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Overview: Pathophysiology of the Kidney

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Basic Kidney Structure and Function

The kidneys are located symmetrically on either side of the vertebrae, starting at the 12th thoracic vertebra and extending down to the 3rd lumbar vertebra. Each adult kidney measures approximately 11 to 12 cm long, 5 to 7.5 cm wide, and 2.5 to 3 cm thick and weighs approximately 115 to 170 g. Each kidney has two general regions: the cortex, the pale outer region, and the medulla, the darker inner portion of the kidney (Figure 1.1). The medulla is divided into cone-shaped regions called the *renal pyramids* (1). Blood is supplied to healthy kidneys through the renal artery, which enters the kidney at the hilus. Approximately 20% of cardiac output circulates to the kidneys. This is far more blood flow than is necessary to supply needed oxygen to the kidneys but is required to allow for their excretory function (2). Urine that has been formed collects in the lower portion of the renal pelvis, which is the expanded upper region of the ureter, and then exits the kidney via the ureter that extends for a length of 22 to 30 cm to provide a connection to the bladder (3).

The basic functional unit of the kidney is the nephron. Each human kidney contains 600,000 to 1.4 million nephrons, which are located in both the cortex and the medulla (4). Within each nephron, there are several well-known microscopic components:

- *The glomerulus/Bowman's capsule/renal corpuscle.* Known as the filtering unit of the kidney, the glomerulus is a network of capillaries surrounded

by a narrow wall of epithelial cells. In the glomerulus, approximately 125 mL/min of filtrate is formed. Bowman's capsule, with its basement membrane, holds the glomerulus, and together they are known as the *renal corpuscle* (4).

- *Proximal convoluted tubule.* The proximal convoluted tubule is a direct continuation of the epithelium of the Bowman's capsule. Controlled reabsorption of filtered glucose, amino acids, sodium, bicarbonate, potassium, chloride, calcium, phosphate, water, and other solutes begins here. In addition, ammonium is produced in the proximal tubule (4).
- *Loop of Henle.* Urine is concentrated in the loop of Henle and may be diluted later as needed. Brenner describes a countercurrent multiplying mechanism, which governs these processes but is not fully understood (4). Water cannot permeate, but sodium can be pumped out. Subsequently, this affects the movement of water in or out of the collecting duct, which is water permeable.
- *Distal tubule.* This portion of the tubule has three parts: (a) the thick ascending limb of the loop of Henle, (b) the macula densa, and (c) the distal convoluted tubule. There is some active transport of sodium chloride in the thick ascending limb of the loop of Henle. This region as a whole absorbs approximately 99% of the water that is filtered by the kidneys back into the body. The result is a more concentrated urine. Some functions of the thick ascending limb of Henle are governed by

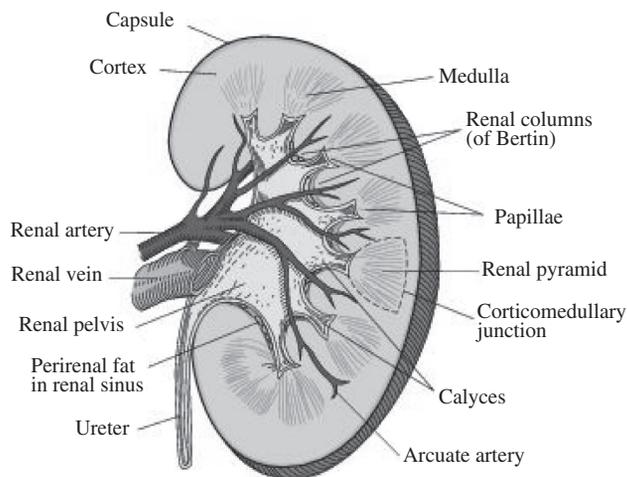


Figure 1.1. Anatomy of a kidney. Reprinted with permission from Figure 2-4 from Brenner BM, ed. *Brenner & Rector's The Kidney*, 8th ed. Philadelphia, PA: Saunders Elsevier; 2008:27.

hormones, including vasopressin, parathyroid hormone, and calcitonin (4).

- **Collecting duct.** The collecting duct contains two types of cells: principal cells and intercalated cells. Principal cells play an important role in the reabsorption of sodium chloride and secretion of potassium. Intercalated cells play an important role in regulating acid-base balance via secretion of hydrogen and bicarbonate (5).

The major functions of the kidneys can be described as (a) excretory, (b) acid-base balance, (c) endocrine, and (d) fluid and electrolyte balance.

Excretory functions of the kidneys include removing excess fluid and waste products. While approximately 180 L of filtrate pass through the kidneys daily, only 1 to 2 L are removed in the urine each day (6). The remaining fluid is retained in the body to support tissues. Substances removed with the urine include urea, vitamins and minerals consumed in excess of the body's requirements, and metabolites of some drugs and poisons. Of course, if blood levels of any of these substances are low, the kidneys promote homeostasis by conserving them to maintain levels within narrowly defined limits.

Acid-base balance is maintained through a buffer system, which maintains the blood's pH at approximately 7.4. Bicarbonate carries hydrogen ions to the kidney, where they are removed from extracellular fluid in the tubules, then reabsorbed in

the proximal tubule and returned to the bloodstream as needed. In addition, phosphate buffers intracellular fluid and is then concentrated in the tubules as water is removed. Other organic compounds, such as citrate, also support acid-base balance. And finally, metabolites of amino acids may be used to moderate acid or base reactions (6).

Several hormones are included in the kidneys' **endocrine function**. Calcitriol, or 1,25-dihydroxy-vitamin D₃, is produced in the kidney and subsequently enhances calcium absorption. In healthy kidneys, the activation of vitamin D and excretion of excess phosphorus set the stage for maintaining healthy bones. (See Chapter 16 for more details.)

The anemia of chronic kidney disease (CKD) is related to altered production of erythropoietin (EPO) in the diseased kidney. Normally, EPO acts on bone marrow to increase the production of red blood cells, thus enhancing the transportation of oxygen throughout the body's tissues. (See Chapter 17 for more details.)

The kidney's role in **fluid and electrolyte balance** is probably its best-known function. The antidiuretic hormone (ADH), also known as *vasopressin*, released from the posterior pituitary gland regulates the water that is reabsorbed into the body. When fluid volume (blood and/or other fluids) is low, ADH is secreted and reduces urine flow, increasing the reabsorption of water in the collecting duct. This mechanism maintains the body's osmolality within a very tight range.

When extracellular volume decreases, perfusion of all body tissues, including the kidney, is reduced. Consequently, the glomerular filtration rate (GFR) is lower, resulting in decreased removal of sodium chloride. This activates the trio of hormones of the renin-angiotensin-aldosterone system to increase blood pressure to maintain adequate tissue perfusion (6).

A person with advanced impairment of kidney function usually experiences edema, uremia (accumulation of waste products in the blood), metabolic acidosis, hypertension, anemia, bone disease, and an increased sensitivity to many drugs.

Types of Kidney Failure

The onset of kidney failure can be sudden, as in acute kidney injury (AKI), or progressive, leading to CKD. Patients with AKI will potentially regain their kidney function, and medical management, including medical nutrition therapy (MNT), may stabilize CKD of certain etiologies. As CKD progresses, renal replacement

therapy such as dialysis or transplantation may be necessary, in combination with appropriate MNT, for survival.

Acute Kidney Injury

Patients with AKI generally have a rapid onset of symptoms occurring over a period of hours to days. Symptoms may start with a small rise in serum creatinine and continue on to a reduced urine volume (oliguria) and ultimately to a complete absence of urine output (anuria) (7). In the United States, AKI typically occurs in the hospital setting and is often secondary to ischemic events and consequent injury to the kidney. It has a high degree of morbidity and mortality despite advancing technology in renal replacement therapy (8). When evaluated radiologically, the kidneys and urinary tract appear normal in size. Due to structural changes that occur with age, elderly patients are especially at risk for AKI when under physiological stress.

The Acute Kidney Injury Network has developed a three-stage classification of AKI according to the percent change in baseline serum creatinine and/or absolute serum creatinine values (9). In addition, identifying AKI as prerenal, renal, or postrenal in its origin remains a key step in evaluating and managing this condition (10). Prerenal AKI results from decreased renal perfusion in an otherwise normal kidney, perhaps due to altered cardiac function and altered glomerular blood flow; with treatment, it can be quickly reversed. AKI may have a renal origin due to underlying structural or functional changes in the kidney. Postrenal

etiologies of AKI may include an obstructive uropathy, with treatment aimed at removing the cause of the obstruction (10).

AKI can occur in previously healthy kidneys. With proper nutrition and appropriate dialytic support, ranging from intermittent hemodialysis to continuous venovenous hemodiafiltration, the kidneys can often repair themselves (11). However, quite often AKI can be superimposed on underlying CKD secondary to diabetes, hypertension, and other conditions. In this scenario, the goal is to return kidney function to baseline by removing the offending agent and avoiding chronic dialysis. (See Chapter 4 for more details.)

Chronic Kidney Disease

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) began in 1997 to produce evidence-based clinical practice guidelines. These guidelines were developed and implemented by physicians and health care providers of the nephrology community. In 2002, NKF-KDOQI outlined a standard for classifying stages of CKD (12). The classification for CKD appears in Table 1.1 (12).

It is important to note that some decrease in kidney function is a normal part of aging. Stage 1 and even stage 2 CKD may be seen in otherwise healthy individuals older than age 60 years. However, even in older adults, reduced kidney function should be monitored to allow appropriate intervention if the decrease in GFR continues into later stages of CKD (13).

Table 1.1. Stages of Chronic Kidney Disease: A Clinical Action Plan

Stage	Description	GFR (mL/min/1.73 m ²)	Action ^a
	At increased risk	<90 with CKD risk factors	Screening; CKD risk reduction
1	Kidney damage with normal or increased GFR	<90	Diagnosis and treatment; treatment of comorbid conditions; slowing progression; CVD risk reduction
2	Mild decrease in GFR	60–89 ^b	Estimating progression
3	Moderate decrease in GFR	30–59	Evaluating and treating complications
4	Severe decrease in GFR	15–29	Preparation for kidney replacement therapy
5	Kidney failure	<15 or dialysis	Renal replacement therapy if uremia is present

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; GFR, glomerular filtration rate.

^aIncludes actions from preceding stages.

^bMay be normal for age.

Source: Reprinted with permission from the National Kidney Foundation KDOQI Clinical Practice Guidelines on Chronic Kidney Disease. *Am J Kidney Dis.* 2002;39(suppl 1):46.

Patients with CKD continually lose GFR over a period of months to years. In many of the underlying conditions, progression of the disease continues even if the kidney is no longer exposed to the initial trigger (14). Eventually, CKD may progress to stage 5, requiring renal replacement therapy such as dialysis or transplantation to sustain life. (See Chapters 3, 5, and 6 for more details.)

Nephrotic Syndrome

Nephrotic syndrome is one of the most serious challenges of clinical nephrology (15). Fundamental alterations of the kidney's glomerular basement membrane allow persistent losses of large amounts of protein in the urine. These changes in the glomerular filtration barrier allow large molecules to pass into the urine (16). These circumstances are most frequently associated with diabetes mellitus, glomerulonephritis, or amyloidosis.

In this context, it should be noted that nephrotic syndrome is not a disease but rather a collection of symptoms that may be seen in CKD of several different etiologies (17). Clinical characteristics include the following:

- Albuminuria (more than 3 g/d urinary albumin losses, with proportionally lesser amounts for children)
- Hypoalbuminemia
- Hypertension
- Hyperlipidemia
- Edema

Because proteinuria (including albuminuria) represents such a high risk for cardiovascular disease and progression of CKD to stage 5, treatment of nephrotic syndrome must include reduction of urinary protein losses. Medical intervention may involve corticosteroids and immunosuppressants in some specific etiologies and angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers to reduce urinary protein losses and to control blood pressure and fluid balance. The latter drugs may be used to reduce proteinuria even when blood pressure is normal (17).

The etiology of elevated lipids in nephrotic syndrome is related to excess production and reduced catabolism of apolipoprotein-B-containing lipoproteins (including chylomicrons and very-low-density lipoproteins). Some patients present with elevated cholesterol, while others have increased cholesterol

and triglycerides (16). Since hyperlipidemia represents increased risk for vascular disease, hydroxymethylglutaryl coenzyme A reductase inhibitors are often used for lipid control. With some disorders, particularly focal sclerosing glomerulonephritis, there may be a proteinuric factor, and the removal of this factor may help manage proteinuria and subsequent hyperlipidemia (18).

The MNT for nephrotic syndrome includes a protein restriction of 0.8 g/kg standard body weight (19,20). This amount seems to reduce proteinuria; however, the patient needs to be closely monitored for malnutrition, and, if needed, the diet can be increased to 1 g/kg to avoid a decline in nutritional status (19,20). Sodium restriction should be based on fluid status and the need to control edema. Potassium and other electrolytes and minerals need to be monitored and the diet individualized. Nutrition therapy for the associated hyperlipidemia may not normalize serum cholesterol levels, and pharmacological therapy, as previously described, is generally required (19–21). It is a clinical challenge to add the recommended interventions for nephrotic syndrome to those already in place for the underlying etiology. More research is needed to identify optimal treatment for nephrotic syndrome.

Conclusion

This chapter has provided a brief overview of normal kidney function and various consequences of kidney disease, along with the many potential etiologies for compromise in kidney function. More detailed information regarding medical treatment and the MNT required at these various stages will be found throughout this publication.

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