevents Strokes and Heart Disease, but Will It Help the Kidneys?

High blood pressure is a silent disease that has no symptoms but is associated with disability and even death. Although high blood pressure causes damage to the kidneys, it is not clear whether kidney damage can easily be undone through blood pressure control. Blood pressure control has been focused on the prevention of stroke and cardiovascular disease.

A systemic review of 123 major clinical trials that took place between 1966 and 2015, including 613,815 patients, showed that a drop in systolic blood pressure by 10 mm reduced the incidence of stroke, heart failure, and coronary artery disease. It reduced all-cause mortality by 13%. Unfortunately, progression of kidney disease to failure was not delayed, although its management in patients with kidney disease is essential to prevent associated comorbidities [5].

This review has been confirmed by the Systolic Blood Pressure Intervention Trial (SPRINT) that demonstrated intensively controlling the blood pressure to a systolic blood pressure of <120 reduces mortality does not reverse kidney disease [6].

With particular attention to the elderly, the Strategy of Blood Pressure Intervention in the Elderly Hypertensive Patients (STEP) trial enrolled persons between 60 and 80 years of age and compared systolic blood pressure targets of 130 and 110 mm Hg. Again, intensive treatment lowered the incidence of stroke, acute coronary artery syndrome, heart failure, coronary stent placement, atrial fibrillation, and death, but once again did not reverse kidney disease [7]. The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Management of Blood Pressure in Chronic Kidney Disease 2021 recommends that the target systolic blood pressure should be <120 mm Hg for most adult patients with CKD who are not receiving dialysis therapy [8].

The blood pressure readings can easily be obtained at home; and out-of-office measurements are now recommended. It is normal for the blood pressure to be lower in the evenings; however, in some cases of hypertension, the blood pressure measurements remain elevated at night. This is more common in chronic kidney disease, as well as in sleep apnea. Since both have been associated with higher risks, nighttime dosing of blood pressure medications, as well as the correction of sleep apnea with continuous positive airway pressure (CPAP), is sometimes advisable.

Malignant Hypertension

In the USA, treatment of hypertension is common, and it is less likely to see a patient present with extremely elevated diastolic blood pressure readings above 130 mm Hg. Termed malignant hypertension, this is a special case of hypertension that is a medical emergency, and requires immediate and intensive treatment in an effort to avoid kidney, heart, or brain damage [9].

How High Blood Pressure Damages the Body

High serum sodium (sNa) concentrations cause high pressure to develop against the blood vessel wall. This pressure stimulates the production of oxygen and free electrons, collectively known as free radicals. These free radicals cause oxidative stress, and this stress decreases the synthesis of nitric oxide. Nitric oxide is a blood vessel wall chemical that causes vessels to dilate. When nitric oxide decreases, the vessels become stiff and resistant to the flow of blood. This resistance puts a heavy workload on the heart, causing the heart muscle to thicken; hence the reason hypertension is frequently associated with heart disease, and even heart failure. Fortunately, blood pressure can be treated and controlled.

The kidney is battered by high blood pressure, and it is the delicate glomerular filters that are the targets for damage. To avoid high pressure damaging the delicate filter, the arteriole that enters the filtering area or glomerulus has the ability to narrow. By narrowing and reducing its internal diameter, there is less pressure entering the glomerulus. At the same time, there are factors that dilate the blood vessel that leaves the filtering space. This blood vessel is the efferent arteriole, which carries blood away from the glomerulus. When it dilates, it reduces the direct pressure against the glomerulus, thus helping to protect the kidney. After a period of time, the ability of the afferent arterioles (which bring blood to the glomerulus) to contract to protect the filter is lost and the subsequent and constant high blood pressure damages the glomerular filter.

In the kidney, the high pressure not only damages the filters, but also causes a series of biochemical reactions. One of the chemicals associated with high pressure is transforming growth factor beta (TGFß), a molecule that increases DNA synthesis, leading to the formation of collagen, a string-like protein that is associated with the formation of scar tissue. Over time the glomerular filters become obliterated by scar tissue. The remaining filters must take on the burden of ridding the body of wastes. Eventually, they also succumb to this burden and drop out. Ultimately, the patient develops kidney failure.

When the heart pumps blood, it generates pressure; this is termed systolic blood pressure. During the period that the heart-pumping chamber is filling, there is a resting or diastolic pressure in the cardiovascular system. If the pumping and resting pressure in the body is elevated, target organs such as the brain and kidney must

endure the consequence. The blood vessels in the brain are often angular which means that the pressure will hit the same point on the blood vessel wall to such an extent that it becomes weakened, causing an aneurysm. If the aneurysm ruptures, it can cause a stroke. Medications and salt restriction can reduce the pressure inside the blood vessels.

Central Aortic Pressure

Although aortic stiffness starts around puberty, it is accelerated in patients with kidney disease. The aorta is composed of two types of connective tissue, collagen and elastin. As can be imagined by the name, elastin is more stretchable while collagen is stiff. With advancing age, collagen replaces elastin. A stiff wall will not absorb as much shock from the pounding pulsating beating of the heart, and the pulse wave travels faster down the blood vessel. It also bounces with greater force off the target organs and damages them over time. If the wave moves at a rate greater than 12 milliseconds, it has been shown to have a higher risk of death [10]. One can measure the central aortic pressure and also get a sense of the stiffness and hardness of the blood vessel walls. Therapy includes reducing salt and weight, ACE or ARB therapy, aldosterone inhibitors, and aerobic exercise.

APOL-1 Gene Variants

Hypertension has long been associated with chronic kidney disease in those of West African ancestry. In this part of the world lives a parasite that causes trypanosomiasis or African sleeping sickness. This parasite is spread by the bite of the tsetse fly, and the disease can be deadly. Thousands of years ago, many West African inhabitants developed immunity to trypanosomiasis through a mutation in the gene that codes the apolipoprotein1 (APOL1) protein; this immunity was passed down from generation to generation. The APOL gene helps protect us from invading organisms, but the trypanosome parasite deactivated APOL1 so that it was no longer protective. The variant that evolved allowed APOL1 to evade deactivation by the trypanosome, and thus destroy the invading parasite. But this also had the tendency to cause hypertension and kidney disease. In those who carry the variant genes, hypertension is 86%, threefold greater than that of the general population [11, 12].

The APOL1 gene and its variants can be stimulated by the interferon that is released in response to many viral organisms, including the human immunodeficiency virus (HIV) and SARS-CoV-2. The interferons can stimulate APOL1 200 fold, and can injure the kidney. The consequence of this is not only kidney injury, but hypertension [13, 14].

Therapy for Hypertension

The first step in managing hypertension to a target value of 120 mm Hg is to assess one's diet and attempt to restrict the intake of sodium. The World Health Organization recommends curtailing the intake of sodium to 2 g per day. The 2021 KDIGO Guidelines echo this recommendation [8]. This is challenging, especially when dining out. Our cultures are centered around food, and unfortunately what was once a necessity for food preservation is now a major source of seasoning and piquancy. Among the difficulties of restricting sodium is that initially foods will taste bland and have little flavor. This abates, for after a while our bodies adjust to the lowered intake of sodium. A person who has adapted to the low-sodium diet will then find that many foods taste overly salty. Reducing sodium in your diet will be discussed in further detail in Chap. 7.

It has also long been established through clinical trials testing diet and lifestyle intervention over a 3–4 year period that even modest reductions in weight loss of at least 4.5 kg and maintained for the next 30 months result in clinically significant reductions in blood pressure [15]. Physical activity decreases weight, lowers the blood pressure, improves quality of life, improves blood sugar control, and lowers the risk of mortality in CKD patients. Clinical guidelines recommend that patients with high blood pressure and CKD undertake moderate-intensity physical exercise for at least 150 min per week, or to a level they can best tolerate based on underlying cardiovascular and physical tolerance [8]. Body mass control and exercise will also be covered in Chaps. 7 and 10.

As for therapy through medication, renin angiotensin system (RAS) blockade with either angiotensin-converting enzyme inhibition (ACEi) or angiotensin II receptor blockade (ARB) is the first line therapy for hypertension because it protects the kidney from vascular damage in a blood pressure independent fashion. It also helps protect the heart. Along with protein and salt restriction, it slows the protein leakage associated with inflammatory conditions that affect the glomerular filter (glomerulonephritis). It is especially valuable in diabetic patients. Many patients who require RAS blockade may also require a diuretic or water pill.

There are two major types of water pills, thiazide and loop diuretics. They work in different ways and in distinct parts of the kidney. Each prevents sodium from being reabsorbed through the kidney tubules. They are highly effective in lowering the blood pressure. A different type of diuretic blocks the kidney hormone, aldosterone, and influences important feedback signals in the kidney that decrease hyperfiltration.

Let us digress to briefly explain hyperfiltration. When eGFR is assessed in hypertension it may appear normal, yet if there is background kidney disease there are fewer functioning nephrons, with the rest of the nephrons forced into doing extra work. They endure higher blood flow rates, and a higher pressure on their delicate filters. These surviving nephrons actually have a higher filtration rate. This is hyperfiltration, and it also occurs with diabetes, obesity, and excessive

dietary protein intake [16, 17]. Hyperfiltration damages the kidneys even while masquerading as healthy kidney function. Diuretic medications such as spironolactone, eplerenone, and finerenone reduce hyperfiltration by blocking aldosterone. The drawback of using them is the side effect of an elevated serum potassium. Finerenone, the newest drug in this class, will cause less hyperkalemia, but serum potassium must still be monitored. Finerenone has been shown to decrease CKD progression in type 2 diabetes (Type2DM) [18]. It has been studied in non-diabetic CKD populations, and shown to decrease proteinuria, an indicator of kidney damage [19]. It has been approved by the US-FDA to reduce the risk of eGFR decline in adult CKD patients with Type 2 DM (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215341s000lbl.pdf).

There are other classes of medications that can reduce the blood pressure. They include calcium channel blockers and beta-blockers. Since lowering blood pressure is critical to reducing some of the side effects of kidney disease, they each have their place as therapeutic agents. Combinations of several drugs may be needed to achieve optimal blood pressure control.

SGLT-2 Inhibitors

The sodium-glucose cotransporter 2 (SGLT-2) inhibitors also trigger the mechanism that decreases hyperfiltration. There are now available to help manage CKD and correct hyperfiltration in both diabetic and non-diabetic populations.

Hyperfiltration is associated with a high blood flow into the kidney. The SGLT-2 inhibitors send back feedback signals that reduce that flow. One SGLT-2 inhibotor, dapagliflozin, slowed the progression of CKD and reduced all-cause mortality in CKD patients who were not diabetic [20], and was approved by the U.S. Food and Drug Administration (US-FDA) to reduce the risk of kidney function decline. (source: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/202293s021lbl.pdf).

A second SGLT-2 inhibitor, empagliflozin, was granted fast-tract designation for the treatment of CKD, and is currently being studied in a clinical trial (source: https://clinicaltrials.gov/ct2/show/NCT03594110).

Conclusion

We are in a dynamic period of unraveling the relationships between blood pressure and kidney disease. The timeline for shifting the paradigm away from hypertension as a causative factor for CKD, as well as for the development of novel therapy that targets the underlying mechanisms of CKD, is moving rapidly.

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Chapter 6
Inflammation in Kidney Disease Glomerulonephritis

Stephen Z. Fadem

Inflammation is a necessary process that allows us to fight environmental toxins, infectious organisms, and cells within our bodies that have mutated and may be dangerous. It is highly complex.

In response to an infection, whether bacterial or viral, our body defense system jumps into action with an instinctive response, putting up a fight against the organism, and at the same time creating antibodies that will be ready the next time an attack occurs. Sometimes the antibody fight against the invading infective agent is also destructive to normal tissues. This "collateral damage" can be acute (short-lived) or chronic.

Inflammation is our immune system's response to stimuli, although not all types of inflammation are related to invading organisms. The body also musters an inflammatory response to many types of stress. Some types of stress are related to what we eat. In this book, we discuss how sugars and carbohydrates, salts, excess fatty foods, tobacco, and a lack of activity can cause insidious harm to organs, particularly the kidneys. We also discuss how specific diseases can harm the kidneys.

The treatment of inflammation depends on its underlying cause, timing, and target organ involvement. With respect to the kidney, an acute urinary tract infection (UTI) can cause an acute inflammatory response as cells in the bladder or kidney swiftly attack invading organisms. The UTI may respond quickly to a course of oral antibiotics. Acute kidney injury (AKI) may follow a complicated surgical procedure, an injury, or exposure to a toxin. It can also accompany an acute, systemic illness. COVID-19 patients commonly sustain an AKI. The AKI generates an intense inflammatory response. As kidney tissues repair themselves, scar tissue and this lingering inflammation may prolong recovery.

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The main factors associated with kidney damage come from inflammation and oxidative stress. These disturb the kidney architecture and anatomy of the blood vessels and the cells inside the kidney that control its function.

Glomerulonephritis

Glomerulonephritis is often the consequence of collateral damage from efforts to fight disease. Examples are autoimmune disorders that occur when antibodies form against the body's own tissues. These may form immune complexes that damage the kidney during efforts at filtration. They can form complexes that deposit in the basement membrane and result in its damage. Alternately, they can stimulate the secretion of increased matrix by the mesangial or housekeeping cells. The extra matrix jams and crowds the glomerular filter, disrupting its function, and even squeezing between the basement membrane and the endothelial cell. Some diseases are related to bacteria, viral organisms, or parasites. Other diseases are the consequence of hypertension or diabetes. Another disease that can affect the kidney is myeloma, a malignant disease where the antibody-forming cells produce too much immunoglobin – a protein component in antibodies. Antibodies can also attack the basement membranes directly (known as anti-glomerular basement membrane or anti-GBM antibody disease), severely damaging them. Amyloidosis is a disease in which abnormal protein substances are deposited in the glomerulus. Many tumors such as Hodgkin's Disease can result in disruption to the immune system, and can also cause glomerular disease. Glomerular diseases can be associated with the use of prescription drugs such as rifampin, penicillamine, or ampicillin. They can also be associated with over-the-counter medications such as non-steroidal anti-inflammatory diseases (NSAIDS), and can also be the result of street drugs such as heroin. They can occur secondary to a variety of infections, particularly COVID-19, HIV, malaria, and *streptococcus*.

The relative lack of oxygen, the inflammatory response, and the oxidative stress stimulates growth factors such as transforming growth factor beta (TGFß). This growth factor sets off a cascade that stimulates the formation of collagen, a component of scar tissue. There is also inhibition of the enzymes that break down collagen. This scar tissue – or fibrosis crowds the functioning part of the glomerulus, and eventually obliterates the glomerular filter. This may manifest as proteinuria or edema, caused by the impaired podocytes leaking protein. Protein losses may exceed 3 g per day and cause what is known as nephrotic syndrome. Impaired kidney function can be a manifestation of glomerulonephritis as the disease progresses. Therapy is aimed blood pressure control, the use of angiotensin blockade, salt and protein restriction, loop diuretics, and immunosuppressive therapy. International guidelines recommend intensive blood pressure control of 125/75 mm Hg for urine protein levels greater than 1 g per day [1]. Albumin is a protein found in the blood, and it falls when urine protein losses are excessive. Severe protein loss is associated with increased blood clot formation, necessitating therapy with anticoagulants

(blood thinners). The decision to use anticoagulants is based upon the serum albumin level. Also, severe protein loss leads to an accumulation of cholesterol and triglycerides in the blood. This should be treated with lipid lowering agents (statins).

Since most types of glomerulonephritis are related to immune alterations, therapy with immunosuppressives may be required. Other therapies include calcineurin inhibitors, rituximab, and mycophenolate mofetil. The calcineurin inhibitors include cyclosporine and tacrolimus. They block the T cell response by inhibiting the signaling protein, calcineurin. They are used to prevent transplant rejection and to treat many types of glomerulonephritis. The use of corticosteroids is also often the first choice of therapy for many types of glomerulonephritis.

Rituximab blocks a different type of immune cell, the B cells. It has been useful in treating lymphoma and other B-cell malignancies. It has also been useful in treating glomerulonephritis. Mycophenolate mofetil inhibits the proliferation of both T and B cells, and it has been useful in treating glomerulonephritis and autoimmune disorders. Cyclophosphamide is a drug that has been used to treat cancer since 1959. It is a derivative of nitrogen mustard that cross-links to DNA and RNA, inhibiting cell growth and protein synthesis. It is also used to treat autoimmune disorders and glomerulonephritis. Azathioprine was first synthesized in 1957, and was used to manage transplant rejection prior to cyclosporine. It inhibits the purine molecules that are precursors to DNA, inhibiting cell growth. Repository corticotrophin is a prolonged release adrenocorticotrophic hormone (ATCH). ACTH is secreted from the pituitary gland and stimulates the adrenal glands to produce corticosteroids. It is used in treating autoimmune disorders, including systemic lupus erythematosus and rheumatoid arthritis, as well as glomerulonephritis.

Types of Glomerulonephritis

Minimal Change Glomerulonephritis

This disease is the most common type of glomerulonephritis in children, and occurs in around 20% of adults who develop idiopathic glomerulonephritis. It can cause massive proteinuria, but often responds to corticosteroids. It has been related to a host of medications, including NSAIDS and lithium. It has also been associated with hepatitis, HIV, leukemia, and lymphoma.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS is a type of glomerulonephritis characterized by scar tissue forming in portions of some glomeruli. It is characterized by proteinuria and may have a worse clinical course than minimal change glomerulonephritis. It can be related to viral infections, including HIV and COVID-19. It can also be inherited. FSGS that is

inherited will not respond to immunosuppressive therapy. It can also be associated with APOL-1 risk variants, and is more common in African Americans.

Membranous Nephropathy (MN)

This is the most common cause of idiopathic nephrotic syndrome in Caucasians. It can also be secondary to malignancy. An antibody, the phospholipase A2 receptor (PLA 2R) antibody, is a marker for idiopathic MN and is elevated in 70–74% of cases. The presence of this antibody may obviate the need for a kidney biopsy. Idiopathic MN responds well to therapy, but often relapses.

Membranoproliferative Glomerulonephritis (MPGN)

MPGN can be caused by infections, autoimmune disorders, or monoclonal gammopathies. It is mediated by immune complexes that crowd the matrix and then split the basement membrane from the capillary. Its prognosis varies on the cause, and it can be characterized by hematuria, proteinuria, and altered kidney function.

IgA Nephropathy

This is suspected with patients present with both proteinuria and hematuria. Its course is varied and may be mild. When associated with heavy proteinuria, it may have a progressive course and should be aggressively treated.

ANCA Nephritis

Anti-neutrophil cytoplasmic antibodies can attack white blood cells and cause severe damage to the glomerulus. It is associated with vasculitis. It may also affect the lungs.

Anti-Glomerular Basement Membrane Disease

Antibodies that are directed against the glomerular basement membrane cause hemorrhage from the kidneys and swift glomerular damage. The disease can also affect the lungs. When the disease affects both the kidneys and lungs, it is referred to as Goodpasture's disease. It was named after Ernest Goodpasture, who described the disease in 1919.

Lupus Nephritis (LN)

Lupus nephritis has six different presentations, each with a specific prognosis. Class I LN has minimal change and Class II is characterized by proliferation of mesangial cells. The symptoms may be mild and the prognosis for both of these classes is excellent. Class III LN is focal can be characterized by proteinuria and hematuria. In Class III less than 50% of the glomeruli are involved. This contrasts with Class IV LN where greater than 50% of glomeruli are involved. Class IV LN is often referred to as proliferative glomerulonephritis, and a common and severe manifestation of LN, Class V LN has similar characteristics as membranous glomerulonephritis. It can exist concurrently with Class III LN. The final class, Class VI LN, is characterized by advanced sclerosis or scar tissue formation in the kidney. At this stage immunosuppressive therapy is not beneficial [2].

Inflammation and Diabetes and Hypertension

The two preceding chapters discuss strategies for managing hypertension and diabetes This chapter discusses how external factors damage the kidney.

When the blood pressure is high, regardless of cause (age, diabetes, hypertension, kidney disease) there is damage to the blood vessel wall because of increased forces against the delicate wall. This is termed endothelial dysfunction and is associated with systemic vascular resistance – a narrowing of the diameter of the blood vessel, worsening hypertension, and atherosclerosis. When the wall is damaged, it leads to oxidative stress and inflammation. Since the glomerular filter contains a large bundle of blood vessels, damage, oxidative stress, inflammation, the release of growth factors like TGFß, matrix deposition, and angiotensin II all cause damage to the essential filtering units. The cells that surround the blood vessels are called podocytes, and they too sustain damage. The mesangium that sits between the blood vessels is also damaged, and as a consequence, releases more matrix proteins that crowd the filter (See Fig. 6.1).

The kidney has a built-in mechanism to protect its delicate filters from high systemic blood pressure. High blood sugars, like high blood pressure, interrupts this feedback mechanism, blocking the kidney from adjusting GFR when needed. This causes the hyperfiltration that was discussed in Chaps. 4 and 5. The strain on the kidney can be controlled with diabetes management [3]. Newer medications like the SGLT2 inhibitors will help restore this mechanism even when the cause of kidney disease is not diabetes.

Any damage towalls inside the blood vessels, regardless of the cause leads to the blockage of a substance known as nitric oxide (NO). Nitric oxide causes the blood vessel walls to relax, and when it decreases, the blood vessels tighten. L-arginine is an amino acid that is synthesized to NO in the endothelial cells. NO reacts with the enzyme guanylate cyclase to dephosphorylate or remove a phosphate from myosin causing the smooth muscle that surrounds the blood vessel to relax. The relaxation

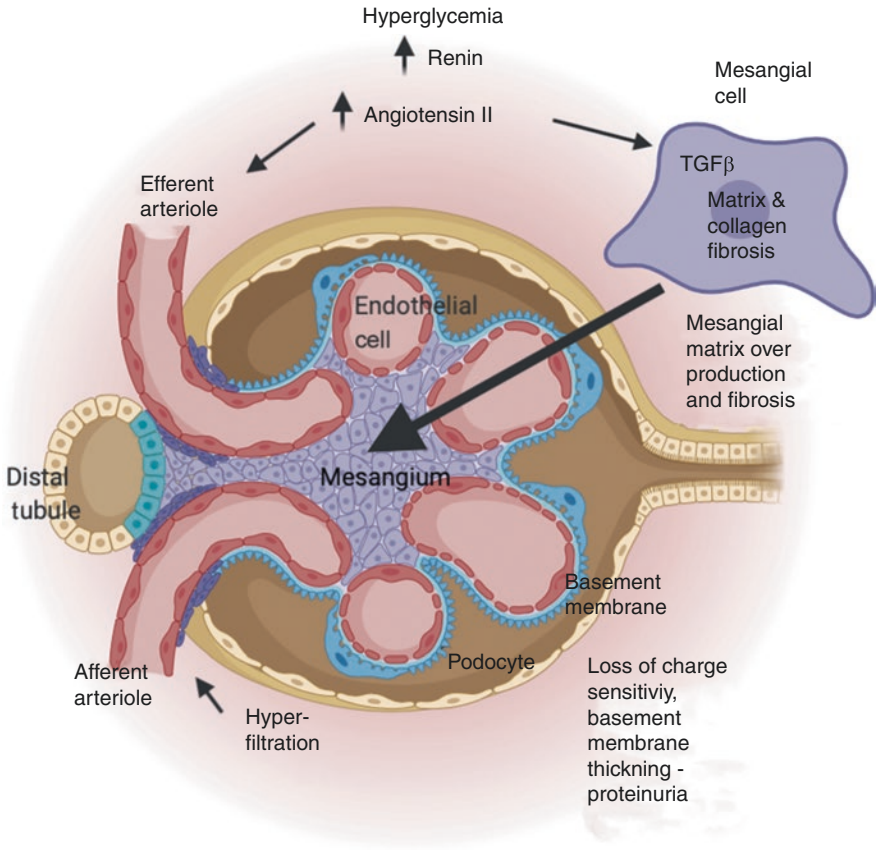

Fig. 6.1 The glomerulus in diabetes and hypertension. (Made with Biorender.com and Adobe Photoshop)

that is caused by guanylate cyclase is inhibited by phosphodiesterase 5 (PDE5). Erectile dysfunction is quite common in the elderly, as well as those with underlying vascular diseases like diabetes, hypertension, and atherosclerosis. It is caused by an inability of the blood vessels feeding the corpus spongiosum in the penis. The development of a drug that blocks inhibition by PDE5 will allow blood vessels to remain in the relaxed state, and allow the corpus spongiosum to fill with blood. These drugs are known as PDE5 inhibitors (sildenafil, tadalafil, and vardenafil), and they have become mainstay therapy for erectile dysfunction.

Metabolic disorders such as diabetes, obesity, or the metabolic syndrome also causes an imbalance between the fuel and energy sources inside the mitochondria, leading to oxidative stress. The mitochondria will be extensively discussed in the appendix. Over time, oxidative stress can damage the mitochondria, leading to damage to the cell.

Hyperglycemia can lead to polymers with proteins and lipids, creating abnormal complexes known as advanced glycation end products (AGES). This causes the release of inflammatory cytokines – cellular hormones that participate in the inflammatory reaction. The two best known are IL-6 and TNF-β. These further stimulate the production of AGES. When cells sense they must fight an infection, they send the signaling molecule NFκB into the nucleus. This causes the release of more cytokines that recruit macrophages and lymphocytes. This also blocks nitric oxide by stimulating the production of free radicals. Free radicals cause harm to mitochondria and other intracellular components.

Hyperglycemia, angiotensin II, and other glomerular diseases stimulate the mesangial cells to elaborate transforming growth factor (TGFß) and to secrete matrix. This is complicated by the relative hypoxic environment that characterizes the disrupted glomerulus. TGFß signals a cascade that produces collagen, leading to scarring in the kidney. It activates a signal pathway that culminates in transcription factors known as Smads being translocated to the nucleus where they activate the genes producing collagen. Mesangial cell collagenase and other proteolytic enzymes are inhibited, leading to collagen accumulation. Angiotensin II is also released and causes tightening of the arteriole exiting the filter, the afferent arteriole. This increases pressure and damage on the filter. Angiotensin blockade is a mainstay on treatment for both diabetes and hypertension.

Podocytes are the cells that line the basement membrane. Like brain cells, they are differentiated to be highly specialized. They cannot be replaced, and when lost do not regenerate. They are sensitive to hypertension, hyperglycemia, and inflammatory changes. Their dropout is the cause for many diseases. They are very sensitive to hyperglycemia, and their dropout is a cause of diabetic nephropathy.

Hyperglycemia activates the renin angiotensin system and increases angiotensin II (Fig. 6.2). This causes efferent constriction and increases filtration pressure, damaging the glomerulus. It also increases transforming growth factor ß (TGFß), resulting in mesangial matrix and fibrosis. Hyperfiltration occurs when the filtration pressure is high. This damages the glomerular filter.

The relationship between kidney disease and inflammation is complex and entails many additional factors. It is highly interesting, and reading about it will embellish one's understanding of the processes that play a role in the progression of kidney disease.

If inflammation is a factor in kidney disease progression, can we stall the progression of kidney disease through the control of inflammation? That is an important question that is being answered by medical research as this book goes to press. This author is a principal investigator of one of the medications that helps block the inflammatory response that can damage the kidney. With respect to the potential for medical breakthroughs, one must wait for our studies to be completed. A medication that is safe and effective will then be reviewed for approval by the FDA.

In the meantime, the modification of lifestyle through dietary control, exercise, and the avoidance of cigarette smoking, may help reduce inflammation. The next chapter is devoted to the dietary measures recommended for patients with CKD.

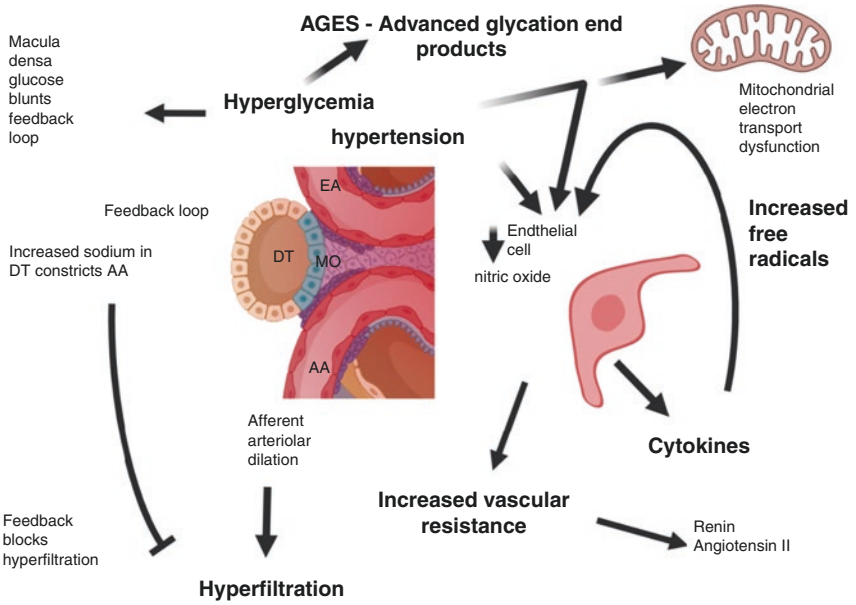

Fig. 6.2 The increased blood flowing through the kidney creates a reflex that causes the afferent arteriole to contract. The increased flow reduces sodium reabsorption causing increased sodium to travel in the tubular fluid to a region in the distal tubule known as the macula densa. Here the distal tubule winds back to the glomerulus to send it signals that there is ample sodium. The swelling causes the arteriole to contract further. This feedback in normal kidneys shuts off the hyperfiltration. Hyperglycemia increases mitochondrial reactive oxygen species (ROS) and advanced glycation end products that also stimulate ROS. Hyperglycemia blocks the tubuloglomerular feedback loop. This blunts afferent arteriole from contracting which allows hyperfiltration. Hyperglycemia increased total peripheral resistance because of vascular endothelial cell damage and the loss of nitric oxide (NO). The result is increase in inflammation, with cytokines and angiotensin II. Thus further damages the kidney. It also causes mitochondrial dysfunction. (Made with Biorender.com and Adobe Photoshop)

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Chapter 7
Diet to Preserve Kidney Function

Kamyar Kalantar-Zadeh, William E. Mitch, and Stephen Z. Fadem

Part 1: Plant-Based Diet in Kidney Disease

It is well known among doctors that consuming more than 1.5 g of protein per kilogram per day (105 g for a 70 kg person) can overwork the kidney filters, causing hyperfiltration. This is especially dangerous in persons with underlying kidney disease since overworking the kidneys can damage them. Many proteins are composed of amino acids that are converted to acids that can harm the kidney [1]. A diet high in animal proteins contain sulfuric and phosphate acids that promote kidney damage [2]. These acid precursors can also increase angiotensin II, which further harms the kidney. Ingestion of red and process meats are the worst culprits [3, 4].

By restricting the dietary protein intake, the arterioles that carry blood into these filters become narrowed, reducing pressure on the delicate filter membranes, and thus protecting them (See Fig. 7.1).

Dietary protein restriction has other benefits. The following table, reproduced from the New England Journal of Medicine, is a good review of the potential benefits of a low-protein diet on not just chronic kidney disease, but on many of the measures with which it is associated (See Table 7.1).

In healthy people, the dietary allowance for protein is 0.8 g/kg/day; and in persons with kidney disease the allowance is even lower, 0.66 g/kg/day. Restricting the dietary protein intake is challenging and, although beneficial, evidence is now emerging that changing the source of proteins might be wiser. A critical review has

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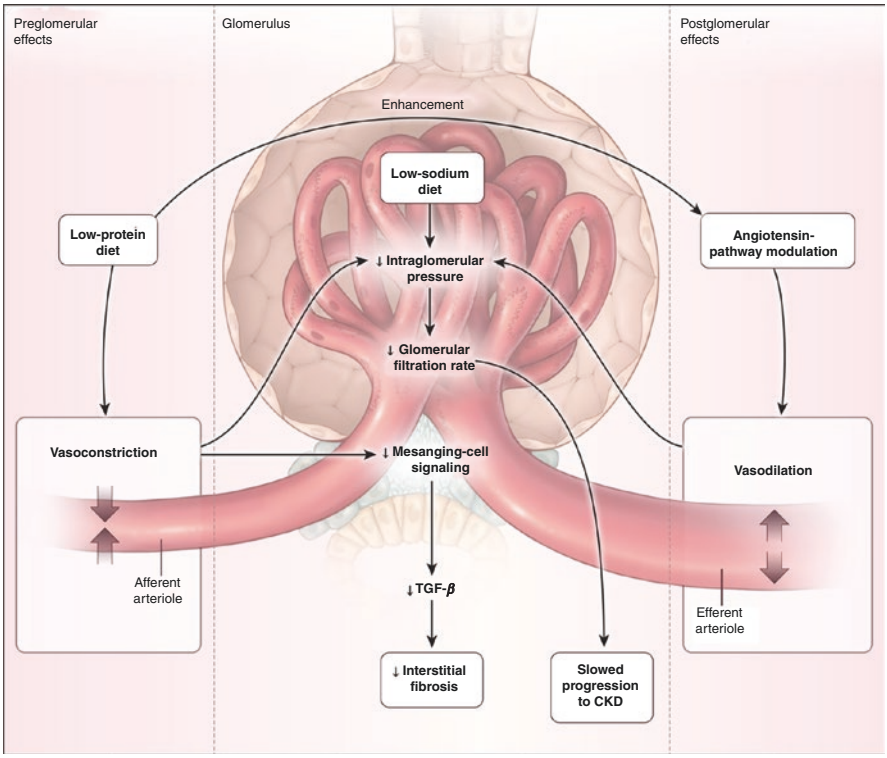

Fig. 7.1 Illustrates how restricting the diameter of the blood vessel entering the glomerular filter (afferent arteriole) can reduce the overall pressure in the filter. The low-protein diet not only restricts the diameter of the vessel entering the filter but helps dilate the vessel exiting the glomerulus (efferent arteriole) (From Kalantar-Zadeh and Fouque [5] used with permission)

demonstrated that while daily red meat consumption increases the risk of CKD progression, the opposite is true when the diet consists of fruits and vegetables. Despite this, the typical person living in the United States consumes less than one third of protein sources from plants.

Our digestive system is shorter and less complicated than that of animals that eat only plants. Animals such as deer, sheep, and antelopes are known as ruminants and have digestive systems specifically designed to more fully breakdown plants. Since we digest plant proteins less completely than ruminants, but still benefit from the fiber, alkali content, and antioxidants found in them, it is a wise strategy to shift the diet to plant-based.

As seen in Table 7.2, a plant-based diet has other benefits that are subsequently discussed. Since the pH of plant amino acids is higher, we ingest less acid. We can eat less saturated fats, absorb less dietary phosphorus, and ingest foods that contain more fiber and antioxidants. It is easier to control one's body mass on a diet richer in vegetables. Vegetables and fruits are less constipating and may not upset the

Table 7.1 Potential benefits and challenges of a low-protein diet (From Kalantar-Zadeh and Fouque [5] used with permission)

Potential benefits and challenges of a low-protein diet (LPD) in the nutritional management of chronic kidney disease (CKD)[a]			
Measure	Potential benefits of LPD	Challenges and risks of LPD	Comments
CKD progression	Synergistic effect with angiotensin-pathway modulators to lower intraglomerular pressure[b]	In first several months, slight drop in GFR may be observed, as shown in MDRD study[c]	Inconclusive results in MDRD study, but small effect size in meta-analyses[d]
Proteinuria	Consistent antiproteinuric effect, which may mitigate hypo-albuminemia	LPD is contrary to notion that DPI must be increased to replace urinary protein loss	Some data suggest that even larger effect may be achieved with DPI of <0.6 g/kg/day
Uremia management and deferral of dialysis	Supported by consistent and biologically plausible data for almost a century	Unlikely to worsen uremia but potential risk of resurfacing or exacerbating PEW	Patients at increased risk for PEW may benefit from supplements (e.g., EAA or KA)
Metabolic acidosis	H^+ generation decreased in proportion to reduction in DPI, especially with larger proportion of plant-based food	The need for >50% HBV protein may prompt higher intake of non-plant-based foods that are more acidogenic	Although >50% HBV protein is recommended, the remainder can be from plant-based foods
Mineral and bone disease	The lower phosphorus content of LPD improves measures of mineral bone disease, including sHPT and high FGF-23	Higher calcium content in some KA preparations may increase calcium load	Additional improvements in bone health are possible by alleviating acidosis
PEW	Ameliorating hypoalbuminemia in patients with proteinuria may help neutralize circulating inflammatory compounds	Weight loss may occur; the habit of LPD intake may continue after starting thrice-weekly hemodialysis, when higher protein intake is recommended	Half of dietary protein source should be HBV protein; liberalize diet during correction of PEW
Cardiovascular and metabolic health	Lower protein intake is associated with lower dietary salt and saturated fat intake and may be less atherogenic, given higher proportion of plant-based food	Higher dietary fat intake (to achieve DEI of 30–35 kcal/kg/day) may confound the goal of achieving a heart-healthy diet	Higher proportions of unsaturated fat and complex carbohydrates recommended

(continued)

Table 7.1 (continued)

Potential benefits and challenges of a low-protein diet (LPD) in the nutritional management of chronic kidney disease (CKD)[a]

Measure	Potential benefits of LPD	Challenges and risks of LPD	Comments
Glycemic control and insulin response	Improvement in insulin resistance is likely	With LPD or VLPD, higher carbohydrate and fat intake (to achieve DEI 30–35 kcal/kg/day) may worsen glycemic control	Given increased insulin half-life and "burnt-out diabetes" with CKD progression, preventing hypoglycemic episodes is prudent
Quality of life and adherence to LPD	Enhanced patient-centeredness, given that many patients seek nutritional therapies and dietary advice	Challenges with adherence; diet fatigue, poor palatability, and cravings reported	Recommend creative recipes and strategies to engage patients
Mortality	There are no convincing data to suggest reduced mortality, although dialysis deferral is a potential mechanism, given high mortality during early dialysis	Increased mortality highly unlikely with DPI of 0.6–0.8 g/kg/day unless severe PEW emerges and is uncorrected	Consider supplements or other corrective strategies whenever PEW is suspected or diagnosed
Hypertension management	MDRD and other data suggest improved BP control	Reduction in BP is more likely a result of concomitant lower salt intake than of LPD itself	Higher potassium intake from more plant-based foods may be a potential mechanism
Microbiome modulation	Improved microbiome profile may be achieved through reduced uremic toxin generation	Possibility of promoting unfavorable microbiome milieu cannot be excluded	Uremia itself can lead to unfavorable microbiome

[a]A diet that provides 0.6–0.8 g of protein per kilogram of body weight per day is recommended most frequently. *BP* denotes blood pressure, *DEI* dietary energy intake, *DPI* dietary protein intake, *EAA* essential amino acids, *FGF-23* fibroblast growth factor 23, *GFR* glomerular filtration rate, *HBV* high biologic value, *KA* ketoacids, *MDRD* Modification of Diet in Renal Disease, *PEW* protein–energy wasting, *sHPT* secondary hyperparathyroidism, and *VLPD* very-low-protein diet

[b]Angiotensin-pathway modulators include angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers.

[c]The MDRD study data were originally presented by Klahr et al. [6] with an additional analysis by Levey et al. [7]

[d]A meta-analysis by Kasiske et al. showed a significant but rather small effect size of an LPD in slowing the CKD progression rate [8]

delicate bacterial balance in the gastrointestinal tract known as the microbiome [5]. Table 7.2 shows the recommended daily intake in patients with CKD according to stage.

The concept of a plant-dominant low protein-diet (PLADO) combines the best of the low-protein diet and the plant-dominant diet. It targets delaying the progression

Table 7.2 Recommended dietary and nutrient intake in adults, according to CKD stage (From Kalantar-Zadeh and Fouque [5] used with permission)

Dietary constituent	Normal kidney function with increased CKD risk	Mild-to-moderate CKD[a]	Advanced CKD[a]	Transition to dialysis[a]	Ongoing dialysis or any stage with existing or imminent PEW
Protein (g/kg/day)	<1.0; increase proportion of plant-based proteins	<1.0 (consider 0.6–0.8 if eGFR <45 ml/min/1.73 m^2 or rapid progression)	0.6–0.8, including 50% HBV protein, or <0.6 with addition of EAA or KA	0.6–0.8 on nondialysis days and >1.0 on dialysis days	1.2–1.4; may require >1.5 if hypercatabolic state develops
Sodium (g/day)[b]	<4 (<3 in patients with hyper-tension)[c]	<4; avoid intake of <1.5 if hyponatremia likely	<3; avoid intake of <1.5 if hyponatremia likely	<3	<3
Potassium (g/day)[d]	4.7 (same as recommended for general population)	4.7 unless frequent or severe hyperkalemia excursions likely	<3 if hyperkalemia occurs frequently during high-fiber intake	<3 if hyperkalemia occurs frequently during high-fiber intake	<3; target high-fiber intake
Phosphorus (mg/day)[e]	<1000; minimize added inorganic phosphorus in preservatives and processed foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus; consider phosphorus binder	<800; minimize added inorganic phosphorus; add phosphorus binder as needed
Calcium (mg/day)	1000–1300 (adjusted for age)	800–1000	800–1000	800–1000 or less	<800
Fibers, alkali, and plant-based foods (g/day)	25–30: target higher proportion (>50%) of plant-based foods (e.g., DASH diet)	25–30 or more; higher proportion (>50%) of plant-based foods	25–30 or more; consider >70% plant-based foods	25–30 or more	25–30 or more; suggest avoiding strict vegan diet

(continued)

Table 7.2 (continued)

Dietary constituent	Normal kidney function with increased CKD risk	Mild-to-moderate CKD[a]	Advanced CKD[a]	Transition to dialysis[a]	Ongoing dialysis or any stage with existing or imminent PEW
Energy (kcal/kg/day)[f]	30–35; adjust to target weight reduction if BMI >30[g]	30–35; increase proportion with LPD	30–35; increase proportion with LPD	30–35	30–35; target higher intake if PEW present or imminent
Fats	Mostly monounsaturated and polyunsaturated lipids including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids

Normal kidney function is defined as an estimated GFR (eGFR) of at least 60 ml per minute per 1.73 m^2 of body-surface area. Patients in this category do not have substantial proteinuria but are at increased risk for CKD because of another condition (e.g., diabetes, hypertension, or polycystic kidney) or a solitary kidney. (A solitary kidney can be a congenital or acquired state, with the latter due to nephrectomy for donation or cancer treatment.) Mild-to-moderate CKD is defined as an eGFR of 30 to less than 60 ml per minute per 1.73 m^2 without substantial proteinuria (<0.3 g of protein per day). Patients with advanced CKD have an eGFR of less than 30 ml per minute per 1.73 m^2 or substantial proteinuria (>0.3 g per day). Patients transitioning to dialysis therapy usually have good residual kidney function. Protein–energy wasting (PEW) is defined according to the criteria of the International Society of Renal Nutrition and Metabolism [9]. In the denominator of the dietary recommendations for protein and energy, kg denotes the ideal body weight (IBW), especially for persons with a body-mass index (BMI, the weight in kilograms divided by the square of the height in meters) above 30. The IBW can be estimated in males as 50.0 + 2.3 kg for each inch over 5 ft (each 2.5 cm over 152.4 cm) and in females as 45.5 + 2.3 kg for each inch over 5 ft. To convert phosphorus to millimoles per day, multiply by .03229. To convert calcium to millimoles per day, multiply by 0.02495. *DASH* denotes Dietary Approaches to Stop Hypertension.

[a]Kidney-transplant recipients may have an eGFR of 30 to less than 60 ml per minute per 1.73 m^2 or less than 30 ml per minute per 1.73 m^2 or may be transitioning to dialysis; the transition-to-dialysis stage includes incremental dialysis preparation. These three subgroups of patients can be approached similarly with respect to dietary management

[b]Patients with certain conditions such as salt-losing nephropathies should not be subjected to sodium restriction

[c]For patients with heart failure, the American Heart Association recommends no more than 2.3 g of sodium per day (equivalent to 1 teaspoon of salt) and suggests an ideal limit of 1.5 g of sodium per day (**https://sodiumbreakup.heart.org/how_much_sodium_should_i_eat**)

[d]Patients who are undergoing peritoneal dialysis and have hypokalemia should have a goal of increasing their potassium intake

[e]Dietary phosphorus should be restricted regardless of the patient's status with respect to hyperphosphatemia

[f]Carbohydrates, which provide 40–60% of the daily energy intake, should be natural (nonrefined) and complex with a high-fiber content

[g]In obese patients, lower energy ranges can be targeted

Fig. 7.2 Salmon is a healthy source of protein

of kidney disease, improving health, reducing heart disease, and delaying aging. Dietary protein intake is restricted to 0.6–0.8 g/kg/day while consuming at least 50% of dietary protein from fruits, vegetables, and nuts. The diet is flexible, not requiring one to become a strict vegetarian or vegan. When consuming proteins, one must consider whether the food consumed is of high biologic value or not. Those that are of limited value lack some of the amino acids that are essential for replacing those that are being eliminated. Fish is an excellent source of amino acids while gelatin and corn are not, as they are lacking in essential amino acids (See Fig. 7.2). This diet is both safe and palatable. Its goal is three-fold: allow slow progression of kidney disease, control proteinuria, and assure an adequate nutritional status [10].

Part 2: Metabolic Acidosis can be Controlled by Eating Fruits and Vegetables

The proteins in our diet are composed of amino acids. Acids are particles known as hydrogen ions (H^+); they carry a positive charge. That charge can be measured by a number that is referred to as the pH. The pH is a quantitative measure of acidity, and is defined as the negative log of the H ion concentration measured in gram-equivalents-liter. What this means that the lower the pH number, the more acid there is in the system; and the higher the pH, the more base is in the system. Since every cell in the body carries out numerous chemical reactions, there must be perfect acid-base balance. The ideal pH of the cell is 7.4. The kidney, lungs, bones, and red blood cells all have a role in controlling excess hydrogen ions. The kidney is the main regulator of acid-base balance and does so through the secretion of H^+.

Many amino acids, including those found in many animal-based foods, have a low pH and contribute acids to the body. Thus, excess acids are derived from some of the amino acids in our diet. Although this sounds contradictory, some amino acids are not acids at all, but instead basic and can help reduce the acid content.

Promptly after the development of kidney disease, even in early Stage 3 CKD, the ability to excrete acids starts to decrease. Even when kidney disease starts very early, there can be an abnormal buildup of acid in the body. This is known as acidosis. The body may adapt by buffering these acids by using bone. Controlling acidosis early is part of the initiative to preserve kidney function. Acids can be in gas form, such ascarbon dioxide. When we have an accumulation of acid in our body, some of that acid can be exhaled as carbon dioxide. Some acid is dissolved in the blood and can dissolve our skeleton. This important point is repeated in nature. The coral that makes reefs is a tiny animal that, like bone cells, secretes a hard calcium skeleton. When the carbon dioxide in the atmosphere is great, more and more is dissolved in seawater, impairing the coral's ability to excrete skeleton. This is because the carbon dioxide uses calcium as a buffer, leaving less for bone or coral reefs. While in nature, the reefs provide a home for fish, we depend on the hard skeletons for mobility (See Fig. 7.3). Acidosis can lead to loss of bone, making a person susceptible to fractures. It can also trigger muscle protein degradation, leading to sarcopenia. Finally, the acidosis that starts when kidney function is impaired stimulates inflammation which causes insulin resistance, fibrosis, and kidney cell injury [11–13]. Dietary acid intake, particularly through ingested animal proteins, predicts and increases the risk of end stage kidney disease [14].

Clinical studies have demonstrated that these actions can be significantly blocked when supplementing one's diet with bicarbonate tablets. Sodium bicarbonate can be purchased over the counter tablets (See Fig. 7.4). It is recommended that one supplement the diet with oral alkali therapy based on the level of bicarbonate that is measured in the blood. Treatments should be designed to maintain a serum bicarbonate level of 23–29 mEq/L. If sodium bicarbonate tables are difficult to ingest, sodium citrate may be substituted. Citrate is metabolized to bicarbonate by the liver.

As many high-protein foods, grains, and sugars are processed to yield foods with a high-acid content, they should be reduced to help control a high dietary acid load. It has further been demonstrated that selecting fruits and vegetables that are rich in

Fig. 7.3 The bones in our body, like coral reefs, are vulnerable to dissolved carbon dioxide (Photograph by Stephen Z. Fadem)

Fig. 7.4 Sodium bicarbonate can be purchased over the counter and is relatively inexpensive

Fig. 7.5 Basic foods that will control metabolic alkalosis (Photograph by Stephen Z. Fadem)

base substances can also protect the kidney (See Fig. 7.5). It is recommended that one consume three helpings per day of either fruits or vegetables to get the equivalent benefit of using bicarbonate tablets [15].

Part 3: Body Mass Control

Obesity is characterized by a body mass index (BMI) of greater than 30 kg/m^2. The BMI is a relationship between height and weight. You can measure yours at http://touchcalc.com/bmi. Obesity is a risk factor for death and disability and causes an estimated five million deaths per year, mainly related to heart disease, diabetes, kidney disease, and cancer. Obesity is common, affecting almost 40% of the US population (http://cdc.com/obesity/data/adult.html). It is the strongest risk factor for developing end-stage renal disease (ESRD) by a factor up to seven fold over those with a normal BMI.

The reason why obesity is so strongly linked to CKD is related to inflammation. All food is valued in calories, a measure of heat generated or, specifically, the amount of energy needed to heat 1 kg of water by 1 °C. The resting or basal metabolic rate (BMR) and exercise-related body metabolism when added together should balance that of the food content consumed. One can download an app for a smartphone that will enable tracking of food and exercise, as well as the calculation of your BMR. Excess food, whether fat, sugars, or proteins, must be stored. The distribution of fat in the body can either be truncal or central (also referred to as visceral). The visceral "pot belly" is associated with heart disease and an insidious inflammatory response that also affects other organs. Fat cells gather the fatty acids, clear them from the circulation, and store them inside the cell [6].

But the body must pay a price, a storage fee of sorts, as this process releases inflammatory molecules, known as cytokines. Cytokines function like hormones, but are secreted by cells, and have effects on other cells. They are generally secreted in response to a threat to the body, and are part of the immune response. They interfere with glucose metabolism and the lining of blood vessel walls. Inflammation also stimulates the formation of damaging fibrosis in the kidney, potentiates cancer, and worsens atherosclerosis. A deeper understanding of how dietary fat stimulates inflammation will be discussed in the appendix.

Central obesity is treated by decreasing calories to reduce their storage. Curbing one's appetite takes more than desire and willpower. It takes knowledge to recognize that some foods can make you hungry rather than satisfy your appetite. Some of the foods that stimulate the appetite do so when insulin release is delayed, as insulin is a powerful appetite stimulant. Carbohydrates are well known to create a craving for food several hours later. Salt tends to make us desire more food, and soda laced with high fructose corn syrup also decreases food satiety. Foods that suppress the appetite include apples, eggs, almonds, green vegetables, salmon, beans, and spices. Cinnamon and ginger are particularly effective and tasty alternatives to curve one's desire to eat.

As one loses weight through caloric restriction, the resting metabolism also decreases. As those of a "riper" vintage can attest, the metabolism naturally declines as we age. The age-related decline in BMR, compounded with a successful diet, can lead to a sense of frustration as one hits a plateau, or even gains weight after a successful period of weight loss. Combating this may be challenging. There are

theories as to the mechanism, and they relate to the mitochondria that we will discuss in detail in the appendix. But the most sensible therapy is to exercise. Becoming more active while dieting is essential for a successful long-term result. Movement is the best medicine.

Another problem associated with dieting and weight loss is that the skin stretches to accommodate the storage of fat in cells. With dieting, these cells shrink, but the skin remains stretched. That may be bothersome for some, in which case plastic surgery is sometimes an option.

Part 4: Sodium

The story of salt parallels the story of the history of mankind itself. Once considered a precious commodity, the word salary comes from salt. Main highways trace the paths animals took to "salt licks," and famous cities like Salzburg, get their names from salt. Prior to refrigeration, salting foods to preserve them was essential. While the role of salt in history cannot be underestimated, it must also be reconciled that our evolutionary history did not include access to saltshakers. Thus, the salt that is recognized as seasoning to improve the flavor of foodmay strain the system that was never designed to handle the large quantities we often consume. Although we can lose salt through skin when we sweat, the major organs tasked with ridding the body of excess salt are the kidneys. Not only must the kidney rid the body of excess salt, but it must use salt to balance the volume of water that our body requires. The kidney works in concert with the heart and the sympathetic nervous system to carry out this assignment.

A salt molecule's journey through the tubule involves numerous and complex biochemical transport mechanisms. The kidney retains salt through the proximal tubule. As the nephron moves into the deeper portion of the kidney, water is abstracted, and salt stays behind. By the time the tubule is at its deepest part – the hairpin turn of the Loop of Henle– the salt content is very high. Here the gradient causes salt movement by diffusion into this part of the kidney. As fluids move upward through the tubule, active transport mechanisms cause further retention of salt. In this area, loop diuretics such as furosemide will stop salt reabsorption, helping to eliminate it. In the distal tubule, the salt is once again reabsorbed so the fluid that leaves to enter the collecting duct is very dilute. Only a fraction of the amount that is filtered is lost in the urine. That fraction generally equals the amount we ingest. Salt moving through the tubule passes the glomerular filter, directing it to clamp down or widen the afferent arteriole that controls filtration. A small salt load will cause the macula densa to send signals for the arteriole to constrict. A large load will cause it to hyperfilter. Hyperfiltration is a major cause of diabetes, and if pressures are high, this also damages the glomerulus. The sodium glucose transporters play a role in this activity, and the SGLT2 inhibitors will cause both a sodium and a glucose loss, decreasing the load of salt that would otherwise cause hyperfiltration (See Fig. 7.6).

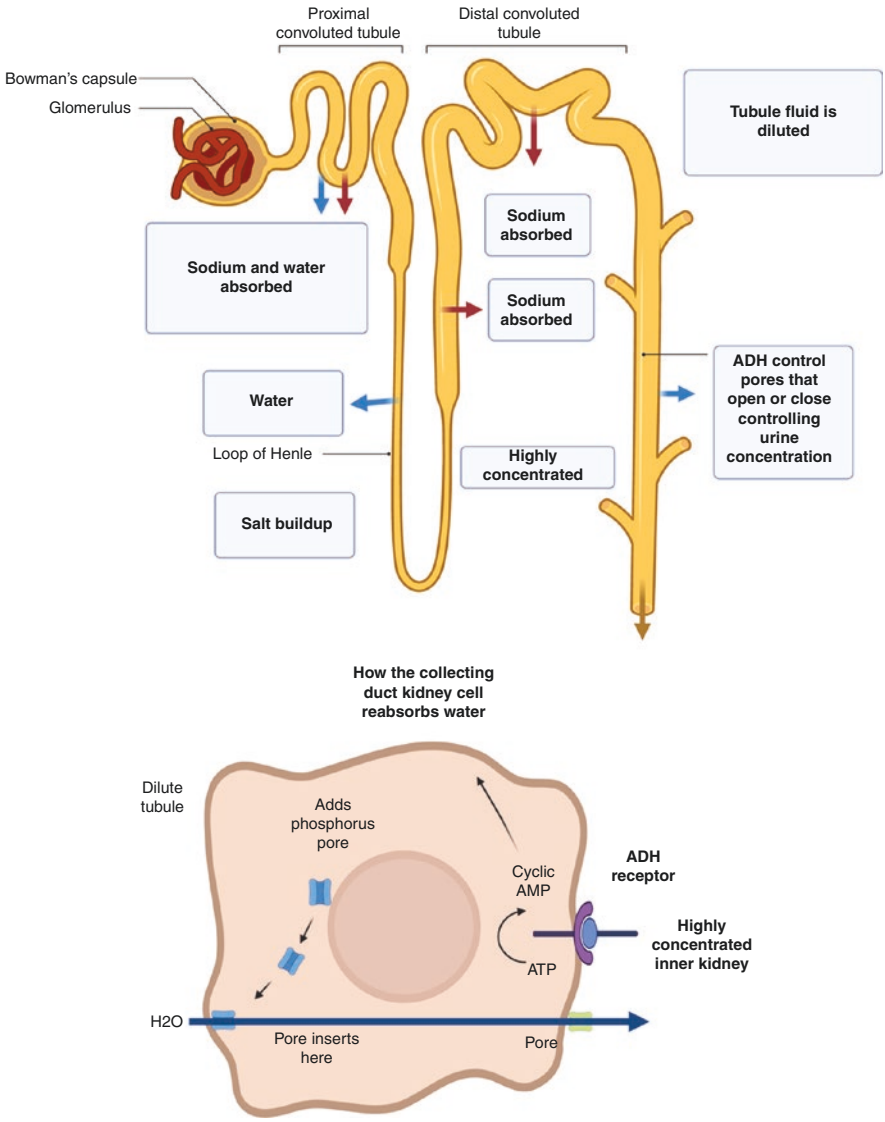

Fig. 7.6 How water is absorbed in the nephron. ADH Antidiuretic hormone (Figure created in Biorender.com and Adobe Photoshop)

The convoluted tubule has pores that open and close to help control the concentration of urine. They are under the control of the antidiuretic hormone that is secreted by the pituitary gland. When hiking on a sweltering summer day, your kidney is told to open its collecting duct pores and expose the urine to the highly concentrated sodium area that was generated in the deep part of the kidney known as the medulla. Meanwhile, closure of the collecting duct allows a very dilute urine to be eliminated (See Fig. 7.6).

Sodium and table salt, or sodium chloride, are often confused. Table salt contains sodium, but the two chemicals are not the same thing. While sodium (Na^+) is an element with a positive charge and an atomic weight of 23 g, Chloride (Cl^-)is negatively charged with an atomic weight of 35 g. One mole of table salt (NaCl or sodium chloride) is 58 g, but one mole of sodium is only 23 g. 10% of that, or 100 mEq or molar equivalent of sodium is 2.3 g. When we measure the serum sodium in our blood, it is 140 mEq/L (140 mEq/L or 140 mmoles/L). Remember, one liter is 1000 cubic centimeters. 2.3 additional grams of sodium in your diet is equivalent to 100 mEq of added sodium, and that means that you will be thirsty until you balance that 100 mEq with 100/140 mEq or 714 cc of water. The kidneys must get rid of that extra fluid, and until this happens, it will put pressure on the walls of the blood vessels that carry fluids around your body.

Reducing the sodium intake will help control the blood pressure and may help delay progression of kidney disease. In a three-year study where patients were assigned to a non-restricted or restricted low sodium diet, the eGFR worsened by 30% in 11% of the non-restricted diet and in only 3.3% of those who were on the restricted sodium diet [8].

Sodium in the diet adds to both hunger and thirst. In addition to helping delay the progression of kidney disease, restricting the dietary sodium will help control the blood pressure with fewer medications. It will also help reduce the incidence of stroke and heart failure. Too much sodium in the diet increases the water retained, diluting the concentration of medications you have taken, often making them less effective [16].

When restricting the dietary sodium intake, it is cautioned not to use salt substitutes without first reviewing the label. Some contain potassium and for persons with a risk to develop hyperkalemia, that can be ill-advised. While shopping in the grocery store, read the labels to check for the sodium content. In addition to limiting foods high in sodium, try to add just a pinch when cooking. Use garlic or pepper instead. Kosher salt, iodized salt, Himalayan salt, etc. are all table salt and contain the same basic mineral. Finally, it is a good idea to take the saltshaker completely off the table. As you reduce the intake of sodium in the diet, you will adapt, and in a short time the food will no longer taste undersalted.

Reducing salt intake is associated with reducing the incidence of stroke and coronary artery disease. Each additional gram of sodium consumed each day beyond the reference value of 2.3 g is associated with a 12% hazard of dying. The National Academy of Science recommends that adults ingest below 1.5 g of sodium per day [17].

Part 5: Phosphorus Management

Phosphorus is present in most of the foods we eat. Dairy products, meats, and plants are well known sources of phosphorus. Of particular concern is its popularity as a food additive, a flavor enhancer, and an emulsifier.

Phosphorus is present in beef, fish, pork, lamb, chicken, and fish. Limiting these foods will help reduce our intake of acids and phosphorus. Ruminants like cattle, deer, and camels are limited to a vegetarian diet. They have four stomachs, regurgitate and rechew their food, known as cud, until it is almost fully digested. We do not fully digest our foods with our one stomach, and plant-based foods pass through our gastrointestinal tracts far less fully digested. Consequently, we do not obtain a great deal of phosphorus from plants. Rennin, also called chymosin, is an enzyme that helps in milk breakdown. It is used in industry in the making of cheese, and it is present in newborn mammals. In humans, it decreases as we grow older. Consequently, the dietary phosphorus from milk products is also not high.

In food processing, phosphorus is added as a preservative to extend the shelf life. With frozen foods, the addition of phosphorus acts as an emulsifier, helping lock in the flavor as the food is thawed. Phosphoric acid also adds flavor to many of the soda products.

Phosphorus is filtered and then reabsorbed in the proximal tubule of the kidney. When kidney function declines, the decrease in filtered load triggers the adaptive hormone fibroblast growth factor (FGF-23) to increase phosphorus excretion. FGF-23 levels start to rise in Stage 2 kidney disease and may damage the heart. Phosphorus is also associated with increased levels of angiotensin II, a hormone that can cause kidney damage, in patients with advanced kidney disease. A dietary restriction of phosphorus and protein will decrease angiotensin and FGF-23. Even in normal individuals, an intake of phosphorus greater than 1400 mg/day is associated with higher mortality [18–21].

The mineral phosphorus is excreted by the kidney but accumulates when kidney function declines. Initially, the kidney response is to increase the release of fibroblast grown factor-23 (FGF-23). This factor helps the kidney adapt by increasing the amount of phosphorus excreted. However, FGF-23 is itself toxic. When the kidneys fail and no longer rid the body of phosphorus, medications that bind the dietary phosphorus are needed. A serum phosphorus measurement will help your doctor assess how much phosphorus has accumulated. When the level is greater than 4 mg/dL, the risk of CKD progression worsens [22].

Part 6: Potassium Management

Potassium is a positively charged mineral that is essential for body function. Its presence inside and outside of the cells creates a difference in charges that helps stabilize the cellular membrane. Having too much or too little affects body functions; it is essential for muscle function and movement. Too little potassium can increase the risk of hypertension, coronary artery disease, or stroke. It can worsen diabetes and aggravate kidney stone formation. It can be associated with one's diet, with the overuse of laxatives or diuretics, and with inflammatory bowel disease (Fig. 7.7).

Fig. 7.7 Some well-known foods high in potassium

Potassium is secreted by the kidneys and may rise when kidney function declines. It is also associated with commonly used medications such as ACE inhibitors or ARB therapy, NSAIDS, or aldosterone blockers. An elevated serum potassium can be secondary to trauma that has caused severe muscle injury.

A type of metabolic acidosis in diabetes patients with CKD occurs when the accompanying hyperkalemia blocks the production of urea, a compound used by the kidney to trap and rid the body of acids. The potassium levels may be high in these patients because of a deficiency in aldosterone. Hyperkalemia and acidosis can also be seen when the urinary tract is obstructed.

Symptoms of hyperkalemia include cramps, weakness, and even trouble walking or paralysis. These signs can indicate a medical injury, or hyperkalemia that can result in an erratic heart function, which can lead to ventricular tachycardia, ventricular fibrillation, and even death.

Part 7: Caloric Restriction

It has been shown in animals that restricting calories will extend lifespan. Some foods work on the same pathway, and as a result have anti-aging properties. It is more enjoyable to find foods that we can eat that will work along the same pathways as calorie restriction. It is refreshing to find that grapes and blueberries may help keep you healthy (See Fig. 7.8). The answer to this question starts in Easter Island.

Rapamycin was first discovered in the soil of Easter Island and has been useful in treating patients undergoing kidney transplantation. It works by acting on a specific site in the cell, the mammalian target of rapamycin (MTOR). Inhibiting mTOR helps repair cells, and stimulating it can be linked to cell growth. Calorie restriction and certain foods can inhibit mTOR.

Fig. 7.8 Can we enjoy healthy eating? (Photograph by Stephen Z. Fadem)

Phosphate is a molecule that when bonded to certain compounds creates a high energy state. Think of energy stored with phosphate bonds as you would a cocked spring. This stored energy can be used for chemical reactions essential to cellular metabolism. Adenosine diphosphate (ADP) is a special molecule that contains two phosphates. Cells convert ADP to adenosine triphosphate (ATP) by breaking down sugar or fat to generate electrons that help drive the chemical reaction to add one phosphate to the ADP molecule. The result, ATP, is a high energy triple phosphate. Sometimes the raw materials that the cell requires to make ATP are too low, forcing the cell to find an alternate pathway, converting two ADP molecules into one ATP and one adenosine monophosphate (AMP). AMP has only one phosphate and is metabolized to uric acid and excreted. Before AMP makes its exit, it first signals an important enzyme, AMP kinase (AMPK). AMPK triggers reactions that conserve and recycle resources, stimulating a recycling process known as autophagy to recycle broken down and worn-out fragments in the cells, and refurbishing them to provide the needed resources for energy. Without AMPK, the mitochondria would have a mismatch between the oxygen and the resource substrates required to make energy. The oxygen would then radicalize and combine with healthy nearby mitochondrial and intercellular components, destroying them. AMPK activation preserves mitochondria and other cell parts. Although AMPK levels decrease as we age, this important enzyme can be stimulated by another enzyme in the foods we enjoy. These are the grapes and blueberries that contain pterostilbenes. Pterostilbenes are sirtuins.

Sirtuins are silent information regulators. These “SIRT” enzymes can transfer an amino acid on certain enzymes from one spot to another, selectively activating them. They are required for AMPK activation and are involved in many processes associated with kidney health. They also work to save telomeres. Telomeres act as “caps” on the tips of DNA, keeping them from fraying and losing information. Once

the telomeres are shortened, the DNA is subject to wear and tear. Many of the components of aging we experience are because our telomeres are too short.

The sirtuins that activate AMPK can help fight the metabolic syndrome, hyperlipidemia, and diabetes, and can thus help preserve kidney function. Staying healthy can be as simple as substituting fresh and simple berries in our diet. Berries, including strawberries, blueberries, blackberries, raspberries, acai berries, and grapes are among the healthiest foods because they are low in calories but high in fiber, vitamin C, and antioxidants. Many berries have proven and impressive health benefits, including lowering blood pressure and cholesterol. They also have strong anti-inflammatory properties. Not just berries and grapes, but other fruits, vegetables, and even dark chocolate may be beneficial. The list includes kale, strawberries, parsley, onions, celery, soy, green tea, and red wine.

Blueberries and grapes are both SIRT foods but act at different parts of the biochemical pathways that delay aging. They have a synergistic action together. Blueberries and many other fruits and vegetables act as antioxidants and reduce the oxidative stress associated with inflammation. While red wine does have resveratrol, it is not ingested in quantities that offer much benefit. One must use caution when consuming alcoholic beverages beyond just a few ounces. Experiments in animals have shown the benefit of pterostilbene, the active component of blueberries. In hospitalized patients with acute kidney injury, large doses of NAD+ precursors and pterostilbene as being safe, but further studies will be needed to demonstrate its effectiveness [23].

Part 8: Flavonoids and Antioxidants

Flavonoids are molecules found in many plants. They dissolve in water and are rich in antioxidant benefits. There are six families of flavonoids. They each contain antioxidants that protect the plant from the oxidizing radiation of sunlight, and thus protect the plant by scavenging for free radicals. They retain those properties when eaten, and thus have an anti-inflammatory benefit. Although we have suggested representative foods in each of the categories, there is considerable overlap. More importantly than the classification, long-term intake of flavonoids are associated with a lower incidence of Alzheimer's Disease [24]. Flavonoids have also been shown to be very promising in the care of patients with kidney disease. In animal models, they have been shown to have an antihypertensive effect, reduce podocyte injury, improve endothelial dysfunction, reduce nephrotoxicity, reduce ischemia/reperfusion injury, promote renal cell regeneration, improve renal function, reduce oxidative stress, decrease carcinogenesis, and decrease the inflammatory response. Further research and study are necessary [25] (Fig. 7.9).

Oxidative stress is a major factor causing kidney damage. Small trials have shown that antioxidants such as lipoic acid and pyridoxine can improve urinary albumin, restore nitric oxide, and lower systolic blood pressure, demonstrating potential benefit. Larger trials are needed [26–30].

Fig. 7.9 Parsley is an example of a low calorie, inexpensive flavonoid that is rich in antioxidants and easy to add to one's diet

Ceylon cinnamon is both an antioxidant and an agent that can lower blood sugar. This antioxidant, working via the same mechanism as cruciferous vegetables and the experimental drug, bardoxolone, is capable of stimulating the release of a transcription factor, nuclear receptor factor 2 (NRF2) from a protein called KEAP1 (Kelch-like ECH-associated protein 1) that is securing it. NRF2 can enter the nucleus of the cell and lead to antioxidant production [31]. Transcription factors are like disk jockeys that play records. Think of DNA as a record collection, and the transcription factor as the DJ. Once the DNA "record" is played, it sends out signals that have certain tasks. In this case, the task is to fight inflammation.

The flavonoids in fruits and vegetables serve as scavengers, reducing oxidative stress. In addition to promoting health, they can be tasty. Eating a healthy food item leaves less of an opportunity to eat goods that are unhealthy. Classic examples of foods to limit or avoid include processed foods. These generally have preservatives that contain sodium or phosphorus. Refined carbohydrates and foods containing excess sugar cause insulin resistance which potentiates inflammation. Fried foods and red meats are less healthy and should be limited.

A healthy and simple breakfast may include two eggs cooked in a cast iron skillet with olive oil. An option is to season with hot sauce; no need to add salt. The egg protein will help build muscle.

An ideal lunch can include a salad with spinach or kale. Mix in tomatoes, blueberries, and walnuts. Use balsamic vinegar and extra virgin olive oil as salad dressing; season with pepper.

An outstanding low-protein dinner idea is to grill Portobello mushrooms and then season them to perfection with garlic and pepper. Although not technically flavonoids, they have antioxidant properties. They can be seasoned and grilled as a delicious protein substitute.

Roast broccoli or cauliflower as a side dish. The ideal protein is salmon. It can be seared and then baked. Garlic and pepper with little or no sodium will create an outstanding flavor.

The ultimate dessert is a delicious bowl of fruit. For additional flavor, sprinkle on some allulose and Ceylon cinnamon. For a snack, shave a small section off a bar of dark chocolate, and add some crushed walnuts or pecans. Sprinkle with allulose or erythritol**.**

Part 9: Supplements for Kidney Patients

Eating a diet low in protein has been shown to preserve kidney function in animal models. Due to conflicting studies, the renal community lost its appetite for the low-protein diet until 2008, when a very well done clinical trial showed that a low-protein diet compared with a regular diet guaranteed better metabolic control, a reduced need for medications, and did not put the patient at risk for malnutrition [32]. Follow-up studies have not demonstrated that the low-protein diet is harmful in ketoanalogue-supplemented very low-protein vegetarian diets [33].

What Are Ketoanalogues?

Amino acids are the ingredients that the body needs to make proteins. If one thinks of it like baking a cake, the body cannot manufacture several amino acid ingredients from "scratch," and they must be included in the diet. Since the body requires essential amino acids to build muscle, and they cannot be manufactured by the body, they must be supplied in the diet. Each amino acid contains nitrogen, and removing the nitrogen but leaving the ketoacid (KA) skeleton creates an ideal supplement for those on a strict diet. These are referred to as ketoanalogues. In persons with kidney disease, there is an excess buildup of nitrogen, and the patient combines this surplus with ketoanalogues to make the amino acids that the body needs.

What is the Current Recommendation for the Low-Protein Diet Plus KA Supplements?

The challenge of successfully restricting dietary protein can be helped by the use of KA supplements; evidence is now suggesting that KA should be included as a supplement for the low-protein diet [34]. We now realize that for each 0.2 g/kg of protein that is restricted, the annual GFR decline will decrease by 1.15 cc/min/1.73 m^2 [7]. In some patients, dietary protein restriction may delay the time until one requires dialysis, but it appears that dialysis is imminent in those whose disease has advanced too far. The low-protein diet, particularly when supplemented by vegetables and fruits, has been shown to be effective in delaying dialysis as kidney disease advances to Stages 4 and 5. In this group a protein restriction of 0.28 g/kg/day is recommended along with the KA supplements [33, 35]. There have been 17 studies analyzing 2996 patients with kidney disease. In persons with advanced kidney disease, (CKD 4 or 5), a very low-protein diet, as opposed to a low-protein diet, is probably necessary to reduce or delay progression to dialysis [36]. This low amount of

protein consumption will require supplementation with KA, and one should consider plant-based proteins instead of animal-based proteins. In persons with mild kidney disease, the low-protein diet does not improve either mortality or the avoidance of dialysis [6, 8, 37], and instead the diet should be modified to include more fruits and vegetables as well as less animal-based protein consumption given evidence that metabolic acidosis and excess protein intake are harmful. The authors of this chapter are currently recommending that persons with advanced kidney disease take a balanced dietary approach based on a supplemented low-protein diet with essential amino acids or their ketoanalogues.

Conclusion

We are discovering that by controlling our diet, we can extend the life of our kidneys; and as a pleasant secondary benefit, help slow the aging process. Healthy options include a plant-based diet, eating fruits and vegetables, avoiding excess phosphorus and sodium. Certain foods, like berries, dark chocolate, green tea, and moderate red wine, may have impressive health benefits. The next chapter discusses better insights into healthy eating.

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Chapter 8
Healthy Diet for Kidney Function

Linda W. Moore

The Functions of Food

The main function of the food we eat is to provide fuel, or energy, needed to keep our bodies working. Food provides three types of fuel: carbohydrates, protein, and fat. These are called macronutrients because they are the nutrients we need in the largest amounts. All three of these fuels are required, and generally in the order mentioned, but the amount of each type varies based on requirements of age, activity, or health status.

Almost all foods contain a mixture of macronutrients. For example, meats (such as beef, chicken, fish) have only protein and some fat; basically, no carbohydrates. Fruits have only carbohydrate – essentially, no protein or fat. Some ingredients used in cooking contain only fat (like oils, butter) or only carbohydrates (like sugar added to coffee or cola). It can get pretty complicated trying to keep up with which foods have which macronutrients. Therefore, it is helpful for understanding foods by grouping them into categories, called food groups, because the types of fuel they provide will be similar within the categories. The main food groups are breads and cereals (or "starches"), fruits, vegetables (usually the "nonstarchy" type like green beans, carrots, onions), meats and meat substitutes (animal products like beef, pork, chicken, turkey, fish and non-animal protein sources like beans, peas, lentils), and dairy foods (like milk, cheese, yogurt). Selecting a variety of foods within these groups to include in a weekly meal pattern can assure that the essential nutrients are available. That means taking care not to eat the same foods every day.

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Grouping foods into categories like these also helps identify the foods that contain certain micronutrients (nutrients required in only small amounts, such as vitamins and minerals). Micronutrients are not sources of fuel but they provide powerful support for bodily functions and certain micronutrients will be specifically important when food needs to be considered as medicine.

The second function of food is to provide pleasure. Our taste sensations are satisfied by the foods we choose to eat. People living in countries where food is abundant have opportunities to indulge in foods to satisfy their appetite as well as their hunger.

> "A good meal ought to begin with hunger." –French Proverb

The sensation of pleasure from food is so strong that we develop food memory. We can recall the aroma of food being prepared and relate that aroma, or even just the thought of the food, to times that are important to us, like holidays or family gatherings or other special times. The memory can be positive or negative and it can include taste, smell, and the physical sensation of the food in our mouth. Considering how powerful food memory can be, it is little wonder that we might be drawn to eat too much of something that we especially like.

> "Tell me what you eat and I will tell you what you are." –Jean Anthelme Brillat-Savarin from *The Physiology of Taste*, 1825

The diet we follow, or the foods we eat, becomes a pattern and changes over time usually related to our environment or to a specific design we might elect based on circumstances. For example, an athlete may eat certain types or amounts of foods related to training for competition or to achieve a certain weight. Pregnancy requires adjustments in diet in order to provide for fetal requirements. Children require less foods to accommodate their small bodies than do adults. Younger adults are more active than older adults and require more food to maintain their weight. As we age, we become less active, yet many people do not make the change in their dietary intake as their activity lessens resulting in overweight and obesity. Many children in our society are eating more and exercising less, then reach adulthood already overweight.

Consequences of Excess

Obesity exacerbates many health conditions and is associated with inflammation which leads to several health-related adverse outcomes. High blood pressure, diabetes, cardiovascular disease, cancer, stroke, osteoarthritis, gallbladder disease, and kidney disease can be traced to excess body weight and the path we took to get there. Almost all obesity is the result of overeating and indulging in the abundance of foods at our fingertips. Whereas it is best to prevent obesity by selecting the appropriate types and amounts of foods, making changes in the diet can result in health improvements after disease diagnosis.

Consider the United States Dietary Guidelines for Adults

For adults, the most recent dietary guidelines (US Dietary Guidelines for Americans, 2020–2025 and available at https:www.dietaryguidelines.gov) suggest that the daily needs of most adults are met by eating about 2½ cups of vegetables, 2 cups of fruits, 6 ounces of grains (at least half should be whole grains), 3 cups of dairy, 5½ ounces of protein foods, and 2 tablespoons of oils [1].

Some Suggestions for Successfully Meeting the Guidelines

1. Vegetables and fruits should include green, red, purple, and orange varieties; in other words, lots of color. Experiment with varieties – carrots do not have to be orange, they also come in purple and yellow varieties. The more colorful the vegetable or fruit, the more of a natural chemical called phytochemicals are present. Phytochemicals are known to have anti-inflammatory properties and are desirable inclusions to our daily food intake. About half of the grains we eat should be whole grains which means they should have the seeds intact or have more of the seed components (like the bran) included instead of refined away and discarded. This can mean using more whole grains in cooking such as substituting whole grains like wheat berries, barley, brown rice, and quinoa as side dishes instead of white rice or potatoes. Dairy foods should be low-fat or fat-free and can be replaced with plant-based substitutes. Protein food choices should be lean to avoid saturated fats and should be seafood, chicken or turkey, nuts, seeds, lentils, or beans most of the time; select red meats only occasionally. Oils should be plant-based oils like olive, canola, or corn instead of solid fats.
2. We should all take care not to overeat. Overeating is especially likely at restaurants and social gatherings; plan ahead to decide to take half of what is served at the restaurant meal home after the meal or share it with someone.
3. Recognize that our favorite foods can be included in a healthy diet; they usually just need to be eaten less frequently or in smaller amounts or both. Not everyone likes blueberries or kale or broccoli but we can find great nutrients in other similar foods like grapes, turnip greens, and zucchini or squash.
4. Start training to limit less-desirable nutrients. We all know what the less-desirable nutrients are: added sugars, saturated fats, sodium, and alcohol. If all four of these are a problem in someone's diet, either try to cut back by reducing the usual amount of each of them or determine to tackle one at a time until reaching the overall goal. For example, if sugary beverages are a problem and cutting them out entirely seems too difficult, try reducing by half or try to dilute them with something that would result in an overall reduction. If adding butter to foods is a habit, try including oils like olive, canola, corn, or other plant-based oils instead – even cutting it to parts like 1-part butter to 3-parts plant-based oil will result in better outcomes while retaining some of the flavor.

Sodium should be reduced to 2300 mg/day or less; this is like not using salt at the table and avoiding foods you know have extra salt added (because you can see it or feel it). It also means being judicious when cooking with salt – try instead to increase the amount of other flavorings like added herbs and no-salt spices.

For alcohol, no more than two drinks per day for men and one drink per day for women is the recommendation for people who consume alcohol. Importantly, the amount of alcohol in beverages should be considered: one 12-ounce beer (5% alcohol) is equivalent to 5 ounces wine or 1½ ounces of liquor. It doesn't take much to exceed these limits. Some beers, for example, can have between 14% and 21% alcohol and many beers are available in 16-ounce or 20-ounce cans.

When a Healthy Diet Needs to Be Adjusted: Kidney Disease

A diagnosis of kidney disease includes some dietary precautions. The main precaution is to understand that the kidneys can no longer seamlessly manage everything and we have to provide assistance by making adjustments in dietary intake. As kidney function deteriorates, food becomes more like medicine. It is still important to eat a variety of foods but a more conscious effort to eat the right foods and get the right amount of food is necessary.

We still need the macronutrients, but the proportion will be altered. When kidney function is only slightly reduced, the proportion of macronutrients may not need to be adjusted. However, eating less protein may help to slow the progression of kidney disease [2]. If the proportion of protein is reduced, however, that means that the proportion of carbohydrates and fats (the other sources of fuel or energy) need to be increased. In the healthy diet mentioned above, the main protein sources are from dairy and protein foods. If these food servings are reduced, how do we get the amount of special nutrients provided by these foods that other foods do not contain or have in lesser amounts? In some circumstances, other foods like fruits, vegetables, and grains will be increased to substitute not only for the energy but also micronutrients. It is not a weight-for-weight substitution, however. For example, reducing the amount of meat by 1–2 ounces cannot be overcome by increasing vegetables by 1–2 ounces. Even substituting plant-based alternatives for meats or dairy does not fully provide the nutrients found in meats. For these reasons, it becomes very important for people with kidney disease to work with specialists regarding their diet.

A dietitian will identify the ways in which the diet can be healthfully altered to include as many of the lost nutrients as possible. Usually, the dietitian will discover the patient's food likes and dislikes, what they typically eat, and try to guide a diet that includes as many of these foods as possible. They will then make recommendations for supplementation of nutrients that cannot be obtained in the special diet for kidney disease, if necessary. All dietitians are trained in the nutrient content of foods and how to adjust foods to obtain the desired results. Some dietitians have specialized training in kidney disease and may more readily understand what needs to be adjusted. The dietitian will work closely with the primary care doctor or

nephrologist in determining the best approach for the patient, their level of kidney function, and the kidney replacement therapy selected by the patient and their doctor. As the trajectory of kidney function and treatment changes, the diet will need to be adjusted. Thus, a long-term relationship with a dietitian is a good idea for patients with kidney disease.

For early kidney disease, where the kidney function is above 60 mL/min/1.73 m^2 (a way of assessing the amount of kidney function a person has), the diet is typically a healthy diet and the US dietary guidelines mentioned above are a good guide to follow. Pay particular attention to the sodium guideline as well as the number of servings suggested from each of the food groups. The dietitian may suggest more plant-based foods and fewer animal sources of proteins while keeping in mind the desired overall nutrient intake [3].

As kidney disease progresses, other nutrients may need to be monitored. For example, if the patient's kidney function is low enough that potassium cannot be regulated by the kidney alone, a dietary restriction may need to be initiated. However, potassium restriction is not a blanket component of the diet for kidney disease. It should be reserved only for those whose blood potassium level cannot be balanced by non-dietary sources. If it becomes a requirement, again be aware that the dietitian can help to make the adjustment while maintaining food likes and dislikes for the patient.

Another nutrient that is monitored in kidney disease is phosphorus. Phosphorus is a mineral found naturally in animal foods and some vegetables. In recent times, phosphorus has been added to many foods as a preservative. The problem is that the kidney regulates the balance between calcium and phosphorus in bones. When kidney function declines, the ability to maintain the calcium-to-phosphorus balance is affected. Thus, dietary phosphorus intake becomes very important for bone health and for protection of blood vessels from build-up of calcium deposits. Complicating the monitoring of dietary phosphorus is the lack of reporting of this nutrient in foods by food manufacturers. The food labels do not list the amount of phosphorus so it is difficult to fully know how much phosphorus we eat. Since the phosphate salt (referred to as inorganic phosphates) is added to processed foods, the best thing to do is check food labels for any mention of "-phos" or "phos-"in the ingredients list and just put that food back on the shelf. There are breakfast cereals without added phosphates but checking the label for the ingredients list is the only way, currently, to know. Most prepared breads, especially quickbreads or quickbread mixes (like muffins, biscuits, pancakes) contain baking powder which contains a calcium phosphate salt. Thus, quickbreads should be eaten sparingly, especially when kidney disease is a concern.

Depending on the type of kidney replacement therapy (such as conservative, dialysis, or transplant), the recommended amount of protein will change. The change in recommended protein amounts is due to either the concern for protecting kidney function and reducing uremic toxins (as for conservative therapy and certain levels of kidney function after a kidney transplant) or for replacing amino acids lost in dialysis (as for hemodialysis or peritoneal dialysis).

A good partnership with a dietitian is recommended for patients with kidney disease. The changes in dietary management are complex and need the attention of

someone trained to navigate the gauntlet of nutritional health with patients who have kidney disease.

A few recipes as examples of the adjustments for kidney disease

Quick Ramen-Like Soup with Baby Bok Choy and Mushrooms: Four Servings

Note: ramen noodles are popular but they are also very salty. A healthy alternative is vermicelli cooked longer than regular instructions (8–10 min instead of the usual 5–7 min).

This recipe can be made with regular noodles (not ramen, they are too salty) and chicken or tempeh (for a regular healthy diet) or with low protein, gluten-free pasta and tempeh (for a conservative kidney disease diet; Fig. 8.1).

Standard recipe	Plant-based protein recipe	Low-protein recipe
4 boneless, skinless chicken thighs	12 ounces tempeh	Chicken or tempeh[a]
8 ounces vermicelli	8 ounces vermicelli	8 ounces low-protein pasta
8 ounces Cremini mushrooms, brushed clean and quartered		
2 heads baby bok choy		
4 tablespoons low sodium soy sauce		
¼ cup lemon juice		
½ cup fresh mint, chopped		
2 tsp cooking oil such as canola or olive oil[a]		

[a]If desired amount of protein needs to be further reduced, add 2 teaspoons of cooking oil to maintain energy provided in the recipe

Fig. 8.1 Quick Ramen-Like soup with baby Bok Choy and mushrooms

1. In a large skillet, sauté the chicken in 2 teaspoons of cooking oil; cook for 3–4 min, stirring occasionally
    - For the tempeh recipe, crumble the tempeh into 2 cups of boiling water and let simmer for 3–4 min. Remove from heat and drain the water off. Pat dry. Return to the skillet with 2 tsp cooking oil and brown, about 3 min.
1. While the chicken (or tempeh) is cooking, fill a medium saucepan ¾ full with water and bring to a boil. Add the pasta and cook for 7–10 min. Remove from heat, drain off the water and set aside.
2. Quarter the mushrooms, chop the bok choy and add to the saucepan with 4 cups of water, and the soy sauce. Bring to a boil and let cook about 4 min. Add lemon juice.
3. Chop the mint and set aside.
4. Assemble in single-serve bowls: noodles, the vegetable and broth mixture, then the chicken (or tempeh); sprinkle with 1 tsp flax seeds and 1 tablespoon chopped mint. Serve hot.

Nutrient values per serving:

- Recipe using vermicelli and chicken: Energy: 612 kcal; Carbohydrate: 116 g, Protein: 40 g; Fat: 26 g; Fiber: 9 g; Sodium: 760 mg; Potassium: 912 mg
- Recipe using vermicelli and tempeh: Energy: 708 kcal; Carbohydrate: 124 g; Protein: 35 g; Fat: 32 g; Fiber: 15 g; Sodium: 703 mg; Potassium: 947 mg
- Recipe using low-protein pasta and chicken: Energy: 610 kcal; Carbohydrate: 122 g; Protein: 25 g; Fat: 26 g; Fiber: 12 g; Sodium: 786 mg; Potassium: 745 mg
- Recipe using low-protein pasta and tempeh: Energy: 706 kcal; Carbohydrate: 130 g; Protein 24 g; Fat: 31 g; Fiber: 18 g; Sodium: 729 mg; Potassium: 780 mg

Thin-Crust Pizza

For this recipe, either dairy cheese may be used or non-dairy cheese substitutes. A regular, thin-crust pizza, homemade or store-bought, regular wheat or gluten-free may be used. Many options are available (Fig. 8.2).

Sauce, Enough for Two Pizzas Plus Extra[a]

- 1 28-ounce can diced tomatoes, drained
- 1 tsp olive oil
- 1 tsp Worcestershire sauce
- 2 garlic cloves, minced

Fig. 8.2 Thin Crust Pizza

- ½ tsp salt
- 1 tsp dried oregano
- 2 tsp dried basil

Cheese, Enough for Two Pizzas

Standard recipe	Plant-based protein recipe
½ cup finely grated parmesan cheese	4 ounces provolone-style, dairy-free cheese, grated
8 ounces part-skim mozzarella cheese, grated	8 ounces mozzarella-style, dairy-free cheese, grated

[a]Extra sauce can be frozen for up to 3 weeks

Place a pizza stone or baking sheet on the top rack of the oven that is 4–5 inches from the broiler element. Preheat the oven to 500 °F.

Process the tomatoes, olive oil, vinegar, Worcestershire sauce, garlic, salt, oregano, and basil in a food processor until smooth, about 20 s. Prepare the crust on a pizza peel or the bottom of another baking sheet that will allow sliding onto the hot baking stone or sheet already in the oven. Place generous ½ cup of sauce on the dough, using the back of a spoon to spread thinly across the circle of dough to nearly the edge of the dough. Sprinkle the cheese mixture over the sauce. Carefully slide the pizza onto the baking stone or sheet in the oven and bake for 10–12 min until cheese is bubbly and beginning to brown. Turn the pizza half-way through the

baking time, making sure not to let the crust burn on the edges. Using tongs, slide the baked pizza onto the transfer peel or baking sheet and transfer to a wire rack to cool slightly and keep moisture from softening the crust. Slice as desired and enjoy!

Thinly sliced meats may be added or small vegetable pieces, if desired. A suggestion for meat substitute is to sauté cauliflower bits until lightly browned and season with ¼ tsp poultry seasoning. Sprinkle on pizza about 5 min before removing from oven.

Nutrient values per serving:

- Recipe using standard wheat crust and dairy cheese: Energy: 661 kcal; Carbohydrate: 80 g, Protein: 36 g; Fat: 20 g; Fiber: 3.6 g; Sodium: 1100 mg; Potassium: 364 mg

Recipe using low-protein, gluten-free crust and dairy-free cheese: Energy: 753 kcal; Carbohydrate: 103 g, Protein: 19 g; Fat: 36 g; Fiber: 16 g; Sodium: 1635 mg; Potassium: 138 mg

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Chapter 9
Muscle Breakdown in Kidney Disease: Mechanisms and Management Strategies

William E. Mitch and Stephen Z. Fadem

Introduction

The muscles are marvelous organs that enable us to bend, stand, run, and lift heavy weights. They are able to "learn" repetitive tasks like dancing, and respond well to conditioning and physical therapy. How is this possible?

Muscles contain fibers – known as muscle fibers or myofibers. They respond to stimuli from the environment, whether it involves training for gymnastics or ballet, physical training, aerobic or resistance exercises. They are perpetually in a state of growth and repair. Muscles are composed of proteins, and turnover of protein is necessary to create new muscle cells or to replace damaged myofibers. The problem in kidney disease is that abnormalities in kidney function stimulate muscle cell breakdown.

The muscle production and breakdown should always remain in balance; otherwise, muscle wasting may occur. In a 70-kg adult, 280 g of protein is synthesized or degraded each day. The standard daily diet for normal adults contains 1 g of protein for each kilogram (1 g/kg/day). These proteins are composed of amino acids containing 16% nitrogen. Thus, the diet contains 11.2 g of nitrogen each day, and we can use nitrogen as a marker of muscle turnover. The amino acids that are consumed enter a free amino acid pool, in which they are either used to make new proteins, or are metabolically destroyed and eliminated by the kidney. Proteins that are broken down into amino acids also contribute to the free amino acid pool (See Fig. 9.1).

When muscles are being built, the process is known as anabolism; when they are being broken down, it is determined to be catabolism. Even a small decrease in the rate of muscle protein synthesis or an increase in muscle protein breakdown caused

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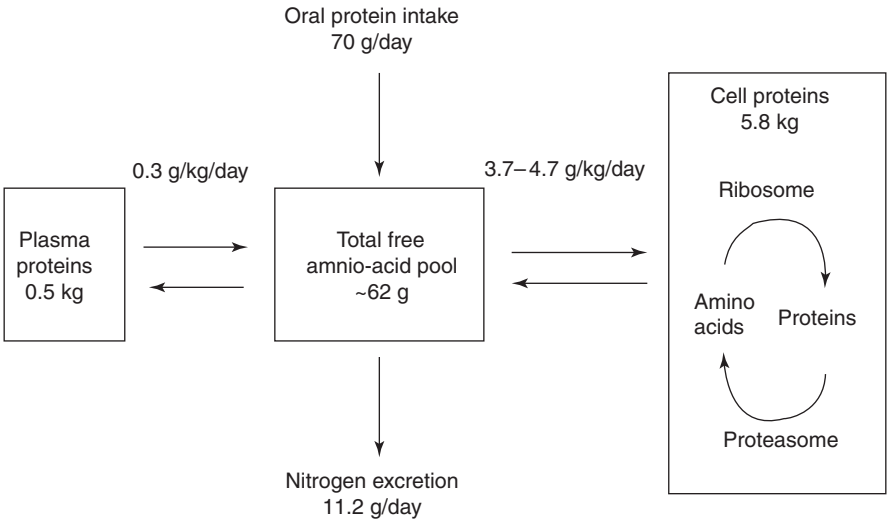

Fig. 9.1 Muscle turnover in normal man. (From Mitch et al. Used with permission of the author [1])

by kidney disease results in a huge loss in muscle mass. We are all familiar with the catabolic process of muscle breakdown in the aged and frail individual or a person with cachexia, a condition which causes extreme weight loss and muscle wasting. Muscle protein wasting also occurs with chronic kidney disease. The kidneys are key in eliminating nitrogen-containing wastes. They also are responsible for controlling acidosis, an important mechanism that stimulates protein degradation.

Mechanisms Causing Muscle Protein Building and Degradation

The cells in organs contain tiny "organelles" that either manufacture or degrade proteins. The ribosome works like an assembly line controlled by genes and holds messenger ribonucleic acid (mRNA) molecules that are coded to send out another molecule, transfer RNA to find a selective amino acid. mRNA acts like a computer program for the manufacturing of protein and codes for the amino acids that are chained into proteins. An example is the COVID-19 vaccine. It also provides mRNA that works on the ribosome to manufacture the SARS-CoV-2 spike protein. Immune cells stimulated by the spike protein are then able to form an antibody to that specific protein. Muscle mRNA molecules create the proteins that form new muscles. The proteins are in a constant state of turnover, being formed into muscle. They are broken down in a predictable fashion. How is this possible?

Cells that are broken down must pass through various metabolic pathways. Research beginning in 1949 demonstrated that our cells contain lysosomes, organelles that digest or break down a variety of proteins and other biomolecules, many of which are worn-out cell parts, including mitochondria. This process is known as autophagy, which means "eating one's self." The lysosomes also engulf and can break down viruses, parasites, and bacteria. They play a key role in several body functions. It was thought at one time that they were essential to muscle breakdown, but Nobel Prize winning science has proven that muscles are broken down by different organelles, the proteasomes. The proteasomes contain enzymes called proteases. They function to break down muscle proteins that have been tagged for destruction. The tag is identified as ubiquitin. Several ubiquitin molecules chain together to tag a muscle. Once tagged, the muscle protein is then plunged into the large proteasome organelle where it is dgested back into amino acids that are then free to make other proteins or be eliminated (See Figs. 9.1 and 9.2) [1].

In normal adults there is a precise balance between protein synthesis and protein degradation. This is necessary because there is a huge amount of protein being turned over daily. The ubiquitin-proteasome system precisely identifies proteins that are being marked for degradation and also controls the levels of protein degradation. Muscle turnover is necessary for survival, but some conditions that turn the ubiquitin system on can lead to muscle loss. These include antigravity (space travel), inactivity or lack of muscle use, viruses like HIV, inflammation, severe infections, starvation, cancer, metabolic acidosis, and CKD [2].

When muscle protein breakdown is profound, it is known as sarcopenia. Sarcopenia occurs with the aging process but is further stimulated by diabetes and kidney disease. Decreased muscle mass, strength, and physical endurance causes a

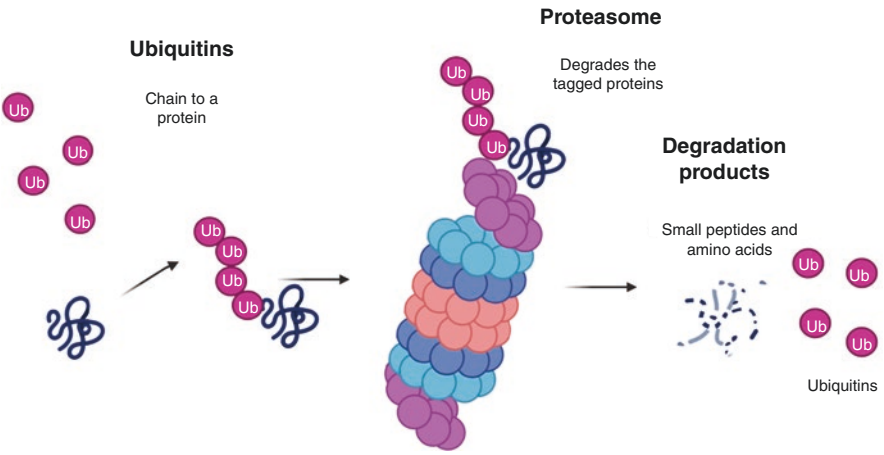

Fig. 9.2 Ubiquitin tags proteins that are marked for degradation by the proteasome. They are then degraded to small protein fragments (peptides) or to amino acids. The ubiquitins return to tag other molecules. (Modified from Mitch et al. [1])

loss of mobility, flexibility, and balance. As muscles weaken, we are at a greater risk for falling and sustaining a fracture.

Regarding kidney disease, the control of the muscle protein breakdown processes that were discussed previously depend upon the key mechanisms that are associated with CKD: poor appetite, vitamin D deficiency, angiotensin II, inflammation, insulin resistance, and metabolic acidosis. These mechanisms turn on metabolic pathways that activate the ubiquitin-proteasome system to promote muscle protein breakdown [3].

There is a scientific basis for administering essential amino acids in order to control growth pathways [4]. Clinical trials indicate that essential amino acids or ketoacid supplements, as well as exercise training, will improve muscle metabolism and slow the progression of kidney disease [5, 6].

At present, a main therapy for the routine treatment of patients with kidney disease is the control of metabolic acidosis. Since kidney disease is associated with metabolic acidosis, and given that acidosis drives muscle protein breakdown, we recommend that metabolic acidosis be controlled by administering sodium bicarbonate, restricting dietary protein, or increasing dietary alkali through foods like fruits and vegetables. As the science advances, other therapies will become available. Investigational drugs must go through a series of clinical trials, and first be approved by the US Food and Drug Administration before they can be accepted as therapy. The next chapter highlightsexercises that might help to preserve muscle mass.

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Chapter 10
Exercises for People with Chronic Kidney Disease and Seniors

Michelle (Misha) L Nguyen and Stephen Z. Fadem

The purpose of these exercises is not to make you Mr. Olympia or the next Simone Biles. These exercises are simple and require only a stationary surface and a resistance band. They may not help you become an athletic superstar, but they are very gratifying.

Resistance bands are inexpensive and can be purchased online or at the store. They also take up less space than weights and machines.

Many training videos and programs use young athletes in top physical shape. But to keep you from being intimidated, these exercises are all being performed by a73-year-old doctor (See Fig. 10.1).

What Are the Benefits of Exercise?

In addition to being associated with living longer, exercise can help with managing weight, preventing chronic diseases, and increasing energy and endurance. It can help reduce bone loss and risk of heart diseases, as well as improve joint pain and stiffness. It may improve memory, lower blood pressure, relieve stress, reduce feelings of anxiety and depression, help with sleeping, and improve overall mood. Regular aerobic exercise may reduce the risk of many conditions, including heart disease, obesity, high blood pressure, type 2 diabetes, stroke, and certain types of

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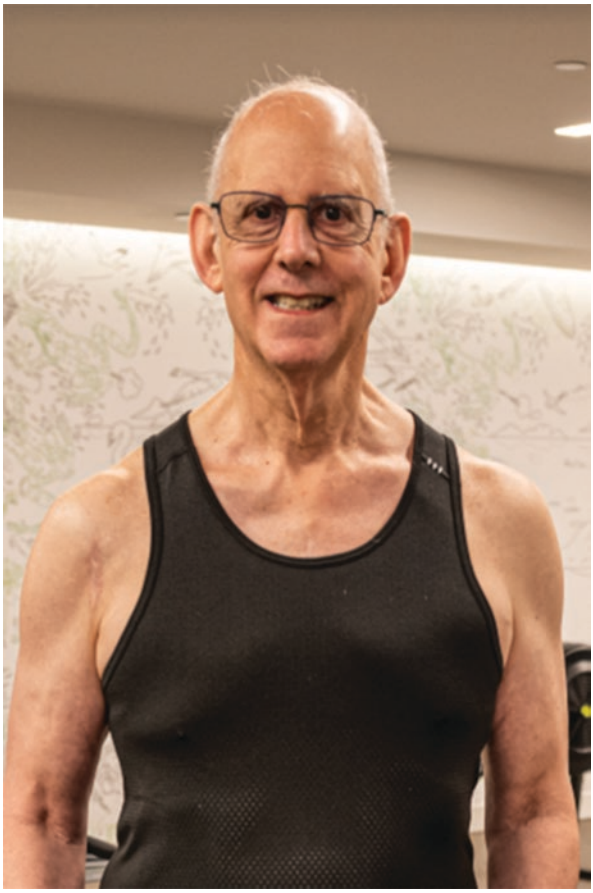

Fig. 10.1 Photograph by MishaFit

cancer. Exercise also helps improve your appearance and helps you remain motivated to stay on a diet.

"If you ain't workin' out, it ain't workin' out." – MishaFit

CKD Patients and Exercise

Resistance and aerobic exercise programs should be designed at relatively low intensity and progressed as slowly as tolerated to avoid injury. Muscle loss due to aging (known as sarcopenia) affects 10% of adults over 50 years old. The prevalence of CKD-related sarcopenia is higher than that of age-related sarcopenia, as was previously described. Resistance exercise, along with amino acid intake, improves muscle mass and function and is considered a meaningful exercise prescription for sarcopenia.

In a study looking at leisure-time physical activity and mortality in patients with chronic kidney disease, data was collected for 4,604 participants with CKD from 1999 through 2012 participating in the National Health and Nutrition Examination Survey (NHANES). Patients were followed for a median of 114 months. Of the 1,440 deaths, there was a 22% higher risk among those who were least active (under 20 min per week). The more active the participant, the lower the risk of death; there was a 43% lower risk when active 1.5–2 h a day [1].

About Exercise

Muscles function to produce force and motion. Skeletal muscles are specialized tissue attached to bones that allows movement. Muscles that are weak and out of condition are prone to injury-related sprains (injury to band of tissues that connect two bones together) or strains (injury to a muscle or to the band of tissues that connect muscle to bone), cramps, or tendonitis. This can lead to pain, spasms, and loss of control.

Stretching is especially important because it helps to keep the muscles flexible, strong, and healthy. Without stretching, muscles shorten and become tight. Flexibility is needed to maintain a range of motion in the joints. A personal trainer possesses the knowledge, skills, and abilities to design a safe and effective fitness program to help you with proper form and make your sessions more enjoyable. A personal trainer can help design the perfect routine to help you achieve your goals, as well as demonstrate the correct form for each exercise. Yoga, Pilates, and Tai Chi are great low-impact activities that help improve balance and core strength.

Strength exercise, or resistance training, increases lean muscle mass and helps make muscles stronger. Balance exercises help prevent falls, reduce the risk of lower-extremity injuries, and stabilize your body's position. Flexibility exercises help stretch muscles, improve physical performance, and allow one to withstand more physical stress.

A Few Tips Before You Begin

- Before beginning an exercise program, you should first consult your healthcare provider and get a physical examination to make sure it is safe to begin.
- These are beginning exercises but will help with strength, balance, posture, and flexibility.
- Don't overdo it. Too much exercise can lead to injuries, exhaustion, and depression.
- Signs of over-training include persistent injuries or muscle pain, irritability and agitation, low energy, higher-than-normal resting heart rate, loss of motivation, and decline in performance.

- Physical therapists, in collaboration with professional trainers, may help to strengthen weak muscles and increase mobility.
- Doctors recommend 150 min of physical activity per week.

Walking

- Just 30 min of walking every day has health benefits that include increased cardiovascular fitness, stronger bones, improved balance, reduced risk of heart disease and stroke. It also boosts energy, reduces excess body fat, boosts immune function, and eases joint pain.
- Walking is a great way to dynamically warm up the body. This may include arm swings, high knees, or butt kicks.
- 5 min of walking or jogging is sufficient enough for most people to avoid injury.
- Stand tall with head up and chin parallel to the ground, keep shoulders down and back, ears aligned above your shoulders, engage your core, swing your arms, step from heel to toe.
- Look for shoes with midsole cushioning made of gel, foam, or air to reduce impact and help with shock absorption.
- Stay hydrated.
- Be cautious of uneven surfaces.

The National Institutes of Health (NIH) recommends that seniors engage in 150 min of moderate aerobic activity such as walking, combined with strength conditioning, balance, and flexibility exercises (See Fig. 10.2).

Core Exercises

The core is the center of the body, consisting of the abdominal muscles, hips, spine, and back muscles. A strong core helps stabilize the entire body and improve one's balance and posture. The core allows the body to rotate and provides momentum to move in any direction. It is important especially for seniors to have a strong core to prevent fall injuries, as well as decrease back pain.

1. *Planks (*Fig. 10.3*)*

    - Start face down in a plank position with forearms and toes touching the floor.
    - Beginners can start on knees.
    - Do not hold your body too low or too high. Aim for a nearly horizontal position.
    - Push your shoulder blades towards the ground.
    - Squeeze glutes tight while tilting pelvis backwards to engage the core.
    - Strengthens core muscles, including abdominal muscles and back muscles.

Fig. 10.2 Walking. (Photograph by MishaFit)

Fig. 10.3 Planks. (Photograph by MishaFit)

- Hold the plank position for 15 s and gradually work up to one minute.
- For plank variation, try rocking planks. While maintaining plank position, engage your core and squeeze the glutes as you rock your body forward until your shoulders move past your hands. Then allow the body to rock back until your heels move past your toes. Repeat back and forth rocking motion.

2. *Scissors* (Fig. 10.4)

- Lie on your back with your hands either at your side or underneath your glutes for added back support.
- Engage your core and press your lower back against the mat.
- With your legs extended straight out, either twist your legs out and above each other or straight up and down.
- Works core muscles, glutes, quadriceps, and adductors.
- Perform 3–4 sets of 45 s with a 15 s rest between sets.

3. *Reverse Crunch* (Fig. 10.5)

- Lie down with knees bent and arms to the side or behind your head for support.
- Exhale as you bring your knees towards your chest and raise your hips off the floor.
- Hold in a reverse crunched position then inhale as you return to starting position. Repeat.
- Start with 3 sets of 8–10 reps. Increase the reps as desired.

Fig. 10.4 Scissors. (Photograph by MishaFit)

Fig. 10.5 Reverse crunch. (Photograph by MishaFit)

Fig. 10.6 Band Pull-Aparts. (Photograph by MishaFit)

Upper Body Exercises

Upper body strength is important for all ages, but particularly for CKD patients and seniors in order to help themselves maintain their independence longer.

1. *Band Pull-Aparts* (Fig. 10.6)

- Grip the resistance band, either with one or two bands, depending on its thickness and your ability to stretch it out.
- Raise the arms to shoulder height, holding bands shoulder width apart.
- Begin with palms down and slowly stretch the band outwards until arms are open wide as you exhale, squeezing and pressing the shoulder blades together. Pause for a few counts.
- Count to 4 as you slowly inhale and bring the band back together.
- Activates back muscles and shoulders.
- Perform 10 reps with palms facing down then 10 reps with palms facing up.

2. *Inclined Push-ups* (Fig. 10.7)

- Place both hands on either side of a box or bench with fingers facing forward.
- Step back into a plank position making sure your body is in a straight line (head is aligned with spine and hips are not sagging).
- Bend your arms slowly as you inhale and lower your chest towards the bench.
- Then engage your core as you exhale and straighten your arms to bring your body back into a straight line.
- Works lower chest, back, shoulders, and triceps.
- Perform three sets of 10–15 reps.

3. *Biceps Curl* (Fig. 10.8)

- Stand with both feet on the resistance band.
- Grab handles with both hands, palms facing forward.
- Slowly exhale as you curl hand towards the shoulders, squeezing biceps and engaging your core. Pause for a few counts.

Fig. 10.7 Inclined Push-ups. (Photograph by MishaFit)

Fig. 10.8 Biceps Curl. (Photograph by MishaFit)

- Inhale as you slowly release arms back to starting position. Repeat.
- Mainly targets the biceps brachii, brachialis, and brachioradialis muscles.
- Perform three sets of 8–15 reps.

4. *Overhead Band Triceps Extensions* (Fig. 10.9)

- Grab one end of a resistance band in each hand behind your head.
- Step with one foot slightly forward.
- Keep your elbows up close to your ears.
- Engage your core.
- Exhale as you extend your arms and squeeze triceps, keeping elbows up.
- Hold for a few counts. Then inhale as you return to starting position.
- Works the long head, lateral head, and medial head of the triceps.
- Perform three sets of 10–15 reps.

Lower Body Exercises

Lower body strength is a key component in helping to preserve independence and overall health in seniors. A strong lower body helps seniors to achieve better balance and prevent injury.

Key benefits to lower body strength training:

- Improves balance
- Lowers risk of falling

Fig. 10.9 Overhead band Triceps Extensions. (Photograph by MishaFit)

- Increases bone strength
- Increases confidence
- Decreases knee injuries
- Boosts stamina
- Avoids muscle imbalances

1. *Sit to Stand* (Fig. 10.10)

   - Sit at the edge of chair and place both feet on the floor shoulder width apart.
   - Stand up slowly as you exhale while engaging your core, ensuring that your knees never cross in front of your toes.
   - Once standing, sit back down slowly as you inhale, keeping knees behind toes.
   - Helps strengthen legs, core, and back.
   - Perform three sets of 10–12 reps.

2. *Stationary Supported Lunge* (Fig. 10.11)

   - Stand tall with feet shoulder width apart.
   - Take a large step backward with one foot. This is your starting position.
   - Inhale and lower the back knee to a 90-degree angle so that both knees are bent. Pause for a few counts.
   - Exhale and slowly press up to starting position, keeping the front knee behind toes and step with feet together. Repeat.
   - Targets the glutes, quadriceps, and hamstrings.
   - Perform three sets of 10–12 reps on each leg.

Fig. 10.10 Sit to Stand. (Photograph by MishaFit)

Fig. 10.11 Stationary Supported Lunge. (Photograph by MishaFit)

3. *Glute Bridges (*Fig. 10.12*)*

- Lie face up on a mat with knees bent and hands by your side, palms facing down, feet flat on the floor.
- Exhale as you lift hips off the ground until your knees, hips, and shoulders form a straight line.

Fig. 10.12 Glute Bridges. (Photograph by MishaFit)

- Hold in a bridge position for a few counts while squeezing your glutes and engaging your core.
- Inhale as you return to starting position and repeat.
- Glute bridge is a great exercise that can be done every day.
- Muscles worked include the glutes, hamstrings, lower back, and abs.
- Aim for two sets of 10 bridges at least 2–3 times a week.

Stretching

Stretching is important for seniors as it allows greater movement and mobility. In addition to reducing the risk of injury, stretching also relieves muscle tension and soreness. It also helps to improve balance and coordination.

1. *Sciatica Stretch* (Fig. 10.13)
   - Lie on your back with both knees bent and feet on the floor.
   - Lift your left leg and cross it over just above the right knee.
   - Grab your left ankle with your right hand.
   - Now reach down your left side and grab your right ankle with your left hand.
   - Pull both ankles.
   - Can be performed at least once per day up to three times per day.
2. *Quad Stretch* (Fig. 10.14)
   - Stand up tall holding a sturdy surface for balance.
   - Grab one foot and pull towards your rear end, keeping your thighs and knees together.

Fig. 10.13 Sciatica Stretch. (Photograph by MishaFit)

Fig. 10.14 Quad Stretch. (Photograph by MishaFit)

Fig. 10.15 Sitting Wide-leg Adductor Stretch. (Photograph by MishaFit)

- Alternatively, this same stretch can be performed lying down on your side, hips lined up so that one is directly above the other, pulling the leg that is on top.
- Try to hold the stretch for 20 s before switching legs.

3. *Sitting Wide-leg Adductor Stretch*(Fig. 10.15)

- Sit on the floor with legs apart in front of you.
- Place your feet against the wall.
- Keep legs straight but slightly bent.
- Reach for the wall.
- Keep your body straight and tall.
- Do not over-stretch for risk of muscle, tendon, or ligament damage.
- Hold stretch position for at least 15 s.
- Repeat as desired.
- Great way to end a session!

Summary

A simple exercise routine helps kidney patients and seniors stay fit. Exercising should be fun and enjoyable. To make a fitness program worthwhile, it must be routine. Remember to always check with your doctor before beginning an exercise program, and stop exercising if you feel sick, weak, or short of breath. There is never a need to overdo these exercises. Exercise is known as the "fountain of youth." It not only improves your overall health, posture, and balance, but it also helps you sleep better, fight diseases better, look and feel better, as well as stay younger, healthier, and happier. So definitely keep on exercising; but if you have not started, remember that it is never too late. First check with your doctor. Then start and stick with your exercise program today!

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Chapter 11
Falls in CKD Patients and Seniors: Causes and Prevention

Stephen Z. Fadem

Introduction

The elderly and those with kidney impairment share many features in common. Falls are quite common in both populations. As we age, falls will be expected to happen to one-third of us; it is the fifth leading cause of death. Not only are kidney patients more likely to fall, but more likely to sustain a fractured hip, a common result of a fall [1]. Besides fractures, falls can cause head injuries, particularly a hemorrhage in either the brain or the area that surrounds it. This can compress the brain; if surgery is not quickly performed, it can result in death.

The most important ways to prevent falls include exercise programs, physical therapy programs, careful management of medications, and strategies to control bone strength.

Why People Fall

Falls in the elderly, the frail, and in those with kidney disease occur for many reasons, among them vision disturbances, gait and balance disorders, dementia, nerve disorders, positional changes in blood pressure (orthostatic hypotension), muscle weakness, and anemia. They can also occur as a side effect of medications that lower the blood pressure too rapidly. Moreover, falls can cause over-sedation, or cause the blood sugar to drop dangerously low. Medications that have a sedating effect can also result in a fall.

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We take for granted that blood vessel tone adjusts when changing from a sitting to a standing position. In persons with advanced diabetes, the blood pressure may fall too low when standing. The reason for these neurological disorders is that the autonomic nervous system automatically controls changes in our blood pressure when we stand. If the nerves are damaged, our blood pressure can drop. This is known as orthostatic hypotension and can lead to an abrupt loss of balance and a fall.

Many of the consequences of chronic diseases result in falls. The kidney patient with diabetes may also have peripheral neuropathy – (damage to nerves outside the brain) which leads to numbness, particularly in the lower extremities. Falls may occur at night when persons with bladder disorders trip while rushing to the bathroom. Heart rhythm disturbances are more common in kidney disease patients, as well as in the elderly. These can result in an abrupt loss of consciousness–fainting or syncope. A lack of activity will cause anemia, muscle, and bone weakness. Patients who have had a stroke, or who have difficulty with their gait for other reasons, are particularly prone to falling.

Vertigo is a spinning sensation caused when the inner ear does not function as it should. It has properties similar to a gyroscope that help us maintain a sense of balance. There are some benign causes of vertigo that can be easily evaluated and managed by a specialist. Sometimes, special exercises are necessary to help retrain the muscles to help us control our balance.

Sarcopenia, or muscle wasting, also leads to falling. Inactivity is a serious cause of muscle wasting even among those in excellent health. The classic example of sarcopenia is the muscle wasting in astronauts who travel out in space in a microgravity environment losing up to 20% of muscle mass on spaceflights lasting 5–11 days [2]. Not only muscle proteins, but bone cells, immune cells, and red blood cells are inhibited by microgravity as well as by inactivity. Meanwhile, cells that store fat and cells that break down bone are stimulated by microgravity [3].

In elderly individuals who do not vigorously exercise, we can expect muscle loss to occur at 1% per year. This is worse in the patient with kidney disease because of metabolic acidosis, inflammation, angiotensin II, and inactivity [4]. As CKD, diabetic, and elderly patients lose muscle mass, they have reduced motor function and may require physical therapy to help them regain stability and balance by aligning sensory information and movement to other muscles and nerves that control posture [5].

Who Is at Risk?

The Centers for Disease Control and Prevention (CDC) has created STEADI (Stopping Elderly Accidents, Deaths, and Injuries), an initiative to help reduce the risk of falling. STEADI is available for download from the CDC website, https://www.cdc.gov/steadi/index.html. The toolkit and algorithm help healthcare providers reduce falls through screening measures, an assessment algorithm, and an intervention program.

The patient who feels unsteady when standing or walking, worries about falling, or has fallen in the past year is at risk for another fall. Aside from history, one should

inquire about prescription drugs–opioids, psychoactive medications, sedatives, or antihypertensive medications. Visual acuity and both lying and standing blood pressure) should also be assessed.

The patient should be asked about potential home hazards such as clutter, throw rugs, or slippery bathroom and bathtub floors.

One can assess gait with three tests, the timed up and go (TUG) test (https://www.cdc.gov/steadi/pdf/TUG_test-print.pdf), the 30-second chair stand test (https://www.cdc.gov/steadi/pdf/STEADI-Assessment-30Sec-508.pdf), or the 4-stage balance test (https://www.cdc.gov/steadi/pdf/4-Stage_Balance_Test-print.pdf). In the TUG test, the patient stands up from a chair, walks to a line 10 feet away, and then back. In the 30-second chair stand test, also referred to as the sit-to-stand test, the patient must stand up from a chair and sit back down for as many times as possible in 30 seconds. The 4-stage balance test helps indicate if a patient is at risk for falling by testing the patient's ability to perform four progressively challenging positions for 10 s each: (1) Parallel stance (with feet side-by-side); (2) Semi-tandem stance (with the instep of one foot touching the big toe of the other); (3) Tandem or Heel-Toe stance (with one foot in front of the other, heel touching toe); (4) One-legged stance (standing on one foot).

Strategies to Prevent Falls

The prevention of falls must therefore start early enough in the course of kidney disease and at an early age. Carefully review each medication with your provider. Have your blood pressure assessed. See your eye doctor, and if necessary your foot doctor. As we age or as kidney disease progresses, we should consider "fall proofing" our homes. Take a look around your house for clutter, loose cords, uneven steps, slippery floors, a lack of proper lighting at the bedside or on stairs, loose throw rugs, and other hazards. Often patients with chronic illnesses such as kidney disease, like seniors, need a strong family-support or friend-support system.

Increasing activity is the best "medicine" to prevent falls, especially with CKD. Taking frequent walks and maintaining vitamin D levels keep bones strong and resistance exercises prevent muscle deterioration. That is why this book encourages you to actively exercise. It shows exercises that are easy to do and that can become part of one's routine. Not only do we all want to strengthen our core and other muscles, but we also want to preserve our sense of balance. Tai chi or Silver Sneakers programs are excellent resources. Community exercise programs are also a good place to start. If possible, seek out a well-supervised exercise area. It helps in the beginning to have a certified personal trainer to guide exercise programing. It is important that simple exercises designed to improve performance, strength, and balance do not result in injury. Begin slow, and work up your exercise capacity. Standing on one leg with and without dumbbells, or performing squats on a Bosu Balance trainer helps build balance (See Figs. 11.1 and 11.2). Achievement with exercise comes with time. Be patient. The following are three of many examples.

Fig. 11.1 Standing on one leg. (Photograph by Michelle L. Nguyen)

Fig. 11.2 Single leg balance dumbbell shoulder press. (Photograph by Michelle L. Nguyen)

Standing on One Leg

- Stand upright with feet together. Beginners should stand close to a wall for balance and support.
- Have a helper nearby if unsteady.
- Life one foot off the ground and try to improve time standing on one foot.
- If able to stand for greater than 60 seconds, stand on a folded mat.

Single Leg Balance Dumbbell Shoulder Press

- Have a helper nearby.
- Maintain and hold your balance while standing on one leg.
- Press the dumbbell above the shoulders in a controlled, slow motion.

BOSU Squats

Photo by Misha

- Make sure you are capable of working on an unstable surface.
- Ideally have a helper standing nearby.
- Beginners can stand on the cushion side of a BOSU balance trainer, with the flat side on the floor.

- The more advanced can try to balance on the flat side, with the cushion side on the floor.
- Bend your knees, pushing your hips back as you squat.
- Make sure to tighten your core and keep your back flat.
- This exercise helps with balance.

CKD patients should undergo screening to determine if they are at risk for a fall. The summary below is modified for the CKD population from STEADI:

1. Address orthostatic hypotension. It is particularly common in diabetics. Patients with orthostatic hypotension that declines 20 mm Hg between lying and standing are at a greater risk of falling within 1 year [6].
2. Adverse health is associated with the number of prescribed drugs. Although many medications are necessary in ill patients, a drug assessment for potential and future benefit vs. risks of harm should be done periodically by one's provider [7]. Medications used for sedation and sleep are associated with falls [8].
3. A systemic review of the literature demonstrated that in healthy, elderly individuals, balance measures improve between 16% and 42% compared to baseline. The activities investigated were resistance and aerobic exercise, balance training, T-bow and wobble board training, aerobic step and stability ball training, adapted physical activity, and Wii Fit training [9]. Tai chi balance training was shown in a clinical trial to be more effective than conventional exercise approaches to reduce the fall incidence [10].
4. It has been demonstrated that many of the accidental injuries that occur in the elderly are preventable with education and environmental intervention [11]. The CDC's STEADI website has an excellent brochure on home fall prevention. (https://www.cdc.gov/steadi/pdf/check_for_safety_brochure-a.pdf).
5. Poor vision, peripheral neuropathy, orthopedic and foot-related disorders are common in patients with CKD, particularly when associated with diabetes. Improved vision, use of proper footwear, and foot and ankle exercises reduce the rate of falls [12, 13].
6. Patients with chronic conditions have a higher fall risk. Cardiovascular disorders such as heart failure and rhythm disturbances, and neurologic disorders such as a stroke or dementia, are associated with multiple features that increase decreased ambulation, poor balance, and falls. In addition, worsening CKD is associated with a higher incidence of hip fractures, also related to falls. Kidney disease is associated with bone loss secondary to excess production of parathyroid hormone (PTH) by tiny glands in the neck. PTH stimulates cells that reabsorb bone. Suppression of PTH is possible with medications, including vitamin D. CKD also causes metabolic acidosis. Metabolic acidosis drives muscle protein breakdown. Control of metabolic acidosis through foods with a high alkali content such as fruits and vegetables, or the administration of sodium bicarbonate tablets preserve muscle mass [14]. Essential amino acids and resistance exercises help promote protein synthesis in CKD, and may improve muscle mass [15, 16].

7. Vitamin D deficiency has been demonstrated to be a risk factor for falls. Clinical trials demonstrate that vitamin D therapy along with calcium, particularly in elderly women, reduced the risk of falls [17]. Vitamin D deficiency is common in CKD and affects not only bone function, but the immune, cardiovascular, and neurologic systems. Vitamin D replacement therapy is recommended in CKD [18].
8. It is critical to understand how to prevent falls. It is recommended to undergo an assessment by your physician to determine your risks of falling, and discuss interventions to prevent future falls during regular physician visits [19, 20].

Here Are a Few Tips to Help Prevent Falls

1. Be careful at night – leave a nightlight on.
2. Use a walker, cane, or hiking sticks when outside on rough terrain. Watch out for small steps and uneven surfaces.
3. Review your medications with your doctor or nurse. Overmedicating can cause dizziness, weakness, or loss of balance.
4. Exercise and take vitamin D supplements to strengthen your muscles and bones.
5. Balance exercises are helpful.
6. Incorporate core exercises and stretching into your routine (See Chap. 10).
7. Consider Tai Chi.
8. Have your eyes checked. Cataracts, glaucoma, and age-related macular degeneration are common in the elderly. Many kidney patients with diabetes have severe eye disease.
9. Wear a hat with a hard rim when walking.
10. Carpeting may make you less steady, but you will hurt yourself more seriously falling on tile or onto a hard floor. Choose carpet flooring because of its slip-resistant surface; the cushion can prevent injuries during a fall.
11. Have foot checks to prevent ulcers or blisters. These may not heal, can become infected, and can lead to complications in patients with diabetes or peripheral vascular disease.
12. Add grab bars to the shower and bath (See Fig. 11.3).
13. Use the handrails on the staircases (See Fig. 11.4).
14. Walking down the stairs as part of an exercise routine will help keep bones strong. Walking up the stairs will build up the lower extremity and gluteus muscles.
15. Choose activities that are age-appropriate. Use your head – don't hit your head.
16. The CDC has a well-written section on falls. (http://cdc.gov/steadi) that you might wish to review.

Fig. 11.3 Add grab bars to your shower

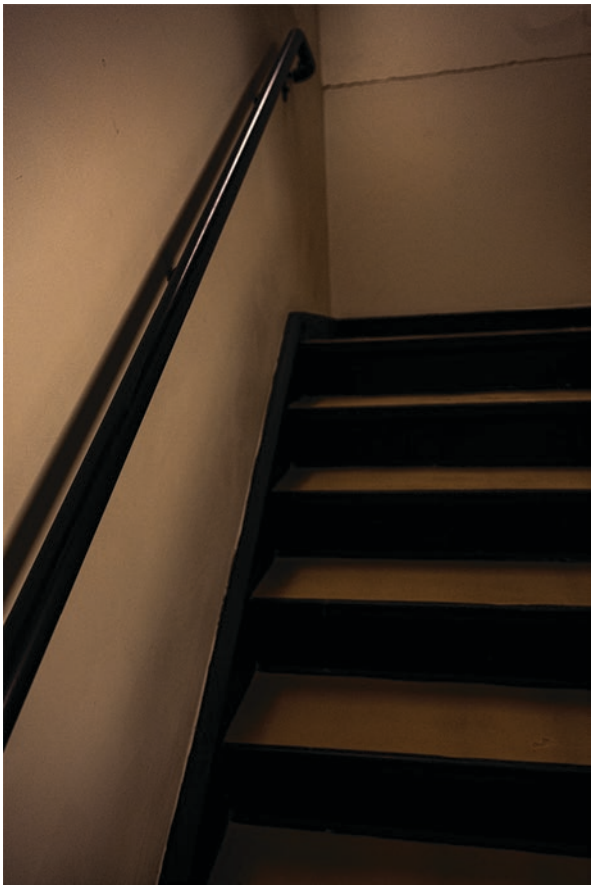

Fig. 11.4 Always use the handrails. Walking down the stairs may help build bone. Walking up the stairs will build up your thigh and gluteus muscles

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Chapter 12
Medications to Avoid with Chronic Kidney Disease

Stephen Z. Fadem

Introduction

Some drugs are eliminated through the kidneys. When the kidneys are damaged, these medications can accumulate in the body and cause damage to body tissues. Some drugs can also damage the kidneys directly when renal function is impaired. In persons where drug metabolism is impaired, medications may have an exaggerated effect; i.e., in those with kidney disease, other chronic illnesses, or the elderly.

Drugs Where the Dose Should Be Reduced or Avoided

It is recommended that if you have CKD, discuss your kidney function levels with your doctors and make them aware of your kidney disease. This may impact the dosage or what drug is prescribed. Next, one should know whether there are risk factors involved with decreased kidney function when taking certain medication. Some medications that are safe for people with normal kidney function can be toxic for those with kidney disease. Sometimes, when drugs of potential nephrotoxicity are required, it is prudent to minimize the risk of toxicity by either reducing the dose or seeking an equivalent alternative. For instance, one might consider using a locally applied topical ointment to attempt achieving the same objective as taking an oral medication. Based on whether you have kidney disease, your doctors should prescribe medications that are eliminated by the kidney differently, modifying either

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the dose, the frequency, or both. You should also be aware that many medications that are readily available over the counter might also cause kidney damage or harmful side effects.

Metformin is a relatively safe drug used in the treatment of diabetes, but in patients with impaired kidney function it can block the cell's ability to make glucose. This is referred to as gluconeogenesis. Without active "fuel" to feed into the mitochondria, the cell reverts to an anaerobic metabolism that results in the accumulation of lactic acid. This is rare when metformin is used as directed [1].

Some drugs are used as diagnostic tools. Gadolinium is used to enhance images in magnetic resonance imaging (MRI) studies. Its metabolism is delayed in CKD, and it can accumulate, leading to a dangerous condition referred to as nephrogenic systemic fibrosis (NSF). NSF is characterized by fibroblast activity and collagen deposition in the skin, and has been a well-known consequence of gadolinium use in CKD patients. One must use an abundance of caution when considering gadolinium-enhanced MRIs in patients with kidney function abnormalities. Newer formulations of gadolinium claim to have greater safety margins, but current guidelines stress avoiding gadolinium with an eGFR <30 cc/min [2].

The statin drugs are commonly used to treat hyperlipidemia, a condition where too much fat accumulates in the blood. On rare occasions, their use can cause muscle cramps, and even more rarely can lead to muscle cell destruction. This is called rhabdomyolysis. A more common cause of rhabdomyolysis is the use of illicit drugs such as methamphetamine or heroin. The statin drugs are metabolized by the liver, and not by the kidney. However, in persons with impaired kidney function, the consequences of muscle breakdown can lead to the impaired excretion of metabolites that can be damaging [3].

Secondary benefits of drug therapy should also be considered. The beta blocker class of hypertension agents are a modes of blood pressure (BP) therapy, as are diuretics and calcium-channel blockers, but coronary artery disease is higher in those over 65 years old using atenolol. Stroke rates are higher in users of beta-blockers when compared with those using calcium-channel blockers [4].

Drugs that Are Toxic to the Kidneys

Medication-induced kidney injury is a common problem in hospitals, but can also happen in the community. Whether a particular drug is toxic to an individual varies on patient characteristics such as coexisting conditions or genetics, and exactly how the drug interacts inside the kidney. Drug-drug interactions are a cause of adverse risk if you have kidney disease. This risk increases as you age.

Medications associated with renal toxicity include analgesics known as non-steroidal inflammatory drugs (NSAIDS). The aforementioned classification of drugs is particularly dangerous in altering both hemodynamic flow and in causing an inflammatory condition referred to as interstitial nephritis. Since they are often used without a doctor's prescription, they are assumed to be safe. However, their

safety actually depends upon how well your kidneys function. When used along with a diuretic (water pill) and with ACE or ARB therapy, they are particularly dangerous.

Proton pump inhibitors (PPIS) are very commonly used to treat gastrointestinal disorders. They are taken for gastrointestinal reflux disorder (GERD), and since they can be purchased over the counter, are also assumed to be safe. However, long-term PPI use may accelerate the progression of kidney disease [5]. PPIs, along with drugs used to treat cancer known as checkpoint inhibitors, have increased the risk of developing inflammatory conditions of the kidney [6].

PPIs may also decrease vitamin B12 absorption, increase the risks for fractures, and lower the serum level of magnesium, an essential mineral in the body. Those using medications for GERD should ask their doctors about their magnesium levels [7, 8].

Antimicrobial agents are used to fight infectious organisms. Many are toxic to the kidney. They include antiviral agents, sulfadiazine, vancomycin, aminoglycoside antibiotics and amphotericin B. A combination of vancomycin-piperacillin-tazobactam is particularly toxic. Aminoglycosides are a family of antibiotics that have been used widely to fight bacteria, but they can directly damage the kidneys. The dose should be either reduced, or the medication avoided. Amphotericin B is a drug used to fight many fungal infections. Although medications such as ciprofloxacin have been reported to cause acute kidney injury, this is fortunately rare. The tuberculosis drug rifampin is also known to cause interstitial nephritis.

Some medications can interfere with the measurement of creatinine directly or through an alteration in serum creatinine, and can also give a false impression of causing kidney failure. The most commonly used medication to do this is trimethoprim. Although trimethoprim/sulfamethoxazole can on occasion cause acute but reversible kidney injury [9], an increment in serum creatinine is more likely explained by interference of the drug with creatinine secretion and elimination across the kidney tubule and into the urine, resulting in a higher blood level [10].

Patients who are undergoing chemotherapy or immunosuppressive therapy for malignancies, arthritis, autoimmune disorders, glomerulonephritis, or an organ transplant, may be prescribed medications that can be harmful based on their dosage, the level of kidney disease, and the association of coexisting conditions. These include methotrexate, cyclosporin A, tacrolimus, cisplatin, ifosfamide, mitomycin, and gemcitabine.

Some chemotherapeutic agents are highly effective in treating an aggressive malignancy. However, the breakdown and obliteration of tumor cells releases its toxic fragments into the circulation. This can lead to a very high purine load. Purines are the products associated with gout. In large amounts, and when the urine acidity is high, they can form uric acid stones in the urine. When physicians are aware that tumor lysis is possible during courses of chemotherapy, they will add alkali to intravenous solutions [11]. Urine crystals can also be formed by antibiotics, although this is rare.

Sodium phosphate has been used as a laxative in patients undergoing endoscopic procedures. However, a load of phosphate in a patient who is volume depleted creates a perfect storm that can damage the kidneys [12]. It is no longer recommended as a bowel preparation therapy for colonoscopies.

Medications that are used to treat blood pressure include ACE inhibitors or ARBs. They are generally well tolerated, but can be toxic in patients who have a partial blockage to the arteries feeding into both kidneys. They can also be toxic when combined with both a diuretic and an NSAID. The use of a diuretic along with ACE or ARB therapy is generally safe and is considered common practice. Caution is advised if your blood pressure is low, you feel dizzy, or feel dehydrated.

Risks of Certain Medications

Medications should be used cautiously in those who are elderly, have decreased renal function, or are frail. Impaired metabolism through the kidneys or liver, a decrease in protein or fat stores, or an accumulative effect may result in an unwanted and hazardous effect.

1. *Changes in blood pressure*

   Diminished blood flow may interfere with kidney function, particularly when the kidneys are impaired. Patients may be vulnerable to drugs commonly used to treat hypertension. Diuretics can be very efficient but can sometimes lead to dehydration. Checking the blood pressure both lying and standing may help alert you to problems that you will need to bring to your doctor's attention.
2. *An exaggerated inflammatory response*

   Since the kidney works as a filter, it is exposed to high concentrations of some medications that trigger inflammation. Antibiotics are by design supposed to attack the membranes and walls of living, invasive organisms. It is easy for an antibiotic to cause damage to the machinery inside the kidney cells. This can occur in the kidney tubules, the glomerular filter, or the interstitial space that surrounds and supports the kidney. Inflammatory cells that have been recruited to the renal area to fight infection may cause collateral damage to fragile kidney structures. This sets up a vicious cycle that may worsen the problem.

   An inflammatory response may directly impact kidney function. Drugs account for the majority of cases of acute interstitial nephritis. Historically, the antibiotic methicillin was the most common culprit, but this drug is no longer in use. Cephalosporins and sulfonamides can cause interstitial nephritis. Diuretics such as thiazide, furosemide, torsemide, metolazone and bumetanide are very commonly used. They too have a sulfonamide structure and can be associated with interstitial nephritis.
3. *Rapid falls in the blood glucose level*

Oral sulfonylurea agents may cause hypoglycemia in CKD patients. It is not advised to use glyburide or glimepiride as their active metabolite is excreted by the kidney, and may accumulate to a higher level in patients with reduced kidney function. An alternative is glipizide, because it is not metabolized to an active metabolite that is excreted by the kidney.

Insulin is metabolized by kidney tubules. When kidney function is reduced, the metabolism of insulin decreases and hypoglycemia may occur. If you are diabetic with CKD, it is important to discuss your diabetic treatment with your providers to assure that the medications you are prescribed will be safe.

Falls are common in kidney patients and in the elderly. They can lead to serious injury. Falls are the fifth leading cause of death in older persons. Steps to avoid falls include making sure that the blood sugar does not fall precipitously low during treatment. If you are diabetic, speak with your doctor about the medications you are taking and the target goals for your diabetes management. The control of diabetes in the elderly should be individualized. Large clinical trials of elderly patients demonstrate that the death rate rises when the HbA1C, an index for glucose control, is <6–6.5%. Overtreatment of diabetes in the elderly can be a risk factor for death [13].

4. *Anticoagulation*

Atrial fibrillation is a clinical condition where the atrial chambers of the heart start beating erratically. This can result in the formation of blood clots in the ventricular or lower heart chamber. These clots can be pumped into the arteries supplying the brain, resulting in a crippling or fatal stroke. Blood thinners are also required when blood clots form in the veins of the lower extremities; these clots can travel directly into the lungs. The use of blood thinners is referred to as anticoagulation. Newer anticoagulation therapies are far safer than warfarin, but an assessment of kidney function is necessary when using an anticoagulant because the dose may need to be adjusted or an alternative medication used. The use of blood thinners is necessary to help avoid this complication, and their benefit outweighs the risk, even in the elderly and those with CKD. While coagulation is generally safe, certain precautions are necessary. If you are receiving a blood thinner, be mindful of the activities in which you are participating. Furthermore, if you have surgery or any medical procedure, alert your doctor that you are taking an anticoagulant. Falling and hitting one's head while on a blood thinner can result in a hemorrhage into the brain or surrounding spaces. Persons taking blood thinners need to be mindful and proactive with respect to falls [14].

5. *Over sedation*

As we age, or develop a chronic illness like kidney disease, it is important that we carefully review our medications with our health providers. The dosage and duration may need to be adjusted. Medications for depression, relaxation, or pain may have an over-sedating effect, particularly when used in combination with other prescribed medications. This can result in being less alert, losing our balance, and even falling.

6. *Hyperkalemia*

   Potassium is an important mineral in many of the foods that we eat. It is eliminated by the kidney, and when kidney function decreases, it may accumulate. A high level of potassium in the blood stream can interfere with how our muscles contract. The heart, being a muscle, may also be affected. Many of the medications that interfere with potassium excretion are popularly used in kidney disease patients. These include the blood pressure medications, converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBS), as well as potassium sparing diuretics (spironolactone, eplerenone, and to a lesser extent finerenone). NSAIDS, trimethoprim-sulfa, and beta-blockers are associated with elevated potassium levels.

Conclusion

The ability to metabolize or excrete drugs decreases with chronic diseases such as CKD. It also decreases with age. You should candidly speak with your doctor to assure that the medication you are about to take is within the FDA safety recommendations. Drug manufacturers and the FDA have worked together to create a label that describes the limitations of a medication. This pertains to the safety of the medication under a variety of conditions including kidney disease.

Information regarding renal dosing is readily available. One can search the FDA website for information about drugs https://www.fda.gov. Many apps that highlight drug toxicity are easily downloadable from the Internet. Among the most popular is http://drugs.com. The information that you acquire from online sources should always be backed up by discussion with your health care providers.

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Chapter 13
Available Treatments If My Kidneys Do Fail

Stephen Z. Fadem

Introduction

When the kidneys fail, there are still several options. The major choices include either dialysis or a kidney transplantation. Although dialysis was first envisioned in 1861, it was not successfully performed for end-stage kidney disease until 1960. Since then it has evolved to become a life-saving procedure for thousands of people. The USRDS (United States Renal Data System) reports that there were 554,038 patients undergoing dialysis in 2018.

Approximately 69,000 perform either hemodialysis or peritoneal dialysis at home. The rest receive dialysis in one of the over 7,700 dialysis centers around the country.

Hemodialysis

Hemodialysis is a treatment that filters wastes from the blood in which an external filter is connected through tubing. In hemodialysis, blood is pumped through a filter that is in contact with a balanced electrolyte solution. Wastes are able to exit the body while the proper proportion of minerals are retained. Hemodialysis requires a surgical procedure whereby an artery and vein are connected in one of the arms. This is known as an arteriovenous fistula. After several weeks, the vessels enlarge and can be easily cannulated. An arteriovenous graft is sometimes used instead and is similar except that a form of Teflon tubing, usually Gore-Tex, is implanted

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between the artery and vein to achieve the same purpose. Dialysis can also be performed through a central venous catheter, although this is less than ideal because of the risk of infection.

Patients can be trained to perform hemodialysis at home, or can travel to a dialysis center where it is performed by a trained staff of nurses and technicians. Hemodialysis patients first began dialyzing at home in 1963. By 1964, a home dialysis machine had been developed in Seattle, Washington. It even contained a veneer surface to match home décor. But despite its early prominence, only 1.8% of patients start hemodialysis at home. In a survey performed by the American Association of Kidney patients, 32% of patients responded they were never educated about home dialysis [1].

Peritoneal Dialysis

Peritoneal dialysis (PD) is a procedure in which the body's own inner abdominal membrane is used as a filter. A balanced solution flows in and out of the abdominal cavity. Wastes cross the body membrane known as the peritoneum. The fluid draws out excess fluid through osmosis but allows the body minerals to remain in balance. It is performed through a series of exchanges. The exchanges can either be performed manually or automated. A plastic catheter is implanted into the abdomen and used for the treatments. Patients and their families learn this procedure during a training session and can perform PD at home. The advantages of PD are that it allows flexibility with regard to one's schedule, and as it can be performed at home and at night, leaving the days free for work or recreation.

Although PD was first used in the 1940s, it was not until flexible catheters and better surgical techniques for their implantation were devised before it became practical. In the 1970s, Jack Moncrieff and Robert Popovich, working in Austin, Texas, developed chronic ambulatory peritoneal dialysis. Although patients must undergo a training program, and PD is performed daily, its advantages are that it enables patients to continue to enjoy a good lifestyle. Patients on PD are more likely to continue working, and it is easier to travel with PD. While mortality rates for both HD and PD have fallen significantly between 2009 and 2018, the mortality rate for PD is around 20% lower than HD. PD is also less costly, and far less labor-intensive. 87.3% of persons who begin renal replacement therapy start with hemodialysis, and only 6.7% begin with home dialysis of either PD or HD. This is in part due to the reality that only around one third of patients ever receive care from the nephrologist prior to starting therapy, and instead present acutely ill to a hospital emergency room where a catheter is placed and the patient discharged to a dialysis center. Early discussion with one's primary care physician and early referral to the nephrologist can result in shared decision-making to determine if either peritoneal dialysis or a

preemptive kidney transplant is more suitable options. Early education can increase the numbers of hemodialysis patients who begin dialysis with an arteriovenous fistula and never require a burdensome hospital stay. Early education can also make patients more aware of their choices for renal replacement therapy. Assessment of quality of life (QOL) using standardized scoring reveals that the PD patients score higher than the HD population at 1 and 2 years after initiation of treatment [2]. As more patients become aware of modalities other than staff-assisted hemodialysis, the numbers of patients selecting peritoneal dialysis will rise.

Kidney Transplantation

A kidney transplant may come from a living related donor, a living unrelated donor, or a deceased person. Patients who are interested in a transplant are evaluated and listed on a national database.

A kidney transplant was performed at the Peter Bent Brigham Hospital (PBBH) in 1946 between a recently deceased accident victim and another patient who developed acute renal failure. The kidney remained outside the body, covered in moist gauze. The transplanted kidney worked long enough to allow the patient's kidney function to recover.

A major barrier to kidney transplantation was the rejection reaction that occurred when trying to transplant tissue foreign to the patient. In 1954, Joseph E. Murray performed a successful kidney transplant at PBBH between a 22-year-old patient with glomerulonephritis and his identical twin brother. This was successful because the immunological systems were identical. In subsequent patients, immunosuppressive agents would be necessary. In 1978, cyclosporin A (CYA) was introduced as an antirejection medication, and ushered in a new era of transplantation, but its success was marred by nephrotoxicity. A newer immunosuppressant, tacrolimus, has overcome many of CYA's disadvantages. It is easier to regulate, reducing the incidence of nephrotoxicity associated with CYA but has a similar mechanisms. mTOR inhibitors are also used, but have a long half-life. Their advantage is that they do not increase the risk of malignancies. Although kidney transplant patients must remain on immunosuppressants, the safety of these medications has greatly improved.

There are currently around 112,000 dialysis patients who await a kidney transplant. Living donor transplantation helps meet the need for a transplant. Donating a kidney is considered safe. A study of CKD among 4000 kidney donors demonstrated that 2.6% had an eGFR <30 ml/min per 1.73 m^2 at a median of 23.9 years [3]. Kidney paired donation has greatly expanded the number of persons receiving a live donor kidney. Originally, these "donor swaps" were between incompatible pairs to overcome the incompatibility of having different blood types. The program has grown in include large chains [4].

Summary

The CDC estimates 15% of the US population has CKD. Yetfewer than 150,000 persons start renal replacement therapy each year. The number of patients who require dialysis depends upon the underlying causes of CKD and how well the disease is managed. As persons at risk become more mindful of their health and realize they have considerable control over the outcome, they will stand a greater chance of delaying or avoiding renal replacement therapy.

In some persons, the need for renal replacement therapy is inexorable. The physician and patient can discuss which modality best suits the individual. The numbers of patients receiving live kidney donations has increased by using kidney paired donations. Newer immunosuppressant therapies have extended the life of the kidney transplant. Receiving a deceased donor kidney transplant doubles the chance of survival over the person waiting on the list. Receiving a living donor kidney transplant quadruples the chance of survival [5]. Survival for both HD and PD has dramatically increased. The higher survival rates for PD, the flexible lifestyle, and the ability to easily remain employed, make it a more practical option.

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Chapter 14
Appendix: The Cell and the Kidney

Stephen Z. Fadem

Introduction

Information in this chapter is designed to give the reader a broader understanding of some of the mechanisms that drive our health. This is but a glimpse into the vast scientific knowledge. Although attempts to make this section highly readable and understandable to those of you who may not have a science background, most of you will probably want to get some online assistance. Recommendations are to start with Internet resources to help with definitions and to gain additional depth.

1. A Typical Cell
2. Inflammation and Obesity
3. What are Mitochondria?
4. How Mitochondria Work?
5. The Story of mTOR
6. mTOR and AMPK
7. The Recycling Systems – Ubiquitin and Autophagy
8. Calculators and the Kidney
9. Implications for Kidney Disease

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A Typical Cell

Mitochondrion The mitochondrion is able to combine phosphate molecules to create energy packets called adenosine triphosphate (ATP) from the breakdown of sugar and fats. Electrons released from chemical reactions carry their electrical charge that creates a force to drive the chemical reaction that produces ATP. The energy is then transferred to the ATP. The electron is then captured by oxygen and left over carbon. The byproduct is carbon dioxide. If the energy process is not well matched free electrons damage cells. This is known as oxidative stress.

Lysosome Lysosomes contain enzymes and can degrade and recycle cellular wastes. They also breakdown bacteria and viruses. When food is scarce they digest damaged cell organelles. This process is known as autophagy.

Vacuole These small sacs are like lysosomes. They help rid the cell of toxins.

Cytoskeleton These are the structural components of cells that help them retain their shape. They are made of filamentous proteins.

Plasma Membrane This is the border of the cell. It is designed to interact with other cells and the environment. The membrane interacts in many ways – receptors permit it to communicate with the outside world, while channels are pathways that enable to transport of minerals into and back out of the cell. Some of the transport mechanisms require energy, and use ATP in the process. Endocytosis is a method where the plasma membrane engulfs a particle, completely surrounding it. It then seals itself creating a vesicle inside the cell.

Nucleus The nucleus is the headquarters of the cell. It contains the genetic material that regulates cell activities. That genetic material is DNA wrapped in a coil. DNA is a sequence of molecules that carry all the codes needed for our body activities – from reproduction to the manufacturing of proteins used in daily life. Transcription factors work like switches. They are molecules that can enter the nucleus to direct DNA activities. When DNA is stimulated by a transcription factor, selected genetic information from that section of the DNA is transcribed onto an mRNA molecule and sent out of the cell to manufacture proteins. This process is guided by the nucleolus. The mRNA is then transported from the nucleus to the ribosome.

Ribosomes The ribosomes are the manufacturing centers where proteins are assembled. The mRNA is able to send another type of RNA to select specific amino acids. These are sequentially laid out in a chain, all based on the RNA code.

Nucleolus This is a small body in the nucleus that helps manufacture and maintain ribosomes, and guides the mRNA in the transcription process.

Rough Endoplasmic Reticulum These are structured layers that surround the nucleus. They hold the ribosomes in place.

Smooth Endoplasmic Reticulum The smooth endoplasmic reticulum produces substances that are required by the cell for its daily housekeeping function.

Golgi Apparatus This is the part of the cell that help package proteins and lipids.

Proteasome A proteasome is an organelle that breaks down targeted proteins into small peptides and amino acids. When stimulated to break down a protein, ubiquitin molecules attach to the protein and direct it to the proteasome where it is digested into simple peptides or back to amino acids. An example is muscle. Muscle proteins are targeted for destruction under a variety of conditions. When this happens, the ubiquitin molecules attach to the muscle protein, and it is broken down.

See Fig. 14.1.

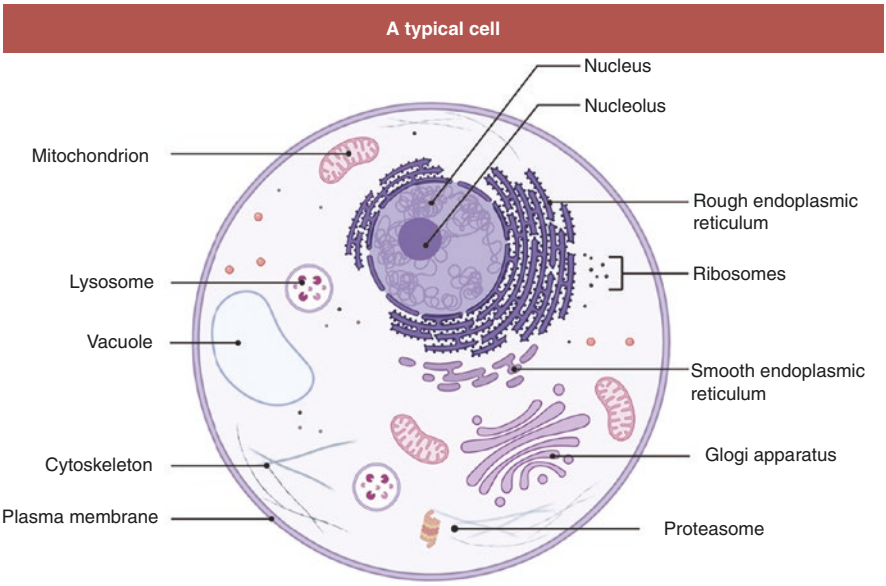


Fig. 14.1 The cell is its own organism with several internal parts known as organelles. (Made with Biorender (biorender.com))

Inflammation and Obesity

Obesity can be politely described as an energy imbalance. It is measured by the body mass index (BMI), which is the ratio of one's weight in kilograms to his or her height (meter squared). The normal value of greater than 25 kg/m^2 is considered overweight, and above 30 kg/m^2 is considered obese. Obesity is linked to heart disease, diabetes, hypertension, and poor health. A study in Israel linked 2.3 million adolescents over a 43-year period. Those who were obese had a 4.9 times higher rate of death from heart disease and 2.6 times the rate of having a stroke [1]. Obesity is also one of the strongest risk factors for CKD.

What we call fat is really a tissue made of adipocytes (fat cells). In truncal obesity – the generalized obesity that enlarges the thighs and booty - the adipocytes store fat in the form of fatty acids. In visceral obesity – that unsightly pot belly – the fatty acids come directly from the liver to their storage site in the abdomen. Visceral obesity has a greater chance of causing heart attacks than truncal obesity. Obesity is not just associated with unsightly and abnormal fat storage in adipocytes, but involved in the metabolism of iron, sugar, lipids, the appetite, and inflammation.

Inflammation is the body's mechanism to respond to an attack by foreign substance. We usually think of inflammation as a reaction to a virus or bacteria, but it can also be an orderly response to something that we have eaten. Inflammation can be triggered by obesity, and affects not only the liver, but the brain, heart, pancreas, and muscle. It is insidious.

When adipocytes start to engulf fatty acids, they switch on inflammatory genes that stimulate the formation of macrophages. The adipocytes release hormones known as adipokines. The two most studied are adiponectin and leptin.

Adiponectin is made of 224 amino acid building blocks. It is released during caloric restriction and causes free fatty acids to undergo an enzyme chemical reaction known as fat oxidation. The enzyme is known as AMP kinase (AMPK). Fat oxidation uses Adenosine monophosphate (AMP), the breakdown product from ATP. The oxidized fatty acids are then cleared from the circulation and stored in adipocytes. In muscle, under the direction of adiponectin, AMPK causes sugar to move into the cell to serve as a substrate for breakdown, induces the breakdown of fatty acids for use as energy, and initiates the synthesis of ATP. This mechanism is activated by the stress of aerobic exercise and initiates high levels of adiponectin; it also helps block inflammation. Exercise training increases the numbers of receptors for adiponectin on cells. Too little adiponectin is induced by obesity, and does the opposite, increasing fat in the circulation. Low levels of adiponectin also increases the hormones that signal inflammation. These are the proinflammatory cytokines. A consequence of this mechanism is the recruitment of bone marrow cells into the fat cells where they are converted to macrophages. These reduce the adiponectin receptors. Macrophages are able to engulf fats to the point of swelling and dying. As they die, they attract calcium that creates a hardened wall on the inside of arteries. This is atherosclerosis – hardening of the arteries.

The other adipokine is leptin. It can reduce the appetite, but during obesity, target cells that control appetite become resistant to its action [2].

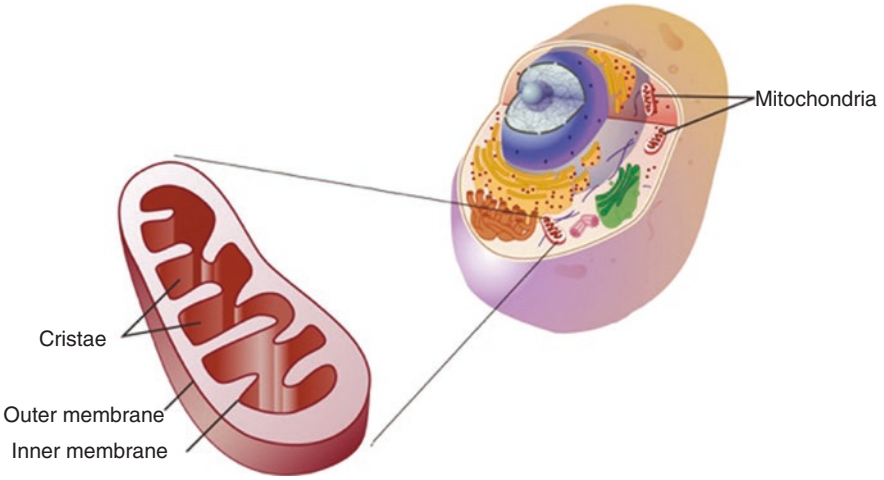


Fig. 14.2 Mitochondria. (Made with Biorender (biorender.com))

What Are Mitochondria?

Mitochondria (See Fig. 14.2) were once independent bacteria, single-celled organisms that had circular DNA instead of a double helix. They somehow became engulfed in the cells of multicellular organisms without being digested. Thus, they coexisted, receiving protection and nutritional support from the rest of the cell, while contributing something vital that made life on earth as we know it possible - the production of energy.

All forms of life must have energy. Although energy takes place in many forms, we are most familiar with the energy associated with electrons. Electrons move from place to place, creating forces that drive biochemical reactions. They are responsible for the light, heat, and motion that we rely on in our homes and in our cells. In the body's cells, this all takes place in the mitochondria. These charge units use electrons to make energy. Electrons activate molecules like adenosine triphosphate (ATP) that can then drive the biochemical reactions that keep us alive. At the end of the activation, another molecule must accept the leftover electrons for safety purposes. That molecule involves oxygen. Electrons that run freely around the cell can become very dangerous.

For around a billion years, cells tried countless combinations to derive a plan that would enable oxygen to drive energy production. Mitochondria are unique bacteria that use oxygen (O_2) from the atmosphere to accept leftover electrons. Phosphorus is an element that can be associated with high energy. Electron charges drive the coupling of phosphorus to a molecular complex known as adenosine diphosphate (ADP) creating ATP, which has a very high-energy state. When ATP is converted back to ADP it releases the energy to drive a chemical reaction. In order to ensure proper disposal of the electrons, the mitochondria convert hydrogen, carbon, and oxygen to carbon dioxide and water. We call this reaction cellular respiration.

Fig. 14.3 Photograph by Stephen Fadem

Sometimes the electrons do not perfectly align with their receptors as they travel through the chain of reactions, leaving unpaired oxygen molecules with only one electron. This is dangerous; these molecules are radical, and are even called free radicals. They seek to pair with other electrons from innocent molecules, damaging or destroying internal cell components. If minor, a cell may recycle the damaged components, but over years minor damage can add up and cause disease.

Mitochondria are the house guests of living cells. In our bodies they provide energy for heart and skeletal muscles, for brain power, kidney function, and just about everything else. While both our moms and dads contributed DNA to our gene pool, the mitochondrial DNA only comes from our mothers. We owe a lot to our mothers. Not only did they give us life but gave us the ability to make energy (See Fig. 14.3).

How Mitochondria Work

A look at the biochemical reactions inside the mitochondria - Made with Biorender.com and Adobe Photoshop.

Mitochondria receive "fuel" – breakdown products from glucose or fat. They break these products down further, releasing electrons (e^-). Pretend you are a sitting on a carbon atom and riding inside a mitochondrion. You start your journey along the famous Krebs's Cycle also known as the Tricarboxylic Acid Cycle. Here you and a paired carbon go through a series of biochemical reactions that gives up

electrons as you travel. You also witness fatty acids releasing electrons through the process of ß oxidation. These electrons are transferred from deep inside the mitochondria to the inner membrane. The transferring molecule is nicotinamide adenine dinucleotide (NAD+). It is also known as a coenzyme. A total of eight electrons are transferred to the electron transport chain. When NAD+ acquires an electron it becomes NADH. Its electrons are then transferred to another biomolecule, flavin mononucleotide (FMN). Like a hot potato, the electrons are transferred through a series of four complexes.

Coenzyme Q is among these electron transfer sites. It hands the electron over to a complex that then moves it to another complex. When the negatively charged electrons are transferred, positively charged protons (H^+) are pumped across the membrane. This creates a positive charge that drives the giant enzyme, ATP synthase to add one more phosphate to ADP creating a high energy bond, and the triple phosphate molecule, ATP. This is like charging a battery. ATP can leave the mitochondria and help drive other biochemical reactions. Some of these reactions help muscles contract, others keep fluids from entering the cells. As a remaining carbon, you attach to oxygen and form carbon dioxide (CO_2). Water is also formed. The oxygen plays an essential role in accepting these hard working electrons, keeping them from causing trouble. Your carbon will soon exit the body through the lungs, and you will be back in the atmosphere. (See Fig. 14.4).

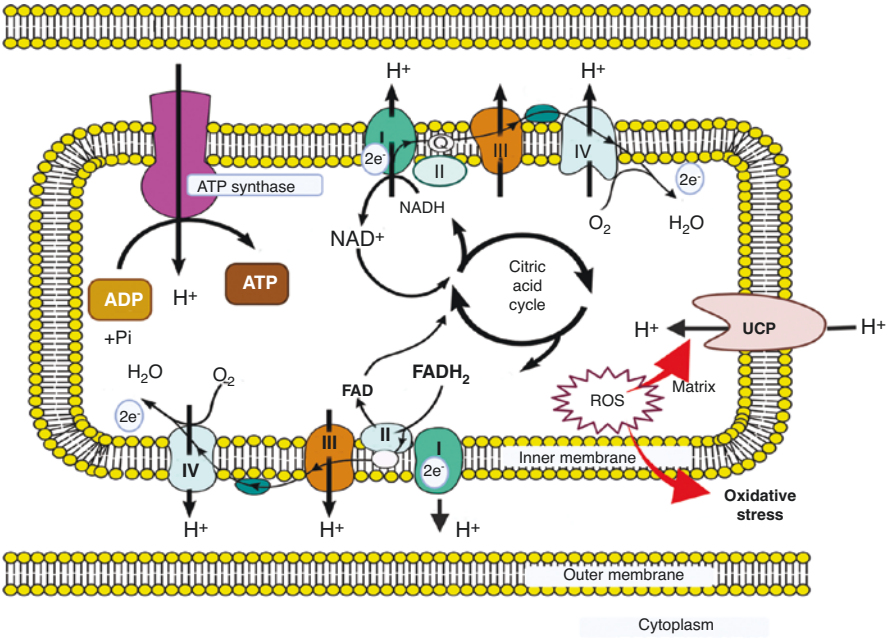


Fig. 14.4 Made with Adobe Photoshop and Biorender (Biorender.com)

Fig. 14.5 The job of this four-barrel carburetor is to correctly mix the fuel and air so that combustion can properly occur. (Photograph by Stephen Fadem)

Just like a carburetor (see Fig. 14.5) the mitochondria must balance fuel and oxygen. During this process, some excess electrons leak and are not captured. These electrons behave as free radicals and damage other part of the mitochondria and cell – this is known as oxidative stress.

There are special channels in the mitochondria, uncoupling channels (UCP), that allow protons (H+) to enter the matrix and neutralize the negatively charged free radicals. This neutralization creates heat. This reduces the stress and is called thermogenesis. This heat occurs in brown fat and can keep animals warm on a cold day. It is the secret behind why polar bears can stay warm in the Artic.

As we age, some of the elements of electron transport chain are not produced in sufficient quantity. The best-known factor is coenzyme Q10. It is identified as Q near complex II in the accompanying figure. Medications such as statins may interfere with the cell's ability to manufacture COQ10.

The coenzymes NAD and FAD are well known. Their precursors are the B complex vitamins, B3 (niacin) and B2 (riboflavin). They serve to move electrons from the mitochondrial matrix after they have been unfettered during the breakdown of carbons or fatty acids, to the electron transport chain.

The Story of mTOR

Easter Island (Rapa Nui) is in the middle of the Pacific Ocean and is characterized by over 1000 statues that were carved centuries ago from volcanic rock, moved to distant locations on the Island, and then erected (See Figs. 14.6 and 14.7). In 1964, an expedition from Canada collected 67 soil samples to try to determine why its inhabitants never were afflicted with tetanus despite walking around without protective footwear and being exposed to horses. The expedition was to be done before the

Fig. 14.6 Rapa Nui – Ranoraku – Easter Island. (Photograph by Stephen Fadem)

Fig. 14.7 Sunrise at Ahu Tongariki – Easter Island. (Photograph by Stephen Fadem)

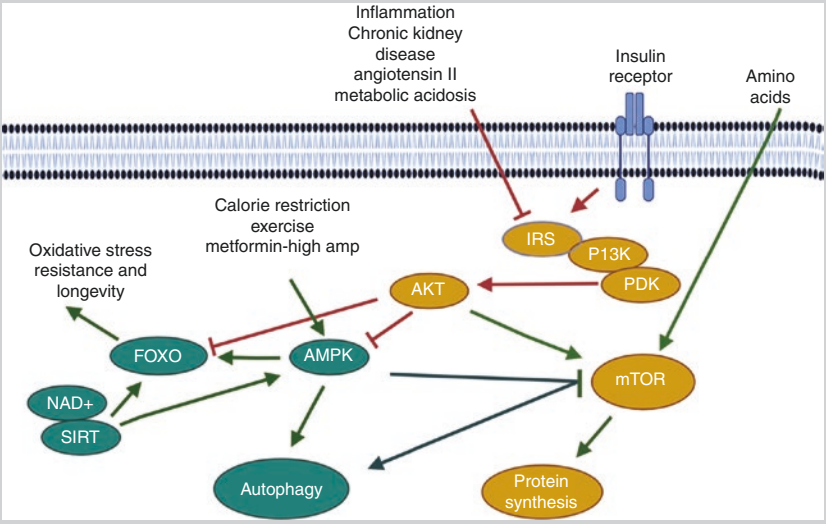
completion of the new runway, fearing that jet travel would change the ecology of this very remote island.

In a fascinating story, the research group at Ayerst Pharmaceuticals identified an anti-infective agent, which was named rapamycin after the island where it was discovered. It later became a major therapy for patients undergoing kidney transplantation. In unraveling the mechanisms of the actions of rapamycin, scientists discovered a key regulator of cellular function – the mammalian (or mechanistic) target of rapamycin.

Mechanisms that turn off mTOR will stimulate autophagy. Autophagy means eating oneself, and the cell devours worn-out parts in order to create the fuel to create energy. Every cell must have energy to survive. This energy is derived by burning fuel – either fats or glucose to make ATP, and then by cycling and recycling ADP to ATP. As a cell goes through its routine, it generates waste products. These are recycled in organelles called lysosomes, and made ready to serve as fuel.

MTOR and AMPK

The Relationships Between Intercellular Actions to Inflammation, Oxidative Stress, Sugar, Angiotensin II, Acidossis and Kidney Disease



mTOR has a dual role as the general contractor of the cell, directing both construction and renovation projects. It is inexorably related to energy conservation, protein synthesis, growth, and recycling.

High blood sugar, inflammation, kidney disease, acidosis, and angiotensin II cause insulin resistance by blocking the insulin receptor substrate (IRS) that enables sugar to enter the cells. Sugar turns off AMPK and turns on mTOR by stimulating a very important enzyme, AKT. The orange ovals with red arrows show the pathways for sugar and the pathway that inflammation uses to reduce IRS. AKT activates mTOR and stimulates protein synthesis [3].

Caloric restriction, aerobic exercise and metformin turn on AMPK, as depicted by the green ovals, and cause energy conservation through the inactivation of mTOR and the subsequent activation of the autophagy recycling mechanism.

Amino acids directly stimulate another complex, the regulator system (RAG) that coordinates signaling pathway to activate mTOR and protein synthesis. Resistance training induces enzymes that produce a product known as phosphatidic acid (PA). This activates mTOR and leads to muscle protein synthesis.

Figure 14.8 is an oversimplified scheme of what is happening inside the cell in response to inflammatory stimuli, stimuli by insulin, calorie restriction/exercise group, and amino acids.

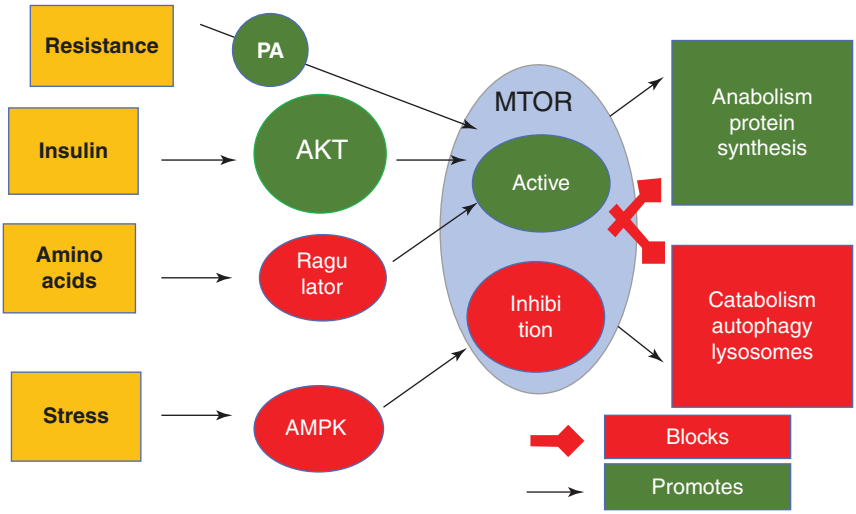


Fig. 14.8 Created with Microsoft PowerPoint

Table 14.1 Abbreviations for Fig. 14.8

Abbreviation	Name	Explanation
IRS	Insulin receptor substrate	Stimulated by insulin but inhibited by inflammation – a key factor in insulin resistance
P13K	Phosphoinositide 3 kinase	Part of the enzyme pathway along with AKT and PDK – responds to insulin and activates mTOR
PDK	Pyruvate dehydrogenase kinase	An enzyme that reacts to insulin
mTOR	Mammalian target of rapamycin	A central enzyme that when inactivated induces autophagy and when activated induces protein synthesis
AKT	AKR mouse strain thymoma	An enzyme that responds to insulin and induces protein synthesis through mTOR
AMPK	Adenosine monophosphate (AMP) kinase	AMP binding to AMPK signals reactions to induce autophagy
FOXO	Forkhead transcription factors	FOXO is activated by reduced insulin signaling, reduces oxidative stress, and increases longevity
NAD+	Nicotinamide riboside that activates sirtuins	A specific molecule electron acceptor and aids with other biochemical reactions
PA	Phosphatidic acid	A lipid critically involved in the activation of mTOR
SIRT	Sirtuins – Silent information regulators	These enzymes depend on NAD+, activate FOXO and AMPK

Each of the abbreviations in Table 14.1 represents a series of biochemical reactions that cause changes to other enzymes in the cascade. These processes either stimulate processes that prolong the life of the cell and help prevent aging, or

alternatively cause the cell to die. While this knowledge is not essential in understanding why kidney patients must avoid overeating, exercise, keeping diabetes in control and avoiding inflammation, it lends support to the arguments that are made for good health. Changing one's lifestyle is difficult, and you deserve to know the rationale before undertaking such a huge task.

The Recycling Systems: Ubiquitin and Autophagy

Figure 14.9 highlights the key differences between two major degradation systems inside the cell.

Ubiquitin - Proteasome	Autophagy - Lysosome
	
Shredder	**Garbage disposal**
The ubiquitin/proteasome system mainly degrades short lived or misfolded proteins. Ubiquitin is a 76 amino acid protein. For targeting, a chain of ubiquitin molecules is attached to the protein selected for degradation. Once selected, the ill-fated protein is transported to the proteasome. **The proteasome can be loosely compared to the paper shredder you are familiar with. It is the proteasome that degrades the protein for recycling or elimination.** **Ubiquitination has important protective and regulatory duties that include degrading defective proteins, regulating important cell processes like HIF (the hypoxia inducible factor that controls hemoglobin) and hepcidin (a molecule that spares iron release when inflammation is present), and tagging muscle proteins for breakdown during metabolic acidosis and kidney disease.**	**Autophagy, phagocytosis, or endocytosis are not limited to proteins but also digests defective cellular organelles and cellular debris. Autophagy can degrade defective mitochondria. The degradation system in autophagy is the lysosome. It can be compared to the garbage disposal.** **Autophagy is regulated by MTOR and AMPK; they oppose each other. AMPK inhibits MTOR and increases autophagy when there is caloric restriction and the body is desperate for fuel. When calories are plentiful, MTOR is stimulated and autophagy is turned off.** **After being activated, an autophagosome forms and surrounds the defective organelle that has been selected for degradation. This defective trash object is called cargo. The autophagosome then fuses with the lysosome and degradation takes place as the enzymes inside the lysosome degrade the cargo.** **Autophagy removes products harmful to the cell and degrades them to small molecules that can either be eliminated or recycled.** **The lysosome has many cellular duties–it helps detect and defend against infection, helps repair membranes, plays a role in metabolism, helps with antigen organization to develop antibodies, assists with energy, and helps regulate amino acid status** **Frontiers in Cell and Developmental Biology | www.frontiersin.org 12 June 2019**

Fig. 14.9 The differences between the ubiquitin/proteasome system and the lysosome system

Calculators and the Kidney

The eGFR Calculator

The Modification of Diet in Renal Disease Clinical Trial was a large clinical study by the National Institute of Health. It was designed to compare protein restriction and blood pressure control in slowing the progression of kidney disease, and showed little actual benefit. Patients with proteinuria had a slower rate of decline in GFR with aggressive BP treatment. The study required an accurate means of measuring kidney function [4]. The data from glomerular filtration rates measured with isotopes is considered highly accurate. This data was compared with several indices of kidney function, and using a best fit analysis, a group of study equations were developed. The calculator first appeared in 1999 using 1628 subjects [5]. The calculator was revised in 2006 as the serum creatinine was standardized to a traceable national mass spectroscopy value. The CKD-Epi creatinine was developed in 2009 using 12,150 subjects worldwide. It reduced the bias inherent in patients with higher values. The KDIGO Guidelines of 2013 adopted this as the standard equation. It is also used in predictive modeling. Cystatin C is also used as a standard for kidney disease. Its advantage is that it is not a muscle metabolite like serum creatinine is, and thus is more accurate in patients with decreased muscle mass. It does not require the race coefficient. A combination serum cystatin C and CKD-Epi GFR equation is also available [6].

The CKD-EPI calculator and predictive model can be found at http://mdrd.com and http://ckd-epi.com.

The CKD-EPI calculator was modified in 2021, and no longer requires a race coefficient for estimating the GFR [7].

Body Mass Index

The body mass index (BMI) was developed in 1832 by Adolphe Quetelet (1796–1874), a Belgian statistician, mathematician, astronomer, and social scientist [8]. It was later adopted as the body mass index in 1972 by the legendary scientist, Ancel Keys (1904–2004), and was used as a body weight index to predict body fat [9]. Today, inexpensive smart scales give us an estimation of body fat using bioimpedance [10].

BMI = weight (kg)/height^2 (meters). Touchcalc automatically converts to metric from feet, inches or pounds.

Underweight	18.49 or below
Normal weight	18.5–24.99
Overweight	15–29.99
Obese	30–39.99
Morbidly obese	40 or over

The BMI calculator can be found at http://touchcalc.com/bmi.

24 Hour Urine Urea Nitrogen

The protein intake calculator was developed by William Mitch to estimate protein intake in CKD patients. It uses a measure of urea nitrogen and adds a non-urea nitrogen value (weight × 0.031 g nitrogen/kg/day). By multiplying this sum by 6.25 one can estimate the amount of dietary protein one is eating, assuming that there is a balance between dietary protein intake and urine urea nitrogen loss. It is based on the principle that dietary proteins are used for repair and rebuilding, and that the body is also constantly degrading proteins at a similar rate. Proteins are metabolically degraded to urea and are mainly eliminated in the urine.

This is helpful because patients with chronic kidney disease are often urged to restrict dietary protein. If you have kidney disease, and are urged to restrict dietary protein intake, this calculation can help you know how well you are following your diet [11].

The calculator is found at http://touchcalc.com/calculators/mitch.

Implications for Kidney Disease

Inflammation

Inflammation, as well as metabolic acidosis, causes the degradation of the insulin receptor substrates. This blocks the insulin pathway and leads to insulin resistance. In insulin resistance, the pancreas must work harder to provide a key enzyme for energy metabolism. Over time, the pancreas wears out. Meanwhile, the hyperglycemia caused by insulin resistance stimulates the inflammatory responses that damage the kidneys and other organs. Inflammation can also be caused by obesity, which decreases adiponectin. Adiponectin helps drive AMPK. AMPK isthe sensing enzyme that blocks mTOR thus stimulating autophagy, a conservation mechanism to help cells conserve the substrates needed to make sufficient ATP.

Eating and Insulin

Sugar that we eat in our diet activates the insulin growth factor receptor on the cell. This turns on several enzymes that stimulate mTOR. It also causes FOXO to leave the cell nucleus, stopping several reactions that fight oxidative stress. In addition, it inhibits AMPK. Metformin, a drug used to treat diabetes, may also work to inhibit AMPK.

Aerobic Exercise and Calorie Restriction

Caloric restriction and aerobic exercising help stimulate AMPK activity. This leads to the regeneration of the substrates required to replace energy through autophagy, the recycling of worn-out cellular components. Worn-out components can cause oxidative stress, so intermittent caloric restriction may have additional benefits.

Resistance Exercise

Along with amino acids, resistance exercise directly stimulates mTOR to promote protein synthesis.This is essential in CKD where muscle breakdown is especially prevalent.

Sirt Foods and Flavonoids

Sirtuins are essential for the AMPK enzyme process to occur. It is not known how effective dietary sirtuins are in promoting AMPK. Flavonoids may stimulate the cell to release transcription factors that promote scavengers to reduce oxidative stress.

Vitamins B_2, B_3, Coenzyme Q_{10}

A clinical trial of 65 participants demonstrated that coenzyme Q_{10} supplements were safe for use in dialysis patients. The larger dose of 1200 mg per day reduced the plasma concentration of F2-isoprostanes, a marker of oxidative stress. The investigators concluded that further studies would be required to make any judgments as to the effectiveness of coenzyme Q_{10} in dialysis patients.

The use of vitamins and micronutrients in CKD is limited by a scarcity of evidence. Although moderate use of over the counter vitamins is safe, their effectiveness in reducing disease progression, decreasing the mortality rate, or benefiting the quality of one's life, has yet to be determined.

Calculators

The use of calculators can give us an idea of our progress, but can also be misleading. More importantly, one should develop a lifestyle and create habits that promote good health. As science advances we will be able to learn more about how kidney

disease progresses, its role to genetics, and how we can prevent its progression. Despite the limitations we encounter, we can use our will power and determination to improve our health, seeking advice from health professionals, modifying our diets, and adjusting our activity routines to make our lives better.

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