Chronic Kidney Disease
Learning Guide series
ACKNOWLEDGEMENTS

EDITOR:

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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 chronic 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

CHRONIC KIDNEY DISEASE (CKD) LEARNING GUIDE

The kidneys play a vital role in elimination of wastes, regulation of blood composition, blood volume and blood pressure, as well as mineral homeostasis.

They are essential for keeping the rest of the body in balance.

Chronic kidney disease (CKD), one form of kidney dysfunction, is increasingly recognized as a major public health concern. The continuum of CKD ranges from mild kidney damage to end-stage renal disease (ESRD). At this stage, kidney function is no longer sufficient to sustain life; therefore, dialysis or kidney transplantation is required.

Complications that arise as CKD advances include anemia, hypertension, systemic disorders of mineral and bone metabolism, cardiovascular disease and widespread effects on other body systems. Early detection and appropriate management can help delay progression to kidney failure and the development of complications.
SECTION 1
OVERVIEW OF CKD

LEARNING OBJECTIVES
After completing this section, you will be able to:

• Define CKD and its stages.
• Discuss the epidemiology, causes and risk factors associated with CKD.
• Understand how CKD is classified.
DEFINITION AND STAGES OF CKD

The kidneys are involved in fluid and electrolyte balance, waste removal and hormone production. Some conditions that can impact kidney function include infections, kidney stones, acute kidney injury (AKI) and chronic kidney disease (CKD).

When the kidneys are damaged or diseased, they can abruptly or progressively lose their ability to perform these vital functions. This results in waste and fluid buildup and abnormal hormonal regulation of blood pressure and mineral homeostasis.

DEFINITION OF CKD

The 2012 Practice Guideline from the Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group define CKD as:1-1

• Kidney damage for >3 months, as characterized by structural or functional abnormalities of the kidney, with or without decreased **glomerular filtration rate (GFR)**, manifested by either:
  — Pathological abnormalities.
  — Markers of kidney damage, including abnormalities in the composition of the blood or urine, or abnormalities in imaging tests.
• GFR <60 mL/min/1.73 m$^2$ for ≥3 months, with or without kidney damage.

GFR is typically used to assess the level of kidney function and to monitor disease progression and treatment response.1-2

One of the major abnormalities seen in CKD is proteinuria, an excess of protein in the urine. KDOQI recommends monitoring levels of the protein **albumin** in the urine as part of the diagnosis of CKD.1-1

FAST FACT

GFR is a measure of the overall filtration rate of all nephrons.1-2 It is considered the best index of overall kidney function in both the healthy and diseased kidney.1 Estimated GFR (eGFR) is calculated with two commonly used equations incorporating the measured serum creatinine concentration, age, sex and ethnic origin.1-1
STAGES OF CKD

KDOQI has identified five stages of CKD, defined according to estimated GFR.\textsuperscript{1-3}

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
<th>GFR RATE (ML/MIN/1.73 M(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>Kidney damage with normal or increased GFR</td>
<td>≥ 90</td>
</tr>
<tr>
<td>G2</td>
<td>Kidney damage with mild decrease in GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>G3a</td>
<td>Mild to moderately decreased GFR</td>
<td>45–59</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderately to severely decreased GFR</td>
<td>30–44</td>
</tr>
<tr>
<td>G4</td>
<td>Severe decrease in GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt; 15 (or dialysis)</td>
</tr>
</tbody>
</table>

Table 1-1: Stages of Chronic Kidney Disease.\textsuperscript{1,3}

A modification of this initial classification system was proposed at the 2004 KDOQI conference. Suffixes can be added: “T” for kidney transplant recipient at all levels of GFR and “D” for people with stage G5 CKD treated with dialysis. A second modification was made in 2012 to divide category 3 into G3a (mild to moderate decrease in GFR) and G3b (moderate to severely decreased GFR).\textsuperscript{1-3}

CKD is associated with a progressive decline in GFR and increased complications over time. Figure 1-1 illustrates the KDOQI conceptual model for the development, progression and complications of CKD.\textsuperscript{1}

Figure 1-1: Conceptual model of CKD continuum: development, progression and complications. “Complications” refers to all complications of CKD and its treatment, including complications of decreased glomerular filtration rate (GFR) and cardiovascular disease.\textsuperscript{1}
Epidemiology

CKD is a major public health problem worldwide.\(^1\)

Prevalence of CKD

Based on U.S. National Health and Nutrition Examination Survey (NHANES) data, the CDC reports that the percentage of adults with CKD Stage G1–G4 remained relatively unchanged from 1999–2016 at about 14% of the U.S adult population. The prevalence of CKD is increasing in the U.S., partially due to the growing number of CKD risk factors, including advanced age, diabetes mellitus, hypertension and obesity.\(^1\)–\(^5\)

Figure 1-2 shows the prevalence of CKD among U.S. adults by CKD stage, based on 1999–2016 NHANES data, determined using creatinine-based GFR estimates.\(^1\)–\(^4\)

Population studies from Australia and Japan have shown similar incidences of CKD. The results of these studies are summarized in Table 1-2.

Table 1-2: Prevalence of CKD in Australia and Japan.

<table>
<thead>
<tr>
<th>eGFR calculation</th>
<th>Australia(^1)–(^5)</th>
<th>Japan(^1)–(^6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of population with eGFR &lt;60 mL/min/1.73 m(^2)</td>
<td>11.4%</td>
<td>19%</td>
</tr>
<tr>
<td>Percentage of population with eGFR &lt;30 mL/min/1.73 m(^2)</td>
<td>0.3%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>
INCIDENCE AND PREVALENCE OF ESRD

The incidence of end-stage renal disease (ESRD), which is defined by the event of initiating renal replacement therapy rather than by GFR, varies widely among countries.

In 2019, the rate of new ESRD cases in the U.S. was approximately 370.2 per million population (pmp) per year. The prevalence of ESRD was approximately 2,203 pmp.1-7

Across 36 European countries, in 2016, an overall incidence of ESRD was 121 cases pmp (ranging from 29 to 251 pmp, depending on region, per year, shown in Figure 1-3. The overall prevalence was 823 pmp per year.1-8

Figure 1-3: Incidence of RRT pmp on 31 December 2016 by country/region, European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry.1-8
CAUSES OF CKD AND ESRD

Diabetes (diabetic nephropathy) and hypertension are the two most common causes of CKD. Other causes include glomerulonephritis and polycystic kidney disease. The causes of ESRD are summarized in Figure 1-4.\(^1\)\(^-\)\(^7\)

![Primary Diagnosis in ESRD Patients](image)

**Figure 1-4:** Causes of ESRD in the U.S. (2019). Diabetes accounts for almost half of the cases of kidney failure and more than one-quarter of cases can be attributed to hypertension.\(^1\)\(^-\)\(^7\)

MORBIDITY AND MORTALITY

CKD is associated with high rates of morbidity and decreased quality of life.\(^3\)

The incidence of hospitalizations among people with CKD is higher than among those without CKD. Some common causes for hospitalization seen in CKD patients include cardiovascular disease (CVD), infections such as pneumonia and bacteremia/septicemia.\(^1\)\(^-\)\(^4\)

Factors that increase the rate of hospitalization in CKD patients include: \(^1\)\(^-\)\(^4\)
- Older age.
- Comorbidities, such as diabetes and congestive heart failure.
- Progression of CKD.
- Dialysis, which increases the risk of infections at the site of catheter placement and mortality.

CKD is also linked to premature mortality. The risk of death is almost doubled by CKD, and more than tripled when people have CKD plus cardiovascular disease (CVD) and diabetes.\(^1\)\(^-\)\(^4\)

**FAST FACT**

Age is one factor affecting kidney function. Normal GFR in individuals aged 30 years or younger is about 125 mL/min/1.73 m\(^2\). After the age of 30 years, GFR decreases by 1 mL/min/1.73 m\(^2\) per year.\(^1\)\(^-\)\(^2\)
HEALTHCARE COSTS

Across healthcare systems, treating CKD has significant costs. For example, in 2017, the United States spent: 1-7

- $84 billion of Medicare was spent on CKD for people over 65 years old.
- An additional $36 billion was spent on ESRD.
- $12 billion was spent on CKD for people under 65 years old.

Expenditures increase dramatically during the transition from CKD to ESRD. Most of these high costs are related to dialysis and hospitalizations for arteriovenous fistula placement, vascular access failure, declotting procedures and infectious complications.1-9,1-10

FAST FACT

Detecting CKD early, and preventing its progression to end-stage renal disease, could potentially improve patient quality of life and help save healthcare dollars.1-11

RISK FACTORS

Several risk factors for the development or progression of CKD have been identified and are presented in Figure 1-5. Risk factors are generally classified as: 1-1

- Susceptibility factors — increase susceptibility to kidney damage.
- Initiating factors — directly initiate kidney damage.
- Progression factors — exacerbate kidney damage or accelerate GFR decline.

In general, people at high risk for CKD include those with diabetes, hypertension and CVD, or those with a family history of these conditions or CKD.1-11

Certain risk factors, including diabetes and hypertension, are considered modifiable risk factors because they may be controlled through treatment or lifestyle changes to help reduce the risk of a patient developing CKD. Other factors, however, such as family history, age, race and ethnicity, are not modifiable.1-1
LEARNING GUIDE: OVERVIEW OF CKD

INITIATING FACTORS:
- Older age
- Certain ethnic populations (Black, Hispanic, Asian, Pacific Islander or Native American Indian)
- Diabetes mellitus
- Hypertension
- Autoimmune diseases
- Systemic infections
- Urinary tract infections
- Urinary stones
- Lower urinary tract obstruction
- Neoplasia
- Family history of CKD
- Recovery from acute kidney injury
- Reduction in kidney mass
- Exposure to certain drugs, chemicals or environmental conditions
- Low birth weight

SUSCEPTIBILITY FACTORS:
- Older age
- Family history of CKD

PROGRESSION FACTORS:
- Higher level of proteinuria
- Hypertension
- Poor glycemic control in diabetes
- Smoking

Figure 1-5: Risk factors for the development and progression of CKD.1,1

COMORBIDITIES

CKD is linked to numerous comorbidities, including diabetes, hypertension and CVD. Prevalence of these conditions tends to rise with increasing stage of disease.1-4

A number of comorbid conditions accompany CKD. These are summarized in Table 1-3.1,1 CVD is considered separately due to its complex relationship with CKD, which incidentally is an independent risk factor for CVD.1 Dyslipidemia, a primary risk factor for CVD, also contributes to CKD development and progression.1,2,12

<table>
<thead>
<tr>
<th>TYPE OF COMORBID CONDITION</th>
<th>EXAMPLES</th>
<th>MANAGEMENT GOALS</th>
</tr>
</thead>
</table>
| Diseases causing CKD        | • Diabetes  
• Hypertension  
• Urinary tract obstruction  
• Acute kidney injury | • Improve CKD  
• Improve functioning and well-being  
• Integration of care with management of CKD |
| Diseases unrelated to CKD   | • Chronic obstructive pulmonary disease (COPD)  
• Degenerative joint disease  
• Alzheimer’s disease  
• Malignancies | • Improve functioning and well-being  
• Integration of care with management of CKD |
| Cardiovascular disease (CVD) | • Atherosclerotic CVD  
• Heart failure  
• Left ventricular hypertrophy | • Evaluation and management of CVD risk factors  
• Possibly improve CKD  
• Improve functioning and well-being  
• Integration of care with management of CKD |

Table 1-3: Classification and management of comorbid conditions in CKD.1,1
CLASSIFICATION AND CLINICAL FEATURES OF CKD

Kidney diseases may be divided into three broad categories based on their etiology and pathology: (1) diabetic, (2) nondiabetic and (3) diseases in the kidney transplant (Table 1-4). Diabetic kidney disease is classified separately because it is the single largest cause of kidney failure.\(^1\)

Regardless of cause, one of the hallmarks of CKD is persistently increased excretion of albumin or other proteins in the urine.\(^1\) As GFR declines, the final common pathway of CKD leads to complications such as hypertension, CVD and uremia.\(^1\).\(^1\)\(^3\)

<table>
<thead>
<tr>
<th>DISEASE</th>
<th>MAJOR CAUSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic kidney disease</td>
<td>• Type 1 diabetes</td>
</tr>
<tr>
<td></td>
<td>• Type 2 diabetes</td>
</tr>
<tr>
<td>Nondiabetic kidney diseases</td>
<td>• Glomerular diseases (affecting the glomeruli), e.g., autoimmune diseases (lupus), systemic infections (hepatitis, human immunodeficiency virus [HIV]), drugs, neoplasia</td>
</tr>
<tr>
<td></td>
<td>• Vascular diseases (affecting the renal vasculature), e.g., large vessel disease, hypertension, small vessel disease (microangiopathy)</td>
</tr>
<tr>
<td></td>
<td>• Tubulointerstitial diseases (affecting the renal tubules and interstitium), e.g., urinary tract infection, stones, obstruction, drug toxicity</td>
</tr>
<tr>
<td></td>
<td>• Cystic diseases, e.g., polycystic kidney disease</td>
</tr>
<tr>
<td></td>
<td>• Acute kidney injury</td>
</tr>
<tr>
<td>Diseases in the kidney transplant</td>
<td>• Chronic rejection</td>
</tr>
<tr>
<td></td>
<td>• Drug toxicity</td>
</tr>
<tr>
<td></td>
<td>• Recurrent disease, e.g., glomerular diseases</td>
</tr>
<tr>
<td></td>
<td>• Transplant glomerulopathy</td>
</tr>
</tbody>
</table>

Table 1-4: Classification of CKD.\(^1\)\(^1\)

FAST FACT
Polycystic kidney disease is one of the most common genetic disorders with the autosomal dominant type, affecting one in 500–1000 live births.\(^1\)\(^4\) It is characterized by the development of cysts (fluid-filled sacs) in the kidney tubules. This leads to progressive kidney dysfunction, which eventually evolves into ESRD.\(^1\)\(^3\)
MARKERS OF POTENTIAL KIDNEY DAMAGE

CKD is typically a silent condition until its late stages. Most patients have no symptoms, or may present with nonspecific complaints such as fatigue, malaise or anorexia.

CLINICAL CONNECTION

The fact that the early stages of CKD are asymptomatic reduces opportunities for preventing adverse outcomes.

SIGNS AND SYMPTOMS

Kidney dysfunction leads to the accumulation of waste products and excess fluid. As CKD progresses, signs and symptoms greatly increase, such that the majority of people with CKD are usually detected shortly before symptomatic kidney failure develops. Potential signs and symptoms are:

**Urinary symptoms**
- Dysuria: Difficult or painful urination
- Nocturia: Excessive urination at night
- Dark-colored urine

**Nonurinary symptoms**
- Edema
- Hypertension
- Arthralgia (joint pain)
- Fatigue
- Fever
- Skin rash
- Weight loss

**Asymptomatic urinalysis abnormalities**
- Hematuria: Blood or red blood cells in the urine
- Pyuria: White blood cell casts, kidney tubular cells and coarse granular casts in urine
- Non-nephrotic proteinuria: <3,500 mg protein in urine/day

**Asymptomatic radiographic abnormalities**
- Hydronephrosis
- Asymmetry of kidney size or function
- Obstructing stones, tumors, cysts or scarring
Related syndromes

• Nephritic syndrome (acute glomerulonephritis, inflammation of glomeruli): Hypertension, edema, hematuria, red blood cell casts

• Nephrotic syndrome: Massive proteinuria (>3,500 mg/day), hyperlipidemia, hypoalbuminemia and edema

• Tubular syndromes: Diverse disorders related to abnormal handling of water or solutes by renal tubules

• Sustained hypertension

ESRD AND UREMIA

As kidney function deteriorates, urea and nitrogenous wastes accumulate in the blood because the kidneys can no longer remove wastes from the body. Symptoms of uremia include anorexia, nausea, vomiting, malaise, muscle weakness, platelet dysfunction, pericarditis, mental status changes, seizures and possibly coma.

Kidney failure is defined as either:

• Stage G5 CKD, corresponding to GFR <15 mL/min/1.73 m², usually accompanied by signs and symptoms of uremia.

• A need to initiate kidney replacement therapy (dialysis or transplantation).

Permanent kidney failure, in which a patient requires dialysis or transplantation to survive, is referred to as end-stage renal disease (ESRD).
REVIEW QUESTIONS: SECTION 1

Answers are provided at the end of this Learning Guide.

1. What is considered to be the leading cause of kidney failure among CKD patients?
   - A Chronic obstructive pulmonary disease
   - B Diabetes
   - C Proteinuria
   - D Hypertension

2. Match the clinical signs of CKD with the correct clinical terms. Write your answers in the spaces provided.

<table>
<thead>
<tr>
<th>CLINICAL TERM</th>
<th>MEDICAL DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Excretion of small abnormal amounts of albumin</td>
</tr>
<tr>
<td></td>
<td>Presence of blood in urine</td>
</tr>
<tr>
<td></td>
<td>Toxic levels of urea in blood</td>
</tr>
</tbody>
</table>

Possible answers: hematuria, microalbuminuria, uremia

3. What is the GFR corresponding to stage G3a CKD?
   - A 60–89 mL/min/1.73 m²
   - B 45–59 mL/min/1.73 m²
   - C 15–29 mL/min/1.73 m²
   - D <15 mL/min/1.73 m²

4. Polycystic kidney disease is a subset of which CKD classification?
   - A Diabetic CKD
   - B ESRD
   - C Nondiabetic CKD
   - D CKD in transplant
SECTION 2
COMPLICATIONS OF CKD

LEARNING OBJECTIVES

After completing this section, you will be able to:

• List the main complications associated with CKD and how they contribute to disease progression.
• Identify the components of CKD–mineral and bone disorder (CKD–MBD) and its clinical consequences.
• Describe the effects of CKD on other body systems.
OVERVIEW

The kidneys regulate many of the body's functions and control numerous processes that maintain homeostasis. As wastes and fluids accumulate due to impaired kidney function, multiple body systems are affected. Figure 2-1 shows complications that arise and manifest as CKD advances. The prevalence of complications is largely based on the level of GFR.

CLINICAL MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

- **Integumentary**: Bruises, pruritus, dry skin, skin color changes, dry brittle hair and nails
- **Cardiovascular**: High blood pressure, increased heart rate, dysrhythmias, electrocardiographic changes, abnormal heart sounds, retinopathy, fluid retention with peripheral edema and/or pulmonary edema
- **Respiratory**: Increased respiratory rate, crackles, decreased blood oxygen
- **Musculoskeletal**: Renal osteodystrophy, decreased calcium, vitamin D impairment, hyperparathyroidism, pathological fractures
- **Gastrointestinal**: Anorexia, nausea, vomiting, halitosis, metallic taste in mouth, bleeding in GI tract
- **Immune**: Increased risk of infection
- **Renal**: Decreased urine output, increased nitrogen, protein in urine, uric acid in urine
- **Hematological**: Anemia, weakness, fatigue, pallor, lethargy, bleeding due to impaired platelet aggregation
- **Neurological**: Peripheral neuropathy, restless legs, change in level of consciousness, lethargy, confusion, encephalopathy, altered motor function
- **Integumentary**: Bruises, pruritus, dry skin, skin color changes, dry brittle hair and nails

**Figure 2-1**: Clinical manifestations of CKD. Note how CKD impacts almost every body system.

ANEMIA

Anemia manifests early in the course of CKD and worsens as kidney function declines. Anemia is categorized by a lessened capacity of the blood to carry enough oxygen, most commonly due to a lower than normal amount of hemoglobin (Hb). Erythropoietin (EPO) is a hormone produced by cells in the kidney. It stimulates erythropoiesis, the formation of red blood cells in bone marrow. Decreased EPO production by the failing kidneys is considered the primary cause of anemia in CKD patients.

**FAST FACT**

Anemia is a recognized independent risk factor for CKD and an important predictive factor for progression to ESRD. The anemia of CKD also amplifies the risk for CVD, which may lead to further kidney dysfunction and culminate in a vicious cycle, termed the cardiorenal anemia syndrome.
HYPERTENSION

Hypertension (high blood pressure) is both a cause and an early complication of CKD.\(^1\)

High blood pressure can directly damage the small blood vessels within nephrons — the functional units of the kidneys. The kidneys then lose their ability to autoregulate GFR and blood pressure, with consequent albuminuria and proteinuria. The proximal tubules then reabsorb excess protein and secrete vasoactive substances that further damage the nephrons. Nephron damage activates the renin-angiotensin-aldosterone system. Increased fluid retention exacerbates the progression of hypertension and nephron loss.\(^{1,2}\)

Overall, the fluid retention associated with hypertension contributes to the development of respiratory and cardiovascular complications.\(^2-1\) Left untreated, hypertension can accelerate CKD progression.\(^3\)

EDEMA

Edema (accumulation of excess fluid in tissues) is an important marker of kidney damage. Edema develops as the kidneys lose their ability to excrete water due to impaired nephron function and resultant decrease in GFR. Other contributing factors include proteinuria and increased renin secretion.\(^2-4\)

Edema associated with kidney disease usually occurs around the eyes, ankles, feet and abdomen.\(^{1,17}\)

CKD–MINERAL AND BONE DISORDER

As CKD advances, it is accompanied by progressive deterioration in mineral and bone metabolism, with disturbances in calcium, phosphorus, vitamin D and parathyroid hormone (PTH) homeostasis.\(^1-3\)

CKD–mineral and bone disorder (CKD–MBD) is a clinical syndrome encompassing mineral, bone and calcific cardiovascular abnormalities that develop as a complication of CKD (summarized in Figure 2-2).\(^1-3,2-4\)

![REDUCED KIDNEY FUNCTION](image)

**Figure 2-2:** Complications caused by disturbances in mineral metabolism in CKD.\(^2,5\)
The components of CKD–MBD (biochemical abnormalities, bone abnormalities and extraskeletal calcification) are closely interrelated, and together, contribute to the high morbidity and mortality observed in people with CKD.3

**BIOCHEMICAL DISTURBANCES**

Calcium and phosphorus homeostasis relies on a complex, tightly regulated system involving parathyroid hormone (PTH), vitamin D and other factors. Abnormalities in mineral metabolism usually originate from failure to maintain this critical regulatory system.2-6

Table 2-1 summarizes the changes in mineral metabolism that occur with advancing CKD.

<table>
<thead>
<tr>
<th>STAGE</th>
<th>GFR RATE (mL/min/1.73 M²)</th>
<th>CHANGE IN SERUM LEVELS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1,25D</td>
</tr>
<tr>
<td>G2</td>
<td>60–89</td>
<td>↓</td>
</tr>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>↓↓</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>↓↓</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>↓↓↓</td>
</tr>
<tr>
<td>G5</td>
<td>&lt;15</td>
<td>↓↓↓↓</td>
</tr>
</tbody>
</table>

**SECONDARY HYPERPARATHYROIDISM (SHPT)**

PTH is the most important regulator of calcium metabolism. It is secreted in response to hypocalcemia and hyperphosphatemia.2-6

Regulation of the vitamin D–PTH axis is disrupted in early CKD.2-7 The net effect is a continuous stimulation of the parathyroid glands and persistent, excessive secretion of PTH. This leads to: 2-8

- Increased calcium release from bone, potentially causing bone disease.
- Reduced activation of vitamin D in the kidneys.
- Decreased calcium absorption from the GI tract.

Secondary hyperparathyroidism (SHPT) begins as early as stage G3a CKD. Most, if not all, untreated people with CKD will develop SHPT, which is associated with increased fracture risk and cardiovascular complications.2-8
BONE DISEASE

Bone disease may occur early in the course of CKD and worsen with progressive kidney dysfunction. By CKD stage G5, bone disease is common, with nearly all patients affected upon dialysis initiation.²⁻⁹

- People with CKD stages G1–G3a often have low bone mineral density (BMD), which is diagnosed as osteopenia or osteoporosis, depending on degree.
- People with more advanced CKD (stages G3b–G5) who display biochemical abnormalities of mineral metabolism are designated as having renal osteodystrophy — a spectrum of bone defects characterized by abnormalities in bone turnover (remodeling), mineralization and volume.¹⁻³, ²⁻⁴
- Both osteoporosis and renal osteodystrophy can increase bone fragility and fractures despite their different pathophysiological backgrounds.¹⁻³

VASCULAR CALCIFICATION

The prevalence of extraosseous tissue calcification (at sites other than bone and teeth) increases with deteriorating kidney function. In CKD, poorly controlled metabolic disease contributes to calcification of the inner and middle layers of arterial walls, and is associated with atherosclerosis (plaque formation) and stiffening of the arteries. Accelerated atherosclerosis in CKD, and especially ESRD, is linked to cardiovascular events and death.¹⁻³, ²⁻¹⁰

CARDIOVASCULAR DISEASE

Cardiovascular disease (CVD) is a well-known complication of CKD. In CKD patients, increased CVD risk is associated with:²⁻¹¹

- Traditional risk factors, such as hypertension, hyperlipidemia and diabetes.
- Nontraditional risk factors, such as anemia, abnormal PTH levels, hyperphosphatemia, inflammation, proteinuria and vascular calcification.

Cardiovascular diseases encountered in CKD include:²⁻⁸

- Left ventricular hypertrophy (LVH) — thickening of the muscle of the lower left chamber of the heart.
- Congestive heart failure (CHF) — inability of the heart to maintain adequate blood circulation causing congestion and edema in body tissues.¹⁻¹⁸
- Peripheral artery disease (PAD) — occlusion of the blood vessels serving the lower extremities leading to pain during activities, resting pain or numbness.
CARDIORENALE SYNDROME

CKD, CVD and CHF share a number of causes (e.g., hypertension, dyslipidemia, diabetes) and risk factors (e.g., older age, obesity). These conditions coexist in a large number of patients.2-2

Recall that kidney dysfunction can negatively impact the heart and circulation, while heart disease can impair kidney function. Consequently, acute or chronic dysfunction of one organ may result in secondary dysfunction of the other. This phenomenon, a simplified version of which is shown in Figure 2-3, is sometimes referred to as the cardiorenal syndrome.2-12

Figure 2-3: Cardiorenal syndrome. Pathophysiologica interactions between the heart and kidney in CKD, CVD and heart failure.2-12
Many of the effects of CKD on other body systems are related to the buildup of uremic toxins as the kidneys fail.

### EFFECTS ON OTHER BODY SYSTEMS

<table>
<thead>
<tr>
<th>SYSTEM</th>
<th>COMPLICATION OF CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Endocrine system</strong>&lt;sup&gt;2-13&lt;/sup&gt;</td>
<td>• Decreased production of kidney-derived hormones (e.g., EPO, 1,25-dihydroxyvitamin D)</td>
</tr>
<tr>
<td></td>
<td>• Impaired production, clearance or response to hormones as a result of uremia</td>
</tr>
<tr>
<td><strong>Gastrointestinal (GI) system</strong>&lt;sup&gt;2-1, 2-13&lt;/sup&gt;</td>
<td>• Elevated levels of urea, metabolic acids, ammonia, metabolic waste products cause GI complaints</td>
</tr>
<tr>
<td></td>
<td>• Manifestations include halitosis (bad breath), mouth ulcers, metallic taste, anorexia, weight loss, nausea, vomiting, hiccups, GI bleeding</td>
</tr>
<tr>
<td><strong>Nervous system</strong>&lt;sup&gt;1-1, 2-1, 2-14&lt;/sup&gt;</td>
<td>• Central nervous system: uremic encephalopathy presents with fatigue, confusion or impaired concentration; may develop to seizures and coma</td>
</tr>
<tr>
<td></td>
<td>• Peripheral nervous system: peripheral neuropathy results from nerve damage due to uremia; characterized by restless leg syndrome, leg pain and sensations of tightness, changes in gait and fine motor movement</td>
</tr>
<tr>
<td><strong>Immune system</strong>&lt;sup&gt;2-1, 2-11&lt;/sup&gt;</td>
<td>• Impaired immune and inflammatory responses and overall immune dysfunction</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of infection</td>
</tr>
<tr>
<td></td>
<td>• Elevated inflammatory markers linked to CVD susceptibility</td>
</tr>
<tr>
<td><strong>Integumentary system</strong>&lt;sup&gt;2-1, 2-15&lt;/sup&gt;</td>
<td>• Uremic pruritus: dry skin, color changes, bruises, mechanical skin damage due to continuous scratching, brittle nails and hair</td>
</tr>
<tr>
<td></td>
<td>• Calcific uremic arteriolopathy: potentially life-threatening vascular disorder of skin and subcutaneous tissue; lesions on the abdomen, buttocks and thigh evolve into painful, necrotic ulcers covered by dry scabs</td>
</tr>
<tr>
<td></td>
<td>• Nephrogenic systemic fibrosis: occurs in people with CKD, acute kidney injury (AKI) and kidney transplants; characterized by painful, progressive fibrosis and thickening of the skin</td>
</tr>
</tbody>
</table>

Table 2-2: Additional complications of CKD.
REVIEW QUESTIONS: SECTION 2

Answers are provided at the end of this Learning Guide.

1. Which condition is linked to decreased production of erythropoietin?
   A. Anemia
   B. Hypertension
   C. Neuropathy
   D. Susceptibility to infection

2. Which biochemical changes are typically associated with CKD progression?
   A. Hyperphosphatemia
   B. Parathyroid hormone elevation
   C. Vitamin D deficiency
   D. All of the above

3. What changes in mineral metabolism occur with progression of CKD?
   A. Elevated parathyroid hormone levels
   B. Hyperphosphatemia
   C. Hypocalcemia
   D. All of the above

4. Name at least two cardiovascular complications associated with CKD.
SECTION 3
DIAGNOSIS AND MONITORING OF CKD

LEARNING OBJECTIVES
After completing this section, you will be able to:

• Understand the importance of medical history and physical examination.
• Explain the tests of blood and urine used to diagnose and monitor CKD.
• Understand how glomerular filtration rate is estimated.
• Understand how imaging studies are used in the evaluation of CKD.
MEDICAL HISTORY

Most people with CKD have no symptoms, or have only nonspecific complaints, such as fatigue, loss of appetite or general malaise. For this reason, people may not be diagnosed until CKD is already advanced. Therefore, a complete medical history is very important. It will entail questions about: 1-17

• Risk factors for CKD, such as hypertension or diabetes.
• Recurrent urinary tract infections or kidney stones.
• Family history of kidney disease.
• Any joint pain, skin rashes, fever or unexplained weight loss.
• Use of prescription and over-the-counter medications, illicit drugs or herbal preparations.

Additionally, a patient’s old medical records should be reviewed, if possible, to determine their previous level of renal functioning. 1-17

PHYSICAL EXAMINATION

A physical examination must be conducted to identify signs of systemic kidney disease and rule out an alternate diagnosis. Specific symptoms include: 1-17

• Urinary symptoms (nocturia, hematuria, dark urine).
• Hypertension.
• Edema.

Blood pressure is classified on the basis of systolic and diastolic blood pressures. In 2017, the American College of Cardiology published the below guidelines (Table 3-1).3-1, 3-2

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SYSTOLIC BLOOD PRESSURE (mmHg)</th>
<th>DIASTOLIC BLOOD PRESSURE (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120 and</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120–129 or</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Hypertension Stage 1</td>
<td>130–139 or 80–89</td>
<td></td>
</tr>
<tr>
<td>Hypertension Stage 2</td>
<td>≥ 140 or ≥ 99</td>
<td></td>
</tr>
</tbody>
</table>

Table 3-1: 2017 Guideline for High Blood Pressure in Adults. 3-1, 3-2
ROUTINE BLOOD TESTS

Biochemical abnormalities are the primary indicators by which CKD and its complications are diagnosed and managed. Common blood tests used to monitor kidney function and complications of CKD are summarized in Table 3-2.

<table>
<thead>
<tr>
<th>CHEMISTRY</th>
<th>NORMAL RANGE</th>
<th>CKD FINDINGS AND IMPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>0.6–1.1 mg/dL (53–98 μmol/L) for females</td>
<td>Increased in CKD</td>
</tr>
<tr>
<td></td>
<td>0.8–1.3 mg/dL (71–116 μmol/L) for males</td>
<td>Can be used to estimate GFR</td>
</tr>
<tr>
<td>Blood urea nitrogen (BUN)</td>
<td>7–20 mg/dL (2.5–7.1 mmol/L)</td>
<td>Increased in CKD</td>
</tr>
<tr>
<td></td>
<td>BUN to creatinine ratio 10:1</td>
<td>Used in conjunction with serum creatinine</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.7–10.2 mg/dL (2.2–2.6 mmol/L)</td>
<td>Decreased in CKD</td>
</tr>
<tr>
<td></td>
<td>Not evident until GFR &lt;30 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.5–4.3 mg/dL (0.81–1.4 mmol/L)</td>
<td>Increased in CKD</td>
</tr>
<tr>
<td></td>
<td>Not evident until GFR &lt;60 mL/min/1.73 m²</td>
<td></td>
</tr>
<tr>
<td>1,25-dihydroxyvitamin D</td>
<td>Summer: 15–80 ng/mL (37.4–200 nmol/L)</td>
<td>Decreased in CKD</td>
</tr>
<tr>
<td></td>
<td>Winter: 14–42 ng/mL (34.9–105 nmol/L)</td>
<td>Not evident until GFR &lt;30 mL/min/1.73 m²</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>12–15.8 g/dL for females 13.3–16.2 g/dL for males</td>
<td>Decreased in CKD</td>
</tr>
<tr>
<td></td>
<td>Low levels warrant further testing</td>
<td></td>
</tr>
<tr>
<td>Parathyroid hormone (PTH)</td>
<td>8–51 pg/mL</td>
<td>Increased in CKD</td>
</tr>
<tr>
<td></td>
<td>High levels cause bone disease</td>
<td></td>
</tr>
</tbody>
</table>

Table 3-2: Blood tests used to assess kidney function and complications of CKD.

CREATININE

Creatinine, a product of muscle breakdown, is produced at a constant daily rate. It is eliminated mostly by glomerular filtration. Creatinine provides an approximate measure of GFR. Creatinine levels: 1-17

- Increase as a marker of kidney damage.
- May be falsely elevated by certain medications that interfere with excretion.

FAST FACT

The serum creatinine level in men is higher than in women because men have greater muscle mass. Creatinine is also higher in younger rather than older individuals, and higher in blacks than in whites. 1-1
**BLOOD UREA NITROGEN (BUN)**

Blood urea nitrogen (BUN), a major end product derived from protein, reflects dietary protein intake as well as the rate of protein breakdown. BUN is excreted by glomerular filtration, but a substantial amount is reabsorbed along the renal tubules. BUN is often used with serum creatinine to measure renal function. BUN levels:

- Vary with respect to blood volume.
- May be increased by high-protein diet, certain medications or urinary tract obstruction.
- May be decreased by a low-protein diet or liver disease.

**SERUM PHOSPHORUS**

When kidney function declines, excretion of phosphorus is diminished and serum phosphorous levels rise. Phosphorous abnormalities may not become evident until CKD stage G3 (GFR <60 mL/min/1.73 m²).

**SERUM CALCIUM**

When elevated phosphorous levels suppress calcitriol (bioactive vitamin D [1,25-dihydroxyvitamin D]) production, calcium absorption from the GI tract decreases. Calcium abnormalities may not become evident until CKD stage G4 (GFR <30 mL/min/1.73 m²).

**SERUM VITAMIN D**

Humans with intact kidney and liver function can make vitamin D₃ from exposure to sunlight and consume vitamin D₂ or D₃ from the diet or dietary supplements. Collectively, vitamins D₂ and D₃ are referred to as vitamin D. Vitamin D is metabolized in the liver to 25-hydroxyvitamin D and then in the kidneys to its active form, 1,25-dihydroxyvitamin D (calcitriol). In people without significant renal disease, vitamin D status is determined by measuring serum levels of 25-hydroxyvitamin D, the primary circulating form of vitamin D.

Levels of vitamin D are inversely related to parathyroid hormone (PTH) levels. Vitamin D deficiency may develop in CKD stages G4 or G5 (GFR <30 mL/min/1.73 m²).

**HEMOGLOBIN**

It is well established that anemia develops during the course of CKD. People with CKD and GFR <60 mL/min/1.73m² should be evaluated for anemia, which consists of:

- Measurement of hemoglobin levels.
- A complete blood count.
- Physical examination for any signs of gastrointestinal bleeding.
ESTIMATES OF GLOMERULAR FILTRATION RATE (eGFR)

Estimates of GFR (eGFR) measure the filtering capacity of the kidneys and are the best overall indication of the level of kidney function. The eGFR is reported in terms of mL/min/1.73 m² (an average body surface area).1-1

CLINICAL CONNECTION
Persistently low or declining GFR indicates CKD. GFR can also be a strong predictor of the time to kidney failure as well as the risk of complications due to CKD.1-1

CREATININE CLEARANCE

Serum creatinine alone is not an accurate index of GFR. The rate of creatinine clearance in the urine is one way to obtain a rough estimate of GFR.1-1

Urinary clearance of creatinine is computed from a timed urine collection (e.g., a 24-hour urine collection) and blood sampling during the collection period. However, timed urinary collections are cumbersome and susceptible to error, and thus are not routinely used.2-4

The amount of creatinine excreted in the urine corresponds to the creatinine filtered by the nephrons (i.e., glomerular filtration) plus the creatinine secreted by the proximal tubules. Because creatinine clearance includes tubular secretion, it overestimates the GFR by 10–40%.1-1

Creatinine clearance can be derived as follows:1-17

\[
\text{CREATININE CLEARANCE (mL/min)} = \frac{\text{Urinary creatinine (mg/dL)} \times \text{Volume of urine (mL/min)}^*}{\text{Plasma creatinine (mg/dL)}}
\]

*If the volume of urine corresponds to a 24-hour collection, the volume is divided by 1,440 (60 min/hour x 24 hours/day).

The normal range for creatinine clearance is 95–105 mL/min/1.73 m².
FAST FACT
Creatinine excretion varies from day to day; thus, creatinine clearance estimates of GFR are imprecise, even from a 24-hour urine collection. Furthermore, urinary excretion of creatinine is lower in CKD, leading to an overestimation of GFR using creatinine clearance.1-1

EQUATIONS TO ESTIMATE GFR
Equations to estimate GFR have been developed to overcome some of the limitations of using creatinine alone. These equations adjust serum creatinine measurements for factors such as age, sex, race and body size.3-5

MODIFICATION OF DIET IN RENAL DISEASE (MDRD) LONG FORMULA
The Modification of Diet in Renal Disease (MDRD) study equation was developed using data from a large sample of people with CKD.3-5 It can be used to estimate GFR up to approximately 90 mL/min/1.73 m².1-1 The original MDRD equation included six parameters: creatinine, albumin, age, sex, race and BUN.3-6

ESTIMATED GFR (mL/min/1.73 m²) =
170 x (Serum creatinine)^-0.999 x (Age)^-0.176 x (BUN)^-0.170 x (Albumin)^0.318

Note: For women, the final value is multiplied by 0.762. For blacks, the final value is multiplied by 1.180.
MDRD 4-PARAMETER FORMULA
The MDRD equation was later simplified into a 4-parameter formula. The 4-parameter MDRD equation requires only serum creatinine value, age, sex and race.1-4

\[
\text{ESTIMATED GFR (mL/min/1.73 m^2) = 175 x (Serum creatinine)^{-1.154} x (Age)^{0.203}}
\]

Notes:
• For women, the final value is multiplied by 0.742. For blacks, the final value is multiplied by 1.212.
• When serum creatinine levels are measured in μmol/L, the value is multiplied by different factors.3-5
• Creatinine should be measured with an assay for which calibration is traceable to an isotope-dilution mass spectrometry (IDMS) method.

CKD-EPI EQUATION
Other equations are also used to estimate GFR. A new equation was recently developed and named the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) equation. This equation is used for large studies because it provides better accuracy and reduced variability.3-7

\[
\text{ESTIMATED GFR (mL/min/1.73 m^2) = 141 x min (Scr / κ, 1)^{α} x max (Scr / κ, 1)^{-1.209} x 0.993^{4α} x 1.018 [if female] x 1.159 [if black]}
\]

Where:
• Scr is serum creatinine in mg/dL
• κ is 0.7 for females and 0.9 for males
• α is -0.329 for females and -0.411 for males
• min indicates the minimum of Scr / κ or 1
• max indicates the maximum of Scr / κ or 1

Both the 4-parameter MDRD equation and the CKD-EPI equation are widely used to estimate eGFR in clinical settings.

CYSTATIN C
Cystatin C is a low molecular weight protein that is freely filtered across the glomerular membrane. It is then reabsorbed and broken down in the renal tubules. Cystatin C is not normally excreted in urine, unless there is kidney damage. However, it can be accurately measured in blood serum;3-5, 3-8
• An increase in serum cystatin C is a marker of declining kidney function
• Urinary excretion is predictive of kidney failure and need for dialysis
• Urine cystatin C is elevated in CKD and acute kidney injury

Unlike serum creatinine, cystatin C levels are not significantly affected by age, sex, race or muscle mass. Thus, cystatin C provides a more accurate estimate of GFR in people with CKD.3-8 Moreover, cystatin C is more sensitive for detecting small decreases in GFR in people with mild renal dysfunction.3-9

Cystatin C has been standardized and a eGFR equation is available for standardized assays.3-7
**URINE TESTS**

Routine assessment of kidney function involves the evaluation of both quantity and quality of urine.\(^{1,15}\)

**SEDIMENTATION**

Analysis of urinary sediment is recommended for people with CKD or who are at increased risk of developing CKD.\(^{1,13}\) Microscopic examination of the urine sample may reveal cells, casts, crystals and microorganisms.\(^{1,17}\)

**Urinary casts** form when a high molecular weight protein derived from epithelial cells of the nephron precipitates within the renal tubules. The protein forms a gel that can trap cell debris, cells, crystals, fat and filtered proteins. Cast production increases when urine is highly concentrated or acidic.\(^{1,1}\)

Formed elements in the urinary sediment may indicate glomerular, tubular or vascular kidney disease. Significant numbers of red blood cells, white blood cells or casts suggest acute or chronic kidney disease that requires further analysis.\(^{1,1}\)

**OSMOLARITY**

The osmolarity of urine is determined by the regulation of the loss of water and solutes in the urine by the kidneys and is maintained at a relatively constant level. If disease alters kidney function, then substances normally not present in urine may appear and increase its osmolarity.\(^{1,15}\)

**URINARY PROTEIN**

Individuals with normal kidney function usually excrete little or no protein in the urine. A persistently high level of protein in the urine is usually a marker of kidney damage. The specific type of protein that is excreted in the urine varies, depending on the type of disease: \(^{1,1}\)

- Urinary albumin is a marker for CKD, diabetes, hypertension and glomerular disease
- Low molecular weight globins are indicative of certain tubulointerstitial diseases
Proteinuria can be considered within the normal physiological range when levels are low and within defined limits. When levels exceed the physiologic range, the terminology used changes in relation to protein levels (see Table 3-3): 3-10

<table>
<thead>
<tr>
<th>ALBUMINURIA</th>
<th>PROTEINURIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiologic range proteinuria</td>
<td>&lt;20 mg/day (15 mcg/min)</td>
</tr>
<tr>
<td>Increased urinary excretion</td>
<td></td>
</tr>
<tr>
<td>of proteins in general</td>
<td></td>
</tr>
<tr>
<td>(e.g., albumin, other specific</td>
<td></td>
</tr>
<tr>
<td>proteins, total protein)</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>30–300 mg/day</td>
</tr>
<tr>
<td>Albumin excretion above</td>
<td>(20–200 mcg/min)</td>
</tr>
<tr>
<td>normal range, but below</td>
<td></td>
</tr>
<tr>
<td>level of detection of tests</td>
<td></td>
</tr>
<tr>
<td>for total protein</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td>&gt;300 mg/day (&gt;200 mcg/min)</td>
</tr>
<tr>
<td>Albumin excretion above</td>
<td></td>
</tr>
<tr>
<td>normal range, detectable</td>
<td></td>
</tr>
<tr>
<td>on tests for total protein</td>
<td></td>
</tr>
<tr>
<td>Nephrotic range proteinuria</td>
<td>–</td>
</tr>
<tr>
<td>Massive excretion of protein</td>
<td></td>
</tr>
</tbody>
</table>

Table 3-3: Terminology Used to Describe Proteinuria. 1-1, 3-10

Proteinuria is a key prognostic finding in CKD, and severity of disease often correlates with the level and persistence of proteinuria over time. Therefore, regular screening for proteinuria is recommended. 1-1

Under most circumstances, a random (or “spot”) urine dipstick test is used to detect and monitor proteinuria. A positive dipstick test for protein should be followed with a quantitative measurement of protein-to-creatinine ratio or albumin-to-creatinine ratio within three months.1-1

**FAST FACT**

Microalbuminuria is the earliest manifestation of diabetic kidney disease. It is typically followed by proteinuria, hypertension and progressively declining GFR, depending on the stage of CKD. 1-1

**URINARY ALBUMIN-TO-CREATININE RATIO (UACR)**

Urinary protein-to-creatinine ratio and the more common and preferred urinary albumin-to-creatinine ratio (UACR) provide accurate estimates of the urinary protein and albumin excretion rate, regardless of hydration status. Urinary proteins and creatinine dissolve easily in water. Therefore, their dilution in urine should be similar and their ratio should be constant. Because the rate of creatinine excretion is relatively steady throughout the day, the UACR in a random urine sample reflects the excretion of protein.1-1
**PTH IMMUNOASSAYS**

Elevated serum parathyroid hormone (PTH) may be the earliest marker of abnormal bone mineral metabolism, detectable before changes in phosphorus and calcium. The following interpretive guidelines for PTH have been proposed:1-1

• <65 pg/mL is predictive of normal bone (normal range 8–51 pg/mL3-2) in people with normal kidney function
• >450 pg/mL reflects a high turnover rate

PTH relates directly to bone turnover, with the caveat that it is not reliably correlated with turnover rate in severe CKD requiring dialysis.1-1

The *Kidney Disease: Improving Global Outcomes (KDIGO)* and KDOQI guidelines recommend periodic monitoring of serum levels of calcium, phosphorus and PTH in all people with CKD stage G3a or higher, according to the schedule in **Table 3-4**.1-3, 3-11

<table>
<thead>
<tr>
<th>CKD STAGE</th>
<th>GFR RANGE (mL/min/1.73 M²)</th>
<th>MEASUREMENT OF PTH</th>
<th>MEASUREMENT OF CALCIUM/PHOSPHORUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>G3a</td>
<td>45–59</td>
<td>According to baseline PTH level and CKD progression</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>G3b</td>
<td>30–44</td>
<td>According to baseline PTH level and CKD progression</td>
<td>Every 6–12 months</td>
</tr>
<tr>
<td>G4</td>
<td>15–29</td>
<td>Every 6–12 months</td>
<td>Every 3–6 months</td>
</tr>
<tr>
<td>G5</td>
<td>&lt; 15 or dialysis</td>
<td>Every 3–6 months</td>
<td>Every 1–3 months</td>
</tr>
</tbody>
</table>

**Table 3-4**: Frequency of serum PTH and calcium/phosphorus monitoring.3-11 Based on KDIGO 2017 recommendations.1-3

PTH levels are measured by immunoassay. Current assays detect biologically active intact PTH (iPTH), rather than fragments of PTH that may be inactive. They are detected as:3-12

• Immunoradiometric (IRMA), meaning that antibodies bound to PTH are detected with a radioactive tag.
• Immunochemiluminescent (ICMA), meaning that antibodies bound to PTH are detected using a tag that emits light when a chemical reagent is added.

**FAST FACT**

Approximately 50% of circulating PTH in people with kidney failure consists of large fragments of PTH, and not the intact form. Older PTH assays detected fragments of PTH. Newer assays are specific for the full-length molecule, designated as “whole,” “bioactive” or “intact” PTH.3-12
KIDNEY IMAGING STUDIES

Imaging studies are recommended for people with CKD and for people who are at an increased risk of developing CKD due to urinary tract stones, infection or obstruction. Imaging studies used to evaluate kidney damage include:

• Ultrasound — Uses high-frequency sound waves that bounce off structures and are converted to images.

• Intravenous pyelography (IVP) — The entire urinary system is visualized through a series of x-ray images, taken sequentially before and after injection of radioactive contrast medium.

• Computed tomography (CT) — Cross-sectional imaging technique uses computerized reconstruction to generate an image “slice”.

• Magnetic resonance imaging (MRI) — Cross-sectional images are obtained by a complex interaction between atoms in the cells and radiofrequency waves in a strong magnetic field.

Each of these imaging techniques is useful for identifying urinary tract obstructions such as kidney stones, cysts and tumors. In ultrasonography, CKD is generally indicated by small kidneys that produce a strong echo.

KIDNEY BIOPSY

A kidney biopsy provides tissue that can be used to help confirm diagnosis and to assess the chronicity and severity of the injury. Renal biopsy is indicated only when the cause of kidney disease cannot be determined by less invasive diagnostic procedures.
EVALUATION OF BONE

In addition to the laboratory parameters discussed earlier, there are a number of evaluations specific to bone. These include markers of bone turnover, bone density and evaluation of bone histology.

![Diagram of evaluation of bone disease in people with CKD](image)

**Figure 3-1:** Evaluation of bone disease in people with CKD. QOL: quality of life.

MARKERS OF BONE TURNOVER

Bone turnover (remodeling) is a coupled process in which resorption of old bone by osteoclasts is followed by formation of new bone by osteoblasts. The process is regulated by PTH, vitamin D metabolites and various other factors.

Biochemical markers that reflect the remodeling process can be measured in blood and/or urine. They include:

- Enzymes or proteins secreted by cells involved in remodeling.
- By-products generated during the resorption or formation of bone.
CLINICAL CONNECTION

In CKD, changes in bone remodeling may be dramatic (such as in renal osteodystrophy); however, most are rather subtle (such as in osteoporosis). Definitive diagnosis of the type of bone disease requires bone biopsy.

BONE MINERAL DENSITY (BMD) MEASUREMENT

Bone mineral density (BMD) can be measured using noninvasive X-ray techniques. A low or decreasing BMD value is indicative of abnormal bones:

- In CKD stages G1–G3b, BMD is an important predictor of fracture risk
- In CKD stages G3b–G5, once CKD–MBD begins to develop, BMD does not predict fractures very well, and routine testing is not recommended
- Following kidney transplant, there is a rapid loss of bone mass and increased fracture risk; regular BMD monitoring is recommended

CLINICAL CONNECTION

As part of the Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994, a correlation was noted between BMD and Cockcroft-Gault eGFR in 13,831 adults older than 20 years old. Low BMD was more prevalent among those with CKD than with normal kidney function.

RADIOGRAPHY

The bone disease component of CKD–MBD may result in fractures, including asymptomatic vertebral fractures. Fractures can be identified on standard radiographs (X-rays).

BONE BIOPSY

Bone biopsy is the gold standard for the diagnosis of renal osteodystrophy. Unfortunately, the procedure is invasive and cannot be readily performed in all patients.

Bone biopsies help to assess bone quality and the underlying pathophysiology of bone disease. In people with CKD stages G3a–G5, bone biopsy may be warranted if there are unexplained fractures, persistent bone pain, unexplained hypercalcemia or hypophosphatemia or possible aluminum toxicity, and before initiating certain treatments.
REVIEW QUESTIONS: SECTION 3

Answers are provided at the end of this Learning Guide.

1. Which measure would you expect to decrease as CKD progresses?
   - A 1,25-dihydroxyvitamin D
   - B Parathyroid hormone
   - C Serum phosphorus
   - D Urinary albumin

2. Which method can be used to estimate glomerular filtration rate (GFR)?
   - A Serum creatinine measurement
   - B Parathyroid hormone (PTH) assay
   - C Serum calcium x phosphorous product
   - D Urinary albumin to creatine ratio

3. Serum creatinine levels vary according to which of the following criteria?
   - A Age
   - B Race
   - C Sex
   - D All of the above

4. How often should serum parathyroid hormone (PTH) levels be measured in people with stage G3a CKD?
   - A Every 1–3 months
   - B Every 3–6 months
   - C Every 6–12 months
   - D Every 12–24 months
SECTION 4
MANAGEMENT OF CKD

LEARNING OBJECTIVES
After completing this section, you will be able to:

• Identify key guidelines for long-term management of people with CKD.
• Recognize treatments that may slow progression of CKD.
• Describe the conditions associated with CKD, and how to manage them.
• Understand renal replacement therapy and renal transplantation.
MANAGEMENT OVERVIEW

Clinical practice guidelines help healthcare providers consistently manage long-term treatment of CKD. Two key organizations publish guidelines for CKD diagnosis, evaluation, classification and treatment:

- The U.S. National Kidney Foundation – Kidney Disease Outcome Quality Initiative (NKF–KDOQI)\(^1\)\(^-\)\(^1\)
- The International Society of Nephrology: Kidney Disease: Improving Global Outcomes (KDIGO)\(^1\)\(^-\)\(^3\)

According to the NKF–KDOQI, a clinical action plan should be developed for each patient, based on the stage of disease as defined in Table 4-1.\(^1\)\(^-\)\(^1\)

<table>
<thead>
<tr>
<th>STAGE</th>
<th>DESCRIPTION</th>
<th>GFR (mL/min/1.73 M(^2))</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>At increased risk</td>
<td>≥ 90 (with CKD risk factors)</td>
<td>Screening, CKD risk reduction</td>
</tr>
<tr>
<td>G2</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90</td>
<td>Diagnosis and treatment&lt;br&gt;Treatment of comorbid conditions&lt;br&gt;Slowing progression&lt;br&gt;Reduction of cardiovascular risks</td>
</tr>
<tr>
<td>G3a</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
<td>Estimating progression</td>
</tr>
<tr>
<td>G3b</td>
<td>Moderate ↓ GFR</td>
<td>45–59</td>
<td>Evaluating and treating complications</td>
</tr>
<tr>
<td>G4</td>
<td>Moderate ↓ GFR</td>
<td>30–44</td>
<td>Evaluating and treating complications</td>
</tr>
<tr>
<td>G5</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
<td>Preparation for renal replacement therapy (dialysis or transplant)</td>
</tr>
<tr>
<td>G5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
<td>Renal replacement therapy, if uremia is present</td>
</tr>
</tbody>
</table>

Table 4-1: Chronic kidney disease: a clinical action plan.\(^1\)\(^-\)\(^1\)
**SLOWING PROGRESSION OF CKD**

The major outcomes of CKD are the progressive loss of kidney function leading to kidney failure and complications such as cardiovascular disease (CVD) and bone disease. Therefore, the goal of medical management of CKD is to slow the progressive loss of kidney function. The rate of GFR decline should be assessed to predict the onset of kidney disease and possible interventions evaluated to slow GFR decline.1-1

In people with CKD, serum creatinine should be measured:1-1

- At least yearly, in order to monitor GFR.
- More frequently than once a year if GFR <60 mL/min/1.73 m² or if there are risk factors for fast progression.

Early interventions to slow the progression of CKD include dietary restrictions, tight control of blood sugar and maintaining blood pressure and blood lipids within a reasonable range, as summarized in Table 4-21-1. The dyslipidemia of CKD primarily is comprised of high triglyceride levels and low HDL cholesterol levels.4-1 Although the NKF-KDIGO recommends following ACC goals, the patients with CKD are known to be challenging to treat and this is particularly true regarding triglyceride management. It is usually recommended that targeted management be made for CKD patients whose triglycerides reach levels of 500 mg/dL. Specific treatment recommendations are not provided in the guide.

<table>
<thead>
<tr>
<th>GOALS</th>
<th>APPROACHES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein intake1-1</td>
<td>Reduce accumulation of toxic urea and creatinine</td>
</tr>
<tr>
<td></td>
<td>• Dietary protein restriction in CKD stages G4–G5 (if not on dialysis)</td>
</tr>
<tr>
<td>Energy intake1-1</td>
<td>Improve nitrogen utilization</td>
</tr>
<tr>
<td></td>
<td>Prevent malnutrition and weight loss</td>
</tr>
<tr>
<td></td>
<td>• Increased caloric intake in CKD stages G4–G5 (if not on dialysis)</td>
</tr>
<tr>
<td>Blood glucose1-1</td>
<td>Control blood glucose in diabetics</td>
</tr>
<tr>
<td></td>
<td>Reduce retinopathy, microalbuminuria, kidney disease, cardiovascular risk</td>
</tr>
<tr>
<td></td>
<td>• Diet, exercise, weight loss</td>
</tr>
<tr>
<td></td>
<td>• Oral antidiabetic medications and/or insulin</td>
</tr>
<tr>
<td>Blood pressure1-1, 4-2</td>
<td>Reduce hypertension, glomerular capillary pressure, protein filtration</td>
</tr>
<tr>
<td>Blood pressure targets:</td>
<td>• CKD stages G1–G4 with proteinuria (&lt;1 g/day) or diabetic kidney disease: &lt;125/75 mmHg</td>
</tr>
<tr>
<td></td>
<td>• CKD stages G1–G4 without proteinuria: &lt;130/80 mmHg</td>
</tr>
<tr>
<td></td>
<td>• In CKD stage G5: Guidelines are not well defined</td>
</tr>
<tr>
<td></td>
<td>• Diet (reduce salt, fluids), exercise</td>
</tr>
<tr>
<td></td>
<td>• Antihypertensive medications: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, beta blockers, calcium channel blockers</td>
</tr>
<tr>
<td>Blood lipids1-1, 4-3, 4-4</td>
<td>Control dyslipidemias and reduce risk of atherosclerosis (rather than slow CKD progression)</td>
</tr>
<tr>
<td>Lipid targets:</td>
<td>• Triglycerides &lt;150 mg/dL 4-5</td>
</tr>
<tr>
<td></td>
<td>• Low-density lipoprotein cholesterol &lt;100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• High-density lipoprotein cholesterol between 30 mg/dL and 60 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Diet, exercise, weight loss</td>
</tr>
<tr>
<td></td>
<td>• Lipid-lowering medications: statins, fibrates, niacin, bile sequestrants</td>
</tr>
</tbody>
</table>

Table 4-2: Approaches to slowing CKD progression.
MANAGING CONDITIONS ASSOCIATED WITH CKD

Decreased GFR is associated with complications in virtually all organ systems. These complications manifest first by high blood pressure and abnormal blood tests, then by symptoms and abnormalities on physical examination. As GFR declines, complications generally worsen. Some important complications to be managed in CKD are malnutrition, anemia, neuropathy, hyperphosphatemia, secondary hyperparathyroidism (SHPT) and bone disease. Management goals and approaches for each are summarized in Table 4-3.

<table>
<thead>
<tr>
<th>GOALS</th>
<th>APPROACHES</th>
</tr>
</thead>
</table>
| Anemia | Correct iron deficiency  
Stimulate red blood cell production and raise hemoglobin levels | • Iron supplements  
• Erythropoiesis-stimulating agents (ESAs): epoetin alfa, epoetin beta, darbepoetin |
| Malnutrition | Evaluate nutritional status  
Address protein energy malnutrition | • Counseling, education  
• Dietary modification |
| Hyperphosphatemia | Reduce blood phosphate levels  
**Phosphate targets:**  
• CKD stages G3 and G4: 2.7–4.6 mg/dL (0.87–1.49 mmol/L)  
• CKD stage G5 and dialysis patients: 3.5–5.5 mg/dL (1.13–1.78 mmol/L) | • Phosphate-restricted diets  
• Oral phosphate binders to reduce phosphate absorption: aluminum hydroxide, calcium salts, non-calcium-based phosphate binders (sevelamer and lanthanum salts) |
| Secondary hyperparathyroidism (SHPT) | Correct hypocalcemia and vitamin D deficiency, reduce PTH levels  
**PTH targets (iPTH assay):**  
• CKD stages G3a–G5: maintain below upper normal limit of assay  
• CKD stage G5 on dialysis: maintain within 2–9x upper normal limit of assay | • Oral calcium salts, increased calcium dialysate concentration  
• Vitamin D, vitamin D analogs  
• Calcimimetics  
• Parathyroidectomy (surgical removal of parathyroid glands) |
| Osteoporosis | Increase BMD, reduce fracture risk in CKD stages G1–G3b without biochemical abnormalities of CKD–MBD or SHPT | • Bone resorption inhibitors: bisphosphonates, raloxifene  
• Bone anabolic: teriparatide (1–34 PTH) |
| Uremic neuropathy | Halt progression of neuropathy | • Renal transplant or dialysis |

*Table 4-3: Managing CKD complications.*
RENAL REPLACEMENT THERAPY (RRT)

People with kidney failure ultimately require dialysis or kidney transplantation to sustain life. Some experts advocate “early initiation of dialysis” or “preemptive” kidney transplantation prior to the onset of kidney failure.1-1

Recall that kidney failure is defined as one of two conditions:
- GFR <15 mL/min/1.73 m², usually accompanied by signs of uremia
- Need to initiate kidney replacement therapy such as dialysis or transplantation for treatment of complications of decreased GFR, which would otherwise increase the risk of mortality and morbidity

Note: Some patients may require dialysis or transplantation at GFR ≥15 mL/min/1.73 m² because of symptoms of uremia.1-1

If kidney function is inadequate, then blood must be cleansed artificially by dialysis. This process separates large solutes from smaller ones by diffusion through a selectively permeable membrane.1-15 Dialysis cannot replace the endocrine function of the kidney — secretion of erythropoietin (involved in red blood cell production) and calcitriol (involved in bone formation). Therefore, dialyzed people need to be supplemented to control for anemia and bone disorder.4-7

HEMODIALYSIS

Hemodialysis directly filters the blood through a membrane and returns it to the body. Dialysate fluid surrounds the membrane and maintains a concentration gradient, so substances diffuse between dialysate and blood:1-15
- Wastes, excess electrolytes and fluid flow from the blood into the dialysate
- The blood is replenished with needed substances from the dialysate

Following filtration, the cleansed blood passes through a mechanism to remove any air, and an agent is added to prevent the blood from clotting. Most people require hemodialysis for 6–12 hours per week, divided into two sessions.1-15

Hemodialysis requires a vascular access site, either in the form of a temporary catheter, or a permanent access that is surgically created:
- Arteriovenous (AV) fistulas connect an artery directly to a vein, usually in the forearm; the vein then thickens, allowing repeated needle insertions 1-19
- Grafts in hemodialysis connect an artery to a vein using a synthetic tube1-19
PERITONEAL DIALYSIS

Peritoneal dialysis uses the **peritoneum** (lining of the abdominal cavity) as a filter because it has a large surface area and numerous blood vessels. Dialysate is drained from a bag through a catheter inserted in the abdomen. Wastes, excess electrolytes and fluid diffuse into the dialysate, and the solution is then drained, discarded and replaced. Each cycle is called an exchange.\(^\text{1-15}\)

- Continuous ambulatory peritoneal dialysis (CAPD) needs no machine — it can be performed at home with the dialysate drained and replenished four times a day and once at night during sleep.\(^\text{1-19}\)
- Continuous cycler-assisted peritoneal dialysis (CCAPD) uses a portable cycler to automatically fill and drain the dialysis solution from the abdomen; a typical schedule involves 3–5 exchanges during the night while the person sleeps, and one exchange during the day.\(^\text{1-19, 4-8}\)
RENAL TRANSPLANTATION

A kidney transplant is the treatment of choice for people with CKD stage G5:1-1, 4-9
• Kidney transplant recipients have a higher mean GFR (usually 30–60 mL/min/1.73 m²) and a better average outcome than dialysis patients
• Risk of death among transplant recipients is less than half of that among people on dialysis

REJECTION RISK

Acute rejection may occur when the recipient mounts an immune response against the kidney. It is accompanied by a decline in kidney function and histological changes in the new kidney. Precautions must be taken to reduce the risk of the new kidney being rejected. 4-9
• Before transplantation, induction treatment with an immunosuppressive agent is initiated to deplete immune cells or modulate immune responses
• Following transplantation, long-term immunosuppressive therapy is required to prevent rejection and deterioration of kidney function — higher doses are given in the first three months, when risk of rejection is greatest

POSTTRANSPLANT BONE DISEASE

Rapid loss of bone mass within the first six months after a kidney transplant leads to osteopenia, which may worsen to the point of osteoporosis. This is accompanied by increased risk of fractures, particularly for the first two years after transplant. Corticosteroids and immunosuppressive therapies contribute to this rapid bone loss.2-9

Bone mineral density (BMD) in transplant recipients should be regularly monitored using dual-energy X-ray absorptiometry (DXA). If osteoporosis develops, then appropriate therapy should be initiated.2-9
REVIEW QUESTIONS: SECTION 4

Answers are provided at the end of this Learning Guide.

1. Which modality may require surgical creation of an arteriovenous fistula?
   - A Continuous ambulatory peritoneal dialysis
   - B Continuous cycling peritoneal dialysis
   - C Hemodialysis
   - D Renal transplant

2. A calcimimetic could be used to treat which complication of CKD?
   - A Anemia
   - B Hypertension
   - C Osteoporosis
   - D SHPT

3. Which measures may help slow CKD progression?
   - A Blood pressure control
   - B Glycemic control
   - C Protein restriction
   - D All of the above

4. At which stage of CKD should preparation for dialysis or transplant begin?
   - A Stage G2
   - B Stage G3a
   - C Stage G4
   - D Stage G5
APPENDIX A: GLOSSARY OF TERMS

**Albumin:** The major plasma protein, approximately 60% of the total, and 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.⁴⁻¹

**Anemia:** Condition categorized by a lessened capacity of the blood to carry enough oxygen, most commonly due to a lower-than-normal amount of red blood cells or hemoglobin.⁵⁻³

**Arteriovenous (AV) fistula:** Surgical connection of an artery directly to a vein, usually in the forearm; causes vein to thicken, allowing repeated needle insertions for hemodialysis.⁵⁻¹⁹

**Atherosclerosis:** Disease characterized by irregularly distributed lipid deposits in the intima of large and medium arteries. Such deposits provoke fibrosis and calcification. Deposits hinder or eventually shut off blood flow.⁶⁻¹⁸

**Comorbidity:** Medical condition other than the primary disease.¹⁻¹

**Creatinine:** A waste product from meat protein in the diet and from the muscles of the body.⁷⁻¹⁹

**Cystatin C:** A low-molecular weight protein produced at a constant rate by all nucleated cells and freely filtered by the glomerulus, which is then reabsorbed and degraded by the tubules. Serves as a novel serum marker of GFR.⁸⁻²

**Diabetes mellitus:** A condition characterized by high blood glucose (sugar); encompasses type 1 and type 2 diabetes.⁹⁻¹⁹

**Dialysate (dialysis solution):** A cleansing liquid used in the two major forms of dialysis — hemodialysis and peritoneal dialysis. This solution contains dextrose (a sugar) and other chemicals similar to those in the body. Dextrose draws wastes and extra fluid from the body into the dialysis solution.⁹⁻¹⁹

**Diastolic blood pressure:** The force exerted by blood on arterial walls during relaxation of the heart muscle; the lowest blood pressure measured in the large arteries.⁴⁻³

**Dyslipidemia:** Abnormal lipid metabolism.⁴⁻⁴

**Edema:** An abnormally high accumulation of tissue fluid.⁴⁻³

**Encephalopathy:** Any disorder of the brain.⁵⁻¹⁸

**Erythropoiesis:** The production of red blood cells.⁴⁻⁵

**Erythropoiesis-stimulating agent (ESA):** Any agent that augments erythropoiesis through direct or indirect action on the erythropoietin receptor. ESAs include epoetin alfa, epoetin beta, and darbepoetin alfa.⁵⁻³

**Erythropoietin (EPO):** A hormone made by the kidneys to help form red blood cells. Lack of this hormone may lead to anemia.⁵⁻¹⁸

**Glomerular filtration rate (GFR):** The amount of filtrate formed in all the renal corpuscles of both kidneys each minute (mL/min).⁵⁻¹⁵

**Hemodialysis (HD):** Use of a machine to remove wastes and extra fluid from the blood after kidney failure; cleaned blood flows through a set of tubes back into the body.⁶⁻¹⁹

**Hemoglobin (Hb):** A protein in red blood cells consisting of the protein globin and the iron-containing red pigment heme, which transports most of the oxygen and some carbon dioxide in blood.⁴⁻³

**Homeostasis:** The condition in which the body’s internal environment remains relatively constant and within physiological limits.⁴⁻³

**Hypercalcemia:** An abnormally high concentration of calcium in blood.⁶⁻¹⁸
Hyperlipidemia: An elevated level of lipids (cholesterol, triglycerides, fatty acids) in the blood.1-18

Hyperphosphatemia: Elevation of phosphorus concentration in blood.1-18

Hypoalbuminemia: Low blood albumin level due to loss of albumin in urine.1-15

Hypophosphatemia: Deficiency of phosphorus in blood.1-18

Insulin: A hormone produced by the pancreas that decreases blood glucose levels. A-3

Kidney Disease: Improving Global Outcomes (KDIGO): Independent, international, nonprofit foundation with a mission to improve the care and outcomes of kidney disease patients worldwide through developing and implementing clinical practice guidelines.1-3

Kidney Disease Outcome Quality Initiative (KDOQI): Workgroup of the National Kidney Foundation; provides recommendations on optimal clinical practices for dialysis, vascular access and anemia in CKD.1-4

Modification of Diet in Renal Disease (MDRD): The MDRD study equation was developed using data from 1,628 people with CKD. It is used to estimate GFR adjusted for body surface area.3-5

National Health and Nutrition Examination Survey (NHANES): Survey conducted by the National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention; uses home interviews and health tests to collect information on health and diet in the U.S.1-6

Nephrotic proteinuria: Persistent massive proteinuria in excess of 3,500 mg/day.1-1

Neuropathy: Any disorder affecting the nervous system.1-18

Osmolarity: The measure of the total number of dissolved particles per liter of solution.1-15

Osteoblast: Cell that makes bone by producing a matrix that then becomes mineralized. A-3

Osteoclast: A large, multinucleated cell that resorbs (breaks down) bone matrix. A-3

Osteopenia: Decrease in bone mass below normal. A-1

Osteoporosis: Decreased bone mass which can result in low-trauma or fragility fractures, especially vertebral, hip, wrist, and thoracic and lumbar spine. A-1

Parathyroid hormone (PTH): A hormone secreted by the principal cells of the parathyroid glands that increases blood calcium level and decreases blood phosphate level. A-3

Parenchyma: The functional part of the kidney. Contains approximately one million nephrons — the filtration units of the kidney.1-15

Pericarditis: Inflammation of the pericardium (the fibrous membrane surrounding the heart).1-18

Peritoneal dialysis (PD): Cleaning the blood by using the lining of the abdominal cavity as a filter. Cleansing liquid, called dialysis solution, is drained from a bag into the abdomen; the solution is then drained from the abdomen, removing extra fluids and wastes.1-49

Peritoneum: The largest serous membrane of the body that lines the abdominal cavity and covers the viscera. A-3
Proteinuria: A condition in which the urine contains a large amount of protein; a sign that the kidneys are not functioning properly.1-19

Pruritus: Itching.1-18

Renal osteodystrophy (ROD): Alteration of bone morphology in people with CKD; one measure of the skeletal component of the systemic disorder of CKD–MBD that is quantifiable by histomorphometry of bone biopsy; common problem for people on dialysis who have hyperphosphatemia or insufficient vitamin D supplementation.1,3,119

Renin: Enzyme released by the kidneys in response to low blood pressure; first step of the renin-angiotensin-aldosterone pathway that regulates aldosterone secretion.4-6

Renin-angiotensin-aldosterone system (RAAS): Pathway that regulates secretion of aldosterone to help control blood volume, blood pressure and levels of Na+, K+ and H+ in the blood.4-6

Risk factor: An attribute associated with increased risk of an outcome. Relationship between risk factor and outcome may be either causal or noncausal.1-1

Secondary hyperparathyroidism (SHPT): A disease associated with CKD that is characterized by increased phosphorous levels and increased PTH, leading to bone disease and other complications.2-6

Systolic blood pressure: The force exerted by blood on arterial walls during contraction of the heart muscle; the highest pressure measured in the large arteries.4-3

Tubulointerstitial diseases: Group of diseases that primarily affect the renal tubules and interstitium.1-17

Type 1 diabetes: Condition in which the body does not produce enough insulin.1-19

Type 2 diabetes: Condition in which the body responds poorly to insulin.1-19

Uremia: Accumulation of toxic levels of urea and other nitrogenous waste products in the blood, usually due to severe kidney malfunction.4-3

Urinary cast: Cylindrical sediment formed when protein precipitates within the renal tubules; may entrap various cells and debris.1-19

Vascular access: In dialysis, the point on the body where a needle or catheter is inserted.1-19


REFERENCES, CONTINUED


REFERENCES, CONTINUED


APPENDIX C: CORRECT RESPONSES

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1. B
2. 
<table>
<thead>
<tr>
<th>CLINICAL TERM</th>
<th>MEDICAL DESCRIPTION</th>
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<tbody>
<tr>
<td>Microalbuminuria</td>
<td>Excretion of small abnormal amounts of albumin</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Presence of blood in urine</td>
</tr>
<tr>
<td>Uremia</td>
<td>Toxic levels of urea in blood</td>
</tr>
</tbody>
</table>
3. B
4. C

SECTION 2
1. A
2. D
3. D
4. Hypertension, atherosclerosis, left ventricular hypertrophy, congestive heart failure, peripheral vascular disease

SECTION 3
1. A
2. A
3. D
4. C

SECTION 4
1. C
2. D
3. D
4. C