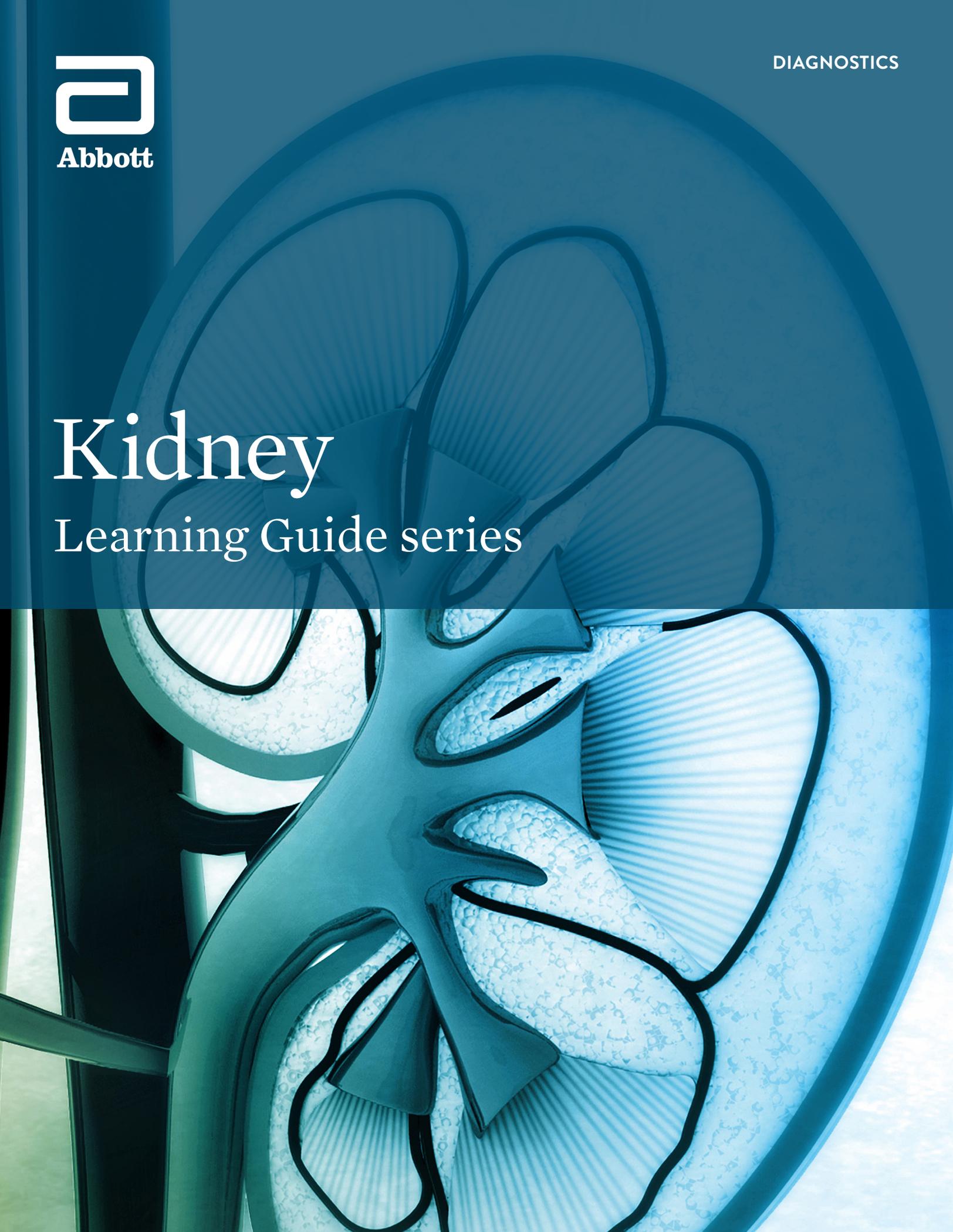




DIAGNOSTICS

Kidney

Learning Guide series



ACKNOWLEDGEMENTS



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ABBOTT DIAGNOSTICS

RENAL EDUCATIONAL SERIES

INTENDED AUDIENCE

This Learning Guide is meant to serve the basic educational needs of healthcare professionals who are involved in the laboratory or manage patients who have or are at risk for kidney disease.

The Renal Educational Series comprises three modules:

- Learning Guide: Kidneys
- Learning Guide: Chronic Kidney Disease (CKD)
- Renal Disease: Shedding Light on Renal Disease

The first module focuses on the structure and function of the kidney. The second and third expand on this foundation, covering the epidemiology, pathophysiology, diagnosis and management of Chronic Kidney Disease (CKD).

HOW TO USE THIS LEARNING GUIDE

To offer you the most benefit from this Learning Guide, each section begins with a set of learning objectives. These will help you focus on the key concepts presented in each section. There is a short quiz at the end of each section designed to help reinforce key concepts covered in that section.

A glossary is included at the end of this Learning Guide for quick reference.

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INTRODUCTION

KIDNEY LEARNING GUIDE

Correct functioning of the urinary system is a critical component of homeostasis in the body. Urine formation and the excretion of wastes is one of the primary functions of the kidneys. The kidneys also help to maintain blood composition, pH and osmolarity, and regulate blood volume, blood pressure and red blood cell production through hormonal mechanisms.

The kidneys are also responsible for producing biologically active vitamin D hormone (calcitriol), which plays a critical role in the regulation of mineral homeostasis, and of calcium and phosphate in particular. The body's delicate mineral balance is orchestrated by complex hormonal feedback mechanisms that involve the kidneys, thyroid and parathyroid glands, bone, and the intestines, and are mediated by parathyroid hormone (PTH), calcitriol and other hormones.¹

SECTION 1

THE KIDNEYS

LEARNING OBJECTIVES

After completing this section, you will be able to:

- Describe the functions of the kidney
- Identify the basic structures of the kidney
- Describe the function of the nephron
- Describe the structures that transport urine out of the body after it exits the kidneys

OVERVIEW OF THE KIDNEYS

The kidneys are a pair of kidney bean–shaped organs located just above the waist, between the **peritoneum** and the back of the abdomen. The two kidneys lie behind the liver and the intestines in the small of the back. They are partially protected by the 11th and 12th pair of ribs.

As shown in **Figure 1-1**, the left kidney is slightly higher than the right, since the liver occupies the space above the kidney on the right side.²

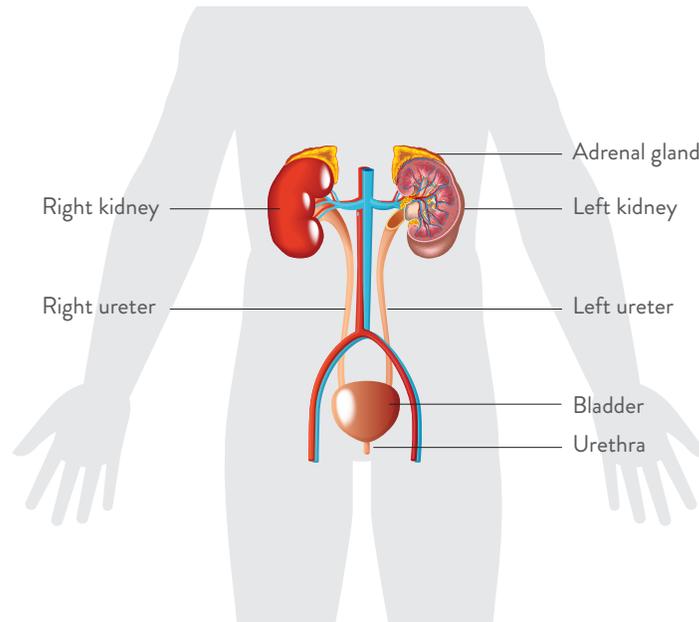


Figure 1-1: The organs of the urinary system.¹⁻¹

FAST FACT

The adrenal glands are a pair of flattened, pyramid-shaped glands that lie on top of the kidneys. They produce the hormones norepinephrine and epinephrine. These two hormones regulate the stress response, which increases heart rate and blood pressure. The adrenal glands also produce aldosterone, which will be discussed later in this module.¹

FUNCTIONS

The kidneys are the hardest working organs of the urinary system. The other components of the urinary system serve mainly as passageways or for storage of urine.

The functions of the kidneys include:¹

- Excreting wastes and foreign substances in the urine
- Regulating various properties of blood, including:
 - **Ionic composition** – by regulating the concentrations of several ions, such as sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), chloride (Cl^-) and phosphate (HPO_4^{2-})
 - **pH** – by excreting hydrogen ions (H^+) and conserving bicarbonate ions (HCO_3^-)
 - **Osmolarity** – by separately regulating the loss of water and solutes in the urine
 - **Blood volume** – by conserving or eliminating water in the urine, blood pressure is increased or decreased
 - **Blood pressure** – by secreting the enzyme **renin**, a component of the **renin-angiotensin-aldosterone (RAA) system**; renin causes an increase in blood pressure
 - **Blood glucose levels** – by synthesizing and releasing new glucose molecules
- Producing **hormones**:
 - **Calcitriol** – the active form of vitamin D, which helps regulate calcium levels
 - **Erythropoietin (EPO)** – which stimulates the production of red blood cells

CLINICAL CONNECTION

The kidneys regulate blood pressure by producing the enzyme renin. An increase in the production of renin results in an increase in blood pressure.¹

Normal kidney functions collectively contribute to the maintenance of **homeostasis**, as summarized by **Figure 1-2**.

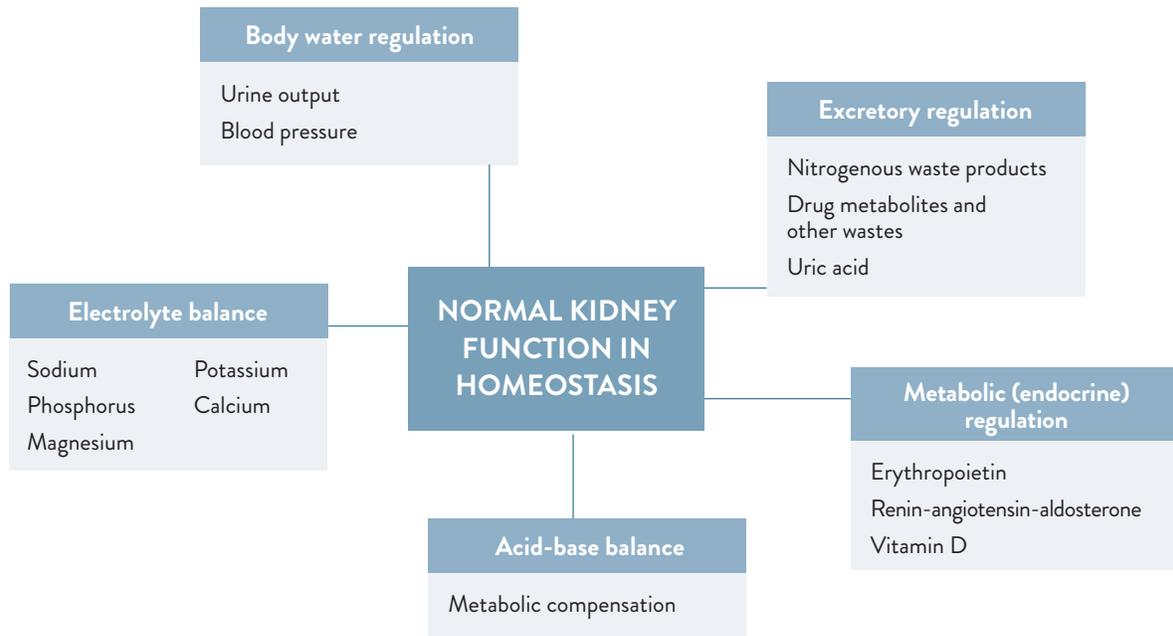


Figure 1-2: The function of the kidneys in the maintenance of homeostasis.^{1,2}

FAST FACT

The main functions of the kidneys are the reabsorption of solutes and water, production of urine, and excretion of wastes. The kidneys also perform several homeostatic functions, including regulation of electrolytes, acid-base balance, and blood pressure. They also produce the hormones vitamin D and erythropoietin.^{1,1}

STRUCTURE OF THE KIDNEYS

FAST FACT

A typical adult kidney is 10–12 cm (4–5 in) long, 5–7 cm (2–3 in) wide, and 3 cm (1 in) thick, roughly the size of a bar of bath soap, and weighs 135–150 g (4.5–5 oz).¹⁻¹

If one was to slice a kidney in half (as illustrated by **Figure 1-3**), two distinct regions would be revealed:

- A superficial, smooth-textured reddish exterior portion called the renal cortex
- A deep, reddish-brown inner region called the renal medulla

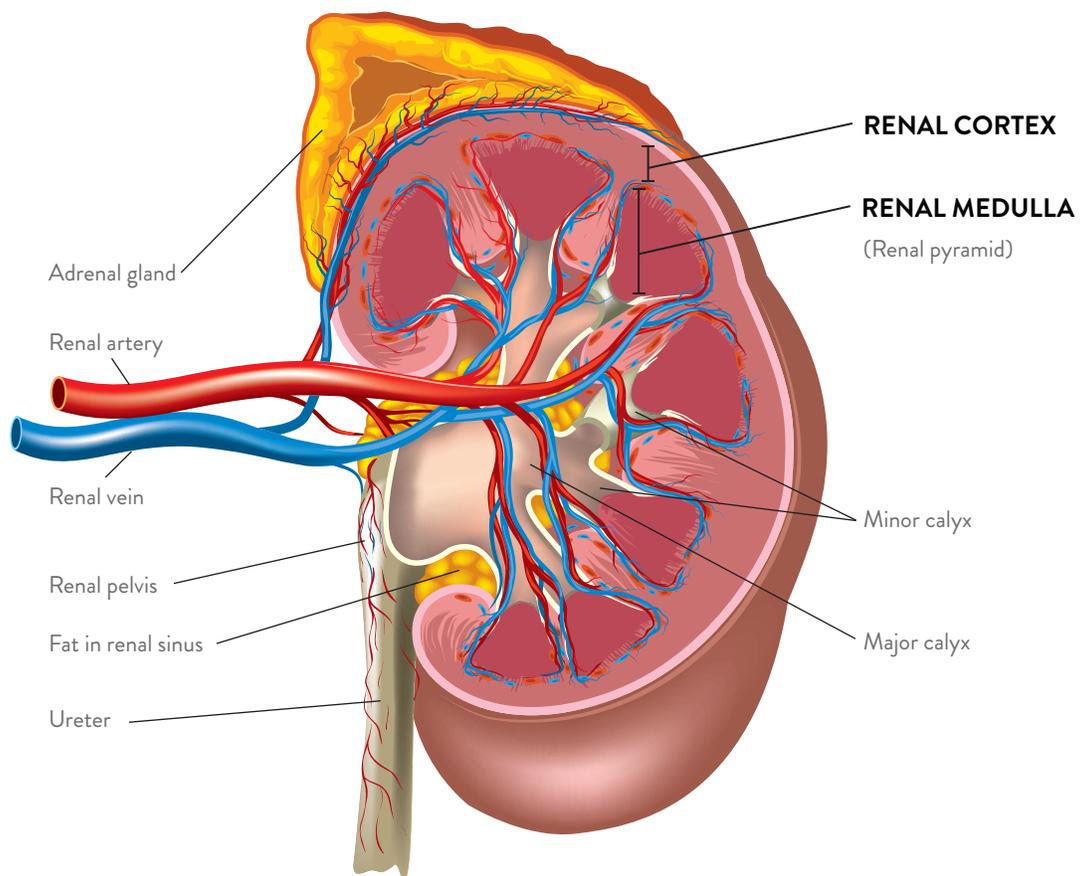


Figure 1-3: Internal anatomy of the kidneys.¹⁻¹

RENAL CORTEX

The renal cortex refers to the smooth-textured area extending from the exterior (renal capsule) to the bases of striated, cone-shaped structures called renal pyramids and into the spaces between them. The renal capsule is the membrane that covers the surface of the kidney.

RENAL MEDULLA

The renal medulla consists of 8–18 renal pyramids. The base of each pyramid faces towards the renal cortex, and the apex of each pyramid, called the renal papilla, points to the renal hilum (the area of the kidney through which the ureter, blood vessels, lymphatic vessels, and nerves emerge).^{1,1} The portions of renal cortex that extend between renal pyramids are called renal columns. A renal lobe consists of^{1,1}:

- A renal pyramid
- The overlying area of renal cortex
- Half of each adjacent renal column

NEPHRON

Together the renal cortex and renal medulla constitute the functional portion of the kidney, called the parenchyma. The **parenchyma** contains approximately one million microscopic structures called **nephrons**, which are the filtration units of the kidney.^{1,1}

FAST FACT

The nephrons are the functional units of the kidneys. Nephrons and collecting ducts perform three basic functions: filtration of the blood, reabsorption of water and solutes, and secretion of wastes from the blood. These processes help to maintain homeostasis within the body.^{1,1}

Each nephron consists of two parts (shown in **Figure 1-4**):¹⁻¹

- A renal corpuscle
- A renal tubule

A renal corpuscle is comprised of the glomerulus (a **capillary** network) plus the glomerular (Bowman's) capsule, a double-walled epithelial cup that surrounds the glomerular capillaries. This configuration creates a thin, porous filtration membrane, which allows passage of water and small solutes, but prevents filtration of most plasma proteins, blood cells, and platelets. The filtered fluid passes into the renal tubule.¹⁻¹

The renal tubule is composed of three main sections, which are (in the order in which fluid passes):¹⁻¹

- Proximal convoluted tubule (attached to the glomerular capsule)
- Loop of Henle (nephron loop)
- Distal convoluted tubule

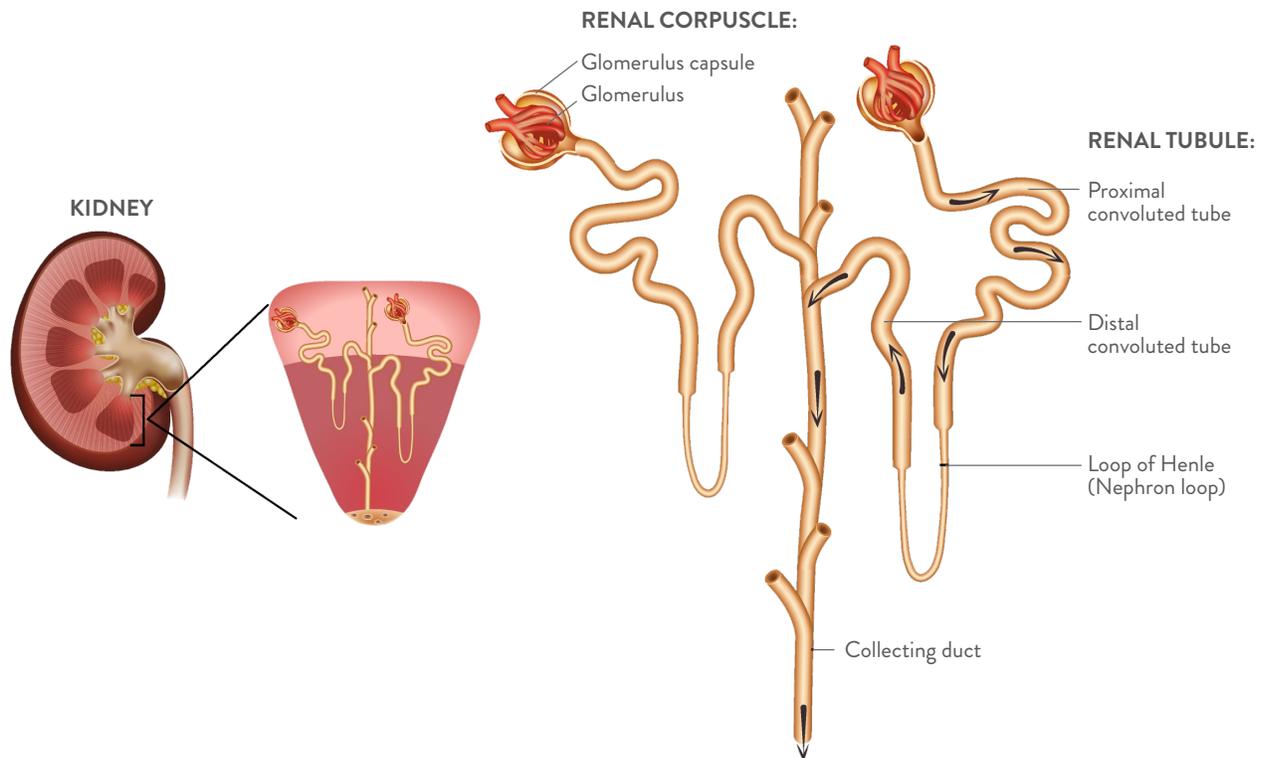


Figure 1-4. The functional components of a nephron.¹⁻¹

PROXIMAL CONVOLUTED TUBULES

The proximal convoluted tubule is attached to the glomerular capsule and is the first structure through which fluid passes. The largest amount of solute and water reabsorption from filtered fluid occurs in the proximal convoluted tubules. Reabsorbed substances include glucose, amino acids, lactic acid, water-soluble vitamins, and ions such as Na^+ , K^+ , Cl^- , Ca^{2+} , Mg^{2+} , HCO_3^- and HPO_4^{2-} . At the same time, waste products such as NH_4^+ , urea and small amounts of creatinine are secreted into urine.¹⁻¹

LOOP OF HENLE

The loop of Henle connects the proximal and distal convoluted tubules. The descending part of this structure dips into the renal medulla. It next makes a hairpin turn and ascends to the renal cortex. Approximately 80–85% of nephrons reside in the outer portion of the renal cortex. The other 15–20% of nephrons exist deep in the cortex. Additional filtered ions and water are reabsorbed from the loop of Henle.¹⁻¹

DISTAL CONVOLUTED TUBULES

Resorption of remaining Na^+ , Cl^- , Ca^{2+} and water continue as fluid flows along the distal convoluted tubule. By the time the fluid reaches the end of the distal convoluted tubule, 90–95% of filtered solutes and water have returned to the bloodstream. Remaining substances that have not been reabsorbed are excreted in the urine.¹⁻¹

DUCTS, CALYCES AND THE RENAL PELVIS

Distal convoluted tubules from several nephrons empty into a single collecting duct. The collecting ducts unite and later converge into large papillary ducts, which then drain into cuplike structures called calyces. Urine then moves into a single large cavity called the renal pelvis, and subsequently through the ureter into the urinary bladder.¹⁻¹

CLINICAL CONNECTION

Acute kidney injury (AKI), an abrupt and sustained decline in renal function, leads to loss of the affected nephrons. In 80% of patients, necrosis (death) of tubular cells, but not glomeruli or surrounding tissues, occurs. Causes of AKI may include oxygen deficiency, sepsis or toxic kidney injury.¹⁻³

RENAL BLOOD SUPPLY

The kidneys are supplied with numerous blood vessels due to their critical function in waste removal and the regulation of blood volume and composition. Despite their small size (less than 0.5% of total body mass), the kidneys receive 20–25% of the volume of blood pumped by the heart while at rest (resting cardiac output). In healthy adults, renal blood flows through both kidneys at a rate of approximately 1200 mL per minute.¹⁻¹

LOWER URINARY TRACT

Urine drains from the kidneys through the ureters into the bladder, and subsequently out through the urethra during urination (**micturition**).^{1,1}

URETERS

There are two **ureters**—one for each kidney. They transport urine from the renal pelvis to the urinary bladder. Along with gravity and hydrostatic pressure, muscular contractions push urine through the ureters. The ureters are long and thick-walled narrow tubes. They measure 25–30 cm (10–12 in) in length and vary in diameter from 1–10 mm between the renal pelvis and the urinary bladder. Like the kidneys, the ureters are positioned behind the peritoneum. They curve at their ends and pass through the wall of the bladder.^{1,1}

Although there is no anatomical valve between each ureter and the bladder, a physiological one exists. As the bladder fills with urine, it compresses the openings to the ureters, and prevents the backflow of urine. If this valve does not operate properly, microbes may travel up the ureters to cause a kidney infection.^{1,1}

URINARY BLADDER

The bladder stores urine. Situated in the pelvic cavity, the **urinary bladder** is a hollow, distensible muscular organ. In males it is directly in front of the rectum, whereas in females it is in front of the vagina and below the uterus. Held in place by folds of the peritoneum, the bladder becomes slightly distended and spherical as it fills with urine. When empty, the bladder collapses. Urinary bladder capacity ranges from 700–800 mL, and is slightly smaller in females due to the position of the uterus.^{1,1}

FAST FACT

When the volume of the bladder exceeds 200–400 mL, pressure within the bladder increases. Stretch receptors in the bladder transmit nerve impulses into the spinal cord, triggering a spinal reflex that gives the sensation of a full bladder. This creates a conscious desire to urinate. By controlling the urethral sphincter and pelvic muscles, a person can initiate or delay urination for a limited period.^{1,1}

URETHRA

The **urethra** carries urine out of the body. It is a small tube that leads from the urinary bladder to the exterior of the body.^{1,1}

- In females, the urethra has a length of 4 cm (1.5 in) and opens to the exterior through the external urethral orifice between the clitoris and the vaginal opening.
- In males, the urethra is approximately 20 cm (8 in) long and extends from the urinary bladder to the exterior, but it first passes through the prostate, then through the deep muscles of the perineum, and lastly through the penis.

REVIEW QUESTIONS: SECTION 1

Answers are provided at the end of this Learning Guide.

1. Which organs constitute the urinary system?

2. What are three functions of the kidneys?

3. At which location is the largest amount of water and solutes reabsorbed into the bloodstream?

- A Distal tubule
- B Glomerulus
- C Proximal tubule
- D Ureter

4. What is the path for fluid through a nephron?

- A Bowman's capsule → proximal convoluted tubule → loop of Henle → distal convoluted tubule
- B Loop of Henle → Bowman's capsule → proximal convoluted tubule → distal convoluted tubule
- C Proximal convoluted tubule → Bowman's capsule → distal convoluted tubule → loop of Henle

5. Complete the table by matching the organ (kidneys, ureters, urethra, urinary bladder) with its function:

FUNCTION	ORGAN
Elimination of urine	
Production of urine	
Storage of urine	
Transport of urine	

SECTION 2

URINE FORMATION, TRANSPORT AND ELIMINATION

LEARNING OBJECTIVES

After completing this section, you will be able to:

- Understand the normal composition of urine
- Describe the process of urine formation
- Describe how glomerular filtration rate (GFR) is related to kidney function
- Identify the differences between the reabsorption and secretion processes

COMPOSITION OF URINE

Routine assessment of kidney function involves the evaluation of both the quantity and quality of urine, as well as the levels of waste in the blood. The analysis of the volume, physical, chemical, and microscopic properties of urine is called a **urinalysis**. It is one test physicians use to assist them in their routine assessment of kidney function and general physical health.¹⁻¹

A normal adult will eliminate 1–2 liters of urine per day. The characteristics of normal urine are listed in **Table 2-1**.

CHARACTERISTIC	DESCRIPTION
Volume	1–2 liters in 24 hours Can vary with fluid intake
Color	Yellow or amber Varies with concentration and diet Certain medications and certain diseases may also affect color
Turbidity	Transparent when freshly voided Becomes turbid (cloudy) upon standing
Odor	Mildly aromatic Becomes ammonia-like upon standing Can also vary with diet and certain diseases
pH	4.6–8.0 (average of 6.0) Varies with diet
Specific gravity (density)	1.001–1.035 Increases as concentration of solutes increases

Table 2-1: Characteristics of Normal Urine.¹⁻¹

WATER AND SALT

Water accounts for approximately 95% of the total volume of urine; the remaining 5% consists of electrolytes. Electrolytes are solutes derived from cellular metabolism and exogenous substances such as drugs. Specific hormones increase reabsorption of water and salts in the renal tubules. Factors such as fluid intake, diet and general health can also influence urine volume.¹⁻¹

INORGANIC SOLUTES

Typical solutes normally present in urine include filtered and secreted electrolytes that are not reabsorbed. Inorganic solutes (ions), such as potassium, are secreted by cells in the collecting duct.¹⁻¹

ORGANIC SOLUTES

A number of organic solutes are also found in urine, including¹⁻¹:

- **Urea** from the breakdown of proteins
- **Creatinine** from the breakdown of creatine phosphate in muscle fibers
- Uric acid generated from the breakdown of nucleic acids
- Urobilinogen from the breakdown of hemoglobin
- Fatty acids, pigments, enzymes and hormones

If body metabolism or kidney function is altered by disease, then substances not normally present may be found in the urine, or normal constituents may appear in abnormal amounts. For example, the presence of glucose in the urine, referred to as glucosuria, usually indicates diabetes mellitus.¹⁻¹

CLINICAL CONNECTION

In diabetes mellitus, the body is unable to produce or use insulin. Because insulin is not available to transport glucose into the cells, excess glucose is excreted in the urine, leading to glucosuria. Because of the high levels of glucose in the fluid being filtered through the renal tubules, the kidneys' ability to reabsorb water is reduced. This leads to excessive urine production, referred to as polyuria.¹

PROTEIN

Normal urine is virtually free of protein. The presence of protein in the urine is called **proteinuria**. This condition can indicate improper functioning of the kidneys. For example, the plasma protein **albumin** usually appears in urine in only trace amounts due to its large size and inability to pass through the tiny openings (fenestrations) in the capillary walls that allow the kidneys to act as filters. If the permeability of filtration membranes increases due to injury, irritation or disease of the kidneys, or due to elevated blood pressure, albumin and other proteins can enter the urine.¹⁻¹ For example, microalbuminuria (small amounts of albumin in the urine) is an early manifestation of kidney disease related to diabetes, hypertension or glomerular damage.²⁻¹

CLINICAL CONNECTION

Several different tests are used to evaluate kidney disease. These tests include measurement of protein or albumin levels in urine and calculation of the rate at which creatinine is cleared in the urine. The urinary albumin-to-creatinine ratio (UACR) is one method of quantifying proteinuria.²⁻¹

Blood tests, as well as urinalysis, can be used to evaluate kidney function. Blood urea nitrogen (BUN) is a test that measures the levels of blood nitrogen from the urea that is generated by the breakdown of amino acids. BUN is elevated when renal disease or obstruction of the urinary tract occurs and glomerular filtration rate (GFR) is decreased or when the renal blood flow is reduced.¹⁻¹

Estimates of GFR (eGFR) are considered the best overall measure of the level of kidney function. To estimate the GFR, prediction equations take into account serum creatinine concentration and some or all of the following variables: age, gender, race and body size.²⁻¹ An emerging method of estimating GFR is based on blood levels of **cystatin C**, a small protein freely filtered by the glomerular membrane and degraded in the proximal tubules.²⁻²

Table 2-2 lists the components of urine, and the amount filtered, reabsorbed and excreted per day.

SUBSTANCE	FILTERED ^a (ENTERS GLOMERULAR CAPSULE PER DAY)	REABSORBED (RETURNED TO BLOOD PER DAY)	URINE (EXCRETED PER DAY)
Water	180 liters	178–179 liters	1–2 liters
Proteins	2.0 g	1.9 g	0.1 g
Sodium ions (Na ⁺)	579 g	575 g	4 g
Chloride ions (Cl ⁻)	640 g	633.7 g	6.3 g
Bicarbonate ions (HCO ₃ ⁻)	275 g	274.97 g	0.03 g
Glucose	162 g	162 g	0 g
Urea	54 g	24 g	30 g ^b
Potassium ions (K ⁺)	29.6 g	29.6 g	2.0 g ^c
Uric acid	8.5 g	7.7 g	0.8 g
Creatinine	1.6 g	0 g	1.6 g
Cystatin C	0.17 g ^d	—	0.017 g

Table 2-2: Substances filtered, reabsorbed and excreted by the healthy kidney.¹⁻¹

^aAssuming GFR is 180 liters per day.

^bIn addition to being filtered and reabsorbed, urea is secreted.

^cAfter virtually all filtered K⁺ is reabsorbed in the convoluted tubules and loop of Henle, a variable amount of K⁺ is secreted in the collecting duct.

^dAssuming normal plasma concentration of 0.96 mg/L and normal urine concentration of 0.095 mg/L.²⁻² Multiplied by GFR of 180 L/day.

GLOMERULAR FILTRATION

As shown in **Figure 2-1**, glomerular filtration is the initial step towards urine production. Water and most of the solutes in blood plasma move across the walls of the glomerular **capillaries** (the smallest of the blood vessels) into the glomerular capsule, and into the renal tubule. Solutes that are in the fluid draining into the renal pelvis stay in the urine and are eventually excreted.^{1,1}

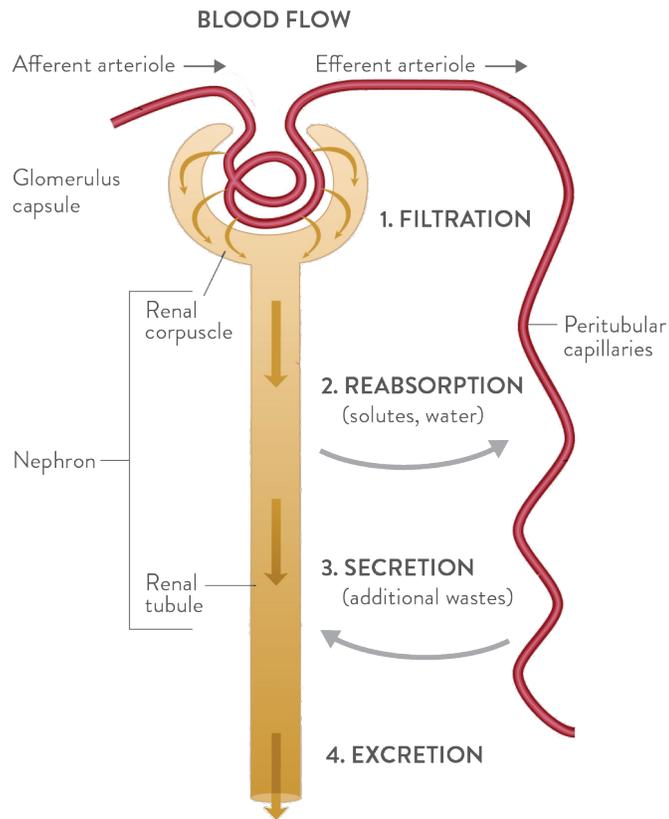


Figure 2-1: Relation of the structure of a nephron to its three basic functions: glomerular filtration, tubular reabsorption and tubular secretion.¹⁻²

FILTRATION PROCESS

Filtration is the first basic function of the **nephron**. The endothelial cells of glomerular capillaries, plus a layer of epithelial cells that encircle the capillaries, form a leaky barrier known as the filtration membrane. It allows the filtration of most water and small solutes, but prevents the filtration of plasma proteins, blood cells and platelets. The filtration membrane is a sandwich-like assembly. A solute's size and charge determine how easily it can pass through glomerular capillary membranes.^{1,1}

Pressure forces fluids and solutes through the capillary membrane. The same process occurs in glomerular capillaries as in other capillaries in the body. However, the volume of fluid filtered by the glomerular capillaries is much greater. Three factors permit this high throughput:¹⁻²

- Glomerular capillaries have a large surface area
- The filtration membrane is thin and porous
- Glomerular capillary blood pressure is high, which creates resistance to the outflow of blood from the glomerulus and promotes filtration by pushing water and solutes through the capillary membrane

Meanwhile, hydrostatic and osmotic pressures oppose filtration by pushing fluid back into the capillaries.¹⁻¹

GLOMERULAR FILTRATION RATE

The **glomerular filtration rate (GFR)** refers to the amount of filtrate formed in all the renal corpuscles of both kidneys each minute. In adults, the average is 125 mL/min for men and 105 mL/min for women. Homeostasis of body fluids dictates that a relatively constant GFR is required.¹⁻¹

- If the GFR is too high, needed substances may pass through the renal tubules and be lost in the urine
- If the GFR is too low, all of the filtrate may be reabsorbed and too few waste products excreted

FAST FACT

Creatinine clearance is a test to measure how efficiently the kidneys remove creatinine and other wastes from the blood. Low creatinine clearance indicates impaired kidney function.²⁻³ Creatinine clearance is related to GFR. Plasma levels of creatinine are stable in healthy individuals because creatinine is produced at a steady rate by muscle. Creatinine in urine comes from excretion of plasma creatinine in the kidneys. There is a steady daily excretion of urine creatinin – however, over short periods of time (hours), the urine creatinine concentration varies with the state of hydration and concentration of urine. By measuring blood and urine creatinine levels over a specific period, the rate of creatinine clearance (mL/min) can be calculated.¹⁻¹

The normal range for serum creatinine is approximately 0.5–1.1 mg/dL in adult females, and approximately 0.6–1.2 mg/dL in adult males. This range may vary by age, gender and weight.²⁻⁴

The kidneys, nervous system and hormones regulate GFR by¹⁻¹:

- Adjusting blood flow into and out of the glomerulus
- Altering the glomerular capillary surface available for filtration

CLINICAL CONNECTION

Acute kidney injury (AKI) is an abrupt reduction in kidney function. It is associated with increased serum creatinine levels, decreased GFR, and oliguria (reduction in urine output) for more than six hours.²⁻⁵ Loss of kidney function in AKI may be reversible, requiring temporary dialysis, or may progress to end-stage renal disease (ESRD), necessitating permanent renal replacement therapy.²⁻⁶

Serum creatinine alone is a poor marker of early renal dysfunction, as it is a functional marker that is not specific for AKI and is influenced by numerous nonrenal factors. Consequently, development of other biomarkers of early kidney damage is an intense area of investigation. Several biomarkers have been identified within the last decade that can detect AKI earlier than creatinine. The most promising of these include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, kidney injury molecule-1 (KIM-1), liver fatty acid binding protein (L-FABP) and interleukin-18 (IL-18).^{1-3, 2-7}

Chronic kidney disease (CKD) refers to a progressive and usually irreversible decline in GFR. CKD occurs in stages, over a prolonged timeframe. A patient with CKD Stage 1 has an estimated GFR (eGFR) ≥ 90 mL/min/1.73 m². By CKD Stage 5, the GFR is diminished to 10–15% of normal (eGFR of < 15 mL/min/1.73 m²). This final stage denotes ESRD, necessitating renal replacement therapy by dialysis or transplant.^{1-1, 2-1}

TUBULAR REABSORPTION AND SECRETION

Approximately 99% of filtered water and many useful solutes are reabsorbed and returned to the blood as fluid flows along the renal tubule and through the collecting duct. As fluid flows through the renal tubule and collecting duct, the tubule and duct cells secrete materials such as wastes, drugs and excess ions into the fluid. Therefore, **tubular reabsorption** returns substances to the blood, and tubular secretion removes substances from the blood.¹⁻¹

REABSORPTION

Reabsorption is the second basic function of the nephron and collecting duct. As fluid flows through the nephron, solutes such as glucose, amino acids, urea and ions, as well as small proteins and peptides, are returned to the blood.

Most reabsorption occurs in the proximal convoluted tubule. Cells along the remaining length of the distal nephron further reabsorb water and selected ions in order to maintain homeostasis.¹⁻¹

FAST FACT

The volume of blood that enters the proximal convoluted tubules every 30 minutes is greater than the total blood plasma volume of the body. This is possible because the normal rate of glomerular filtration is so high.¹⁻¹

SECRETION

The third function of nephrons and collecting ducts is **tubular secretion**, the transfer of substances such as hydrogen ions (H^+), potassium (K^+), ammonium ions (NH_4^+), certain drugs from the blood and tubule cells into the tubular fluid. There are two critical outcomes to tubular secretion: the secretion of H^+ helps to control blood pH, and the secretion of other waste products helps eliminate them from the body.¹⁻¹ In healthy individuals, creatinine is not secreted in significant amounts by the kidneys. Creatinine entering the urine comes from passive glomerular filtration. In severe renal disease, when plasma creatinine is high, active tubular secretion becomes important.

CLINICAL CONNECTION

Several low molecular weight proteins and enzymes are filtered through the glomerulus and subsequently reabsorbed in the proximal tubule. Tubular injury may increase the concentration of these proteins in the urine even though less is being filtered.²⁻⁸ Serum cystatin C is a marker of decreased GFR, whereas urine cystatin C is a marker of tubular injury.²⁻⁹

Acute kidney injury (AKI) induces the expression of a number of proteins in the renal tubules. These proteins are excreted in urine and are thus being evaluated as specific biomarkers to help diagnose AKI and potentially differentiate between different subtypes and pathologies of kidney injury. They include interleukin-18 (IL-18) and neutrophil gelatinase-associated lipocalin (NGAL).^{1-3, 2-7, 2-10}

HORMONAL REGULATION

Tubular reabsorption and tubular secretion are regulated by hormones, which are described in **Table 2-3**. These hormones will be discussed in greater detail in the next section.

HORMONE	MAJOR STIMULI THAT TRIGGER RELEASE	EFFECTS
Angiotensin II	Low blood volume or low blood pressure stimulates renin-induced production of angiotensin II	Increases reabsorption of Na^+ , other solutes and water, which increases blood volume
Aldosterone	Increased angiotensin II level and increased level of plasma K^+ promotes release of aldosterone by adrenal cortex	Increases secretion of K^+ and reabsorption of Na^+ , Cl^- Increases reabsorption of water, which increases blood volume
Antidiuretic hormone (ADH) or vasopressin	Increased osmolarity of extracellular fluid or decreased blood volume promotes release of ADH from the posterior pituitary gland	Increases facultative reabsorption of water, which decreases osmolarity of body fluids
B-Natriuretic peptide (BNP)	Stretching of the ventricles and atria of the heart stimulates secretion of BNP	Increases excretion of Na^+ in urine (natriuresis) Increases urine output (diuresis) Decreases blood volume

Table 2-3: Hormonal regulation of tubular reabsorption and tubular secretion.¹⁻¹

REVIEW QUESTIONS: SECTION 2

Answers are provided at the end of this Learning Guide.

1. Where does filtration take place?

- A Collecting duct
- B Distal tubule
- C Glomerulus
- D Proximal tubule

2. Which of the following is not normally found in urine?

- A Creatinine
- B Glucose
- C Urea
- D Water
- E All of the above

3. What is currently considered the best way to assess kidney function?

- A Blood urea nitrogen (BUN)
- B Creatinine clearance rate
- C Estimates of glomerular filtration rate (GFR)
- D Urinary albumin-to-creatinine ratio

4. During tubular reabsorption, ____% of filtered water is reabsorbed.

- A 50
- B 75
- C 99

SECTION 3

RENAL REGULATION OF BLOOD COMPOSITION AND VOLUME

LEARNING OBJECTIVES

After completing this section, you will be able to:

- Summarize the role of the kidneys in regulating blood composition
- Understand how hormones act on the kidneys to regulate blood volume and pressure

REGULATION OF BLOOD COMPOSITION

To perform correctly, the cells of the body require stable **osmolarity**, stable pH and glucose levels, and constant removal of wastes. These functions are provided, in part or in whole, by the kidneys.¹⁻¹

FAST FACT

The osmolarity of a solution is a measure of the total number of dissolved particles (molecules and/or ions) per liter of solution. A similar term, **osmolality**, is the number of particles of solute per kilogram of water. Most body fluids and solutions used clinically are dilute, in which case there is less than a 1% difference between the two measures.¹⁻¹

IONIC COMPOSITION AND OSMOLARITY

The kidneys maintain a relatively constant blood osmolarity by regulating the loss of water and solutes. Reabsorption in the nephron collecting ducts helps to maintain this balance.¹⁻¹

Most solute and water reabsorption from filtered fluid occurs in the proximal convoluted tubules. Sodium (Na^+) ions are the major contributor to osmolarity and fluid volumes. Other ions, such as potassium (K^+), calcium (Ca^{2+}), and chloride (Cl^-), must also be maintained within tight control to ensure proper cellular functioning.¹⁻¹

CLINICAL CONNECTION

Parathyroid hormone (PTH) is a major regulator of the levels of calcium (Ca^{2+}), magnesium (Mg^{2+}) and phosphate (HPO_4^{2-}) ions in the blood. The specific action of PTH is to increase the number and activity of cells called **osteoclasts** that break down mineralized bone. This releases calcium and phosphates from bone into the blood.

PTH also acts on the kidneys. It slows the rate at which calcium and magnesium ions are lost from the blood into the urine, and it increases the loss of phosphate from the blood into the urine. PTH also stimulates the formation of calcitriol (the active form of vitamin D, often referred to as 1,25 dihydroxy Vitamin D).¹

ACID-BASE BALANCE AND BICARBONATE

To regulate acid-base balance (pH), the kidneys excrete variable amounts of hydrogen ions (H^+) into the urine and conserve bicarbonate ions (HCO_3^-), which buffer H^+ in the blood. The equilibrium between these two ions regulates blood pH. Slight changes in concentration can cause significant alterations in physiologic functions.¹⁻¹

UREA WASTE

Urea is generated from the breakdown of amino acids, and some is normally excreted in urine. After being filtered in the glomerulus, variable amounts of urea are reabsorbed or secreted in the tubules and collecting ducts. If the glomerular filtration rate decreases significantly, such as with renal disease, urea is not effectively eliminated in the urine and collects in the blood. This can be confirmed by the measurement of blood urea nitrogen (BUN).¹⁻¹

BLOOD GLUCOSE AND GLUCONEOGENESIS

The kidneys are able to synthesize and release new glucose molecules from substances other than glycogen or simple sugars in a process called gluconeogenesis. The kidneys convert the amino acid glutamine to glucose, thus helping to maintain normal blood glucose levels.^{1,1-1}

RED BLOOD CELLS

The kidneys regulate red blood cell formation through a hormone called **erythropoietin (EPO)**.³⁻¹ EPO is produced by the kidneys and increases the number of red blood cell precursors. In renal failure, EPO levels decrease and red blood cell production declines.³⁻¹

CLINICAL CONNECTION

Anemia (the condition of having too few red blood cells) is common in patients with chronic kidney disease due to a lack of erythropoietin.²⁻³

REGULATION OF BLOOD VOLUME AND PRESSURE

Four different hormones affect the absorption of sodium ions, chloride ions and water, as well as the secretion of potassium ions by the renal tubules. The most important regulators of electrolyte reabsorption and secretion are angiotensin II and aldosterone. The major hormone for regulating water reabsorption is antidiuretic hormone (ADH). B-natriuretic peptide (BNP), and, to a lesser degree, atrial natriuretic peptide (ANP), also play a role in inhibiting both electrolyte and water reabsorption.¹

RENIN-ANGIOTENSIN-ALDOSTERONE (RAA) SYSTEM

The renin-angiotensin-aldosterone system controls the secretion of aldosterone hormone by the adrenal glands that lie on top of the kidneys. Aldosterone regulates the homeostasis of two mineral ions – sodium (Na^+) and potassium (K^+) – and helps to adjust blood pressure and blood volume.¹

Figure 3-1 summarizes the effects of renin, angiotensin and aldosterone.¹

- Dehydration, sodium deficiency or hemorrhage decrease blood volume and blood pressure
- Low blood pressure stimulates the kidneys to secrete **renin**, an enzyme that converts angiotensinogen (a plasma protein produced in the liver) to angiotensin I
- Angiotensin I travels through the bloodstream to the lungs, where angiotensin-converting enzyme (ACE) converts it to the active hormone, angiotensin II
- Angiotensin II stimulates:
 - Contraction of smooth muscle in the walls of arterioles, which helps raise blood pressure towards normal
 - Secretion of aldosterone by the adrenal glands
- Upon reaching the kidneys, aldosterone increases:
 - Reabsorption of sodium and water, so that less is lost in the urine
 - Secretion of potassium and hydrogen ions into the urine
- Blood volume and blood pressure increase due to increased water reabsorption

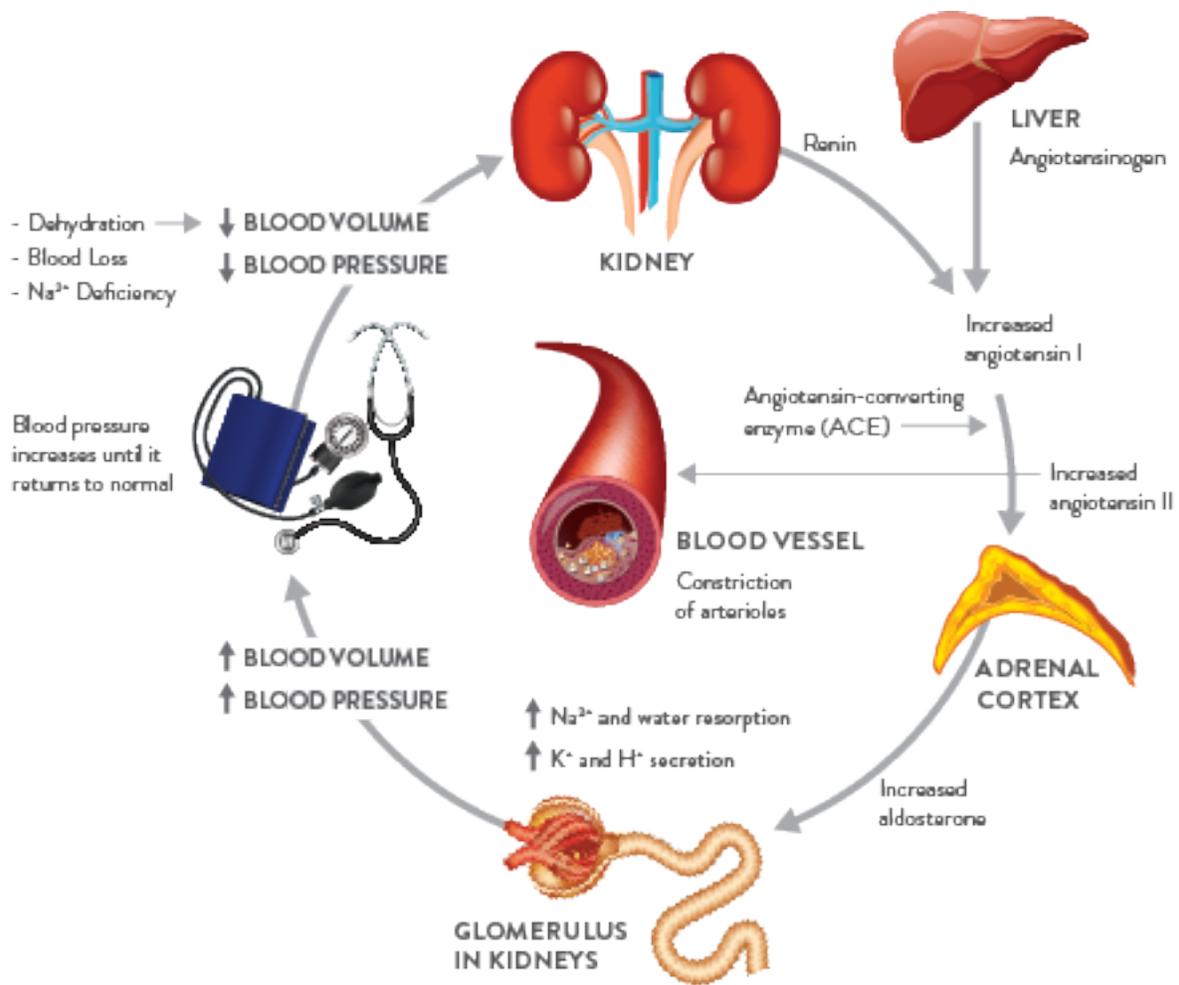


Figure 3-1. The regulation of aldosterone secretion by the renin-angiotensin-aldosterone system.¹

ANTIDIURETIC HORMONE (VASOPRESSIN)

Antidiuretic hormone (also known as ADH or vasopressin) is released by the pituitary gland at the base of the brain. ADH regulates water reabsorption by increasing the water permeability of cells in the distal convoluted tubule and collecting duct.

- When ADH concentrations are high, the kidneys produce as little as 400 to 500 mL of concentrated urine. This serves to retain fluid in the body and raise blood pressure.
- When ADH levels are low, the kidneys produce a large amount of dilute urine.

The regulation of ADH involves a negative feedback loop, shown in **Figure 3-2¹**:

- The hypothalamus (a region of the brain that coordinates many hormonal and homeostatic processes) detects an increase in osmolarity (i.e., a decrease in water concentration and a concomitant increase in solutes).
- The hypothalamus stimulates the pituitary gland to secrete ADH.
- ADH makes the cells of the kidneys more permeable to water and increases water reabsorption.
- Plasma osmolarity decreases and homeostasis is restored in the body, which subsequently stops the release of ADH.

A precipitous decrease in blood volume (e.g., due to hemorrhage or severe dehydration) is also a stimulus for ADH.¹¹

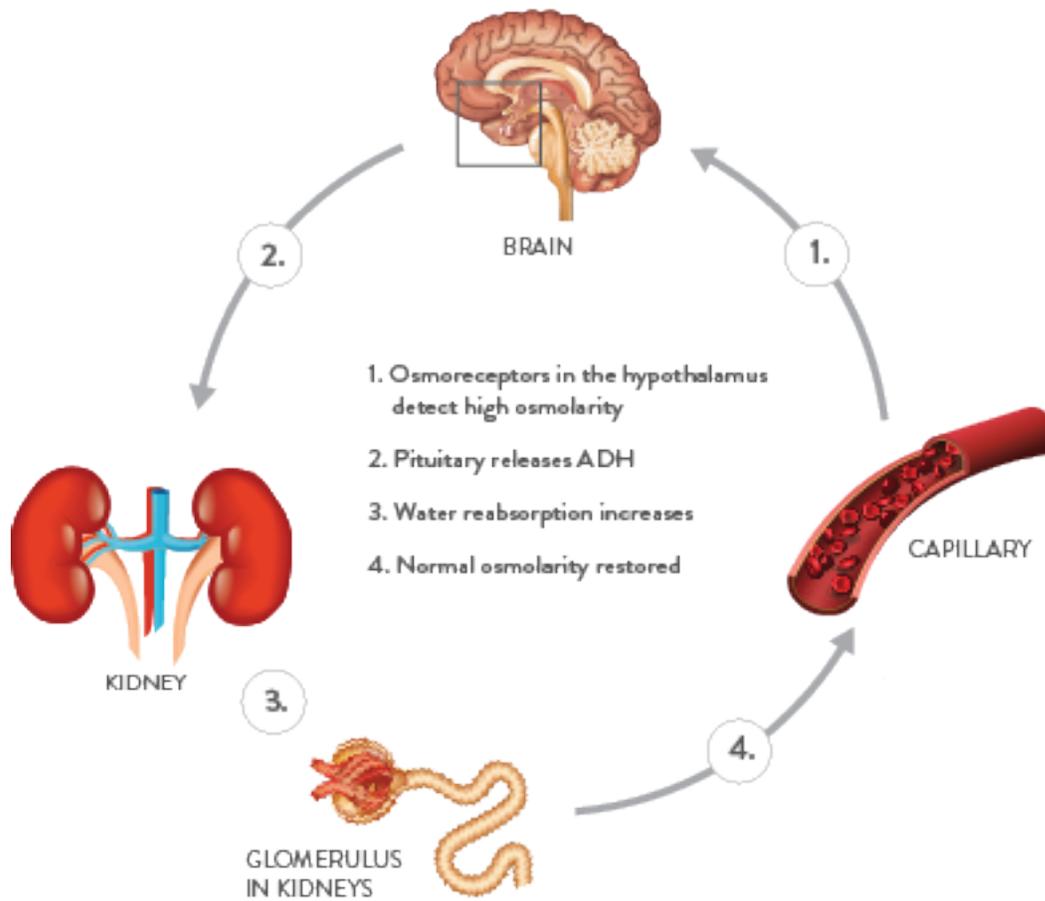


Figure 3-2: Negative feedback regulation of water reabsorption by ADH.

B-NATRIURETIC PEPTIDE (BNP)

A significant increase in blood volume stimulates the release of B-Natriuretic Peptide (BNP) from the heart. The importance of BNP for normal tubular function is unclear, but it can:

- Inhibit reabsorption of sodium ions and water in the proximal convoluted tubule and collecting duct
- Suppress the secretion of aldosterone and ADH, thereby increasing the excretion of sodium in the urine and increasing urine output

Both of these actions decrease blood volume and blood pressure.¹¹ BNP (or its precursor, NT-pro-BNP) can be measured in many clinical laboratories to assess fluid overload.

REVIEW QUESTIONS: SECTION 3

Answers are provided at the end of this Learning Guide.

1. Which of the following ions has the greatest influence on osmolarity?
 - A Calcium
 - B Phosphate
 - C Potassium
 - D Sodium

2. The kidneys respond to increases in blood pressure by:
 - A Excreting more water
 - B Filtering less sodium
 - C Filtering more sodium
 - D Reabsorbing more water

3. If glomerular filtration rate declines, what is the effect on blood urea levels?
 - A Increase
 - B Decrease

SECTION 4

MINERAL HOMEOSTASIS

LEARNING OBJECTIVES

After completing this section, you will be able to:

- Understand calcium and phosphorus homeostasis
- Relate the parathyroid axis to the endocrine function of the kidney
- Distinguish between calcium absorption, resorption and reabsorption

OVERVIEW OF MINERAL HOMEOSTASIS

Stable levels of inorganic minerals such as calcium (Ca^{2+}), phosphate (HPO_4^{2-}) and magnesium (Mg^{2+}) are critical for normal physiological functioning. For example, calcium is essential for skeletal structure, proper functioning of nerve and muscle cells, blood clotting, and the function of numerous enzymes.⁴⁻¹

Maintaining homeostasis of minerals is a finely tuned balancing act involving **absorption** from the gastrointestinal (GI) tract, reabsorption and secretion by the kidneys, and storage and **resorption** from bone.¹ As illustrated in **Figure 4-1**, calcium homeostasis is maintained through a complex hormonal feedback loop that involves^{1, 4-1}:

- **Calcitriol** (also called 1,25-dihydroxyvitamin D_3 or $1,25[\text{OH}]_2\text{D}_3$), the active form of vitamin D, produced by the kidneys
- **Parathyroid hormone (PTH)**, produced by the parathyroid glands in the neck

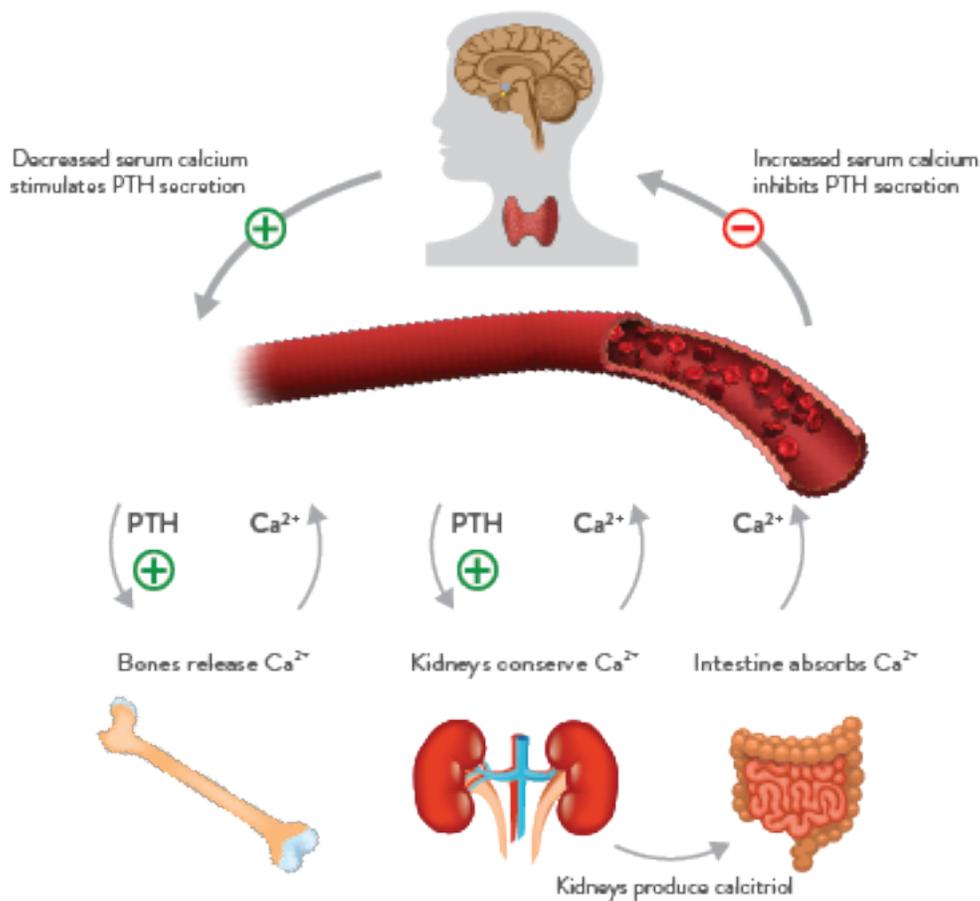


Figure 4-1: The parathyroid axis: a feedback loop involving parathyroid hormone (PTH) and calcitriol ($1,25[\text{OH}]_2\text{D}_3$) maintains calcium homeostasis.¹

INTESTINAL ABSORPTION

As food is digested, dietary minerals are absorbed from the intestines. Calcitriol promotes the absorption of calcium and other minerals from the GI tract to the bloodstream.⁴⁻¹

RENAL EXCRETION

The kidneys filter and excrete minerals in the urine. PTH, the major regulator of mineral levels in the blood, acts on the kidneys in three ways:¹

- Decreasing secretion of calcium and magnesium into the urine, thus raising their levels in the blood
- Increasing excretion of phosphate in urine, thus lowering levels in the blood
- Inducing conversion of inactive vitamin D to calcitriol by the kidneys

BONE REMODELING AND RESORPTION

Bone is a mineral reservoir that stores 99% of the body's calcium, along with other minerals. Bone tissue is constantly remodeled and repaired, removing old bone and replacing it with new bone.⁴⁻¹

- Cells called osteoclasts resorb (break down) old bone, releasing minerals such as calcium
- Bone-building cells called osteoblasts form new bone, depositing minerals in the process

To maintain a constant level of calcium in the blood, the rate of bone remodeling is tightly controlled by hormones.^{4-1, 4-2, 4-3}

- PTH stimulates resorption by osteoclasts, releasing calcium into the bloodstream
- Calcitriol, produced by the kidneys, promotes normal bone mineralization and opposes PTH production
- Calcitonin, produced by the thyroid gland, plays a lesser role by inhibiting osteoclasts and promoting calcium deposition by osteoblasts

FAST FACT

What is the difference between absorption, reabsorption and resorption?

Absorption is the intake of fluids or other substances by cells of mucous membranes, such as the absorption of calcium by the intestines.⁴⁻⁴

Reabsorption is the return of most of the filtered water and many of the filtered solutes to the bloodstream from the kidneys.¹⁻¹

Resorption is the removal of minerals and collagen fibers from bone by osteoclasts.⁴⁻¹

All three of these processes are stimulated directly by PTH or indirectly by activated vitamin D, which the kidneys produce in response to PTH.¹

IMPORTANCE OF VITAMIN D

Vitamin D is an essential nutrient required for the optimal absorption of dietary calcium and phosphate and for normal bone formation.⁴⁻³

It is important to note that vitamin D itself is biologically inactive. A two-step process in the liver and then the kidney converts it to the active metabolite 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃), also known as calcitriol.⁴⁻³

The classical actions of vitamin D in kidneys, bone, parathyroid glands and the intestines pertain to maintaining calcium levels within a precise range to ensure normal cellular physiology and skeletal integrity.^{4-2, 4-3}

Table 4-1 summarizes the classical calcemic effects of vitamin D.

TISSUE	EFFECTS
Intestine	Enhances absorption of dietary calcium and phosphate ⁴⁻³
Kidney	Self-regulates vitamin D activation and degradation ⁴⁻³ Enhances renal calcium reabsorption ⁴⁻²
Parathyroid	Inhibits both PTH synthesis and secretion, as well as parathyroid cell growth ⁴⁻³
Bone	Helps sustain normal bone mineralization and remodeling ⁴⁻²

Table 4-1: Classical calcemic effects of vitamin D in various tissues.

REVIEW QUESTIONS: SECTION 4

Answers are provided at the end of this Learning Guide.

1. Where does activation of vitamin D to calcitriol take place?
 - A Bone
 - B Gut
 - C Kidneys
 - D Thyroid

2. Which is an effect of calcitriol?
 - A Decreases absorption of dietary calcium and phosphate
 - B Increases PTH synthesis and secretion
 - C Promotes tubular secretion of calcium
 - D Sustains normal bone mineralization

3. Which is an effect of parathyroid hormone?
 - A Increases absorption of dietary calcium and phosphate
 - B Promotes bone resorption
 - C Reduces serum calcium levels
 - D Stimulates bone formation

APPENDIX

APPENDIX A:
GLOSSARY OF TERMS

APPENDIX B:
REFERENCES

APPENDIX C:
CORRECT RESPONSES

APPENDIX A: GLOSSARY OF TERMS

Absorption: Intake of fluids or other substances by cells of mucous membranes.⁴⁻⁴

Albumin: The major plasma protein, approximately 60% of the total, that is responsible for much of the osmotic pressure of the plasma. It acts as a transport protein for fatty acids, drugs and hormones among others. It is synthesized in the liver and its concentration is decreased in the context of renal disease.^{A-1}

Aldosterone: A hormone produced by the adrenal cortex that promotes resorption of sodium and water by the kidneys and excretion of phosphorus in the urine.⁴⁻⁴

Anemia: Condition of the blood in which the number of functional red blood cells or their hemoglobin content is below normal.⁴⁻⁴

Antidiuretic hormone (ADH): Hormone produced by the hypothalamus, which stimulates reabsorption of water from the renal tubules and vasoconstriction of arterioles, raising blood pressure. Also called vasopressin.⁴⁻⁴

Calcitonin: A hormone produced by the thyroid gland that can lower the amount of blood calcium and phosphates by inhibiting bone resorption and by accelerating uptake of calcium and phosphate into bone.⁴⁻⁴

Calcitriol: The metabolically active form of the steroid hormone vitamin D, which is essential for the dietary absorption of calcium and phosphate. Also called 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D₃).^{A-2}

Capillary: Microscopic blood vessel located between an arteriole and venule through which materials are exchanged between blood and interstitial fluid.⁴⁻⁴

Creatinine: A waste product from meat protein in the diet and from the muscles of the body.²⁻³

Cystatin C: A low-molecular-weight protein produced at a constant rate by all nucleated cells, freely filtered by the glomerulus, and almost completely degraded in the proximal renal tubules. Serves as a novel serum marker of GFR.^{2-2, A-3}

Erythropoietin (EPO): A hormone made by the kidneys to help form red blood cells. Lack of this hormone may lead to anemia.²⁻³

Glomerular filtration rate (GFR): The amount of filtrate formed in all the renal corpuscles of both kidneys each minute (mL/min).¹⁻¹

Homeostasis: The condition in which the body's internal environment remains relatively constant and within physiological limits.⁴⁻⁴

Hormone: A mediator released in one part of the body that regulates the activity of cells in another part of the body.¹

Micturition: The act of expelling urine from the urinary bladder. Also called urination.¹⁻¹

Nephron: The working units of the kidneys, which remove wastes and extra fluids from the blood. Each kidney consists of about one million nephrons.²⁻³

Osmolality: The measure of the total number of dissolved particles per kilogram of water.¹⁻¹

Osmolarity: The measure of the total number of dissolved particles per liter of solution.¹⁻¹

Osteoblast: Cell that participates in bone formation by secreting some organic components and inorganic salts.⁴⁻⁴

Osteoclast: A large, multinucleated cell that resorbs (destroys) bone matrix.⁴⁻⁴

Parathyroid hormone (PTH): A hormone secreted by the parathyroid glands that increases blood calcium level and decreases blood phosphate level.⁴⁻⁴

Parenchyma: The functional part of the kidneys. Contains approximately one million nephrons – the filtration units of the kidneys.¹⁻¹

GLOSSARY OF TERMS, CONTINUED

Peritoneum: The largest serous membrane of the body that lines the abdominal cavity and covers the viscera.⁴⁻⁴

Proteinuria: A condition in which the urine contains a large amount of protein, a sign that the kidneys are not functioning properly.²⁻³

Reabsorption, tubular: The return of most of the filtered water and filtered solutes to the bloodstream by the kidneys.¹⁻¹

Renin: Enzyme released by the kidneys in response to low blood pressure – the first step of the renin-angiotensin-aldosterone pathway that regulates aldosterone secretion.¹

Renin-angiotensin-aldosterone (RAA) system: Pathway that regulates secretion of aldosterone to help control blood volume, blood pressure and levels of Na⁺, K⁺ and H⁺ in the blood.¹

Resorption: The removal of minerals and collagen fibers from bone.⁴⁻¹

Secretion, tubular: Movement of substances from the blood into the renal tubular fluid.⁴⁻⁴

Specific gravity: The ratio of the weight of a volume of a substance to the weight of an equal volume of distilled water.¹⁻¹

Urea: A waste product found in the blood and caused by the normal breakdown of protein in the liver.²⁻³

Ureter: One of two tubules that connect the kidney with the urinary bladder.⁴⁻⁴

Urethra: Duct from the urinary bladder that conveys urine to the exterior.⁴⁻⁴

Urinalysis: Analysis of the volume and physical, chemical and microscopic properties of urine.⁴⁻⁴

Urinary bladder: Hollow muscular organ located in the pelvic cavity, behind the pubic bone; receives urine via the ureters and stores it until excreted via the urethra.⁴⁻⁴

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APPENDIX C: CORRECT RESPONSES

SECTION 1

1. The kidneys, ureters, urinary bladder, and urethra
2. Any three of the following:
 - Regulation of blood ionic composition and pH
 - Regulation of blood volume and pressure
 - Maintenance of relatively constant blood osmolarity
 - Production of hormones calcitriol and erythropoietin
 - Regulation of blood glucose levels
 - Excretion of wastes and foreign substances
3. C
4. A

5.

FUNCTION	ORGAN
Elimination of urine	Urethra
Production of urine	Kidneys
Storage of urine	Urinary bladder
Transport of urine	Ureters

SECTION 2

1. C
2. B
3. C
4. C

SECTION 3

1. D
2. A
3. A

SECTION 4

1. C
2. D
3. B

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