Diabetes and Renal Disease

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- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
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Faculty

Diane Thompson, RN, MSN, CDE, CLNC, has an extensive history in nursing and nursing education. She possesses a strong background in diabetes and cardiac care, starting her professional career at the cardiac care area of the Cleveland Clinic in Cleveland, Ohio. Ms. Thompson took the knowledge and experience she learned from the Cleveland Clinic and transferred it into the home health arena in rural Ohio, after which she moved to Florida and obtained further knowledge while working as a PRN nurse in all areas, including medical/surgical, intensive care, emergency, critical care, and cardiology. With a desire to have a specific area to concentrate her profession, Ms. Thompson accepted a position as a pneumonia case manager, which led into a diabetes case manager career.

Ms. Thompson has been employed in diabetes care since 2001, when she was hired as a diabetes case manager. After the completion of 1,000 hours of education to diabetes patients, Ms. Thompson earned her certification as a diabetes educator in 2003. From 2006 to 2018, Ms. Thompson was the Director of Diabetes Healthways at Munroe Regional Medical Center in Ocala, Florida. As the director of the diabetes center, Ms. Thompson was responsible for the hospital diabetes clinicians, hospital wound care clinicians, and out-patient education program. Today, she is the nurse manager of a heart, vascular, and pulmonary ambulatory clinic at Metro Health System in Cleveland, Ohio. Ms. Thompson has also lectured at the local, state, and national level regarding diabetes and the hospital management of hyperglycemia. Ms. Thompson is a member of the ADA, AADE, Florida Nurses Association, and the National Alliance of Certified Legal Nurse Consultants.

Ms. Thompson acknowledges her family as her greatest accomplishment. She is a wife of more than 30 years and a mother of a daughter and son, of which she is very proud. Ms. Thompson credits her husband for the support needed to set a goal and achieve it. He has been by her side through nursing school and completion of her Bachelor's degree and Master's degree, which she was awarded in 2015 from Jacksonville University in Florida.

Faculty Disclosure

Contributing faculty, Diane Thompson, RN, MSN, CDE, CLNC, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planner/Director Disclosure

The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses and allied health professionals involved in the care of patients with diabetes.

A complete Works Cited list begins on page 24.

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Course Objective

Renal failure is a life-changing event that can be prevented or delayed with proper understanding and education on behalf of the healthcare professional and the patient. The purpose of this course is to provide nurses with the information necessary to identify renal complications of diabetes and educate patients with diabetes regarding the steps necessary to prevent renal disease.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the epidemiology of diabetes and renal disease in the United States.
2. Identify criteria for the diagnosis of diabetes.
3. Discuss the essential functions of the kidney.
4. Evaluate the causes, diagnosis, and treatment of acute renal failure.
5. Analyze the various stages of chronic kidney disease, including diabetic nephropathy.
6. Utilize standards of care for the treatment and prevention of renal disease in patients with diabetes.
7. Discuss the educational needs for patients with diabetes to prevent or delay renal disease.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The range of changes in the kidney that occur among individuals diagnosed with diabetes is referred to as diabetic nephropathy or diabetic kidney disease. The effects of diabetes on the renal system can range from mild to severe. At the severe end of the spectrum is clinically apparent, or overt, diabetic kidney disease, which is characterized by persistent proteinuria, hypertension, and a progressive decline in kidney function [1].

Diabetes is the leading cause of kidney failure in the United States, accounting for 44% of new cases [2]. In 2018, 131,636 individuals in the United States began treatment for end-stage renal disease requiring dialysis or transplantation [3]. In the United States, annual end-stage renal disease costs are estimated to be $49.2 billion, with a greater incidence and associated cost among racial minorities [3].

The increased prevalence of chronic kidney disease in the United States is generally the result of two major factors: the increased incidence in type 2 diabetes overall and the innovative therapeutic approaches that have permitted individuals diagnosed with diabetes to live longer [1].

AN OVERVIEW OF DIABETES

EPIDEMIOLOGY

Diabetes is a progressive disease process influencing fuel metabolism by the body [4]. Carbohydrate, protein, and fat metabolism are altered when insulin, the mediator of fuel, is not available. Insulin deficiency can result from defects in insulin secretion and/or diminished tissue response to insulin. The result of this defect in insulin secretion and/or insulin resistance is hyperglycemia [5]. The chronic metabolic dysregulation associated with diabetes can result in long-standing damage to various organs, including the eyes, kidneys, nerves, heart, and blood vessels [6].

According to the American Diabetes Association (ADA), as of 2020, 10.5% of the U.S. population, or 34.2 million Americans, have a diagnosis of diabetes. In addition, an estimated 7.3 million people have diabetes but remain undiagnosed [7]. By 2025, it is predicted that 15% to 20% of all Americans will have a diagnosis of diabetes or impaired glucose tolerance [8].

The scope of the diabetes problem is vast and diverse, particularly among geographical regions. In 2018, the prevalence of diabetes in the United States varied from 6.6% in Colorado to 13.4% in West Virginia [9]. Genetics, race, age, and lifestyle significantly influence the onset and progression of the disease process [5]. Although all races and ethnicities can develop diabetes, the prevalence is greatest among persons of Native American/Alaska Native (14.7%) and Hispanic (12.5%) heritage [10]. The prevalence in non-Hispanic Black Americans is 11.7%, whereas the prevalence in White Americans is 7.5% [10]. The highest prevalence of diabetes in the United States is observed in Native Americans in the Southwest, where an estimated 16.0% of the population has the disease [11].

The most rapid increase in diabetes prevalence in the last decade has been among adolescents. Historically, children and adolescents with hyperglycemia have been diagnosed with type 1 diabetes, a result of the body being unable to produce adequate amounts of insulin. However, it is now estimated that as many as 45% of juvenile-onset cases of diabetes are type 2 [8]. Furthermore, it has been predicted that children born in this millennium will have a one in three chance of developing diabetes in their lifetime; among high-risk ethnic groups, the estimate is as high as one in two [12].

DIAGNOSTIC CRITERIA FOR TYPE 2 DIABETES			
Stage	**Fasting Plasma Glucose Level**	**Two-Hour Postprandial Plasma Glucose Level**	**Glycated Hemoglobin (HbA1c)**
Euglycemia	≤100 mg/dL	<140 mg/dL	<5.7%
Prediabetes	>100 mg/dL but <126 mg/dL	≥140 mg/dL but <200 mg/dL	5.7% to 6.4%
Diabetes[a]	≥126 mg/dL	≥200 mg/dL	≥6.5%
[a]A random blood glucose level ≥200 mg/dL with symptoms of hyperglycemia is also indicative of diabetes.			
Source: [14; 17]			*Table 1*

DIAGNOSIS

The most common types of diabetes are type 1 and type 2. However, gestational diabetes is also relatively common and is a source of significant morbidity and mortality. Gestational diabetes is first recognized in pregnancy, usually after 24 weeks of gestation, and typically resolves after the birth of the child [13]. Other less common types of diabetes include [8; 14]:

- Maturity-onset diabetes of the young: A genetic, autosomal-dominant defect of the pancreatic beta cells, resulting in insulin deficiency and decreased insulin release without the presence of insulin resistance and obesity. This form of diabetes typically develops in patients younger than 25 years of age. It is a different clinical entity than type 2 diabetes of the adolescent, which presents with insulin resistance.
- Diabetes related to diseases of the exocrine pancreas, such as cystic fibrosis, and various endocrine diseases, such as Cushing syndrome, acromegaly, and chromocytoma
- Drug-induced diabetes resulting from the use of certain medications, particularly high-dose corticosteroids

The U.S. Preventive Services Task Force (USPSTF) recommends that all adults 45 years of age and older be screened for type 2 diabetes either every three years or annually if they have any risk factors [15]. The USPSTF also recommends screening for abnormal blood glucose as part of a cardiovascular risk assessment in adults 35 to 70 years of age who are overweight or obese [16]. In addition, individuals of any age who are at risk for or are suspected of having diabetes should be screened. Established risk factors for type 2 diabetes include:

- Age 45 years and older
- Body mass index (BMI) greater than or equal to 25
- Family history of type 2 diabetes
- Habitual physical inactivity
- Race/ethnicity (e.g., African American, Hispanic American, Native American, Alaska Native, or Pacific Islander)
- Impaired glucose tolerance or elevated fasting glucose
- Previous history of gestational diabetes or giving birth to a child weighing more than 9 pounds
- Hypertension (i.e., blood pressure greater than 140/90 mm Hg in adults)
- Abnormal lipid levels (i.e., high-density lipoprotein [HDL] level <35 mg/dL and/or triglyceride level >250 mg/dL)
- Polycystic ovary syndrome
- History of vascular disease
- Acanthosis nigricans (most common among individuals of African descent)

The diagnostic criteria for type 2 diabetes are fairly straightforward and are based on fasting plasma glucose and postprandial plasma glucose levels (***Table 1***). After a diagnosis of type 2 diabetes has been definitively made, education on self-care management is necessary in order to obtain euglycemia and prevent complications related to the detrimental effects of hyperglycemia [17]. It is estimated that as many as 90% of patients with type 2 diabetes will require oral medications to achieve adequate glucose control within five years of diagnosis [18]. When glucose levels cannot be adequately controlled with oral medications, the use of injectable medications is necessary. If elevated blood glucose levels are untreated and continue to rise, the result can be hyperosmolar hyperglycemic nonketotic syndrome and ultimately death [19].

PHYSIOLOGY OF THE RENAL SYSTEM

GLOMERULAR FILTRATION AND TUBULAR RESORPTION

It is approximated that the glomerular filtration rate (GFR) in a healthy individual with two properly functioning kidneys is 90–120 mL/min/1.73 m^2 [20]. The approximate mass cutoff of substances for filtration is 70 kDa [21]. Substances greater than the 70 kDa cutoff are often retained during filtration; smaller particles are excreted in the urine.

After filtration at the glomerulus (a network of capillaries supplied by the afferent arteriole and drained by the efferent arteriole), most of the sodium and, under normal conditions, virtually all of the potassium and glucose are actively resorbed from the tubular fluid in the proximal tubule [22]. Water is resorbed osmotically and regulated by antidiuretic hormone (vasopressin) [20]. In addition to absorption, a number of substances are secreted into the tubular fluid through the action of transporters along the renal tubule, including organic anions and cations such as creatinine, histamine, many drugs, and toxins [21].

Typically, approximately 30 mL/min of isotonic filtration is delivered to the loop of Henle, where a countercurrent multiplier mechanism achieves concentration of the urine [21]. The loop of Henle is the portion of the nephron formed by the descending and ascending limbs of the renal tubule [20]. This loop passes down into the medulla of the kidney, where secretion of sodium, chloride, and urea takes place. The thick ascending limb is impermeable to water but allows resorption of sodium, chloride, potassium, calcium, and bicarbonate. Due to the low water and high solute resorption in the loop of Henle, the filtration leaves the ascending limb hypo-osmotic [23].

Under customary circumstances, no more than roughly 5–10 mL/min of glomerular filtrate is delivered to the collecting ducts. Water absorption in the collecting ducts occurs directly through water channels controlled by vasopressin [20]. Under the control of aldosterone, sodium resorption from tubular fluid occurs in different types of cells in the renal collecting ducts. Many acids, including phosphoric and sulfuric acid, are not volatile and therefore cannot be excreted by the lungs. These compounds, termed "fixed acids," must be excreted as salts through the kidney [21]. Urinary excretion of fixed acids also occurs in the collecting duct. Although it deals with less than one-tenth of the total glomerular filtrate, the collecting duct is the site of regulation of urine volume and the site at which water, sodium, acid-base, and potassium balance are achieved [23]. The collecting duct is under hormonal control, in contrast to the proximal tubule, the actions of which are generally a simple function of volume and composition of tubular fluid and constitutively active transporters. In addition, the collecting duct is the last region of the renal tubule traversed before the remaining 1–2 mL/min of the original glomerular filtrate exits into the functional roles of the proximal and distal renal tubules.

RENAL REGULATION OF BLOOD PRESSURE

The kidneys maintain the circulating blood volume by fluid balancing and by altering peripheral vascular resistance via the angiotensin-aldosterone system [23]. First, the sodium concentration in the proximal tubular fluid is sensed at the macula densa, part of the juxtaglomerular apparatus. The juxtaglomerular apparatus also assesses the perfusion pressure, an important indicator of intravascular volume status under normal circumstances. Through the action of these two sensors, either low sodium or low perfusion pressure acts as a stimulus to renin release [21]. Renin, a protease made in the juxtaglomerular cells, cleaves angiotensinogen in the blood to generate angiotensin I, which is then cleaved to angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II raises blood pressure by triggering vasoconstriction directly and by stimulating aldosterone secretion, resulting in sodium and water retention by the collecting duct [20]. All of these effects expand the extracellular fluid and consequently renal perfusion pressure, completing a homeostatic negative feedback loop that alleviates the initial stimulus for renin release [21].

Intravascular volume depletion also triggers vasopressin release. Receptors in the carotid body and elsewhere sense a fall in blood pressure and active autonomic neural pathways, including fibers that go to the hypothalamus, where vasopressin release is controlled. Vasopressin is released and travels via the bloodstream throughout the body. At the collecting duct renal tubular apical plasma membrane, vasopressin facilitates insertion of water channels. This results in reabsorption of free water [21].

RENAL REGULATION OF CALCIUM METABOLISM

The kidney plays a number of important roles in calcium and phosphate homeostasis [21]. The kidney converts vitamin D from food sources into an active form for use in the body [23]. First, the kidney is the site of 1 α-hydroxylation or 24-hydroxylation of 25-hydroxycholecalciferol, the hepatic metabolite of vitamin D. This increases calcium absorption from the gut. Second, the kidney is the site of action of parathyroid hormone, resulting in calcium retention and phosphate wasting in the urine [21]. When the kidneys fail, and the body is unable to convert dietary vitamin D to its active form, calcium is poorly absorbed, and bone disease can result [23].

REGULATION OF RENAL FUNCTION

The kidney regulates the GFR in response to the solute concentration in the distal renal tubule via a process known as tubuloglomerular feedback [21]. When an excessive concentration of sodium and chloride in the tubular fluid is sensed by the macula densa, afferent arteriolar vasoconstriction is triggered [20]. This diminishes the GFR so that the renal tubule has a smaller solute load per unit, allowing sodium to be more efficiently reclaimed from tubular fluid. A variety of vasoactive substances, including prostaglandins, nitric oxide, and peptides (e.g., endothelin, bradykinin), contribute to the humoral control of tubuloglomerular feedback [21].

An additional challenge for the kidney is the regulation of renal cortical versus medullary blood flow [21]. Renal cortical blood flow must be sufficient to adequately maintain GFRs that are able to clear renally excreted waste efficiently without exceeding the capacity of the renal tubules for solute reabsorp-

tion [22]. Likewise, medullary blood flow can disrupt the osmolar gradient achieved by the countercurrent exchange mechanism. Insufficient medullary blood flow can result in anoxic injury to the renal tubule [21]. The redistribution of blood flow from the cortex to the medulla involves preferentially supplying blood, and therefore oxygen, to those nephrons with loops of Henle that dip down into the inner medulla [23].

Active transport of substances into or out of the tubules involves substances to move against an electrochemical gradient, which requires energy in the form of adenosine triphosphate (ATP) [23]. Most medullary oxygen consumption is devoted to generating ATP that fuels the array of active transporters involved in reabsorption of solute in the loop of Henle. Thus, when oxygen demand exceeds available supply, regulatory mechanisms tend to limit the workload of the ATP-consuming transporters. These regulatory mechanisms diminish the solute delivered to the loop of Henle by decreasing the GFR [21]. Renal blood flow is also preferentially shunted to medullary nephrons. This action provides for both decreased GFR and, at the same time, redistributes blood flow from the cortex to the medulla [23].

Pathologic conditions may affect the volume and nature of urine that is excreted [20]. Adaptations in the kidney due to injury can also be thought of as a form of regulation. For example, the loss of nephrons results in compensatory glomerular hyperfiltration, increased GFR per nephron, and renal hypertrophy [23]. While hyperfiltration may be adaptive in the short term, allowing maintenance of the total renal GFR, an inexorable, gradual progression to chronic renal failure is believed to begin when hyperfiltration is present [21].

There are other clinically important adaptations to injury. Poor renal perfusion from any cause results in responses that improve perfusion through afferent arteriolar vasodilation and efferent arteriolar vasoconstriction in response to hormonal and neural cues [21]. These regulatory effects are reinforced by inputs sensing sodium balance. Alteration of sodium balance is another way to influence blood pressure and renal perfusion pressure [22]. Sympathetic innervation by the renal nerves influences renin release. Renal prostaglandins play an important role in vasodilation, particularly in individuals with chronically poor renal perfusion [21].

ACUTE RENAL FAILURE

Acute renal failure is a heterogeneous group of disorders characterized by widespread, rapid deterioration of renal function, resulting in accumulation of nitrogenous wastes in the blood that customarily would be excreted in the urine [21]. The most common origin of acute renal failure is impaired renal blood flow. In these patients, the GFR decreases in response to lower filtration pressures. Diminished perfusion can result from renal vasoconstriction, hypotension, hypovolemia, hemorrhage, or inadequate cardiac output [24].

Individuals with acute kidney injury demonstrate a rapid onset of symptoms, including minimal urinary output and elevation in blood urea nitrogen (BUN), creatinine, and electrolytes [1]. Depending on the cause and on when the individual seeks medical attention, there may be other presenting characteristics as well, such as a decrease in GFR. Oliguria is commonly, but not always, observed [21].

CLASSIFICATION

There are three etiologic categories of acute renal failure: prerenal, intrarenal, and postrenal.

Prerenal Kidney Failure

Prerenal failure, the most common type of acute kidney injury, is caused by renal hypoperfusion (most likely from dehydration) and does not usually result in structural kidney damage [25]. Some individuals are dependent on prostaglandin-mediated vasodilation to maintain renal hypoperfusion and can develop renal failure simply from the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs). Likewise, individuals with renal hypoperfusion (e.g., renal artery stenosis, congestive heart failure, internal small vessel disease) who are dependent on angiotensin II-mediated vasoconstriction of the efferent renal arteriole to maintain renal perfusion pressure may develop acute renal failure upon administration of ACE inhibitors [26].

Intrarenal Kidney Failure

Intrarenal kidney failure, the result of damage to the renal parenchyma, may be a result of prolonged prerenal kidney injury (leading to acute tubular necrosis), toxins, interstitial nephritis, or acute glomerulonephritis [25]. Intrarenal causes of acute renal injury may result in rhabdomyolysis, in which myoglobin, released in the bloodstream after a crush injury to muscle, precipitates in the renal tubules.

Sepsis is one of the most common origins of acute renal failure. As a complication of sepsis, acute renal failure involves a combination of prerenal and intrarenal factors. The prerenal factor is renal hypoperfusion as a consequence of the hypotensive, low systemic vascular resistance septic state. The intrarenal component may be a consequence of the cytokine dysregulation that characterizes the sepsis syndrome, including elevated blood levels of tumor necrosis factor, interleukin-1, and interleukin-6, which contribute to intrarenal inflammation, sclerosis, and obstruction.

Postrenal Kidney Failure

Postrenal (obstructive) acute kidney failure results from physical obstruction of urine outflow and may be caused by neoplasm, prostatic enlargement, bladder dysfunction, or nephrolithiasis [25; 27]. Renal stones may also result in these types of injuries.

TREATMENT

The primary goal of treatment for acute renal failure is to maintain life until renal function has been recovered. Management principals directly related to physiologic alterations generally include correcting fluid and electrolyte disturbances, treating infection, maintaining nutrition, and remembering that drugs and their metabolites are not excreted [24]. Typically, with adequate dialytic support and nutritional interventions, the condition will reverse itself [1]. However, regardless of the origin, if the acute injury is left untreated, it can result in acute tubular necrosis, with sloughing of cells that make up the renal tubule. Depending on the rapidity of treatment, the time between onset of initial injury and eventual acute tubular necrosis varies. Acute renal failure may be irreversible or reversible, with either prevention of or recovery from acute tubular necrosis [21].

CHRONIC RENAL FAILURE

Progressive and irreversible loss of nephrons decreases the GFR and affects vital processes, with changes manifested throughout all organ systems [24]. Individuals with chronic renal failure and uremia show a constellation of symptoms, signs, and laboratory abnormalities, which is a reflection of the long-standing and progressive nature of renal impairment and the effects upon a multitude of tissues. As a result, osteodystrophy, neuropathy, and anemia are typical initial findings for individuals with newly diagnosed chronic renal failure in addition to elevated BUN and serum creatinine [21].

The most common cause of chronic renal failure is diabetes, followed closely by hypertension and glomerulonephritis; polycystic kidney disease, obstruction, and infection are less common causes [28]. In chronic renal failure, there are two theories to account for the adaptation to loss of renal function: the adaptive response and the intact nephron response [24].

The adaptive response depends on the location of injury; for example tubulointerstitial disease damage is primarily within the tubular or medullary parts of the nephron [24]. Whereas acute injury to the kidney is characterized by necrosis and sloughing of tubular epithelial cells, often followed by their regeneration and re-establishment of normal architecture, chronic injury causes irreversible loss of nephrons [21]. Alterations in tubuloglomerular feedback occur, resulting in renal vasodilation [1]. As a result, a greater functional burden is born by fewer nephrons, manifested as an increase in glomerular filtration pressure and hyperfiltration. The compensatory hyperfiltration, which can be thought of as a form of hypertension at the level of the individual nephron, predisposes to fibrosis and scarring [21].

In the intact nephron theory, the loss of nephron mass with progressive kidney damage triggers the remaining nephrons to sustain normal renal function. These nephrons are capable of a compensatory expansion in their rates of reabsorption and secretion and can maintain a constant rate of excretion in the presence of a declining GFR [24]. Therefore, the rate of nephron destruction and loss increases, speeding the progression to uremia, the complex of symptoms and signs that occurs when residual renal function is inadequate [21].

The clinical manifestations of chronic renal failure are often described using the term uremia. Uremia refers to a number of symptoms caused as a result of declining renal function and the accumulation of toxins in the plasma [24]. It has a number of effects on metabolism, including a decrease in a basal body temperature (perhaps due to decreased sodium, potassium, and ATP activity) and diminished lipoprotein lipase activity with accelerated atherosclerosis [21].

The pathogenesis of chronic renal failure results in part from a combination of the toxic effects of [21]:

- Retained products normally excreted by the kidneys (e.g., nitrogen-containing products of protein metabolism)
- Normal products, such as hormones, now present in increased amounts
- Loss of normal products of the kidney (e.g., erythropoietin)

Excretory failure also results in fluid shifts, with increased intracellular sodium and water and decreased intracellular potassium. These alterations may contribute to subtle alterations in the function of a host of enzymes and transport systems [21].

CLINICAL MANIFESTATIONS

Clinical manifestations related to chronic renal failure may be related to many body systems and imbalances (***Table 2***) [21]. Individuals with chronic renal failure typically exhibit differential degrees of sodium and fluid excess, reflecting loss of the renal route of salt and water excretion. Hyperkalemia is a serious problem, especially for individuals with a GFR less than 5 mL/min/1.73 m^2. The diminished capacity to excrete acid and generate buffers in chronic renal failure results in mild, moderate, or severe acidosis. In addition, several disorders of phosphate, calcium, and bone metabolism are observed in chronic renal failure as a result of diminished absorption of calcium from the gut, overproduction of parathyroid hormone, alteration in vitamin D metabolism, and chronic metabolic acidosis.

SIGNS AND SYMPTOMS OF UREMIA AND THEIR RESPONSE TO TREATMENT			
Abnormality	**Improves with an optimal program of dialysis and related therapy**	**Can persist or progress despite an optimal program**	**Develops only after initiation of dialysis therapy**
Volume expansion and contraction	X		
Hypernatremia and hyponatremia	X		
Hyperkalemia and hypokalemia	X		
Metabolic acidosis	X		
Hypocalcemia	X		
Renal osteodystrophy	X	X	
Osteomalacia			X
Carbohydrate intolerance	X		
Hypothermia	X		
Hypertriglyceridemia		X	
Protein-calorie malnutrition	X	X	
Impaired growth and development		X	
Infertility and sexual dysfunction		X	
Amenorrhea		X	
Fatigue	X		
Sleep disorders		X	
Impaired mentation	X		
Lethargy	X		
Asterixis	X		
Muscular irritability	X		
Peripheral neuropathy	X	X	
Restless leg syndrome	X	X	
Paralysis	X	X	
Myoclonus	X		
Seizures	X	X	
Coma	X		
Muscle cramps			X
Dialysis disequilibrium syndrome			X
Dialysis dementia			X
Myopathy		X	X
Arterial hypertension	X	X	
Congestive heart failure or pulmonary edema	X		
Pericarditis	X		
Cardiomyopathy	X	X	
Uremic lung	X		
Accelerated atherosclerosis		X	X
Hypotension and arrhythmias			X
Skin pallor	X	X	

Table 2 continues on next page.

SIGNS AND SYMPTOMS OF UREMIA AND THEIR RESPONSE TO TREATMENT *(Continued)*			
Abnormality	**Improves with an optimal program of dialysis and related therapy**	**Can persist or progress despite an optimal program**	**Develops only after initiation of dialysis therapy**
Hyperpigmentation	X	X	X
Pruritus		X	
Ecchymoses	X	X	
Uremic frost	X		
Anorexia	X		
Nausea and vomiting	X		
Uremic fetor	X		
Gastroenteritis	X		
Peptic ulcer	X	X	
Gastrointestinal bleeding	X	X	X
Hepatitis			X
Refractory ascites on hemodialysis			X
Peritonitis			X
Normocytic, normochromic anemia		X	
Microcytic anemia			X
Lymphocytopenia		X	
Bleeding diathesis		X	X
Increased susceptibility to infection	X	X	
Splenomegaly and hypersplenism		X	
Leukopenia			X
Hypocomplementemia			X
Source: [21]			*Table 2*

Central nervous system symptoms are related to alterations in nerve conduction due to metabolic encephalopathy from a wide variety of causes. Congestive heart failure and pulmonary edema can develop and are most commonly related to sodium and volume overload. When present, anemia is chiefly due to a lack of erythropoietin production and loss of its stimulatory effect on erythropoiesis.

Gastrointestinal symptoms are common among patients with end-stage renal disease, with almost 80% of patients on dialysis reporting various gastrointestinal complaints [29]. Many individuals with uremia have peptic ulcer disease thought to be a consequence of secondary hyperparathyroidism. A variety of additional gastrointestinal abnormalities and syndromes can occur in patients with renal disease, including uremic gastroenteritis (characterized by mucosal ulcerations with blood loss) and uremic fetor (a distinctive bad breath due to degradation of urea to ammonia by enzymes in saliva) [29].

Uremia causes sex hormone imbalances as well. Low estrogen levels lead to a high incidence of amenorrhea and difficulties carrying a pregnancy to term. Low testosterone levels lead to impotence, oligospermia, and germinal cell dysphagia.

Skin changes can arise from many of the effects of chronic renal failure. Pallor is generally related to anemia, while gray discoloration is the result of transfusion-related hemochromatosis. Pruritus and excoriations related to calcium deposits develop secondary to hyperparathyroidism, and skin color changes appear due to accumulated pigmented metabolites.

DIABETIC NEPHROPATHY

As noted, diabetes is the most common primary diagnosis in persons with chronic kidney failure, accounting for 44% of new cases in the United States [2]. Advanced glycosylated end-products, activation of polyol pathways, glucotoxicity, and protein kinase C, all consequences of diabetes, contribute to renal tissue injury [24]. Glycosylation of proteins in the capillary basement membrane may stimulate mesangial expansion [1]. The excessive passage of protein through the glomerulus is thought to result in the increased width of the glomerular basement membrane, microaneurysms, and intestinal inflammation [5]. Glomerular hypertension, inflammation, and oxidative stress worsen albuminuria, with angiotensin II and mechanical stress factors contributing to this process [30].

Albuminuria is a well-known marker of poor renal outcomes in individuals with type 2 diabetes [31]. Persistent albuminuria is present in the earliest stage of nephropathy in type 1 diabetes and is a marker for development of nephropathy in type 2 diabetes [21]. Albuminuria has been shown to be a predictor of poor cardiovascular outcomes; therefore, serum albumin should be measured in all individuals with diabetes and hypertension and steps should be taken to suppress albuminuria to prevent further renal and cardiovascular events [31].

Kimmelstiel Wilson nodules (nodular glomerulosclerosis) are a classic feature of diabetic damage to the kidney [32]. If Kimmelstiel Wilson nodes are present on biopsy, this is positive for diabetic nephropathy. The pathology of these nodes is related to histologic renal changes [5]. Progressive histologic changes in glomeruli are indistinguishable in type 1 and type 2 diabetes and occur to some degree in the majority of individuals [33]. The mesangium surrounding the glomerular vessels is increased due to the deposition of basement membrane-like material and can encroach on the glomerular vessels; the afferent and efferent glomerular arteries are also sclerosed. Glomerulosclerosis is usually diffuse; however, in some cases, it is associated with nodular sclerosis [33].

Research has demonstrated that hypertension, hyperglycemia, and high triglyceride concentrations are associated with an elevation in albumin-to-creatinine level independent of the type of diabetes [34]. Glucagon and growth hormone are both elevated in poorly controlled diabetes and have been shown to produce glomerular hyperfiltration, a phase that generally precedes glomerular alterations in patients with type 1 diabetes. Changes in circulating levels of angiotensin II, catecholamines, and prostaglandins, or altered responsiveness to these vasoactive hormones, may also result in hyperfiltration [1]. It is unclear whether this early hyperfiltration phase occurs in type 2 diabetes. It has been proposed that the presence of atherosclerotic lesions in older individuals with type 2 diabetes may prevent hyperfiltration and thus account for the lower incidence of overt clinical nephropathy in these individuals [35; 36; 37].

STAGES OF RENAL DYSFUNCTION AND NEPHROPATHY IN TYPE 2 DIABETES	
Stage	**Description**
Stage 1	Normal serum creatinine and somewhat elevated GFR (but not to the same extent as in type 1 diabetes). Some individuals may have microalbuminuria at clinical diagnosis due to undiagnosed diabetes. Blood pressure may be elevated, as essential hypertension may be related to metabolic syndrome and type 2 diabetes.
Stage 2	After the diagnosis and treatment of hyperglycemia, abnormal albuminuria may be found (or it may be reduced if initially increased). In some studies, GFR has been found to be moderately decreased. Blood pressure has a tendency to increase over time.
Stage 3	Microalbuminuria typically develops after some years with diabetes as a result of blood pressure elevation and lack of glycemic control. Hypertension is quite common in such individuals. GFR may still be normal; however, it tends to decrease progressively.
Stage 4	Overt diabetic nephropathy. After 10 to 20 years with diabetes, proteinuria typically develops. GFR declines variably related to metabolic control and blood pressure; even borderline blood pressure elevation should be carefully treated. Cardiovascular disease is common. On biopsy, these individuals typically have lesions, but a few will not show any changes or nondiabetic lesions. Biopsy is generally not indicated.
Stage 5	The late stage, just before or with renal insufficiency.
Source: [40]	*Table 3*

Learning to recognize chronic kidney disease in its earliest stages and understanding the measures necessary to prevent the progression and associated complications are essential (***Table 3***) [38]. Early in the course of diabetes, the histologic changes in renal glomeruli are accompanied by microalbuminuria, a urinary loss of albumin that cannot be detected by routine urinalysis dipstick methods. Albuminuria is thought to be due to a decrease in the heparan sulfate content of the thickened glomerular capillary basement membrane. Heparan sulfate prevents the excretion of highly negatively charged proteins, such as albumin, through the basement membrane; its loss therefore allows for increased albumin filtration [39].

If glomerular lesions worsen, proteinuria increases and overt nephropathy develops. Diabetic nephropathy is defined clinically by the presence of more than 300–500 mg of urinary protein per day, an amount that can be detected by routine urinalysis [1]. In diabetic nephropathy, proteinuria continues to increase as renal function decreases. Therefore, end-stage renal disease is preceded by massive, nephritic-range proteinuria (greater than 4 mg/dL) [1]. Renal hemodynamic changes play a role in the pathogenesis of diabetic kidney disease.

Glomerular hypertension and the associated renal vasodilation and hyperfiltration increase glomerular protein filtration, leading to proteinuria and glomerulosclerosis [1]. Individuals with type 2 diabetes often have hypertension at the time of diagnosis, whereas individuals with type 1 diabetes usually do not develop hypertension until after the onset of nephropathy. In either case, hypertension worsens as renal function deteriorates. When hypertension is present in patients with diabetes, the initiation of therapy with either an ACE inhibitor or an angiotensin II receptor blocker (ARB) is indicated [41].

RISK FACTORS

As discussed, diabetes is a primary risk factor for the development of chronic kidney disease. Race and age also appear to be factors. Compared with whites, new cases of end-stage renal disease in 2018 were 3.4 times greater in African Americans, 1.9 times greater in American Indians/Alaska Natives, and 1.3 times greater in Asian Americans [3]. From 2007 to 2016, the presence of end-stage renal disease resulting from hypertension was 2.7 times higher in Native Hawaiians/Pacific Islanders than White Americans and 1.2 times greater than Black Americans [42].

Hypertension is considered to be a critical factor in the formation of diabetic renal failure. Systemic hypertension is present in 50% of individuals newly diagnosed with type 2 diabetes, but it is rarely present in those with type 1 diabetes without nephropathy [43]. The proportion of individuals with type 2 diabetes with hypertension increases with the advancement of kidney disease, occurring in 80% of patients with microalbuminuria and more than 90% of patients with macroalbuminuria [43]. But even small increases may impact the kidneys. High pressure in the renal capillaries is believed to affect renal function before it can be detected by the systemic blood pressure [5]. Antihypertensive therapy has been proven to reduce the incidence of albuminuria, preserve renal function, and slow the decline of GFR in individuals with diabetic kidney disease [1; 44]. Elevated systolic blood pressure may be more predictive of kidney disease progression than elevated diastolic blood pressure [5].

Nephrotoxic drugs (including aminoglycosides and NSAIDs) may accelerate dysfunction and should be used with discretion. Monitoring drug levels with corresponding reduction in medication dosage is advised for individuals with renal impairment [26]. Gadolinium-based radiocontrast dyes may also accelerate dysfunction and should be avoided in individuals with diabetes unless there are no alternative options. If dyes are necessary for diagnostic tests, hydration must be maintained prior to and after the study [5]. The U.S. Food and Drug Administration (FDA) has published guidelines for the appropriate use of gadolinium-based contrast dyes specific both to the patient's level of renal function and the particular brand of dye being used [45]. The FDA also has added a "black box" warning to the insert for gadolinium-based contrast that states clinicians should screen all patients for kidney disease prior to administration of the agents [45].

Contrast induced nephropathy (CIN) is a rare disorder caused by the use of certain contrast dyes in diagnostic tests, such as computerized tomography (CT) or angiograms. In most instances, no problems with the use of these dyes have been reported. However, the risk for CIN can increase for individuals with diabetes and chronic kidney disease. The overall incidence of CIN is 5% to 38%, depending on the presence of risk factors [46]. Risk factors include preexisting renal disease (i.e., serum creatinine greater than 1.4 mg/dL or eGFR less than 60 mL/min/1.73 m^2), age older than 75 years, diabetic nephropathy, sepsis, congestive heart failure, and hypovolemia [47; 48]. In patients with advanced kidney disease, the risk increases to 30% to 40%. The risk of CIN in patients with both chronic kidney disease and diabetes is 20% to 50%. Symptoms include fatigue, poor appetite, edema in the feet and ankles, and dry, itchy skin [49].

PREVENTION

Good glycemic control is the mainstay of therapy for preventing and delaying further disease progression. Maintaining a glycated hemoglobin (HbA1c) level less than 7% reduces the risk of renal complications [1]. The relationship between glycemic control and renal disease has been well documented by the Diabetes Control and Complication Trial, the Stockholm Intervention Study, the Kumamoto Study, and the United Kingdom Prospective Diabetes Study (UKPDS) [5]. According to these studies, for every 1% decrease in HbA1c, there is a 35% reduc-

tion in the risk for complications such as diabetic nephropathy [1]. As noted, optimal glycemic control also reduces microalbuminuria, proteinuria, and the size of the hypertrophied kidney [5]. Furthermore, increased blood glucose concentrations are associated with increased GFRs [5]. Fasting blood glucose level targets are [1]:

- <120 mg/dL in patients with chronic kidney disease
- <140 mg/dL in patients on hemodialysis
- <160 mg/dL in patients on peritoneal dialysis

HbA1c should be checked twice every year if glucose levels are controlled or quarterly if glucose levels are uncontrolled. HbA1c levels within 10% of normal have been shown to be highly protective and associated with a lack of target organ damage [50; 51]. However, studies have shown an increase in morbidity in the elderly with tight controls [52]. It may be prudent for older patients to maintain HbA1c levels no lower than 6%.

Blood pressure management is also an important part of preventing renal disease in patients with diabetes. A target blood pressure of less than 130/80 mm Hg has been advised. However, tighter control is necessary in the presence of nephropathy; 120/70 mm Hg is suggested for these patients [1].

In adult patients with stages 1 through 4 chronic kidney disease, the Department of Veterans Affairs Guideline Panel suggests intensive blood pressure management beyond a target of less than 140/90 mmHg, to reduce mortality in patients with estimated glomerular filtration rate below 60 mL/minute/1.73 m^2.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed November 8, 2021.)

Strength of Recommendation: Weak for

TREATMENT

ACE Inhibitors and Angiotensin-Receptor Blockers

An ACE inhibitor or an ARB is traditionally used as a first-line or preferred therapy for the management of hypertension in individuals with diabetes, particularly those with or at risk for nephropathy [53]. For nonpregnant adults, blood pressure goals should be maintained at less than 120/80 mm Hg [5]. ACE inhibitors and ARBs diminish the risk of diabetic nephropathy and reduce the risk of cardiovascular events [54].

A treatment plan including ACE inhibitors or ARBs is recommended for all individuals with type 1 diabetes and microalbuminuria, even if they are normotensive, as a high proportion of individuals with type 1 diabetes progress from microalbuminuria to overt nephropathy and subsequently end-stage renal disease [5]. Research has demonstrated that ACE inhibitors and ARBs can help preserve kidney function in individuals with chronic renal failure [55]. The use of an ACE inhibitor or an ARB for normotensive persons with type 2 diabetes is less well-substantiated due to the less predictable rate of progression from microalbuminuria to nephropathy and end-stage renal disease in these patients. However, should an individual with type 2 diabetes develop hypertension or show an increase in microalbuminuria, the use of an ACE inhibitor or an ARB is warranted [5].

Sodium-Glucose Cotransporter 2 Inhibitors

For people with type 2 diabetes and diabetic kidney disease, the ADA recommends use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor to reduce chronic kidney disease progression and cardiovascular events in patients with an estimated GFR ≥20 mL/min/1.73 m^2 and urinary albumin ≥200 mg/g creatinine [79]. These agents may also be useful for patients with GFR ≥20 mL/min/1.73 m^2 and normal to 200 mg/g creatinine urinary albumin.

Erythropoiesis-Stimulating Agents

Anemia may occur in individuals with diabetic nephropathy even prior to the onset of advanced renal failure. This tendency is the result of erythropoietin deficiency [54]. Erythropoietin, typically manufactured in the kidney, is a hormone that stimulates the bone marrow to produce red blood cells [1]. Erythropoiesis-stimulating agent treatment should be initiated when hemoglobin levels are less than 11 g/dL, with a target hemoglobin level of 11–12 g/dL and a target hematocrit of 30% to 33% [56]. The potential risk of hypertension with erythropoietin therapy should be taken into consideration prior to initiating treatment [54; 57]. Monthly hematocrit measurements are necessary during therapy so the dosage can be titrated as necessary. Measurements of serum iron and ferritin levels are recommended before initiating erythropoietin therapy and periodically during treatment to determine whether iron therapy should be initiated.

The Department of Veterans Affairs Guideline Panel recommends against offering erythropoiesis-stimulating agents to patients with chronic kidney disease for the purpose of achieving a hemoglobin target greater than 11.5 g/dL due to increased risk of stroke and hypertension.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPGFinal5082142020.pdf. Last accessed November 8, 2021.)

Strength of Recommendation: Strong against

Intravenous or subcutaneous erythropoiesis-stimulating agents are typically administered three times per week, frequently in combination with dialysis. Two erythropoiesis-stimulating agents are available for the treatment of anemia in individuals with chronic renal failure: darbepoetin alfa (Aranesp) and epoetin alfa (Epogen, Procrit). Peginesatide (Omontys) has been discontinued [58]. In 2007, the drug manufacturers agreed to post a black box warning that these agents should be used to maintain hemoglobin levels no greater than 11–12 g/dL. Higher levels have been found to increase the risk of serious cardiovascular events and death [5; 59].

The typical starting dosage of epoetin alfa is 50–100 units/kg three times per week [60]. The dose is then titrated to hemoglobin levels not to exceed 12 g/dL. For darbepoetin alfa, the dose is 0.45 mcg/kg once per week or 0.75 mcg/kg every two weeks [60].

After dialysis is initiated, erythropoietin can be given intravenously, eliminating the need for injections. When given IV during dialysis, higher doses of erythropoietin are needed, leading to higher costs. Therefore, some payers have required patients to remain on subcutaneously administered erythropoietin even after initiation of dialysis. In 2011, the FDA recommended more conservative dosing of epoetin alfa and other erythropoiesis-stimulating agents in patients with chronic kidney disease [59]. In their statement, the FDA asserted that erythropoiesis-stimulating agent therapy should be individualized to the patient and the lowest possible dose given to reduce the need for transfusions.

Side effects related to erythropoiesis-stimulating agent therapy can include hypertension (specifically for individuals in whom hematocrit increases more than 0.2% per day), nausea, vomiting, fever, headache, pruritus, and rash [60]. However, the use of an erythropoiesis-stimulating agent is associated with an improved quality of life, and some studies have shown an atherogenic effect on HDL as the anemia is corrected [5].

Hemodialysis

Hemodialysis is the most common treatment for kidney failure [61]. It removes waste products and excessive fluids from the vascular system by passing the blood through a semipermeable membrane [55]. Although hemodialysis is efficient in removing solutes, it does not remove all metabolites [23]. The artificial membrane allows for the flow of some molecules, such as urea, creatinine, potassium, sodium, and phosphorus, while preventing the removal of larger molecules, such as proteins [55].

Hemodialysis access should be placed at least six months prior to initiation of renal replacement therapy, as proper access takes months to properly heal. Up to 80% of patients presenting for initial dialysis are dialyzed via temporary venous catheters due to a lack of established access [61]. Hemodialysis can be provided via three major different types of access: an arteriovenous (AV) fistula, an AV graft, or a temporary venous catheter. In its 2006 guideline for vascular access, the National Kidney Foundation endorsed a goal for at least 65% of all patients on hemodialysis to have a working AV fistula by 2009 [62]. In the 2019 update of the guideline, the vascular access Work Group emphasizes a more patient-focused approach that takes into account each patient's needs and preferences when choosing access type [63]. As of 2018, reporting institutions dialyzed 65.7% of all patients on hemodialysis via AV fistulas [3].

AV fistulas are created surgically by attaching an artery directly to a vein. Generally placed in the forearm, AV fistulas may be categorized as radial-cephalic, brachial-cephalic, or brachial-basilic based on the vein and technique used [64; 65]. Generally, the radial-cephalic, having a lower anatomical position in the forearm, is preferred for first access as it preserves the higher veins for later use. After anastomosis, the resultant increase in blood flow to the vein results in thickening of the venous wall, allowing it to withstand the numerous punctures required for hemodialysis [65]. AV fistulas generally require at least three months to fully mature. AV fistulas are recommended as the first form of access, and they should be promoted in all eligible patients who choose hemodialysis, as they improve outcomes and reduce costs compared with central venous catheters [66]. They also offer the best access for longevity and have the lowest association with morbidity and mortality [67]. However, multiple studies suggest that certain subgroups of patients (i.e., the elderly and those with limited life-expectancy) may benefit from alternative forms of access. As stated, a patient-centered, individualized approach to the choice of access may indicate the use of a method other than AV fistula [68; 69]. AV fistulas are not without complications, and the overall patency rate is only 50% after five years [65].

AV grafts are generally considered to be inferior to AV fistulas and superior to temporary catheters, but fewer than half are patent after five years [70]. These grafts are often used for patients who lack veins large enough to create fistulas. The determination of need for graft placement versus fistula is accomplished via vein mapping and clinical evaluation.

AV graft formation is accomplished by implantation of a synthetic tube that connects a vein and an artery. Dialysis is then performed by cannulating the synthetic graft. Synthetic grafts have higher rates of infection and clotting and, as noted, generally fail sooner than fistulas [71].

Temporary catheters are the least preferred method of access for hemodialysis, but one of the most frequently used. However, according to data from Centers for Medicare and Medicaid Services, catheter use in the United States declined from approximately 28% in 2006 to 24% in 2007 [72].

Indications for hemodialysis include [23]:

- BUN exceeding 90 mg/dL
- Serum creatinine greater than or equal to 9 mg/dL
- Hyperkalemia
- Drug toxicity
- Intravascular or extravascular fluid overload
- Metabolic acidosis
- Symptoms of uremia (e.g., pericarditis, gastrointestinal bleeding)
- Changes in mentation
- Contraindications to other modes of dialysis

Hemodialysis is contraindicated if any of the following are present [23]:

- Hemodynamic instability
- Inability to anticoagulate
- Lack of access to circulation

Insulin requirements and diabetes management may become more complicated during dialysis [5]. Glucose is removed with hemodialysis; however, insulin remains active, which may lead to hypoglycemia during treatment. It may be necessary to have adjusted insulin doses for both dialysis and nondialysis days. Increased self-monitoring of blood glucose during treatment is necessary to evaluate the appropriate insulin dose [5].

Peritoneal Dialysis

Although it is not often used, peritoneal dialysis is a possible alternative to hemodialysis [5]. Only an estimated 9% of individuals with end-stage renal disease use this therapy [61]. Peritoneal dialysis filters blood through the peritoneal membrane that lines the abdominal cavity [1]. During peritoneal dialysis, the dialysate left in the abdomen overnight will often be adjusted to a lesser concentration of glucose, because during the extended dwell time the glucose will be absorbed. An alternative to adjusting the solution concentration is to add fast-acting insulin to the dialysate or administer insulin subcutaneously prior to bedtime [5]. Over several years of treatment with peritoneal dialysis, the filtration capacity of the peritoneal membrane tends to decrease as a result of peritoneal inflammation and frank infection; this is known as ultrafiltration failure [73].

There are three types of peritoneal dialysis available: continuous ambulatory peritoneal dialysis (CAPD) continuous cyclic peritoneal dialysis (CCPD) (also referred to as automated peritoneal dialysis), and intermittent peritoneal dialysis (IPD) [1]. With CAPD, the patient exchanges new dialysate every 4 to 6 hours over the course of 24 hours. The dialysate passes from a plastic bag through a catheter and stays in the individual's abdomen with the catheter sealed. The dialysate is then drained after several hours, and the process begins again with fresh dialysate.

Similar to CAPD, CCPD uses a machine connected to a catheter to automatically fill and drain the dialysate from the individual's abdomen. This is usually performed at night as the patient is sleeping.

IPD involves the same type of machine as CCPD to fill and drain the dialysate solution from the individual's abdomen. However, this therapy uses multiple short exchanges of dialysate every few days. IPD treatments take longer than CCPD, and assistance from a family member, friend, or health professional is required. This older strategy has largely been abandoned in favor of CAPD or CCPD, but it remains an option for patients who cannot receive dialysis at home or who have poor vascular access [74; 75].

Indications for the use of peritoneal dialysis include [23]:

- Uremia
- Volume overload
- Electrolyte imbalance
- Hemodynamic instability
- Lack of access to circulation
- Removal of high-molecular-weight toxins
- Severe cardiovascular disease
- Inability to anticoagulate
- Contraindication(s) for hemodialysis

Contraindications for peritoneal dialysis include:

- Recent abdominal surgery
- History of abdominal surgeries with adhesions and scarring
- Significant pulmonary disease
- Need for rapid fluid removal
- Peritonitis

Renal Transplantation

The ultimate plan in end-stage renal failure is for transplantation of a healthy kidney [73]. For many individuals, kidney transplant restores renal function to normal parameters, allowing the individual to gain greater independence and return to normal life activities [55]. Transplant outcomes are more successful today than in the past due to immunosuppressive drugs and sophisticated tissue match procedures [5]. At 90.1%, the five-year survival rate for transplant patients is more than twice the 43.9% survival rate for patients on dialysis [3]. However, recipients must take antirejection medications on a daily basis for as long as the kidney remains viable.

Kidney transplant can be performed using a kidney from a living relative donor, a living unrelated donor, or a suitable cadaveric donor [1]. Allocation of all transplants in the United States is managed by the United Network for Organ Sharing (UNOS). Kidney transplant guidelines place the highest considerations on histocompatibility and time spent on the transplant list [76]. The median adult wait time for a cadaver kidney is just over four years [3]. When the kidney is procured from the donor or cadaver, the ureter, renal vein, and renal artery are dissected, leaving as much length as possible [23].

Potential complications of renal transplantation in patients with diabetes include rejection of the transplanted organ, infection, extended wound healing times, an increase in insulin requirements as a result of restored kidney function, and increased insulin resistance from the effects of steroid therapy, immunosuppressive medications, or weight gain [5]. Individuals with diabetes must take additional insulin following transplantation. The newly functioning kidney catabolizes insulin once again and post-transplant steroid therapy affects blood glucose levels, making patients susceptible to hyperglycemia [1]. Renal transplantation is an optimal choice for individuals who value their independence highly and are able to participate actively in their care [55].

PATIENT EDUCATION

An intensive and multifactorial management approach is required for patients with diabetes and renal disease in order to address all risk determinants. This strategy should include lifestyle modifications (e.g., smoking cessation, weight management and reduction, increased physical activity, dietary changes) coupled with therapeutic achievement of evidence-based blood pressure, blood glucose, and lipid goals [77]. All individuals with type 1 or type 2 diabetes must be educated regarding the need for screening to assess kidney function regularly. In patients with type 1 diabetes, screening should be completed within five years of diagnosis and then annually thereafter. For patients with type 2 diabetes, screening should begin at diagnosis and continue annually thereafter [1].

Additional screening should include testing for anemia, osteodystrophy, potassium levels, and cholesterol. Discussion regarding each testing method and rationale for each test should be completed yearly with all patients with diabetes [5]. Patient education should include the normal, expected, and problem range values. A record-keeping device, such as a diary, to manage and share results with all healthcare providers may be helpful. Collaboration with the nephrology team is crucial to the individual's care and management [1].

Medical management minimizes the loss of kidney function and complications related to this loss; this includes the control of blood pressure and blood glucose levels [1]. Patient education related to the control and management of diabetic nephropathy should include information regarding the control of hypertension with a goal of 120/80 mm Hg. Patients taking an antihypertensive should be given information regarding the agent's mechanism of action, duration of action, maximum dosages, and possible side effects. Specific instructions should include continuing to take medications prescribed even if hypertensive symptoms improve [5].

NUTRITIONAL CONSIDERATIONS FOR PATIENTS WITH RENAL DISEASE					
Nutrient	**Stage of Renal Disease**				
	Preclinical Nephropathy (Stages 1–3)	**Progressive Nephropathy (Stage 4)**	**Hemodialysis**	**Peritoneal Dialysis**	**Transplantation**
Energy (calories)	30–35 kcal/kg/day adequate to achieve and maintain healthy body weight	30–35 kcal/kg/day adequate to achieve and maintain healthy body weight	30–35 kcal/kg/day adequate to achieve and maintain healthy body weight	30–35 kcal/kg/day, allowing for dialysate kilocalories	30–35 kcal/kg/day adequate to achieve and maintain healthy body weight
Protein	<10% of kcal 0.8–1.0 g/kg/day	8% to 10% of kcal 0.6–0.8 g/kg/day 50% HBV	12% to 20% of kcal 1.2 g/kg/day 50% HBV	12% to 20% of kcal 1.2–1.3 g/kg/day 50% HBV	0.8–1.0 g/kg/day in stable protein After surgery: 1.2–1.3 g/kg/day
Carbohydrate	50% to 60% of kcal	50% to 60% of kcal	50% to 60% of kcal	50% to 60% of kcal	50% to 60% of kcal
Fiber	14 g/1,000 kcal	14 g/1,000 kcal	14 g/1,000 kcal	14 g/1,000 kcal	14 g/1,000 kcal
Fat	30% of kcal <10% saturated fat with an emphasis on MUFA <200 mg cholesterol/day	25% to 35% of kcal <10% saturated fat with an emphasis on MUFA <200 mg cholesterol/day	25% of 35% of kcal <10% saturated fat with an emphasis on MUFA <200 mg cholesterol/day	25% of 35% of kcal <10% saturated fat with an emphasis on MUFA <200 mg cholesterol/day	25% of 35% of kcal <10% saturated fat with an emphasis on MUFA <200 mg cholesterol/day
Sodium	≤2,400 mg/day	≤2,400 mg/day	≤2,400 mg/day	≤2,400 mg/day Monitor fluid balance	≤2,400 mg/day
Potassium	No restrictions	Monitor labs 2.4 g/d if hyperkalemic	Adjust to serum levels	Unrestricted if serum levels are normal	Unrestricted unless hyperkalemic
Phosphorus	Maintain serum values WNL Adjust for protein	10–12 mg/g protein or 10 mg/kg/day	10–12 mg/g protein or 800–1,000 mg/day Adjust for protein	10–12 mg/g protein or 800–1,000 mg/day Adjust for protein	DRI Supplement as needed
Calcium	1.0–1.5 g/day Maintain serum levels WNL	1.0–1.5 g/day Daily limit including binder load: <2.0 g/day	Daily limit including binder load: <2.0 g/day	Daily limit including binder load: <2.0 g/day	0.8–1.5 g/day
Fluid	No restrictions	Output plus 1,000 mL	Output plus 1,000 mL	Maintain balance	Unrestricted unless overloaded

DRI = dietary reference intakes; HBV = high biologic value; Kcal = kilocalories; MUFA = monounsaturated fatty acids; WNL = within normal limits.

Source: [1] *Table 4*

Because blood pressure management is a key component of the treatment plan for individuals with diabetic nephropathy, home blood pressure monitoring should be encouraged between healthcare provider visits [32]. Other therapeutic regimens for individuals with nephropathy include optimal glycemic control, prevention of or early intervention for urinary tract infections, and low-protein diets. A major aspect of initial treatment should consist of education regarding lifestyle modifications, including weight loss, reduction of sodium intake, limited alcohol consumption, and appropriate physical activity [5].

Research has demonstrated that a low-protein diet may be beneficial in some individuals whose nephropathy appears to be progressing, but this can be complicated for patients with diabetes who are already on restrictive diets [1]. In addition to a nephrology referral, these patients should be referred to a registered dietitian, preferably a certified diabetes educator [5]. The team may then develop a meal plan that is adequate, palatable, and realistic for the patient, taking into consideration additional nutrient needs and renal disease stage (***Table 4***). Additional protein restrictions may be warranted in the later stages of chronic kidney disease in order to slow disease progression for patients on dialysis [1].

In the adult with stage 3–5 CKD and diabetes, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative asserts it is reasonable to prescribe, under close clinical supervision, a dietary protein intake of 0.6–0.8 g/kg body weight per day to maintain a stable nutritional status and optimize glycemic control.

(https://www.ajkd.org/article/S0272-6386(20)30726-5/fulltext. Last accessed November 8, 2021.)

Level of Evidence: Expert Opinion/Consensus Statement

Although it is necessary for individuals with diabetes to become aware of the complication of nephropathy, it is important to always emphasize what the individual can do to maintain good health and continue normal activities. Scare tactics can lead to patients "giving up," particularly if they are having difficulty accepting the disease process. Most individuals with diabetes are sufficiently motivated by their desire to alleviate the consequence of uncontrolled diabetes and will not require additional coaching [1].

HEALTH LITERACY

Healthcare professionals should be sensitive to the complex issues that arise when presenting information and instructions to individuals with diabetes and nephropathy. These patients receive multiple complicated instructions from a team of healthcare providers [5]. To compound this, health literacy in general has been found to be low among patients in the United States [1]. According to data from the first ever National Assessment of Adult Literacy (NAAL), only 12% of adults in the United States had proficient health literacy and more than one-third (77 million adults) would have difficulty with common health tasks (e.g., following directions on a prescription) [78]. In addition, 80% of individuals forget what their healthcare provider tells them as soon as they leave the office, and 50% of recalled information is incorrect.

LABORATORY ANALYSIS		
Test	**Patient A's Results**	**Target Range**
Hemoglobin	8.7 g/dL	11.0–12.0 g/dL
Creatinine	2.2 mg/dL	0.6–1.2 mg/dL
GFR	49 mL/min/1.73 m^2	90–120 mL/min/1.73 m^2
Serum albumin	3.3 g/dL	≥4.0 g/dL
HbA1c	8.8%	<7.0%
LDL	143 mg/dL	<100 mg/dL
HDL	43 mg/dL	>40 mg/dL (preferably >60 mg/dL)
Glucose (random)	186 mg/dL	<140 mg/dL
Albumin-to-creatinine ratio	281 mg/g	<30 mg/g
Calcium	8.7 mg/dL	8.4–9.5 mg/dL
Phosphorus	4.2 mg/dL	2.7–4.6 mg/dL
Plasma parathyroid hormone	77 pg/mL	35–70 pg/mL

Source: Compiled by Author *Table 5*

CASE STUDY

Patient A is an African American woman, 53 years of age, with a 17-year history of type 2 diabetes, hypertension, and hyperlipidemia and a 35-year history of smoking. She had been referred to a diabetes clinic for intensive diabetes self-management education and training over this period. She presents in the office with shortness of breath, pruritus, and pitting edema of bilateral extremities. Her blood pressure is 165/92 mm Hg, heart rate 94 beats per minute (regular rate and rhythm), and respiration 26 breaths per minute. She is 5 feet 3 inches tall and weighs 202 pounds (BMI: 35.8). Blood is taken and sent to the laboratory for analysis, which reveals some abnormal findings (***Table 5***).

Based on the serum biomarker results, Patient A is diagnosed with stage 3 chronic kidney disease, with a GFR of 49 mL/min/1.73 m^2 and profound microalbuminuria. This diagnosis is substantiated by the noted elevation in random blood glucose levels and HbA1c.

Patient A is also experiencing anemia, with a hemoglobin level of 8.7 g/dL, and early signs of a bone and mineral metabolism disorder. She is considered at high risk for a cardiovascular event due to her long history of diabetes, hypertension, tobacco abuse, and hyperlipidemia, all of which appear to be uncontrolled.

Patient A attends diabetes self-management classes taught by a registered nurse and a registered dietitian. A 24-hour food recall demonstrated a high-protein diet and difficulty complying with the low-carbohydrate plan necessary to control her blood glucose levels. Over a period of six months, the patient lost and regained 10 pounds. She generally does not eat breakfast, has a salad at her desk at work for lunch, and typically stops at a fast food restaurant or orders delivery for dinner due to worsening fatigue and loss of energy. Patient A lives alone and does not enjoy cooking for one person. She also admits to not sleeping well and frequently eating in the middle of the night. Goals for treatment include glucose management, regulation of blood pressure, smoking cessation education, and lowered protein intake.

A meal plan is created for Patient A geared toward weight loss; the plan is low carbohydrate without being high protein in order to prevent further damage to the kidneys. Meal planning is simplified and incorporates homemade quick-fix meals or slow cooker recipes that should reduce the fat intake associated with a predominantly fast food diet. Specific emphasis is given to the need to refrain from high-protein foods and to eat at regular intervals throughout the day, including breakfast.

The need for physical activity is vital for Patient A and should help with weight loss, stress control, and blood pressure management. The patient is encouraged to wear a pedometer and work up to walking 10,000 steps each day. She is encouraged to start slowly and increase activity gradually.

Adherence to medications is an important part of Patient A's treatment plan. She is prescribed medications for many of her existing conditions including diabetes, hypertension, anemia, and cardiovascular disease. Instructions for her diabetes medications include the rationale for maintaining adequate glucose control. Patient A's history reveals a lack of glycemic control, so medication adherence is paramount and patient education includes insulin therapy instructions. The nurse also discusses the action, dosage, side effects, and need for a newly prescribed ACE inhibitor. Patient A is instructed to monitor her blood pressure at home and to report any high or low reading to her primary care provider.

Anemia education is completed, with further explanation regarding the need for additional testing to determine if supplemental iron or an erythropoiesis-stimulating agent is necessary. To prevent damage related to cardiovascular disease, Patient A is started on a statin to help decrease her lipid levels in conjunction with a low-fat diet. A vitamin D supplement is also recommended due to the elevated parathyroid hormone level.

Lastly, Patient A is encouraged to conduct self-blood glucose monitoring, maintain regular check-ups with her healthcare team, and follow-up with a nephrologist to further impede kidney disease progression. With education and understanding, Patient A can maintain her current kidney function. However, if she continues on her current path, progression into end-stage renal disease could be inevitable.

CONCLUSION

It is estimated that 34.2 million Americans have diabetes [7]. Because diabetes is the leading cause of end-stage renal disease leading to long-term hemodialysis in the United States, it is inevitable that healthcare professionals will encounter patients with this complication. An understanding of the relationship between diabetes and renal disease will ensure that appropriate diagnosis and treatment are given as this population grows.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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