Diabetes Special Offer

Expires March 31, 2021

This Special Offer includes:

Diabetes and Renal Disease
Diabetic Hypoglycemia
Sexual Dysfunction in Patients with Diabetes

NetCE
Continuing Education

Diabetes and Renal Disease

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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

Division Planner

Jane C. Norman, RN, MSN, CNE, PhD

Division Planner Disclosure

The division planner has 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.

Accreditations & Approvals

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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.

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 2014, 120,000 individuals in the United States began treatment for end-stage renal disease requiring dialysis or transplantation [2]. In the United States, annual end-stage renal disease costs are estimated to be $35.4 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), the prevalence of diagnosed diabetes increased by 382% from 1988 to 2014 [7]. As of 2017, 9.4% of the U.S. population, or 30.3 million Americans, have a diagnosis of diabetes. In addition, an estimated 7.2 million people have diabetes but remain undiagnosed [8]. By 2025, it is predicted that 15% to 20% of all Americans will have a diagnosis of diabetes or impaired glucose tolerance [9].

The scope of the diabetes problem is vast and diverse, particularly among geographical regions. In 2015, the prevalence of diabetes in the United States varied from 6.4% in Colorado to 13.6% in Mississippi [8]. 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 and non-Hispanic black heritage [10]. The prevalence of diabetes, both diagnosed and undiagnosed, is 16.09% in Native Americans, compared to an overall national rate of 11.5% in adults [10]. The prevalence in non-Hispanic black Americans is 17.7%, nearly twice as high as that of white Americans (9.3%) [10]. The highest prevalence of diabetes in the United States is observed in Native Americans in the Southwest, where an estimated 22.0% of the population has the disease [10].

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 [9]. 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 [11].

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: [13; 16]			*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 [12]. Other less common types of diabetes include [9; 13]:

- 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 [14]. The USPSTF also recommends screening for abnormal blood glucose as part of a cardiovascular risk assessment in adults 40 to 70 years of age who are overweight or obese [15]. 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 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 [16]. 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 [17]. 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 [18].

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 [19]. The approximate mass cutoff of substances for filtration is 70 kDa [20]. 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 [21]. Water is resorbed osmotically and regulated by antidiuretic hormone (vasopressin) [19]. 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 [20].

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 [20]. The loop of Henle is the portion of the nephron formed by the descending and ascending limbs of the renal tubule [19]. 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 [22].

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 [19]. 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 [20]. 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 [22]. 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 [22]. 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 [20]. 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 [19]. 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 [20].

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 [20].

RENAL REGULATION OF CALCIUM METABOLISM

The kidney plays a number of important roles in calcium and phosphate homeostasis [20]. The kidney converts vitamin D from food sources into an active form for use in the body [22]. 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 [20]. 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 [22].

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 [20]. When an excessive concentration of sodium and chloride in the tubular fluid is sensed by the macula densa, afferent arteriolar vasoconstriction is triggered [19]. 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 [20].

An additional challenge for the kidney is the regulation of renal cortical versus medullary blood flow [20]. 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 reabsorption [21]. 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 [20]. The redistribution of blood flow from the cortex to the medulla involves pref-

erentially supplying blood, and therefore oxygen, to those nephrons with loops of Henle that dip down into the inner medulla [22].

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) [22]. 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 [20]. 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 [22].

Pathologic conditions may affect the volume and nature of urine that is excreted [19]. 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 [22]. 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 [20].

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 [20]. 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 [21]. 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 [20].

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 [20]. 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 [23].

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 [20].

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 [24]. 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 [25].

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 [24]. 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 [24; 26]. 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 [23]. 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 [20].

CHRONIC RENAL FAILURE

Progressive and irreversible loss of nephrons decreases the GFR and affects vital processes, with changes manifested throughout all organ systems [23]. 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 [20].

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 [27]. 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 [23].

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 [23]. 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 [20]. 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 scaring [20].

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 [23]. 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 [20].

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 [23]. 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 [20].

The pathogenesis of chronic renal failure results in part from a combination of the toxic effects of [20]:

- 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 [20].

CLINICAL MANIFESTATIONS

Clinical manifestations related to chronic renal failure may be related to many body systems and imbalances (***Table 2***) [20]. 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.

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 [28]. 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) [28].

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	
Hyperpigmentation	X	X	X
Pruritus		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**
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: [20]			*Table 2*

Uremia causes sex hormone imbalances as well. Low estrogen levels leading 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 [23]. 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 [29].

Albuminuria is a well-known marker of poor renal outcomes in individuals with type 2 diabetes [30]. 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 [20]. 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 [30].

Kimmelstiel Wilson nodules (nodular glomerulosclerosis) are a classic feature of diabetic damage to the kidney [31]. 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 [32]. 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 [32].

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 [33]. 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 [34].

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***) [35]. 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 [36].

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 ACE inhibitor therapy is indicated [38].

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: [37]	*Table 3*

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 are 9.5 times greater in Native Hawaiians/Pacific Islanders, 3.7 times greater in African Americans, 1.5 times greater in American Indians/Alaska Natives, and 1.3 times greater in Asian Americans [3]. In 2014–2016, the presence of end-stage renal disease resulting from hypertension was five times higher in Native Hawaiians/Pacific Islanders than their white counterparts of similar age [3].

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 [39]. 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 [39]. But even small increases may impact the kidneys. High pressure in the renal capillaries is believed to effect 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; 40]. 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 [25]. 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 [41]. 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 [41].

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 [42]. Risk factors include pre-existing 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 [43; 44]. 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 [45].

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% reduction 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 [46; 47]. However, studies have shown an increase in morbidity in the elderly with tight controls [48]. 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 recommends that blood pressure targets should be less than 140/90 mm Hg. (https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG2014.pdf. Last accessed November 12, 2018.)

Strength of Recommendation: Strong

TREATMENT

ACE Inhibitors and Angiotensin-Receptor Blockers

An ACE inhibitor or an angiotensin-receptor blocker 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 [49]. For nonpregnant adults, blood pressure goals should be maintained at less than 120/80 mm Hg [5]. ACE inhibitors and angiotensin-receptor blockers diminish the risk of diabetic nephropathy and reduce the risk of cardiovascular events [50].

A treatment plan including ACE inhibitors or angiotensin-receptor blockers 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 angiotensin-receptor blockers can help preserve kidney function in individuals with chronic renal failure [51]. The use of an ACE inhibitor or angiotensin-receptor blocker 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 angiotensin-receptor blocker is warranted [5].

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 [50]. 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% [52]. The potential risk of hypertension with erythropoietin therapy should be taken into consideration prior to initiating treatment [50; 53]. 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 the increased risk of stroke and hypertension.

(https://www.healthquality.va.gov/guidelines/CD/ckd/VADoDCKDCPG2014.pdf. Last accessed November 12, 2018.)

Strength of Recommendation: Strong

Intravenous or subcutaneous erythropoiesis-stimulating agents are typically administered three times per week, frequently in combination with dialysis. Three erythropoiesis-stimulating agents are available for the treatment of anemia in individuals with chronic renal failure: darbepoetin alfa (Aranesp), epoetin alfa (Epogen, Procrit), and peginesatide (Omontys). 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; 54].

The typical starting dosage of epoetin alfa is 50–100 units/kg three times per week [55]. 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 [55]. The dosing for peginesatide is individualized to the lowest dose necessary in order to avoid the need for transfusion [56]. This agent is given only monthly to patients on dialysis.

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 [54]. 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 [55]. 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 [3]. It removes waste products and excessive fluids from the vascular system by passing the blood through a semipermeable membrane [51]. Although hemodialysis is efficient in removing solutes, it does not remove all metabolites [22]. 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 [51].

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 [3]. Hemodialysis can be provided via three major different types of access: an AV fistula, an AV graft, or a temporary venous catheter. The National Kidney Foundation endorsed a goal for at least 65% of all patients on hemodialysis to have a working AV fistula by 2009, but this goal was not met [57]. As of 2017, reporting institutions dialyzed 62.8% 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 [58; 59]. 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 [59]. 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 [60]. They also offer the best access for longevity and have the lowest association with morbidity and mortality [61]. 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. A patient-centered, individualized approach to the choice of access may indicate the use of a method other than AV fistula [62; 63]. AV fistulas are not without complications, and the overall patency rate is only 50% after five years [59].

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 [64]. 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 [65].

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 [66].

Indications for hemodialysis include [22]:

- 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 [22]:

- 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 [3]. 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 [67].

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 [68; 69].

Indications for the use of peritoneal dialysis include [22]:

- 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 Transplant

The ultimate plan in end-stage renal failure is for transplantation of a healthy kidney [67]. For many individuals, kidney transplant restores renal function to normal parameters, allowing the individual to gain greater independence and return to normal life activities [51]. Transplant outcomes are more successful today than in the past due to immunosuppressive drugs and sophisticated tissue match procedures [5]. At 80.5%, the five-year survival rate for transplant patients is more than twice the 47.1% 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. Kidney transplant guidelines place the highest considerations on histocompatibility and time spent on the transplant list [70]. The median adult wait time for a cadaver kidney is 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 [22].

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 [51].

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 [71]. 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].

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 [31]. 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].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For adults with CKD without diabetes, not on dialysis, with estimated GFR less than 50 mL/min/1.73 m^2, the American Dietetic Association recommends a protein-controlled diet providing 0.6 g to 0.8 g dietary protein per kg of body weight per day.

(https://www.andeal.org/topic.cfm?cat=3927. Last accessed November 12, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

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*

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*

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) [72]. 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.

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 30.3 million Americans have diabetes [8]. 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.

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Diabetic Hypoglycemia

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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.

Division Planner

Jane C. Norman, RN, MSN, CNE, PhD

Division Planner Disclosure

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

Audience

This course is designed for nurses in any healthcare venue and dietitians with a desire to better understand the causes, recognition, and treatment of hypoglycemia in a variety of settings.

A complete Works Cited list begins on page 22.

Accreditations & Approvals

In support of improving patient care, NetCE is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide nurses and healthcare professionals with a foundation of understanding hypoglycemia in order to assure the highest quality of care is provided to patients.

Learning Objectives

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

1. Define hypoglycemia and its effects on community health.
2. Describe the pathophysiology of hypoglycemia.
3. Outline risk factors for hypoglycemic events, including the use of specific herbal medications.
4. List signs and symptoms of hypoglycemia.
5. Identify causes of hypoglycemia, including medications and non-medication-related factors.
6. Compare treatment options for hypoglycemia.
7. Describe education topics to incorporate into patient teaching regarding hypoglycemia prevention.

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

Diabetes is a complex, multifaceted disease state, and healthcare providers involved in the care of patients with diabetes require in-depth knowledge of all aspects of the disease [1]. Optimal glycemic control and management for patients with diabetes has been proven to decrease both macrovascular complications (e.g., cardiovascular disease, peripheral vascular disease, cerebrovascular disease) and microvascular complications (e.g., nephropathy, neuropathy, retinopathy) [2; 68]. These findings are supported by the results of the Diabetes Prevention Program Outcomes Study and other large-scale studies [3]. Unfortunately, available diabetes treatment regimens are imperfect. Often considered a fact of the disease, iatrogenic hypoglycemia (commonly driven by insulin) is a limiting factor in successful, optimal glycemic control and management [4; 5; 6; 7]. Hypoglycemia occurs with both types of diabetes but impacts those with type 1 diabetes with lower glycated hemoglobin (HbA1c) percentages more prevalently than those with other forms of the disease [8]. This is due to specific defenses against the falling plasma glucose concentrations that continue in individuals with functioning pancreatic alpha and beta cells [9].

Patients with type 1 diabetes striving to achieve glycemic control may have symptomatic hypoglycemia up to 10 times per week, with asymptomatic events occurring more often [10]. On average, type 1 diabetes patients suffer an average of two episodes of symptomatic hypoglycemia per week, often at night [9]. An estimated 4% to 10% of deaths among individuals with type 1 diabetes are attributed to hypoglycemia [11]. Studies have revealed a wide range of episodic hypoglycemia in patients with type 1 diabetes, from 62 to 170 episodes per 100 patient-years with tight glycemic control [12]. These estimates, however, are often based on reported episodes, which may be lower than actual events because they are generally limited to severe episodes that require medical treatment. In contrast, the same studies revealed that patients with type 2 diabetes experienced between 3 and 73 hypoglycemic episodes per 100 patient-years [12].

AN OVERVIEW OF HYPOGLYCEMIA

Identifying a definitive and concrete blood glucose level that indicates hypoglycemia has been controversial. Similar to the adjustments needed for survival with chronic acidosis or chronic anemia, the body of those with chronic hyperglycemia can adapt to regulate vital operations and maintain function [12]. Patients with uncontrolled diabetes may function with elevated blood glucose levels, causing symptoms of hypoglycemia when the levels are brought back within an acceptable range [4].

Hypoglycemia is defined as a blood glucose level of less than 70 mg/dL and the start of cognitive alteration [5]. Cognitive impairment is classically observed in patients with functioning autonomic and central nervous systems when blood glucose levels fall to less than 60 mg/dL [8]. Hypoglycemia is generally best diagnosed utilizing the Whipple triad: autonomic and/or central nervous system symptoms, a low plasma glucose concentration, and relief of symptoms with treatment [12; 13]. It is important to remember that symptoms of hypoglycemia can instigate anxiety and fear [1].

PHYSIOLOGY OF FUEL METABOLISM

Glucose regulation is maintained by a sophisticated mechanism of regulatory and counter-regulatory reactions. When an individual consumes food, specifically carbohydrates, sugars are released into the blood circulatory system [1]. The chemical reactions to this sugar introduction help maintain homeostasis in the body.

Phases of Insulin Response

The concentration of plasma glucose is dependent on the rate glucose enters the circulation in contrast to the rate it is removed [14]. The fuel homeostasis within the body can be explained in a five-phase approach. Phase 1, or the fed state, occurs immediately and up to 3.9 hours after consumption of food. During this phase, the circulating glucose predominantly comes from an exogenous source. Plasma insulin levels are elevated, glucagon levels are minimal, and triglycerides are synthesized in the liver. Insulin impedes the breakdown of glycogen and triglyceride reservoirs. The brain and other glucose-dependent organs utilize some of the glucose absorbed from the intestinal tract, and the excess glucose is stored in the liver, muscle, adipose tissue, and other tissues for use later.

Phase 2 occurs 4 to 15.9 hours after consumption of food and is referred to as the postabsorptive state. In phase 2, blood glucose originates from the breakdown of glycogen and hepatic gluconeogenesis. There is a decrease in plasma insulin levels, and glucagon levels begin to increase. Anabolism (energy storage) ends in this phase and catabolism (energy production) begins. There is a mobilization of carbohydrate and lipid stores. Hepatic glycogen breakdown provides maintenance of circulating plasma glucose to ensure an adequate supply of glucose to the brain and other organs. Adipocyte triglyceride begins to breakdown, and free fatty acids are released into the circulatory system for use by the liver and skeletal muscle as the primary energy source and as a substrate for gluconeogenesis. The brain continues to utilize glucose, provided mainly by gluconeogenesis, due to its inability to use free fatty acids.

Phase 3 is the early starvation state. About 16 to 47.9 hours after the consumption of food, the blood glucose is generated from hepatic gluconeogenesis and glycogenolysis. Gluconeogenesis continues to generate most of the hepatic glucose. In this phase of starvation, lactate makes up half of the gluconeogenesis substrate along with amino acids (specifically alanine) and glycerol. The secretion of insulin is suppressed and counter-regulatory hormone (glucagon, cortisol, growth hormone, and epinephrine) secretion is stimulated.

Phase 4 begins 48 hours to 23 days after food consumption. During this preliminary prolonged starvation state, blood glucose originates from hepatic and renal gluconeogenesis. Within 60 hours of starvation, gluconeogenesis provides more than 97% of hepatic glucose output. The secretion of insulin is distinctly diminished and counter-regulatory hormone secretion is stimulated.

Phase 5, or the secondary prolonged starvation state, begins 24 days after food consumption. Blood glucose during this phase originates from hepatic and renal gluconeogenesis, just as in phase 4. However, in phase 5 the rate of glucose being utilized by the brain and the rate of gluconeogenesis diminishes.

The relationship between the glucoregulatory and counter-regulatory hormones and the many factors that contribute to the fuel metabolism should be considered. There is a sophisticated relationship between the metabolic-regulatory hormones insulin (a glucoregulatory hormone), glucagon, and epinephrine (counter-regulatory hormones). When insulin is elevated, glucagon and epinephrine are suppressed [15]. This process occurs to prevent the continued rise of endogenous glucose levels. Conversely when insulin levels decline in response to diminished circulating glucose levels, glucagon and epinephrine respond by increasing. These relationships are maintained when normal homeostasis is maintained. In the presence of diabetes, there is a disruption of this homeostasis [16].

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

Hypoglycemia is a result of one of two different issues: hyperinsulinemia (resulting from too much exogenous insulin, an insulin-secreting pancreatic tumor, or excessive oral diabetes medication) or iatrogenic issues (alteration in glucose counter-regulation) [12]. Hypoglycemia can be a complication of insulin therapy in both type 1 and type 2 diabetes or of oral medications that stimulate the pancreatic beta cells in the islets of Langerhans [17]. Symptoms of hypoglycemia tend to have a greater severity when they are the result of hyperinsulinemia due to the prevention in the formation of alternative fuels, such as free fatty acids or ketones [8].

Iatrogenic hypoglycemia is the consequence of the relationship of relative insulin surplus (also referred to as absolute insulin surplus) and compromised physiologic and behavioral responses to falling plasma glucose levels in patients with type 1 diabetes and patients with insulin-deficient type 2 diabetes [4; 13]. Normally, a decrease in insulin release is the first physiologic defense. An increase in glucagon production is the second, and the third physiologic defense is epinephrine [15]. Epinephrine limits the clearance of glucose in insulin-sensitive tissues. The result of each of these defenses is a sympathoadrenal response, primarily a sympathetic neural response, to hypoglycemia initiating neurogenic symptoms. As a result, behavioral protections, such as hunger, take effect [1]. In some cases, these natural defenses may be compromised.

Chronic hypoglycemia can result in hypoglycemia-associated autonomic failure (HAAF), a syndrome characterized by both defective glucose counter-regulation and hypoglycemia unawareness. This response is common in patients with type 1 diabetes, but can also occur in patients with advanced type 2 diabetes. In patients with HAAF, the epinephrine response to ensuing hypoglycemia is decreased, with adjustments in insulin and glucagon absent [18]. These patients will also experience fewer symptoms of low blood glucose levels due to a decrease in the sympathoadrenal response, resulting in an unawareness of the condition or the need to correct it [12]. Tight control of blood glucose levels and avoidance of hypoglycemia can reverse HAAF within two to three weeks [18].

Research has also indicated that recurrent hypoglycemia can result in increased nitric oxide production by the ventromedial hypothalamus, a mechanism that triggers response to hypoglycemia in patients with HAAF [19]. However, prolonged or excessive nitric oxide production causes an impaired counter-regulatory response. In an animal study, blocking this action with the use of the antioxidant *N*-acetylcysteine prevented the development of an impaired counter-regulatory response [19].

Nocturnal Hypoglycemia

Nocturnal hypoglycemia is another concern for some diabetes patients. Sleep impairs the counter-regulatory response to hypoglycemia in individuals with or without diabetes [20]. This impairment is caused by a decreased epinephrine response to dropping blood glucose levels during sleep. The result is an increased susceptibility to asymptomatic nocturnal hypoglycemia, particularly for patients with type 1 diabetes. Because it has been established that recurrent hypoglycemia can result in further deficits in counter-regulatory hormone responses, regular nocturnal hypoglycemia can trigger a cycle of hypoglycemia, impaired counter regulatory responses, and decreased awareness of low blood glucose levels while awake or asleep. Patients who experience recurrent asymptomatic nocturnal hypoglycemia are at increased risk for more frequent and severe hypoglycemia [8].

Some patients will experience a rebound reaction to hypoglycemia known as the Somogyi phenomenon [21]. This condition almost exclusively occurs in patients who take long-acting insulin and occurs most often following nocturnal hypoglycemia [21]. Untreated hypoglycemia or a rapid decrease in blood glucose triggers a release of counter-regulatory hormones, resulting in an episode of hyperglycemia and a period of insulin resistance that can persist for hours to days. The insulin resistance and hyperglycemia can lead to ketonuria or ketonemia [1].

Recognition and diagnosis of the Somogyi phenomenon is difficult, and it is important that healthcare providers thoroughly assess signs and symptoms of nocturnal hypoglycemia. This can be done nicely by utilizing continuous glucose monitoring [5]. This option involves placing a small sensor under the skin that monitors interstitial fluid [22]. The sensor device transmits an electronic signal to a monitor every five minutes. These levels are stored for up to 72 hours.

RISK FACTORS

The first step in developing a plan for the prevention and treatment of hypoglycemia is having a solid knowledge of risk factors and strategies to avoid or address those factors [5]. Reduction of hypoglycemia risk factors is an important aspect of the education process for patients with either type 1 or type 2 diabetes. Hypoglycemia risk reduction involves addressing the issues of hypoglycemia at every patient contact [5]. The principals of aggressive glycemic control are necessary to prevent hypoglycemia and include patient education, frequent self-monitoring of blood glucose (SMBG), flexible insulin (or other medication) regimens, individualized glycemic goals, and continuous professional guidance [23]. Finally, healthcare providers should consider both conventional risk factors and those indicative of compromised defenses against hypoglycemia and adjust treatment accordingly [9].

INSULIN

Inaccurately timed, an incorrect type, or excessive doses of insulin can result in hypoglycemia. In addition, there can be a diminished exogenous glucose source as a result of a missed meal, skipped snack, extended fast, or exercise [1; 5]. The duration of insulin therapy may also be a risk factor for hypoglycemia [24].

WEIGHT LOSS

When patients with diabetes experience weight loss, there is a corresponding increase in insulin sensitivity. Along with weight loss, improved fitness enhances insulin sensitivity by increasing muscle mass and optimizing glucose utilization. If these patients continue on a pre-weight-loss medication or insulin regimen, there is a greater potential of hypoglycemia [9].

ALCOHOL USE

Use of alcohol also increases the risk of experiencing hypoglycemia. Ethanol impedes gluconeogenesis and inhibits cortisol and hormone responses to hypoglycemia. Severe hypoglycemia can occur when ethanol consumption is coupled with lack of food or overnight fast, resulting in glycogen depletion [8]. Hypoglycemia can be prevented in this case by eating while ingesting any alcohol and limiting alcohol intake [25].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the Academy of Nutrition and Dietetics, alcohol consumption may place adults with diabetes at increased risk for delayed hypoglycemia, especially if using insulin or insulin secretagogues. Therefore, adults with diabetes should be advised that if they choose to drink alcohol, they should do so in moderation (i.e., one drink per day or less for adult women and two drinks per day or less for adult men).

(https://www.andeal.org/topic.cfm?menu=5305&cat=5595. Last accessed February 5, 2020.)

Level of Evidence/Strength of Recommendation: Weak, Conditional

HAAF

As discussed, iatrogenic hypoglycemia is the result of the interplay of relative insulin excess and compromised physiologic and behavioral defenses against dropping plasma glucose concentrations. Risk factors for HAAF include insulin deficiencies, a history of severe hypoglycemia or hypoglycemia unawareness, and aggressive glycemic control therapy [9].

HORMONES AND PREGNANCY

Women with diabetes who are of child-bearing age should be acutely aware of potential hypoglycemic episodes. Women are at an increased risk of hypoglycemic events at specific points in their lives, such as at the start of each menstrual cycle, as a result of decreased levels of progesterone. After conception and early in the first trimester, the risk of hypoglycemia is amplified as a result of increases in peripheral utilization and storage of glucose. Late in the third trimester, nocturnal hypoglycemia becomes a concern, as a bedtime snack may be insufficient to meet the intensified fetal demands for glucose. Lastly, during the postpartum phase, the risk of hypoglycemia results from the loss of placental hormones [1].

AGING

As the aging process progresses, an individual's risk of hypoglycemia increases as a result of various behavioral and physical changes. The production of counter-regulatory hormones that are so important to preventing hypoglycemia begins to slow [12]. Additionally, elderly patients frequently are prescribed many medications for various conditions, making polypharmacy a concern. Polypharmacy is relatively common among patients with type 1 and type 2 diabetes due to the multiple comorbidities associated with the disease. However, drugs may interact and increase the risk for hypoglycemia [26].

Behavioral changes, including cognitive decline and changes in eating habits, can also affect hypoglycemia risk [27; 28]. Elderly patients often have erratic nourishment or caloric intake, and this coupled with oral medications that increase insulin secretion or exogenous insulin significantly increases the potential for hypoglycemia [1]. Even when adequate calories are consumed, the older adult's intestinal absorption of those calories is slowed. As a patient ages, the adrenergic response to low blood glucose diminishes or disappears [12]. Additionally, the preliminary symptoms of hypoglycemia, for instance lack of motor skills or confusion, may be misdiagnosed or unrecognized [26].

DEPRESSION

In one study of more than 4,000 patients, individuals with diabetes and major depressive disorder were found to be more likely to experience frequent episodes of hypoglycemia than those without depression [29]. In addition, the time to first severe episode of hypoglycemia is shorter in depressed patients.

COMPLEMENTARY AND ALTERNATIVE THERAPIES

It is imperative to investigate individuals' use of any alternate therapies due to concerns associated with the usage. Research has demonstrated that only 40% of individuals inform their primary care providers of their use of complementary or alternative therapy [30]. Furthermore, the National Health Interview Survey has shown that 26.2% of patients with diabetes used some form of complementary or alternative therapy in the past year for treatment and/or wellness [31; 69]. Therefore, inquiring about the use of these therapies, particularly the use of herbal medications, should be incorporated into each instance of patient contact.

The use of some complementary or alternative therapies can increase the risk of hypoglycemia and may be a concern for many reasons. Some concerns include:

- Potential side effects
- Drug interactions
- Product variability
- Lack of product standardization
- Possibility of contamination
- Possibility of misidentification

Side effects and drug interactions are the two most significant areas of concern. Serious side effects have been experienced by patients taking complementary therapies, and the risk of drug interactions is a particular concern for patients with existing conditions, such as diabetes. Concomitant use of complementary therapies in these patients may result in toxicity secondary to exaggerated or subtherapeutic effects of their medication [32].

There are 10 botanical or complementary therapies that pose a specific risk of hypoglycemia in patients with diabetes. These include cinnamon, fenugreek, bitter melon, ginseng, nopal, aloe, banaba, caiapo, bilberry, and milk thistle [33].

Cinnamon

Cinnamon is derived from the bark of an evergreen tree that grows in tropical climates. This product has an active compound, hydroxychalcone, that may lower blood glucose and lipid levels in patients with diabetes, although research has been mixed [34; 35]. Some patients will take cinnamon to help control blood glucose levels despite the lack of proof of efficacy. It is possible that the effects of hydroxychalcone may potentiate the effects of secretagogue agents, increasing the risk of hypoglycemia [32].

Fenugreek

Fenugreek is a member of the *Leguminosae* family along with chickpeas, green peas, and peanuts. Historically, this herb was used to induce labor, but today it is used for diabetes, loss of appetite, and stimulation of milk production in breastfeeding women [36]. The active compounds of fenugreek include saponins and glycosides, and the seeds contain alkaloids, 4-hydroxyisoleucine, and fenugreekine, which delay gastric emptying, resulting in slow carbohydrate absorption, glucose transport inhibition, increased insulin receptors, improved peripheral glucose utilization, and possible stimulation of insulin secretion [32]. In diabetes patients, these effects may result in hypoglycemia [33].

Bitter Melon

Bitter melon is a vegetable cultivated in India, Asia, South America, and Africa and may also be known as bitter gourd, bitter apple, bitter cucumber, karolla, or karela. It is the most widely used diabetes treatment in Ayurveda, a form of traditional medicine originating in India [37; 38]. The active compounds in this vegetable include momordin, charantin, polypeptide P, and vicine. Use of bitter melon, usually in the form of juice or tea, can cause hypoglycemia, hypoglycemia-induced coma, increased tissue uptake of glucose, inhibition of enzymes involved in glucose production, and enhanced glucose oxidation of glucose-6-phosphate-dehydrogenase pathways [32]. Specific attention is required and intensive education is necessary when bitter melon is taken in conjunction with an insulin secretagogue [1].

Ginseng

Ginseng is a popular botanical product traditionally used to support overall health and the immune system [39]. The active ingredient in ginseng is ginsenoside, which decreases carbohydrate absorption in portal circulation and may increase glucose transport and modulation of insulin secretion when taken with an insulin secretagogue [33]. However, it is important to note that there is no conclusive evidence supporting any health benefits of ginseng [39].

Nopal

Nopal, also known as prickly pear, is a member of the cactus family and is a food source in Mexico. It is also used as an antihyperglycemic in Mexican culture [40]. The active compounds in nopales are mucopolysaccharide fibers and pectin, which slow the absorption of carbohydrate, decrease lipid absorption, and increase insulin sensitivity [32; 40]. As a result, there may be an improvement in blood glucose levels without hypoglycemia, but further research is necessary to confirm the efficacy and safety of this use. In the United States, the use of nopal is usually limited to Mexican and Native American populations [1].

Aloe Vera

Aloe vera is a common desert plant belonging to the family *Liliaceae*. The gel of aloe leaves has traditionally been used topically to soothe and heal wounds [41]. The active chemical constituent of aloe is glucomannan, a polysaccharide similar to guar gum and glycoprotein. Glucomannan has the potential to increase and promote glucose uptake. As a result, hypoglycemia can occur when aloe is consumed, particularly when used in combination with a secretagogue [32].

Banaba

Banaba is a type of crape myrtle commonly found in the Philippines, India, Malaysia, and Australia [32]. Commonly used as a tea to treat diabetes and promote weight loss, banaba has the chemical components corsolic acid and ellagitannin, which stimulate glucose uptake [33]. Banaba also has an insulin-like activity secondary to activation of insulin receptor tyrosine kinase or inhibition of tyrosine phosphate. Concurrent use of banaba and oral diabetes medication or insulin may result in an increased risk for hypoglycemia [32].

Caiapo

Caiapo is a form of white sweet potato cultivated in the mountains of Japan and South America. The botanical product is commonly used by Native Americans to decrease thirst and promote weight loss [32]. The active compound in caiapo is acidic glycoprotein, which decreases insulin resistance and improves insulin sensitivity. As a result, there is an increased potential for hypoglycemia, particularly when used with a secretagogue.

Bilberry

Bilberry is a plant related to the American blueberry, huckleberry, and cranberry. Two forms of bilberry may be used: the berry and the leaf. The fruit is used for circulatory problems, diarrhea, eye disorders, and menstrual cramps, while the leaf is used for other conditions, including diabetes [42]. The active compounds of bilberry leaf are anthocyanosides and chromium [32]. These components increase the potential for hypoglycemia due to the decreased vascular permeability and redistribution of microvascular blood flow. Research is still being completed to determine the exact mechanism by which bilberry lowers blood glucose [33].

Milk Thistle

Milk thistle is related to daisies and other thistles and has been used extensively for various hepatic disorders [43]. The active components are silybin, silychristin, and silydianin. These compounds inhibit the hepatotoxin-binding hepatocyte membrane receptors and decrease glutathione oxidation [32]. The resultant blood glucose-lowering effects and potential for hypoglycemia are being studied [1].

Case Study

Patient A arrives at her primary care provider's office for a routine examination. She is a Native American woman, 45 years of age, who is 5 feet 4 inches tall and weighs 205 pounds, with a body mass index of 35.3 kg/m^2. Her physician is concerned because of her family history of type 2 diabetes, heart disease, and stroke. Patient A has a past medical history of hypertension and hyperlipidemia. Her blood work reveals an HbA1c of 8.0% (estimated average glucose: 183 mg/dL) and a fasting blood glucose level of 173 mg/dL. A diagnosis of type 2 diabetes is confirmed by further blood work. Patient A is reluctant to start medications and asks her primary care provider if he knows of any alternative therapies she could use instead. After a thorough explanation regarding the benefits of glycemic control in respect to her family and personal past medical history, Patient A agrees to start taking metformin. She is also referred to a diabetes self-management education program recognized by the American Diabetes Association (ADA) for information regarding SMBG, medication management, exercise, blood glucose goals and behavior change, and culturally sensitive meal planning.

Patient A returns in three months for a follow-up evaluation of her progress. Her HbA1c remains 8.0% (estimated average glucose: 183 mg/dL), and she states her fasting blood glucose levels are 185–220 mg/dL. She states she has been adherent to her meal plan and has been working outside more often to increase her activity level. She appears frustrated with the lack of improvement.

Her primary care provider decides to add a sulfonylurea to the patient's therapy to increase insulin production. Patient A is started on glipizide 10 mg twice per day. Additional education is completed regarding the action of glipizide as well as the potential side effects and the importance of eating meals on a consistent schedule to prevent hypoglycemia. The patient and her daughter were both instructed on recognition of signs and symptoms of hypoglycemia and treatment options. Patient A is able to verbalize all instructions given.

One month later, Patient A's daughter calls the primary care provider in the mid-morning to report that her mother was working out in the yard and became dizzy, shaky, sweaty, and confused. She is instructed to check Patient A's blood glucose level and treat for possible hypoglycemia. After the patient's blood glucose levels are stabilized, the daughter is told to bring the patient to the clinic. The initial blood glucose level is 43 mg/dL. After Patient A consumes 6 ounces of orange juice, the blood glucose is rechecked in 15 minutes. The result is 87 mg/dL.

At the clinic, the certified diabetes educator assesses Patient A's medication understanding and adherence. No adverse practices are identified, so further information gathering is completed.

***Rationale and comments**: From the information gathered so far, it is unclear what caused Patient A's hypoglycemia. Additional areas should be explored, including:*

- *Timing of medication and meals*
- *Breakfast intake*
- *Blood glucose level prior to working in the yard*
- *Other episodes of hypoglycemia*
- *Fasting blood glucose levels*

The diabetes educator requests Patient A recall her breakfast, which reveals the intake of two scrambled eggs, one slice of whole-wheat toast with butter, half of a banana, 8 ounces of fat-free milk, and a cup of tea. The educator also inquires about any use of holistic or herbal remedies. Patient A becomes quiet and is hesitant to answer, but finally reveals she has been drinking bilberry tea every morning and using nopal and bitter melon in most of her meals. The patient indicates she did not share this with her primary care provider because she did not feel it was important. The diabetes educator informs Patient A about the potential interactions of many herbal medications and the impact they could be having on her diabetes and other conditions. The importance of including these medications in her conversations

with all of her healthcare providers is stressed. As a result, Patient A's primary care provider decides to decrease her glipizide to 5 mg twice a day. The patient is also instructed to call the diabetes nurse with a week of blood glucose levels to determine the success of the change in therapy.

SIGNS AND SYMPTOMS OF HYPOGLYCEMIA

Hypoglycemia is a serious and real threat to diabetes patients. Patient education must emphasize the early recognition of hypoglycemic states to assure the condition is treated promptly [44].

Symptoms of hypoglycemia are categorized by the acute response and progress in severity of the reaction. Initially, symptoms of hypoglycemia are a result of adrenergic effects that occur secondary to the release of catecholamine. These symptoms include sweating, weakness, shakiness, tremors, anxiety, faintness, tachycardia, and palpitations [45].

As hypoglycemia progresses and plasma blood glucose levels continue to decrease, the reaction to the lack of glucose becomes more severe. Symptoms in this stage are the result of the deficit of glucose in the central nervous system and include confusion, irritability, diplopia, inappropriate affect, motor incoordination, headache, abnormal behavior, weakness, and convulsions. The most severe of the central nervous system symptoms are diabetic coma and death [45].

More than half of all severe hypoglycemia episodes occur during sleep, when symptoms are less likely to be detected or recognized [21]. Nocturnal hypoglycemia most typically is caused by excessive insulin therapy and, with great cause for concern, usually does not awaken the person. Patients should be aware of symptoms that may indicate nocturnal hypoglycemia, such as morning headaches, feeling "foggy" in the morning, difficulty awakening, psychologic changes, exhaustion, restlessness while sleeping, night sweats, nightmares, and loud respirations [8]. Additionally, unusually high blood glucose levels after breakfast or lunch or detection of a small amount of ketones but no glucose in the morning urine are signs of nocturnal hypoglycemia [21].

CASE STUDY

Patient B is a white adolescent, 15 years of age, with a five-year history of type 1 diabetes. He is on multiple daily injections of insulin glargine for his background insulin and a rapid-acting insulin analog for meal and correction boluses. Patient B has experienced a roller-coaster effect with his glucose levels, and he has had difficulty in school recently due to fatigue and headaches. Patient B states he has not been sleeping well at night and wakes up exhausted. When asked to recall his blood glucose levels, he states his morning glucose levels have ranged between 189 mg/dL and 215 mg/dL. The primary care physician suspects nocturnal hypoglycemia and possible Somogyi phenomenon.

***Rationale and comments**: Nocturnal hypoglycemia is indicated by several signs and symptoms. The patient has experienced:*

- *Headaches and fatigue*
- *High blood glucose levels in the morning*
- *Waking up exhausted*

These are all signs of nocturnal hypoglycemia.

The physician instructs Patient B to assess his blood glucose level at 3 a.m. to identify if Somogyi phenomenon is an issue. She also prescribes the use of a continuous glucose sensor to assess blood glucose patterns and hyperglycemia/hypoglycemia events that may be occurring without being noticed.

CAUSES OF HYPOGLYCEMIA

The frequency of hypoglycemia in patients with diabetes is due primarily to abnormalities in glucose counter-regulation. There is a multitude of potential causes of hypoglycemia, including, but not limited to, excessive oral and injectable medications, physical activity, illness, and inappropriate patient practices [1].

ORAL MEDICATIONS

The appropriate use of diabetes medications requires an understanding of the mechanisms of action of each agent. This understanding should decrease incidents of hypoglycemia. Patients taking oral medications for diabetes who may be at an increased risk for hypoglycemia are often thin, are taking an insulin secretagogue, and/or have erratic eating patterns. This is especially true when a patient is taking medications with a rapid onset of action.

Sulfonylurea medications, such as tolbutamide, tolazamide, chlorpropamide, glyburide, glipizide, and glimepiride, are associated with an increased risk for hypoglycemia due to their mechanisms of action. Sulfonylurea preparations appear to acutely lower blood glucose levels by stimulating the release of insulin from the pancreas, an effect dependent upon functioning beta cells in the pancreatic islets [46; 70]. These agents close the energy-sensitive potassium channel in the cell membrane of the pancreatic beta cell. By accomplishing this, there is an increased amount of available insulin [44]. It is important to note that individuals with impaired first-phase insulin release will experience a diminished effect from sulfonylurea therapy [1].

The nonsulfonylurea secretagogues, or glinides, are hypoglycemic agents with the potential to reduce blood glucose levels to below normal. Within this classification of hypoglycemic agents there are two medications: repaglinide and nateglinide [47; 70]. These agents lower blood glucose levels by stimulating the release of insulin from functioning beta cells in the pancreas. Insulin release is glucose-dependent and diminishes at low glucose concentrations. These agents are most effective when taken just prior to the first intake of a meal [47]. This results in a greater insulin release during the first phase.

INSULIN

Insulin can be divided into two categories: basal and bolus. Healthy pancreatic beta cells release insulin into the blood stream throughout the day. This basal or background insulin enables stored fat and glucose to be released in the correct amounts to enable adequate metabolism during times when a person is not eating. This steady insulin level throughout the day regulates glucose production by the liver, the production and release of fat as fuel, and the entry of particular amino acids into cells for the creation of enzymes and structural proteins. Individuals without diabetes release about half of their total daily insulin requirements as background insulin to fulfill these needs [21]. As food is consumed, it is converted to glucose and other energy precursors by the digestive system. In response to rising blood glucose levels, the beta cells of the pancreas are stimulated to produce and release insulin. This is known as bolus insulin release [1].

When an individual's pancreatic beta cells are no longer proficient in producing enough or any insulin, exogenous insulin is required [1]. This can be accomplished utilizing many differing preparations. Previous therapies were formulated from beef or pork insulin, which were the only available synthetic forms of human insulin. Today, recombinant human insulin is available and is used by most persons requiring insulin therapy. The modern human recombinant insulin differs from the pork insulin by only one amino acid and beef preparations by

three amino acids [21]. Insulin injections, in small amounts, provide the body with the needed hormone to adjust to plasma glucose levels. However, unregulated and sustained hyperinsulinemia is common with exogenous insulin [9].

Unfortunately, hypoglycemia is the most important limiting factor for insulin adjustments to improve glycemic control. The risk of hypoglycemia depends on multiple factors, including age, weight, degree of insulin resistance, duration of the disease process, duration of insulin therapy, degree of glycemic control, and past history of episodes. In addition, there are casual factors that can instigate an episode of hypoglycemia, such as over administration of insulin, dietary transgressions, unplanned strenuous exercise while taking insulin, excessive alcohol intake, and hypoglycemia unawareness [5]. According to various studies, the annual incidence of severe hypoglycemia in the person with type 2 diabetes is 2% to 13% [48; 49]. Although the severe hypoglycemia experienced by the insulin-treated type 2 diabetes group is not trivial, the rate of severe hypoglycemia demonstrated by the type 1 diabetes individual during the Diabetes Control and Complication Trial was far greater. Of individuals treated with intensive insulin therapy during this study, 65% suffered severe hypoglycemic reactions requiring assistance from another individual for recovery [12].

Patients using insulin for the treatment of diabetes require extensive education regarding preparation of the syringe, as inaccurate dosing is a significant threat. If a patient is unable to fully visualize the small incremental markings on the syringe, the chance of dosing error is increased. The result of medication errors can be severe hypoglycemia, seizures, and possibly even death. For patients with poor vision, the insulin pen may be a better option and may increase the safety for the individual. Patients should demonstrate their techniques for preparation of the syringe, site selection and preparation, and administration. This allows for a thorough assessment of potential risk factors for hypoglycemia [1].

The development of hypoglycemia is a concern for all individuals on an insulin therapy regimen. Education should include information regarding oral and injectable combination medication management, exercise considerations, and specific patient-centered issues to maintain safe use of medications in daily life [1].

Injectable medications alone or in combination with another antihyperglycemic agent increase the potential for an adverse hypoglycemia reaction [50]. Preventative measures include not skipping meals, eating prior to exercise, and appropriately timing insulin bolus therapy [50; 51].

EVIDENCE-BASED PRACTICE RECOMMENDATION

For individuals using fixed insulin doses (or insulin secretagogues), the Academy of Nutrition and Dietetics asserts that consistent carbohydrate intake with respect to time and amount can result in improved glycemic control and reduce risk for hypoglycemia.

(https://www.andeal.org/topic.cfm?menu=5305&cat=5595. Last accessed February 5, 2020.)

Level of Evidence/Strength of Recommendation: Fair, Conditional

Accurate and frequent SMBG is recommended for all patients who use insulin. SMBG can help prevent hypoglycemia and provide information relevant to adjusting food intake, activity level, and medication [5]. Patients should report frequent blood glucose levels below 70 mg/dL to their primary care provider [52]. This will allow for the fine tuning of the insulin regimen, which should result in optimized glycemic control and reduction of adverse outcomes [1]. Nocturnal hypoglycemia can be an issue for patients taking insulin, and those who have or who are suspected to have nocturnal hypoglycemia as a result of insulin therapy should monitor their blood glucose levels [1].

For patients on an insulin regimen, exercise can significantly increase the potential for hypoglycemia [53]. Education related to exercise should focus on the assessment of pre-exercise blood glucose levels and determination if additional carbohydrates are needed. The risk for hypoglycemia increases as the duration or intensity of the activity increases. SMBG also can be used to monitor how psychologic and physical stressors influence glycemic responses [54]. Correlating SMBG results with the presence of stressors can help the patient manage them better for glycemic control.

Case Study

Patient I is an African American man, 72 years of age, with a 15-year history of type 2 diabetes. He has experienced diabetes-related complications, including a transient ischemic attack, angioplasty for coronary heart disease, renal impairment, and hypertension. His glycemic control has diminished steadily over the past two years to a current HbA1c of 8.9% (estimated average glucose: 209 mg/dL). Patient I has been very hesitant to start insulin therapy because of the experiences of past family members. He states, "As soon as I start on the needle, my life is over." After multiple educational opportunities regarding the benefits of good glycemic control and how it can diminish the adverse effects of his diabetes, Patient I ultimately agrees to a change in treatment therapy to include insulin injections. The physician prescribes neutral protamine Hagedorn (NPH) insulin 10 units twice per day due to cost factors over the more expensive long-acting insulin.

One morning, Patient I's wife calls emergency services reporting that Patient I is combative, confused, sweating, and beginning to lose consciousness. She is able to pour a large glass of orange juice in his mouth. She states, "I wanted to make sure it worked, so I put 5 tablespoons of sugar in it." When the patient arrives in the emergency department his blood glucose level is 357 mg/dL and he is complaining of chest pain. The decision is made to admit Patient I for further observation and glucose management. He is ordered weight-based insulin correction for glucose control. His NPH insulin is put on hold. The next morning, Patient I has a blood glucose level of 313 mg/dL. His glucose is covered, and the physician orders his home dose of NPH insulin 10 units. Patient I refuses his dose because it made him, "sicker than I was before. I was brought here because it doesn't work." The nurse explains the action of the insulin in relationship to his blood glucose levels and the action of the NPH, again stressing the benefits of adequate glucose control and the detrimental effects of hyperglycemia. The patient remains adamant that he is not going to take insulin again. His primary care provider discusses the need for the insulin therapy, and Patient I agrees to take the insulin while he is in the hospital and staff is around in case he "gets into trouble." After 24 hours, the patient has blood glucose levels less than 150 mg/dL and states he is feeling better than he has in many months. Through education regarding insulin, the connection is made between the increased perception of health and the decrease in blood glucose levels.

Patient I agrees to try insulin at home again. When it is time for his next dose of NPH, the nurse brings in the vial and a syringe to assess his ability to successfully draw up the 10 units of insulin. Observation reveals that the patient is struggling to complete the task competently and has actually drawn up 16 units of insulin opposed to 10 units. When his attention is drawn to the excessive amount of insulin in the syringe, he states, "Those little lines are so hard to see even with my glasses on. I figured the amount is so small it shouldn't hurt me." Patient I also struggles to manipulate the vial and syringe to the extent of the needle bending within the bottle.

***Rationale and comments**: There are several options available to Patient I to ensure he is receiving the correct amount of insulin. A Magni-Guide may be helpful to increase visualization of the syringe markings. A refrigerator vial stabilization device may also be considered to allow for greater stabilization of the needle when preparing the insulin syringe. The wife's willingness to learn how to draw up insulin into the syringe should be assessed. Once taught, her ability to accurately prepare the insulin syringe should be observed. Finally, the best option may be utilizing an insulin pen, which can increase patient safety.*

The treatment options are discussed with Patient I and his wife, and they decide to investigate the use of an insulin pen. The patient calls his insurance company to evaluate the coverage and is happy to hear the insulin pen is covered due to his recent hypoglycemia experience. Patient I and his wife are both taught how to dial the correct amount of insulin units, how to change insulin pen needles, and how to appropriately dispose of needles. Both individuals are able to perform all vital components taught regarding insulin pen usage and safely return home.

INSULIN PUMP THERAPY

Some patients may use a form of insulin delivery known as continuous subcutaneous insulin therapy, or insulin pump therapy. Insulin pumps are small, battery-operated microcomputers that resemble a standard pager device in size and appearance. This therapy is used most often for individuals with type 1 diabetes, although it is an option for some patients with type 2 diabetes. In contrast to multiple daily injections of rapid- and long-acting insulins, the insulin pump delivery system works to mimic normal pancreatic function [21]. This is accomplished by the steady release of precise amounts of insulin from the pump to achieve the basal or background insulin the body requires and optimize metabolic homeostasis. Likewise, when food is consumed, the individual or care provider enters the amount of carbohydrate and the pump calculates the correct dose and recommends a bolus dose. The individual can accept or enter an alternate bolus. Insulin pumps only use rapid-acting insulin to increase the ability of the pump to imitate normal pancreatic functioning [1].

In 2016, the U.S. Food and Drug Administration (FDA) approved the first automated insulin-delivery device for individuals 14 years of age and older with type 1 diabetes [55]. The device is a hybrid closed-looped system that automatically monitors glucose and provides appropriate basal insulin doses. It measures glucose levels every five minutes and automatically administers or withholds insulin, depending on the level of glucose measured. The device requires little to no input from the user.

A major advantage of insulin pumps is the opportunity for tight blood glucose control. This is possible because insulin delivery becomes very similar to the normal physiologic pattern. Pumps also offer the benefit of a more normal lifestyle, allowing users more flexibility with meal and activity patterns.

Although patients utilizing insulin pump therapy have been proven to achieve better glycemic control, they are not immune to hypoglycemia, and even with the introduction of this technology, hypoglycemia rates have been relatively unchanged for decades. Inappropriate carbohydrate counting or overriding the recommended bolus dose can lead to overdosing and ultimately hypoglycemia. Furthermore, if a meal bolus is programmed and delivered and the meal is interrupted or missed, hypoglycemia may result. As when any form of insulin is injected into the body, the potential of hypoglycemia is increased with planned or unexpected exercise. Lastly, stress can increase the release of adrenocorticotropic hormone and corticotrophin-releasing hormone, resulting in an increase in circulating blood glucose [17]. This stress can be the result of positive or happy events or as a response to negative events. If the pump was programmed for deliveries to meet known stress needs, hypoglycemia may develop when the stressors are removed without adjusting the total insulin delivery [21].

The ADA provides guidelines for the selection of patients appropriate for pump use [56]. Candidates should be highly motivated to take a great deal of responsibility for the care of their diabetes on a day-to-day basis. This includes the ability to count carbohydrate grams, to calculate appropriate bolus dosing, to make adjustments for varying activity patterns, and to monitor blood glucose four to seven times per day.

Case Study

Patient K is a defense attorney in a busy, prestigious law firm. She has dealt with type 1 diabetes since her diagnosis at the age of 13 years. She was started on an insulin pump in order to level out her blood glucose control and improve her overall health and has been happy with the results. Patient K is invited to play in a softball game prior to the barbeque at the annual neighborhood picnic. She feels it would be a good idea to get a little exercise because she has spent much of the day sitting and relaxing while talking with her friends. In the middle of the game, the patient suddenly becomes weak, diaphoretic, shaky, and confused—clear signs of hypoglycemia.

***Rationale and comments**: Several factors most likely contributed to Patient K developing hypoglycemia, the most significant being her engagement in exercise (unplanned) prior to eating her meal. In addition, the patient is away from the stress of her job and is relaxing, which is lowering her stress hormones. Together, these conditions are to blame for her hypoglycemic episode.*

EXERCISE

Individuals on an insulin therapy regimen should have a clear understanding of the risk of hypoglycemia related to exercise. Strenuous or aerobic exercise raises the blood glucose levels initially, but these levels will decrease as the body re-establishes its stores [57]. Although an initial increase in blood glucose levels will be seen, the potential for hypoglycemia can last up to 72 hours after stopping exercise. This is due to the physiologic reaction of fuel mobilization for energy release. When an individual is exercising at maximal levels, the body's energy level demands increase up to 20-fold in comparison to the resting state. In an attempt to maintain homeostasis and prevent hypoglycemia, several regulatory mechanisms are activated. Initially, skeletal muscles break down their own stores of glycogen, triglycerides, and free fatty acids from adipose tissue. In order to mobilize extramuscular stores, hormonal adjustments are essential. In the early phase of exercise, hepatic glucose production is increased by a reduction of insulin levels and unchanged glucagon levels. In subsequent stages, glucagon and catecholamine levels are elevated. As a result, glucose levels in healthy individuals remain fairly constant during exercise. When individuals with diabetes engage in moderate- or high-intensity exercise on a regular basis, however, the result is a decrease in blood glucose levels and increased insulin sensitivity [57]. Helping patients with diabetes to understand this sophisticated balance of fuel and energy metabolism is vital in the prevention of hypoglycemia [1].

Individual glycemic response patterns can differ markedly with exercise; therefore, the Academy of Nutrition and Dietetics recommends that persons with diabetes taking insulin or insulin secretagogues use glucose monitoring and recognition of glucose patterns to make decisions to exercise safely.

(https://www.andeal.org/topic.cfm?menu=5305&cat=5595. Last accessed February 5, 2020.)

Level of Evidence/Strength of Recommendation: Consensus, Conditional

PATIENT ISSUES

Other significant causes of hypoglycemia are patient behaviors and choices. Patient-related risk factors, such as meal timing and accurate administration of medications, are particular concerns when insulin or oral antihyperglycemic agents that increase the production of insulin from the pancreatic beta cells are used [58]. Meal timing is a key component of insulin, sulfonylurea, and nonsulfonylurea insulin secretagogue therapy.

Also, vision and manual dexterity are necessary to administer injectable medications and should be assessed in all individuals new to insulin therapy. Likewise, cognitive function is a consideration when caring for persons utilizing any medication, oral or injectable. Rapid-acting oral agents, such as repaglinide and nateglinide, are taken just prior to the first bite of a meal; if short-term memory is an issue, special caution and instructions are required [1]. In many cases, clear and complete patient education may alleviate these factors. However, if cognitive or physical deficits are an issue, involvement of a caregiver and/or the use of adaptive tools may be necessary.

Case Study

Patient G is a white man, 85 years of age, with a long history of type 2 diabetes. The nurse conducts a home health care visit for home assessment and medication evaluation. The patient indicates that his blood glucose levels are consistently in the high 200s, including in the mornings and at night. The nurse reviews the medications remaining in his weekly pill box to assess medication adherence and notes that he has been missing multiple medications throughout the week, including the medication to help control his blood glucose levels. Patient G states that when he realizes he has missed the medication, he is afraid to take it. The nurse informs the patient's physician of the findings, and the patient's regimen is changed to repaglinide 2 mg just prior to each of the three biggest meals. The instructions are given to Patient G, and he states understanding and is able to verbalize when to take the medication.

The nurse returns to Patient G's home three days later to assess his tolerance to the new medication. When the nurse arrives at 9 a.m., the patient is in a state of confusion, diaphoresis, and shakiness. His blood glucose level is 48 mg/dL. The nurse provides adequate treatment, and Patient G is then able to help determine what precipitated the episode of hypoglycemia. The patient reports that he took the repaglinide pill at 7:15 a.m., but he had not consumed breakfast. The nurse works with Patient G to develop a plan to avoid skipping meals. They decide that the patient will make his breakfast each day and elicit the assistance of his daughter to remind him to take the repaglinide when she talks to him each morning. The daughter also agrees to check in after lunch and dinner to assure that the patient is taking the repaglinide as he should at all meals.

TREATMENT OF HYPOGLYCEMIA

Treatment of hypoglycemia is fairly straightforward when the cause is known. When symptoms are mild-to-moderate and the patient is able to communicate and swallow, treatment is usually administered via the oral route. In most cases, hypoglycemia may be reversed by adhering to the 15:15 rule [1]. The 15:15 rule is simply defined as utilizing 15 grams of carbohydrate and rechecking the blood glucose in 15 minutes. If the blood glucose level is less than 70 mg/dL, with or without the presence of hypoglycemia symptoms, another 15 grams of carbohydrate should be administered and the blood glucose level should be checked again [58; 59]. When the blood glucose level is greater than 70 mg/dL, treatment should be stopped. Examples of foods that provide 15 grams of carbohydrate include three glucose tablets (sold in most pharmacies), one-half can of regular soda, 4 ounces of fruit juice, 2 tablespoons of raisins, 1 tablespoon of sugar, or 8 ounces of non-fat milk [1].

It may take up to 30 minutes for complete resolution of hypoglycemia symptoms following treatment. A common mistake when treating hypoglycemia is continuing the administration of glucose regardless of blood glucose levels because symptoms persist. This can lead to overtreatment and rebound hyperglycemia. When the blood glucose level is greater than 70 mg/dL, the individual should consume a snack consisting of a carbohydrate and a protein to prevent rebound hypoglycemia. This snack could include half of a peanut butter sandwich, crackers and cheese, or half of a ham or turkey sandwich [58].

Episodes of severe hypoglycemia, in which the individual has the potential of becoming comatose, combative, and/or unable to swallow, require more direct and immediate treatment [1]. In cases when a person may be combative but still able to swallow, treatment options include administering a tube of glucose gel or 1 to 2 tablespoons of honey into the cheek to raise blood glucose levels [21]. When the individual is no longer able to cooperate or is unconscious, the options decrease significantly. In cases when the individual is in an acute care facility and has an intravenous access line, the treatment is 50% dextrose. The dose of dextrose is calculated using the formula (100 - blood glucose level) x 0.4. This equation will indicate the amount of 50% dextrose in milliliters to be administered intravenously [1].

Although this treatment is very effective, hypoglycemia does not always occur within the hospital or when intravenous access is available. In these instances, the option for treatment is glucagon [58]. Glucagon is a polypeptide hormone typically secreted by the alpha cells of the pancreas. It increases the blood glucose level by stimulating the liver to change stored glycogen to glucose. Glucagon opposes the action of insulin, and it is used as an injection to reverse hypoglycemia and insulin shock in patients with diabetes. Glucagon also increases the use of fats and excess amino acids for energy production [60]. Glucagon can be given intramuscularly, intravenously, or subcutaneously. For individuals who weigh 20 kg or more, the appropriate dose is 1 mg. For children weighing less than 20 kg, the appropriate dose is 0.5 mg or 20–30 mcg/kg. Treatment can be repeated if unsuccessful but should not exceed a maximum of 1 mg for children [50]. In 2019, the FDA approved the first non-injection glucagon therapy for the treatment of severe hypoglycemia in persons 4 years of age or older [67]. The new product is a nasal powder packaged in a single-use dispenser. Glucagon can be kept at room temperature, and it is suggested that it should be available at all times [1].

Treatment of mild, moderate, or severe hypoglycemia in patients who use insulin pumps is similar to the treatment of all patients. However, because insulin pumps administer a rapid-acting insulin analog with a short half-life, removal of the pump may resolve mild-to-moderate hypoglycemia symptoms independent of any other intervention, depending on severity. In cases of severe hypoglycemia, treatment should be provided as described, with the additional need to immediately remove the insulin pump to prevent resistance to hypoglycemia treatment [21].

PATIENT EDUCATION

Prevention is the best and most effective intervention for hypoglycemia. Hypoglycemia prevention is a key patient education topic and should be discussed at every interaction with the individual. Education should include information regarding oral medication management, insulin therapy, exercise considerations, SMBG, and specific patient-centered issues to maintain safe use of medications in daily life [1]. Many healthcare providers believe self-management education is best completed by a certified diabetes educator prepared to do this type of formal education. This is true, but consistent reinforcement is needed and is best done by each healthcare provider in the form of teachable moments while interacting with the patient [61]. Individuals who actively manage their own diabetes care have better outcomes than those who do not. For these reasons, an educational approach that facilitates informed decision making on the part of the patient is widely advocated [62]. It is important to tailor teaching to each individual's specific literacy and comfort level. This will guide the educational interaction. Encompassing a variety of theories and teaching styles is paramount [63]. Patient education is a vital aspect in preventing adverse effects and detrimental outcomes related to medication therapy with diabetes. Each category of medication is associated with specific instructions to prevent hypoglycemic episodes [1].

For patients receiving medication therapy for diabetes, strategies to prevent hypoglycemia include not skipping meals and eating prior to exercise. Additionally, patients should be advised regarding the proper steps if a medication dose is missed. Most medication preparations should be taken as soon as the missed dose is realized, but there are a few exceptions. If the medication is either repaglinide or nateglinide or if it is too close to the time of the next dose, the missed dose should be skipped [50].

Patients should also receive thorough education related to the signs and symptoms of hypoglycemia [5]:

- Dizziness/lightheadedness
- Numbness or tingling around the mouth
- Palpitations
- Confusion
- Shaking
- Sweating
- Irritability/nervousness
- Hunger
- Headache
- Weakness

These signs and symptoms of hypoglycemia should be stressed at each patient education session.

Patient education regarding the treatment of hypoglycemia consists mainly of reinforcement of the 15:15 rule. It is critical that each patient, as well as the support person or caregiver, is aware of the steps to be taken in cases of severe hypoglycemia, when the individual is unable to swallow and has a potential of choking. In these situations, the only treatment available is an intramuscular injection of glucagon [12].

ORAL MEDICATIONS

Fundamental topics for all individuals taking a medication to prevent and/or correct hyperglycemia include [1; 50; 58]:

- Adherence to the medication regimen
- Adherence to the meal and exercise regimen
- Importance of wearing medical identification at all times
- Physician notification of frequent hypoglycemia or continued, unresolved hyperglycemia

Sulfonylurea medications should be taken with breakfast or the first main meal of the day to maximize effect and safety [50]. Patients taking a sulfonylurea should also space meals no more than four hours apart and avoid situations when meals have the potential of being missed [1]. Patients may carry a rapid-acting glucose source, such as glucose tablets or gel, in order to swiftly treat the onset of hypoglycemia in the initial stages [50]. Safe alcohol practices are also essential when a treatment regimen includes a sulfonylurea agent [58].

As with the sulfonylureas, timing is essential for the prevention of hypoglycemia when utilizing nonsulfonylurea secretagogues (i.e., repaglinide and nateglinide). Patients should be instructed to take the medication no more than 30 minutes prior to the meal; often, the medication is taken with the first bite of the meal [50; 58]. If a meal is to be skipped, the patient should also skip the prescribed dose of the medication [50].

Patients prescribed acarbose or miglitol require special consideration. These patients (and/or caregivers) should receive instruction regarding the need to take the medication with the first bite of each main meal [50]. Instruction regarding the action of these alpha-glucosidase inhibitors and the prompt treatment of hypoglycemia with simple sugar sources is imperative. Patients also benefit from carrying glucose tablets or gel at all times [58].

INSULIN

When an individual is being treated with insulin, patient education needs include the signs and symptoms of hypoglycemia, treatment of hypoglycemia, safe preparation of insulin syringes, and meal planning [58]. Healthcare professionals should assess each patient's ability to adequately see the markings on the small insulin syringe. If this cannot be satisfactorily met, visual aids (e.g., magnifiers) or insulin pens should be considered.

Caregivers and close family members or friends should receive information regarding prevention and treatment of hypoglycemia and providing a safe environment for the individual should hypoglycemia occur [1]. Instructions should be provided regarding preparation of glucagon, including how to inject the saline from the prefilled syringe into the glass vial of powdered hormone and appropriate injection sites (e.g., the upper arm, leg, or buttock) [21].

Emphasis on accurate and frequent SMBG and reporting frequent blood glucose levels less than 70 mg/dL to a primary care provider is an essential tool in the education process [22]. Communication between the individual, the certified diabetes educator, and the primary care provider is an optimal approach to incorporate into the education plan [58].

PHYSICAL ACTIVITY

The greatest potential for exercise-related hypoglycemia occurs when a person is receiving insulin therapy, although it may occur in patients taking oral glucose-lowering medications as well [64]. For these patients, education related to exercise should focus on the assessment of pre-exercise blood glucose levels, consumption of additional carbohydrates as needed, and having a carbohydrate source available if symptoms of hypoglycemia develop. It is also important to note that hypoglycemia risk increases as the duration or intensity of the activity increases. If assessment of blood glucose prior to exercise reveals a level less than 100 mg/dL, the individual should consume 25–50 grams of carbohydrate before engaging in physical activity. If the blood glucose level is 100–180 mg/dL, the patient should consume 10–15 grams of carbohydrate [1]. Patients should avoid exercise when their insulin or medication therapy is at peak effect. Lastly, patients should be advised to inject insulin away from muscles that will be the focus of exercise, as when a muscle is used, blood flow and utilization of glucose transport to the skeletal muscle increase [1].

NOCTURNAL HYPOGLYCEMIA

Patients who experience or who are suspected of having nocturnal hypoglycemia should be advised to monitor blood glucose levels prior to going to bed. When the blood glucose is less than 110 mg/dL, the patient should consume a snack that includes a carbohydrate and a protein. The specific signs and symptoms of nocturnal hypoglycemia should be explained, including the need to notify the primary care provider of suspected episodes. If an episode of nocturnal hypoglycemia occurs, the patient will be instructed to measure blood glucose levels at 3 a.m.; these levels are useful when creating a treatment plan [1].

PATIENT BEHAVIORS

Behavioral issues should be an aspect of patient education as well. Meal planning, particularly the need to count carbohydrates and adhere to dietary limitations, should be assessed. A food diary can assist in determining areas of focus for the individual and caregiver when hypoglycemia is occurring and cause is in question [65].

An additional area of educational focus is the issue of safety while driving [66]. The use of appropriate self-care skills and safety precautions should be taught and frequently reinforced in patients who drive. Emphasis should be placed on blood glucose monitoring prior to operation of a vehicle and frequent monitoring (every two hours) while on extended trips. Patients should be advised to refrain from driving when signs and symptoms of hypoglycemia are present [65]. Finally, a rapid-acting glucose source should always be available in the vehicle to treat any signs of hypoglycemia, although tablets should not be stored in the vehicle [66]. As always, wearing medical identification indicating that the patient has diabetes is important [65].

CONCLUSION

Hypoglycemia is a serious complication of diabetes and is most commonly experienced by patients who use oral medication or insulin to control the disease. In healthy people, hypoglycemia is prevented by a sophisticated interaction of the fuel metabolism and regulation of the body's counter-regulatory hormones. Causes of homeostatic imbalance include overdose of oral medication therapy, excessive insulin therapy, exercise, and inappropriate patient practices.

Recognition of hypoglycemia and knowledge of the treatment are critical concepts for healthcare providers to incorporate into the education plan of all diabetes patients, especially those who have just initiated medication therapy or have been newly prescribed an insulin regimen. Strategically placed assessment questions allow healthcare providers to illicit critical information regarding symptoms and signs the individual or caregiver may not recognize as hypoglycemia.

Finally, communication is essential to the prevention and understanding of hypoglycemia. In addition to the primary care team (i.e., the individual, support person or caregiver, the primary care provider, and the certified diabetes educator), other members may be added to improve care, including an exercise physiologist, registered dietitian, and pharmacist. All members of the education team should provide consistent information regarding the prevention, recognition, and treatment of hypoglycemia at each patient contact. This approach will provide the best possible level of understanding in order to obtain optimal glycemic control and minimize the adverse effects of hypoglycemia.

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Sexual Dysfunction in Patients with Diabetes

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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. (A complete biography appears at the end of this course.)

Faculty Disclosure

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

Division Planners

Jane C. Norman, RN, MSN, CNE, PhD
Alice Yick Flanagan, PhD, MSW

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

Audience

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The purpose of NetCE is to provide challenging curricula to assist healthcare professionals to raise their levels of expertise while fulfilling their continuing education requirements, thereby improving the quality of healthcare.

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Course Objective

The purpose of this course is to provide healthcare providers with the information necessary to identify and address sexual problems in patients with diabetes.

Learning Objectives

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

1. Identify the prevalence of diabetes in the United States and risk factors for its development.
2. Describe the basics of sexual physiology in both men and women.
3. Identify possible causes of sexual dysfunction in patients with diabetes.
4. Evaluate the impact of various lifestyle interventions on sexual functioning in patients with diabetes.
5. Compare and contrast available pharmacologic treatments for sexual dysfunction.
6. Discuss other possible treatments for sexual dysfunction.
7. Outline the psychosocial impact of sexual dysfunction on patients with diabetes.

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

As the number of diabetes cases in the United States continues to rise, the associated complications of the disease have become major public health issues. The complication of sexual dysfunction is often not discussed or addressed, although it is a relatively common occurrence among patients with type 1 or type 2 diabetes.

Human sexuality is a dynamic and multifaceted construct consisting of interplay between interpersonal, biologic, psychologic, and cultural factors. Sexuality impacts many aspects of life, and an individuals' sexual self-schema is an evolving concept [1]. For patients experiencing sexual dysfunction, the issue can have major repercussions, from conflict in their relationships to loss of their perceived identify and self-esteem. Feelings of loss, sadness, and tension are common.

Primary education often covers the topic of diabetes without addressing the impact of sexual dysfunction on adults with the disease and their partners. However, healthcare professionals are in a unique position to provide education, support, empathy, and encouragement to these patients, allowing them to lead the best possible life, with minimal stressors as a result of the disease process. A thorough understanding of the relationship between diabetes and sexual dysfunction will allow healthcare professionals to improve the quality of life of patients living with diabetes. Screening of sexual dysfunction should become a part of the routine care of patients with diabetes.

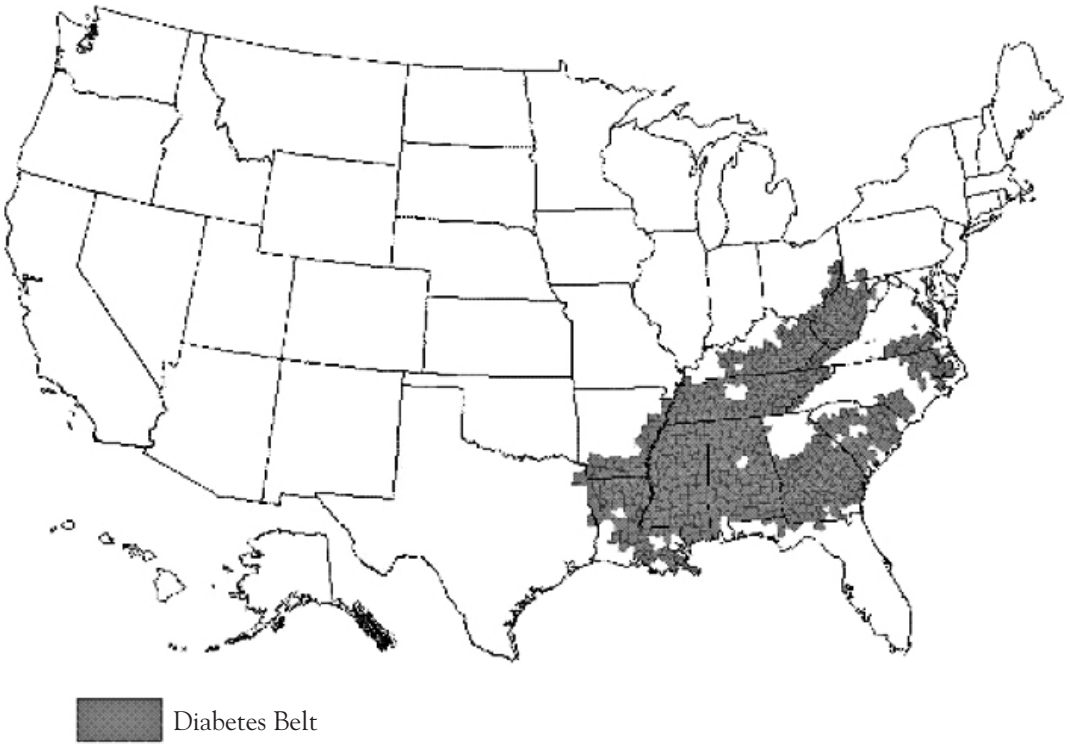
OVERVIEW OF DIABETES

DIABETES EPIDEMIOLOGY

Diabetes, known clinically as diabetes mellitus, is a progressive disease process affecting the fuel metabolism functioning within the body [2]. According to the American Diabetes Association (ADA), the prevalence of diabetes has increased eightfold since 1958, with the sharpest increase occurring in the 2000s [3]. As of 2015, 9.4% of the U.S. population, or 30.3 million Americans, had diabetes [4]. Unfortunately, 7.2 million of these individuals were unaware of their diabetes diagnosis. Diabetes has been considered epidemic since the 1970s, and the percentage of Americans expected to have diabetes or prediabetes is estimated to reach 15.5% and 30%, respectively, by the year 2030 [9].

The scope of the problem is vast and diverse, particularly among geographic regions. The Centers for Disease Control and Prevention has identified a "diabetes belt" in the United States, consisting of 644 counties in 15 states, where 11.7% of the adult population has diagnosed diabetes, compared with an 8.5% average in other counties (***Figure 1***) [56]. Although this represents a particularly dense geographic concentration of disease, there are many other counties and groups of counties outside of this belt with prevalences as high or higher. Many of the counties outside of the "diabetes belt" with especially prevalent diabetes have high Native American populations; one such example are several counties in northeastern Arizona, northwestern New Mexico, and southern Utah [3].

THE DIABETES BELT



Source: [56] *Figure 1*

Genetics, race, age, and lifestyle significantly influence the onset and progression of the disease process [6]. Although all races and ethnicities can develop diabetes, the prevalence is greatest among non-Hispanic blacks, Mexicans, and Native Americans/Alaska Natives [4; 57; 58; 59]. The incidence of diagnosed diabetes is estimated to be 12.7% among non-Hispanic blacks 18 years of age and older, compared with the overall U.S. rate of 9.4%. The prevalence of diabetes among persons of Hispanic descent who are 18 years of age or older is 12.2% [58]. Among the subdivisions of Hispanic groups, diabetes prevalence rates are 8.5% for Central/South Americans, 9% for Cubans, 12% for Puerto Ricans, and 13.8% for Mexicans.

In addition to being at high-risk for diabetes, Mexican Americans are 40% more likely to die from the disease than their non-Hispanic white counterparts [4]. However, Native Americans/Alaska Natives present the greatest risk for the development of type 2 diabetes; their risk is nearly three times greater than that of white Americans [59]. It is estimated that approximately 17.6% of Native Americans/Alaska Natives 18 years of age and older have type 2 diabetes. The highest prevalence of diabetes in the United States is observed in certain Native American groups of the Southwest, where an estimated 22.2% of the population has the disease [4]. The highest rate of diabetes for any population (worldwide) has been reported to occur in the Pima Indians of Arizona [60].

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 46% of juvenile-onset cases of diabetes are type 2 [61]. 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 [10].

DIAGNOSIS

As discussed, 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 around the 24th week of gestation, and typically resolves after the birth of the child [3]. Other less common types of diabetes include [5; 8]:

- Maturity-onset diabetes of the young (MODY): 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

All adults older than 45 years of age should be screened for type 2 diabetes every three years or every two years if they have any risk factors [8; 23]. In addition, individuals of any age who are at risk for or are suspect of having diabetes should be screened. Established risk factors for type 2 diabetes include:

- Age older than 45 years
- Body mass index (BMI) greater than or equal to 25 kg/m^2
- 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 (IGT) 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 ovarian 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, postprandial plasma glucose levels, or glycosylated hemoglobin (HbA_{1c}) testing (***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 [3]. 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 [3]. 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 (HHNS) and ultimately death [7].

DIAGNOSTIC CRITERIA FOR TYPE 2 DIABETES		
Stage	**Fasting Plasma Glucose Level**	**Two-Hour Postprandial Plasma Glucose Level**
Euglycemia	<100 mg/dL	<140 mg/dL
Prediabetes	≥100 mg/dL but <126 mg/dL	≥140 mg/dL but <200 mg/dL
Diabetes	≥126 mg/dL	≥200 mg/dL

Source: [5; 8] *Table 1*

AN OVERVIEW OF SEXUAL PHYSIOLOGY

Human sexuality is increasingly recognized as an important aspect of an individual's health and quality of life throughout the lifespan. Sexual activity has been associated with health benefits and longevity [11]. However, older adults engaging in sexual activity has long been a taboo, allowing for the perpetuation of myths regarding sexuality later in life. In fact, a regular sex life can continue throughout life. Data derived from the National Social Life, Health, and Aging Project indicate that more than half of individuals 75 to 85 years of age are sexually active, and physical health is significantly correlated with sexual activity and many aspects of sexual function, regardless of age [11].

In order to understand sexual dysfunction in patients with diabetes, it is important to have a solid comprehension of the normal functioning of the male and female reproductive systems. In theory, men and women experience similar physiologic changes (i.e., vasodilation) in response to sexual arousal. However, men are believed to follow a general linear pattern during sexual activity: excitement, arousal, plateau, orgasm, and resolution. Women, on the other hand, are thought to follow a non-linear model of sexual response including emotional intimacy, sexual stimuli, and emotional and physical satisfaction [12].

Sexual maturation and function in women involve the secretion of hormones, primarily estrogen and androgens [13]. Estrogen is an umbrella term that encompasses three similar hormones: estradiol, estrone, and estriol. The presence of estrogen induces the cervical mucosa to produce abundant fluid secretions, which in addition to providing lubrication, enhances the survival and mobility of sperm [14]. The presence of estrogen also protects the vaginal tissues by facilitating nitric oxide synthesis, the enzyme involved in the control of vaginal and clitoral arterial blood flow. When estrogen levels decrease, women experience difficulties with vaginal lubrication, low sexual desire, painful intercourse, and/or difficulties with orgasm [12]. Androgens, which are primarily considered a male sex hormone, are also a part of normal female sexuality. In women, androgens activate sebaceous glands, which play a role in activation of sexual desire and libido functions [14].

Male sexual functioning is centered on the erectile reflex. Erectile tissue consists of vascular chambers, supplied with blood via arterioles, within the corpora cavernosa and corpus spongiosum [13]. Typically, the arterioles are constricted, resulting in minimal blood flow through the erectile tissues. However, in the presence of sexual stimulation, the arterioles dilate and fill with blood, expanding the erectile tissue and resulting in erection. The process of formation and maintenance of an erection is under the control of the autonomic nervous system, but it can be stimulated or inhibited by central nervous system input, such as stress,

medications, and visual stimuli [14]. Impotence is defined as the inability to consistently maintain sufficient rigidity for sexual intercourse and may be the result of arterial, venous, neurogenic, or psychogenic causes [15].

Diabetes can impact all areas of sexual function due to the presence of vascular impairments, endothelial dysfunction, neurologic derangements, and hormonal changes [1]. The exact cause of sexual dysfunction can be difficult to elucidate and is most likely a result of a combination of these factors.

EVIDENCE-BASED PRACTICE RECOMMENDATION

The U.S. Preventive Services Task Force concludes that clinicians should assess all male patients with diabetes for erectile dysfunction.

(https://www.guideline.gov/summaries/summary/47767. Last accessed March 7, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

POSSIBLE CAUSES OF SEXUAL DYSFUNCTION IN PATIENTS WITH DIABETES

VASCULAR DISEASE

Blood flow is directly related to driving pressure and inversely related to arteriolar resistance, which is dependent on the net effects of systemically circulating substances, such as catecholamines, angiotensin, and prostaglandins [16]. Vascular endothelial thickening and its consequences are most associated with chronic cardiovascular diseases such as coronary artery disease and peripheral vascular disease, the presence of which greatly increases the risk for myocardial infarction and stroke [1]. In patients with diabetes, atherosclerosis is often present, as evidenced by fatty streaking, intimal plaques, and calcification of vessels. Changes in platelet activity, with an increase in adhesiveness and tendency to aggregation, have been observed in patients with diabetes, although it is not clear whether this is a primary alteration as a consequence of diabetes or if it occurs secondary to occlusive arterial disease [17].

When the vasculature is weakened due to narrowing related to fatty streak formation or rupture, the result is ischemia. Ischemia is the reversible cellular injury that occurs when tissue demands for oxygen exceed the supply. The result is an imbalance in oxygen supply and demand that results in tissue hypoxia, decreased energy substrate, and the buildup of toxic metabolites. Ultimately, ischemia results in alteration in tissue function [16].

This process of weakening vasculature and alteration of tissue function can lead to obstruction of the genital arteries and consequent symptomatic sexual dysfunction in both men and women [1]. Diffuse atherosclerosis, a common finding in patients with diabetes, may affect the penile, clitoral, or vaginal vasculature in addition to the circulatory beds of the heart, brain, and lower extremities. There may be a discrete narrowing in the external iliac artery that diverts the blood supply from penile circulation [18].

In women, estrogen acts as a vasoprotector, which diminishes the effects of atherosclerotic disease on female sexuality in the childbearing years. However, as estrogen levels drop, often during perimenopause and menopause, arterial blood flow to the pelvis may be compromised. This is termed clitoral and vaginal vascular insufficiency syndrome and may cause delayed vaginal engorgement, diminished vaginal lubrication, pain or discomfort with intercourse, diminished vaginal sensation, diminished vaginal orgasm, and diminished clitoral sensation or orgasm [19; 20]. There is some evidence that hormone replacement therapy in postmenopausal women increases clitoral blood flow, but this must be weighed against the possible risks associated with the therapy [21].

Although erectile dysfunction is associated with cardiovascular risk factors and atherosclerosis, it is not known whether the presence of erectile dysfunction is predictive of future cardiovascular events. In one study, all-cause deaths occurred in 11.3% of individuals who reported erectile dysfunction at baseline, but in only 5.6% of individuals who reported no or mild erectile dysfunction [22].

Autonomic Neuropathy

Autonomic neuropathy significantly impacts the survival and quality of life of an individual with diabetes. The autonomic nervous system consists of the afferent and efferent systems, involving both the parasympathetic and sympathetic nervous systems, and may involve any organ within the body. Disturbances in the autonomic nervous system may be functional (e.g., gastroparesis, ketoacidosis) or organic (e.g., lost nerve fibers) [23]. With autonomic neuropathy, there is damage to the autonomic, motor, and/or sensory nerves as a result of metabolic or vascular derangement in individuals with long-standing diabetes [24].

Studies of men with diabetes who experience erectile dysfunction have suggested that neurologic abnormalities, primarily autonomic neuropathy, are present in up to 80% of the cases [18]. The primary abnormalities are related to the autonomic nervous system, which is responsible for engorgement [18]. Neurologic impotence, usually in the form of erectile dysfunction or retrograde ejaculation, can result from diabetic autonomic neuropathy [24].

The erectile tissue and neurologic innervation of the female genitalia are homologous to the male, which may contribute to the observation that women with diabetes have more arousal phase dysfunction [18]. In women without dysfunction, vaginal lubrication is initiated by increased blood flow through the vaginal capillary plexus. During this process, arterial dilation occurs [12]. In women with peripheral nervous system disease, such as that seen with diabetes, the sexual response cycle is stunted, resulting in decreased lubrication, vaginal wall thickening, and difficulty or inability to achieve orgasm [20].

OBESITY

Individuals with diabetes (particularly type 2) tend to be overweight or obese, and this may be a confounding factor for patients experiencing sexual dysfunction. Vascular, endothelial, neurogenic, endocrine, and psychologic factors may all play a role [25]. Obesity and sexuality is a prevailing area of study for researchers, although many studies have been small in scale and focus primarily on the obese male with erectile dysfunction or obese women awaiting bariatric surgery. One study of 12,364 French men and women between 18 and 69 years of age revealed that obese men and women were at a greater risk of negative sexual outcomes than their nonobese counterparts [26]. The research uncovered the fact that obese women were 30% less likely to report a sexual partner in the previous 12 months than women of a healthy weight. Obese men were 70% less likely to report more than one partner in the same time period and greater than 2.6 times more likely to report erectile dysfunction than their nonobese counterparts [26]. However, the study did not determine the cause of sexual inactivity/dysfunction, and the actual etiology may be physical or psychologic (or both) in nature. When an individual views him/herself as visually unappealing, the emotion may be internalized and result in sexual avoidance, even when the individual is in a committed relationship [25].

Obesity is often the result of insulin resistance in diabetes and is associated with dyslipidemia and endothelial and smooth muscle dysfunction, each of which is associated with sexual dysfunction [27]. A strong inverse relationship has been identified between the incidence of metabolic syndrome and testosterone levels (total and unbound, or "free") as well as sex hormone-binding globulin levels. The association is strongest for the dyslipidemia and waist circumference components of metabolic syndrome when compared with elevated triglycerides, hypertension, or glucose intolerance [28]. As such, diminished levels of testosterone should also be considered, along with vascular and neuropathic etiologies, when evaluating erectile dysfunction in overweight patients with poorly controlled diabetes [25].

CASE STUDY

Patient T is large man, 44 years of age, who is admitted to the emergency department with complaints of nausea, vomiting, and excessive urination. He and his wife had been out riding their motorcycles over the past weekend and eating a high-fat diet, as they do most weekends. They decided to come to the emergency department suspecting food poisoning. He is a white male with seasonal allergies and hypertension, but no other significant medical history. His surgical history is positive for an appendectomy at 15 years of age without complications. His family history is positive for type 2 diabetes, coronary artery disease, cerebrovascular accident, hyperlipidemia, hypertension, and obesity. Upon physical assessment, Patient T is alert and oriented. His height is 5 feet 10 inches; weight 239 pounds without shoes; BMI 34.4 kg/m^2; blood pressure 146/82 mm Hg on medications; pulse 83 beats per minute, regular rate and rhythm; and oral temperature 37 degrees Celsius. His lungs are clear to auscultation, and heart sounds are clear, without rubs or murmurs auscultated. The abdomen is soft and nontender in all quadrants. Peripheral pulses are present at +2 at all extremities. Patient T's feet are free from lesions, with a positive Babinski reflex, and all extremities are warm to touch and responsive to monofilament test. Laboratory results include:

- HbA_{1c}: 8.1% (estimated average glucose: 186 mg/dL)
- Random blood glucose: 321 mg/dL
- Blood urea nitrogen (BUN): 22 mg/dL
- Creatinine: 0.9 mg/dL
- Alanine transaminase: 16 U/L
- HDL: 31 mg/dL
- Low-density lipoprotein (LDL): 122 mg/dL
- Triglycerides: 201 mg/dL
- Microalbumin: 312 mcg/mg

The patient reports that the only medications he is currently taking are over-the-counter cetirizine (Zyrtec) and chlorthalidone 25 mg/day for hypertension.

The emergency physician diagnoses Patient T with new-onset type 2 diabetes and refers him to the inpatient diabetes educator for survival skills education. He is discharged on metformin 1000 mg twice daily and blood glucose monitoring twice a day for the next month. In addition, Patient T is instructed to follow-up with his primary care provider within the next 72 hours for further diabetes evaluation.

The certified diabetes educator meets with the patient and his wife to provide information on metformin, a biguanide. Education focuses on the drug's mechanism of action, lifestyle modification (especially diet), and recognition and treatment of hyperglycemia.

Patient T is provided with a blood glucose monitor and instructed on the frequency, use, and importance to the management of diabetes. He is informed of the discharge order to monitor his glucose levels twice daily. The diabetes educator encourages him to alternate the times of his monitoring to obtain the greatest amount of information to guide management decisions. Patient T and his wife ask many questions and are able to verbalize the instructions given.

At the conclusion of the visit, Patient T's wife timidly asks if there are any other things diabetes could affect. The educator begins to list the many possible chronic complications, but the wife stops her and states that the patient has recently had problems performing. Patient T, mortified, states he is fine, but his wife disagrees, stating she loves him and wants their physical relationship back. When asked how long the problem had been occurring, the patient states that the problems began in the last month. The educator provides information regarding the impact of stress, elevated glucose levels, diet, and obesity on erectile function.

As a first step, the educator encourages Patient T to obtain better glycemic control, improve his diet, and manage any stress he may be experiencing. Because these are all modifiable conditions, they should be addressed first and may resolve the sexual dysfunction. If the condition remains a persistent issue, the patient is instructed to discuss further options (e.g., medication) with his primary care provider. Patient T and his wife are agreeable to this plan and appear more comfortable and relaxed.

TREATMENT OPTIONS

In the treatment of sexual dysfunction, the first and most important goal is to identify and treat any reversible cause(s). Education is an essential part of this process, as patient investment and compliance with lifestyle changes and treatments is necessary [22]. Patients and their significant others should have a solid understanding of diabetes-related and other causes of sexual dysfunction and of the available treatment options [6]. Due to the more overtly physiologic nature of male sexual dysfunction, many options exist for the treatment of sexual dysfunction in men. However, the same cannot be stated for women. In both sexes, the appropriate first step is to address modifiable factors, such as controlling of blood glucose levels, adoption of a healthy diet, and counseling [25]. In men, first-line therapy for erectile dysfunction (the most common cause of male sexual dysfunction) consists of pharmacotherapy with a phosphodiesterase-5 inhibitor (i.e., sildenafil, vardenafil, or tadalafil) and/or testosterone replacement in hypogonadal men [29]. Other mechanical and surgical options are available. Women also have some medical treatment options, although education and psychotherapy (e.g., individual and couple therapy, cognitive-behavioral therapy, physiotherapy) are the most common approaches [30]. As with all patients with diabetes, education regarding diet (such as adopting the Mediterranean diet), exercise (aerobic and anaerobic exercise), control of blood glucose levels, and smoking cessation should be provided and reinforced regularly [25].

LIFESTYLE INTERVENTIONS

The first step in addressing sexual dysfunction in most patients is to make changes in one's lifestyle, particularly for women, for whom pharmacologic and surgical options are limited. This includes obtaining adequate rest, engaging in effective stress management techniques, and regular exercise [30]. Regular physical activity is protective against the development of sexual problems in patients with diabetes [29; 31]. Weight loss may also be helpful for some patients. In fact, obesity nearly doubles the risk of erectile dysfunction, and even modest improvement in weight may result in better sexual functioning [29]. Smoking is associated with an increase in the risk of erectile dysfunction, and given the implications of smoking for all patients, cessation should be encouraged.

Engaging in noncoital intimacy (e.g., sensate-focus exercises) and enhancing stimulation and eliminating routine, with the use of erotic materials, masturbation, and devices, may improve sexual response, particularly among women [32]. Some women have experienced success with pelvic floor muscle training (Kegel exercises), a process for strengthening the pubococcygeus and levator ani muscles [33]. With this training, the individual should alternate constriction and release of the muscles of the pelvic floor. These exercises should be done rapidly 10 to 20 times [24].

Steps should also be taken to decrease pain associated with intercourse by changing positions, ensuring full arousal, or practicing biofeedback [32]. Topical lubricants can improve the comfort of sex, especially for those experiencing vaginal dryness, and many over-the-counter products are available [25]. Lubricants add temporary moisture to vaginal tissue, allowing for easier penetration, but these products do not increase blood flow to the genitals and may not improve disorders of desire. Only water- or silicone-based (not oil-based) products should be utilized. Silicone-based lubricants are not absorbed by the skin, resulting in longer efficacy compared to water-based formulations.

However, because these products are not absorbed, they must be washed completely off with soap and water following sexual activity [12].

PSYCHOSOCIAL INTERVENTIONS

Marriage counseling or sex therapy may be required for cases in which sexual dysfunction has been long standing in the relationship [6]. In severe cases, individuals have reported the absence of a sexual physical relationship with their significant other for more than 10 years. Truth, honesty, and openness are essential goals for therapy in order to initiate the healing process. Because the task may seem insurmountable to the couple, encouragement regarding the re-establishment of a healthy relationship will be fundamental [25].

Discussion of the issues related to sexual dysfunction can potentiate an already fragile state. Stress increases relationship friction and can worsen sexual dysfunction; therefore, management of stress is crucial [25]. Stress is subjective in nature, and a patients' self-described stress level should not be discounted. Members of the healthcare team have an important role assisting patients and their partners to modify their appraisals of typical and atypical stressors related to diabetes and complications associated with the disease process. Providing individuals with more effective coping strategies is often necessary [34].

PHARMACOTHERAPY

When education and control of modifiable factors do not result in improvements or resolution, medical treatments will be required [25]. In general, pharmacotherapy is used for male sexual dysfunction, but research into drugs for female sexual dysfunction is ongoing. Prior to the initiation of any therapeutic option, the individual should be mandated to refrain from the use of alcohol and all forms of tobacco. The patient's current medications should also be assessed for the presence of medication that might contribute to sexual dysfunction [23]. If possible, these medications should be eliminated or replaced.

The ability of a man to initiate and maintain an erection is dependent on the presence of nitric oxide and cyclic guanosine monophosphate. Phosphodiesterase-5 enzyme inhibitors used to address erectile dysfunction, including sildenafil, vardenafil, tadalafil, and avanafil, act by increasing nitric oxide and cyclic guanosine monophosphate levels, both of which may be diminished in men with diabetes [23]. These medications are absolutely contraindicated in individuals being treated with nitroglycerine or other nitrate-containing medications due to the potential for severe hypotension and fatal cardiac events [6].

The National Institute for Health and Care Excellence recommends that clinicians consider a phosphodiesterase-5 inhibitor to treat problematic erectile dysfunction in men with type 2 diabetes, initially choosing the drug with the lowest acquisition cost and taking into account any contraindications.

(https://www.guideline.gov/summaries/summary/49931. Last accessed March 7, 2018.)

Level of Evidence: Expert Opinion/Consensus Statement

Phosphodiesterase-5 enzyme inhibitors have also been studied for improvements in sexual arousal and functioning in women, although their use is off-label. To date, these agents have not been shown to be effective in women, a fact that is attributed partially to gender differences in physiologic and psychologic components of sexual response [35]. For women without arousal or desire problems, these agents might be helpful, but additional research is necessary before they can be recommended [35].

Sildenafil

Sildenafil, marketed in the United States as Viagra, is typically given in tablet form in dosages ranging from 20 mg to 100 mg [36; 37]. The usual dose is 50 mg taken one hour (range: 30 minutes to four hours) before sexual activity. Sildenafil acts to increase the effect of nitric oxide by inhibiting phosphodiesterase-5, which is responsible for degradation of cyclic guanosine monophosphate in the corpus cavernosum [36]. When sexual stimulation produces local release of nitric oxide, inhibition of phosphodiesterase-5 by sildenafil causes increased levels of cyclic guanosine monophosphate in the corpus cavernosum, resulting in smooth muscle relaxation and inflow of blood. The medication is only effective in the presence of sexual stimulation. The effect of sildenafil on sexual arousal in women has been studied but is unclear, and data from clinical trials are limited.

The most common adverse reactions are headache and dyspepsia [37]. Other less common side effects include flushing, insomnia, diarrhea, myalgia, epistaxis, dyspnea, abnormal vision (e.g., color changes, light sensitivity, blurred vision), pyrexia, erythema, paresthesia, nasal congestion, and increased liver enzymes [37]. In rare cases, myocardial infarction, hemorrhage, and transient ischemic attack have been reported [36; 37]. If severe reactions or vision or hearing changes develop, the patient should be advised to contact his healthcare provider as soon as possible.

Possible drug-drug interactions can occur with beta-blockers, loop and potassium-sparing diuretics, cytochrome P450 inducers, rifampin, delavirdine, protease inhibitors, hepatic isoenzyme inhibitors, antiretroviral medications, and isosorbide [36]. High-fat meals may reduce absorption, so patients should be advised to take sildenafil on an empty stomach. Grapefruit may increase the drug level while delaying absorption and should be avoided.

Patient teaching for those taking sildenafil should focus on the avoidance of adverse events and safe administration. First, individuals must be cautioned to avoid use of nitrates or advise their primary care or emergency care providers of the use of this medication. Patients should also be aware of the potential cardiac risk with sexual activity, especially in the presence of cardiovascular risk factors. If symptoms such as chest pain, dizziness, or nausea occur during sexual activity, the activity should be halted and a healthcare provider be contacted. Erections lasting greater than four hours and priapism (i.e., painful erection lasting longer than six hours) may occur, and immediate medical attention is required in these cases to prevent permanent penile tissue damage. Finally, education regarding the prevention of sexually transmitted infections is necessary, as sildenafil does not prevent the spread of these diseases.

Vardenafil

Vardenafil (Levitra, Staxyn) is given in an enteric-coated or oral disintegrating tablet taken by mouth as a single dose, as needed, one hour prior to sexual activity [36]. Dosage range is 5–20 mg and based on effectiveness and tolerance, with a maximum of 20 mg daily. The medication should be taken on an empty stomach for maximum efficacy.

Vardenafil acts by increasing cyclic guanosine monophosphate levels, prolonging smooth muscle relaxation, and promoting blood flow into the corpus cavernosum [36]. Potential adverse reactions include headache, dizziness, flushing, decrease or loss of hearing, tinnitus, rhinitis, sinusitis, dyspepsia, nausea, back pain, and flu-like symptoms [37]. A transient decrease in supine blood pressure may also occur. Possible drug-drug interactions have been noted with alpha-blockers, nitrates, antiarrhythmics (e.g., quinidine, procainamide, amiodarone, sotalol), erythromycin, indinavir, itraconazole, ketoconazole, and ritonavir [36]. As with sildenafil, high-fat meals may reduce peak drug levels.

The patient education needs for vardenafil are similar to those outlined for sildenafil. Evaluation of the individual's cardiac risk prior to the initiation of the medication is necessary. Other general topics should include risk of priapism, vision/hearing changes, safe and effective administration practices, and when to contact a healthcare provider.

Tadalafil

Tadalafil, which is sold as Cialis and Adcirca in the United States, is available in enteric-coated tablets. The typical dose is 10 mg daily taken at least 30 minutes prior to sexual activity, which is titrated to a greater dose as needed [36]. Creatinine clearance must be assessed by the healthcare provider prior to initiating the medication. Unlike the other medications, tadalafil may improve erectile function for up to 36 hours after a single dose [37].

As with sildenafil and vardenafil, tadalafil increases cyclic guanosine monophosphate levels, prolongs smooth muscle relaxation, and promotes blood flow into the corpus cavernosum. Adverse reactions may include dizziness, headache, flushing, myalgia, decrease or loss of hearing, nasal congestion, tinnitus, dyspnea, back pain, limb pain, hypertension, and dyspepsia [37]. Tadalafil has been associated with interactions with alpha-blockers, nitrates, erythromycin, itraconazole, ketoconazole, ritonavir, and rifampin [37]. Dosing should be adjusted or the medication discontinued if taken with protease inhibitors, potent CYP3A4 inhibitors, or potent CYP3A4 inducers. Coadministration with nitrates may cause a serious decrease in blood pressure, leading to an increased risk of myocardial infarction or stroke [36]. Patients should be advised to seek immediate medical attention if chest pain develops after taking the medication. Alcohol use may increase the incidence of certain side effects, including headache, dizziness, orthostatic hypotension, and tachycardia; avoidance of alcohol is advised. Grapefruit should also be avoided.

Information regarding the transmission and prevention of sexually transmitted infections should be provided. Additional patient education may focus on appropriate administration, recognition of adverse effects, and times to contact a healthcare provider.

Avanafil

Avanafil is a second-generation phosphodiesterase-5 enzyme inhibitor that was approved for use in April 2012 [51]. The usual initial dose is 100 mg, taken 15 minutes before sexual activity [37]. The recommended dose with concomitant alpha blocker or CYP34A inhibitor use is 50 mg [37]. Although avanafil does potentiate nitroglycerin-induced hypotension, the effects of the agent on heart rate and blood pressure are less than those of the first-generation phosphodiesterase-5 enzyme inhibitors. Nonetheless, its use is not recommended in patients taking nitrates [37]. The side effects of avanafil are similar to the effects observed with other erectile dysfunction drugs, with headaches and flushing being the most common. Grapefruit potentiates the effect and toxicity of avanafil, and alcohol should also be avoided. Avanafil may be taken with food, including foods with fat. Studies have shown that this agent is effective in men with erectile dysfunction, including those with diabetes, and that it has a low rate of discontinuation (2.8%) due to adverse effects even at the maximum dose of 200 mg, which most men eventually progressed to in clinical trials [52; 53].

Agents for Female Sexual Dysfunction

In 2009, flibanserin was submitted for approval by the U.S. Food and Drug Administration (FDA) for the treatment of hypoactive sexual desire disorder in women. This medication acts by blocking serotonin, which has been shown to inhibit sexual function. Post hoc analysis of data from studies of flibanserin's antidepressant properties found that the agent significantly improved self-reported sexual function, although this was not replicated in later direct studies [38; 39]. The difference could be

partly attributed to the different populations studied (i.e., the general public compared to women with major depressive disorder). In 2010, the FDA's Reproductive Health Drugs Advisory Committee voted that flibanserin was not significantly more effective than placebo and that the potential benefits did not outweigh the risk of adverse events [39]. In 2013, the FDA again denied approval of flibanserin after the pharmaceutical company resubmitted a new drug application with data from 14 additional clinical trials; the same reasons for denial were cited [54]. However, after additional data were provided, in 2015 the FDA approved flibanserin to treat hypoactive sexual desire disorder in premenopausal women [55]. The drug includes a boxed warning due to an increased risk for severe hypotension and syncope when taken along with alcohol. One 100-mg tablet is taken daily at bedtime [37].

Androgen Therapy

An estimated 30% of men with erectile dysfunction fail to respond to first-line drugs, and low testosterone levels maybe a contributing factor [41]. Androgen therapy, usually in the form of testosterone therapy, may be used in the treatment of male and female dysfunction, although its use in women is controversial and off-label [25; 32]. Benefits have been noted for women who are postmenopausal and not taking estrogen replacement [40]. Older age is associated with lower levels of testosterone.

Testosterone replacement, often in the form of a transdermal gel or a patch, may be utilized, with the goal of increasing desire and stimulation. Transdermal testosterone is a 1% gel in 25 mg or 50 mg per unit dose packaged in a 1.25 gram per non-aerosol metered pump or a 1.62% gel in 20.25 mg or 40.5 mg per unit dose [36]. It is applied to the shoulder or upper arm, where it can be covered by a short-sleeved shirt, being careful to use gloves for application. The skin should be clean, dry, and intact. Gel is typically applied in the morning. The maximum dosages of the 1% and 1.62% gels are 100 mg and 81 mg, respectively [37]. The patch is available in 2-mg and 4-mg strengths, but the initial dose is usually 4 mg (as a single patch) [37]. The dose is then adjusted according to serum testosterone levels. The patch should be placed on the clean, dry skin of the back, abdomen, upper arm, or thigh at night, with the site rotated to avoid irritation [37]. Other preparations are available.

In men, possible adverse reactions to topical testosterone include stroke, asthenia, depression, headache, gastrointestinal bleeding, prostatitis, prostate abnormalities, urinary tract infections, cholestatic hepatitis, reversible jaundice, hypernatremia, hyperkalemia, hypercalcemia, hyperphosphatemia, hypercholesterolemia, pruritus, acne, allergic contact dermatitis, gynecomastia, breast tenderness, and flu-like symptoms [36]. In women, side effects include decreased HDL levels, acne, hirsutism, clitorimegaly, and voice deepening [32].

Concurrent use of topical testosterone and corticosteroids may increase edema, and use with insulin may alter insulin dosage requirements [36]. Adverse interactions have also been noted with oral anticoagulants. Oxyphenbutazone levels may increase when utilized in combination with testosterone gel or patch, and propranolol clearance may increase when utilized in combination with testosterone gel or patch [36]. When applying the gel, it is important to prime the pump by pumping three times and discarding the gel prior to the first use. For the best results, patients should refrain from bathing or swimming for five hours after application.

When used to treat sexual dysfunction in individuals with diabetes, topical testosterone may decrease glucose levels and alter symptoms of hypoglycemia. Patients should be advised to report this and other possible side effects, including priapism, nausea and vomiting, changes in skin color, ankle edema, or sudden weight gain, to their care provider. In addition, patients' female partners should be monitored for signs of virilization, such as acne or changes in body hair distribution.

Estrogen Replacement

Estrogen plays an important role in normal female sexual functioning by maintaining the integrity of the female genital tissue, and low estrogen levels can create an excessively sensitive vaginal environment, whereby touch that was once pleasurable becomes annoying, painful, or irritating [12]. Low levels of serum estrogen can also cause vaginal wall atrophy, thinning of the vaginal mucosa, and an elevated pH level, which leads to changes in the vaginal flora and increases the risk for vaginal and urinary tract infections [25]. The major cause of low estrogen levels is menopause, and most women will experience a change in sexual function during this period [20]. Sexual complaints have been associated with serum estrogen levels less than 50 pg/mL.

Estrogen hormone replacement therapy has been used for years to treat symptoms of menopause, but more recent research has indicated that its use may place women at increased risk for stroke and certain cancers [42; 43]. However, estrogen replacement can improve sexual functioning and satisfaction, including clitoral sensitivity, increased libido, and improvements in urogenital atrophy [44]. Estrogen may be taken alone or in conjunction with progesterone or testosterone. It is important to weigh the possible benefits against the risks of hormone replacement.

Intracavernosal or Intraurethral Alprostadil

For patients who do not respond to the first-line therapies of lifestyle change, pharmacotherapy, and/or testosterone replacement, intracavernosal or intraurethral alprostadil may be effective in improving erectile functioning. This second-line therapy consists of the injection of alprostadil, a prostaglandin, into the corpora cavernosa or the insertion of a suppository containing alprostadil into the urethra. The active ingredient is absorbed in to the penile tissue, facilitating smooth muscle relaxation and aiding in tumescence, an effect that lasts approximately 30 to 60 minutes [18]. The dosage should be individualized according to response to dose, etiology of erectile dysfunction, and agent being used [37]. After the initial appointment establishes the correct dose, the patient may self-administer alprostadil 10 to 15 minutes prior to sexual activity up to three times per week, with at least 24 hours between doses. If the medication is administered intraurethrally, the patient should be advised to urinate prior to insertion.

Oral stimulation should be avoided while using this medication and administration method. If the patient's female partner experiences vaginal bleeding or itching or if she may be pregnant, barrier contraception (e.g., a condom) should be used during intercourse [25].

Patients tend to prefer the intracavernosal method over the intraurethral administration as it is better tolerated and more effective [29]. Common side effects with intraurethral administration of alprostadil include penile pain, urethral burning or bleeding, dizziness, and testicular pain, while the intracavernosal administration is associated with penile pain, prolonged erection, injection site hematoma, and headache [29; 37]. With either medication, prolonged erections and priapism are serious concerns. If a rigid erection lasts longer than four hours, the patient should be instructed to contact his healthcare provider.

VACUUM PUMP DEVICES

Vacuum pump devices or constrictors are a viable alternative to medication therapy or medication failure. They are non-invasive, have few side effects, and are generally well tolerated [7]. To use, the vacuum tube is lubricated and placed over the penis, with a constriction band situated over the end. A battery- or hand-operated pump is initiated, and a vacuum is produced. Sitting back or lying down may improve the tightness of the seal. For patients with larger abdomens who are unable to visualize the pelvic area, assistance applying the pump may be necessary. When significant tumescence is produced, the band is moved to the base of

the penis, the vacuum is released, and the cylinder is removed. The band can safely remain in place for 30 minutes. These devices do not produce a full erection, and the base will remain flaccid; however, sufficient rigidity is obtained for sexual activity in 80% to 90% of cases [18].

Thorough education regarding appropriate application and use of vacuum devices is essential for successful outcomes and prevention of injury. Patients should be encouraged to practice the application process to gain confidence and to use sufficient lubrication to avoid friction injury. It may be necessary for patients to remove hair from their pubic area in order to obtain the tightest seal possible.

PROSTHESES

The implantation of an inflatable penile prosthesis is a surgical option for the treatment of impotence in men who have not responded to first- or second-line therapies [7]. The prostheses are implanted by a urologist as a pair and are made primarily of a silicone polymer. The three main types of prostheses are malleable, inflatable, and mechanical [18]. The cost varies significantly based on the type of prosthesis selected.

After it is implanted, the individual or his significant other may inflate the prosthesis by pressing on the pump, which transfers fluid from the reservoir to the cylinders within the penis. The implant may be deflated after sexual activity by pressing on the deflation valve at the base of the device. This will cause the device to return the fluid from the implant to the reservoir [25].

Patients should be instructed to watch for signs and symptoms of infection and to alert their healthcare provider of any discharge or seepage from the tip of the penis. In addition, patients should be aware of potential signs of complications, such as mechanical failure, extrusion of the device, pain, and bruising. These discoveries should be communicated to a primary care provider without delay [18].

PSYCHOSOCIAL IMPACT OF SEXUAL DYSFUNCTION

Sexual intimacy is a taboo subject in many cultures, and men and women may feel uncomfortable discussing it, even with healthcare providers [25]. In addition, some patients are less engaged in discussing health issues, particularly conditions like diabetes, depression, or sexual dysfunction. However, if left untreated, diabetes and sexual dysfunction can have significant negative ramifications on mental and physical health. This is an important consideration, as psychologic stress can exacerbate existing issues, including sexual dysfunction, leading to a cycle of despair and dysfunction. In one study, men and women with diabetes and sexual dysfunction reported more depressive symptoms than those without sexual dysfunction [45]. Emotional factors that may interfere with sexual arousal, causing or worsening sexual dysfunction, include [46]:

- Poor communication or conflict with a partner
- Depression
- Anxiety
- Stress
- Fatigue

Sexual and emotional issues do not just impact the individual. They can impair personal relationships and generate challenges of trust, intimacy, and closeness. Patients or partners may experience feelings of distance or withdrawal emotionally as well as physically. Partners of patients with diabetes and sexual dysfunction may not experience enjoyment or may dread being unable to bring their partner to orgasm. This can lead to issues of negative self-worth, fears of abandonment or betrayal, and loss of intimacy [25]. By presenting clear information regarding how sexual health can be impacted by diabetes, stress, cardiovascular issues, and low hormone levels, healthcare professionals can help patients successfully manage this significant personal issue [46].

Sexuality and virility are important aspects of an individual's self-perception and beliefs about one's role in society. This can be compounded in cultures that highly value youth, masculinity/femininity, and/or virility/fertility (including many Western cultures). Healthcare professionals may assess patients for impaired self-esteem with interview techniques and quality of life questionnaires [25].

Individuals with diabetes have an increased risk of depression compared to the general public. Approximately 10% to 15% of individuals with diabetes meet the criteria for comorbid depression prior to being diagnosed with sexual dysfunction [47]. In women with diabetes, in particular, depression is a significant predictor of sexual dysfunction, as is the quality of the partner relationship [20; 45]. To a lesser extent, depression and psychologic problems impair diabetic men's sexuality as well [48]. Symptoms of depression include [18]:

- Apathy and self-imposed social isolation
- An inability to perform activities of daily living
- Disruption of sleep patterns
- Memory impairment
- Mood swings
- Frustration
- Despair/hopelessness
- Suicidal ideation

In addition to the organic impact of depression on sexual arousal and function, the medications used to treat depression can also cause impaired sexual response [20; 49]. Antidepressants associated with the greatest rates of sexual side effects include selective serotonin reuptake inhibitors (e.g., paroxetine, sertraline), serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine), tricyclic antidepressants (e.g., amitriptyline, clomipramine), and monoamine oxidase inhibitors (e.g., isocarboxazid) [50]. If possible, antidepressants with fewer sexual side effects, such as bupropion, should be selected for patients with diabetes.

Clinical guidelines for the treatment of depression have been established and may be applied, with few alterations, to patients with diabetes diagnosed with major depressive disorder. However, the most effective approach and treatment for individuals with diabetes and minor subclinical depression (dysthymia) are less clear, although it should be addressed fully before it advances to major depression [47]. In many cases, these patients will benefit from referral to a mental health expert for psychotherapy, support groups, and/or pharmacologic intervention.

Some individuals with diabetes will have a decreased interest in sexual intimacy due to feelings of constant fatigue. This may be the result of physical or psychologic factors (or a combination). If fatigue occurs secondary to depression, antidepressant treatment should improve the symptom.

Often, patients experiencing sexual dysfunction may be angry, anxious, or self-loathing. These types of feelings make it difficult for the individual to clearly communicate with his or her significant other. If relationship problems are present, referral to a counselor, therapist, or psychologist for individual and couple's counseling is indicated. The couple may also be provided with techniques to improve their sexual relationship, including [25]:

- Redefining pleasure in the relationship
- Mood-setting techniques
- Cuddling
- Scheduled intimacy
- Erotic media

Providing education regarding medications or alternate forms of counseling has been proven beneficial for the management of depression and/or anxiety, and this should result in improvements in sexual function [25]. Individuals should be advised to contact their healthcare provider if they experience depressed mood or anxiety for more than two weeks [46].

Patient teaching for successful understanding and management of psychologic distress stemming from sexual dysfunction should include the following key points [25]:

- A good sexual relationship requires more than a pill.
- Open communication is imperative.
- Relationship building and bonding may be required.
- Counseling regarding individual expectations may be needed.
- A positive and encouraging attitude is essential for both individuals.
- Keep the end result in the forefront of the discussion.
- Encourage alternate ways for expression of pleasure.

CASE STUDIES

CASE STUDY 1

Patient K is an active white man, 75 years of age, presenting to his physician's office for his three-month diabetes evaluation. He has a positive history of diabetes for the past 20 years, and a 28-year history of hypertension and hypercholesterolemia. Past surgical history is positive for bilateral knee replacement 10 years ago, two angioplasties with stents within the past five years, and non-emergent coronary artery bypass surgery two years ago. He continues to smoke despite multiple attempts to stop and strong advisement by all providers involved in his care.

Currently, his blood pressure is 152/84 mm Hg, and his pulse is 78 beats per minute, regular rate and rhythm. He is 5 feet 10 inches tall and weighs 252 pounds. Laboratory analysis reveals the following results:

- HbA_{1c}: 8.0% (normal range: 4.6% to 7.1%)
- Total cholesterol: 178 mg/dL (normal range: <200 mg/dL)
- LDL: 108 mg/dL (normal range: <130 mg/dL)
- HDL: 43 mg/dL (normal range: 30–75 mg/dL)
- Triglycerides: 188 mg/dL (normal range: 40–170 mg/dL)
- BUN: 13 mg/dL (normal range: 6–23 mg/dL)
- Creatinine: 1.2 mg/dL (normal range: 0.6–1.5 mg/dL)
- Potassium: 4.3 mEq/L (normal range: <8 mEq/L)
- Sodium: 38 mEq/L (normal range: 10–40 mEq/L)

The patient's current medications include:

- Metformin: 2000 mg daily in two divided doses
- Glimepiride: 4 mg each morning
- Pioglitazone: 30 mg each morning
- Digoxin: 0.5 mg daily
- Atenolol: 50 mg daily
- Ezetimibe: 10 mg daily
- Aspirin: 81 mg daily

Patient K's wife of 46 years, Mrs. K, accompanies him to the visit. While reviewing the results of the patient's laboratory tests and blood glucose results, Dr. G detects tension between the patient and his wife. When his wife attempts to ask a question regarding Patient K's blood glucose levels, he snaps at her to leave him alone and stop nagging. Mrs. K leaves the office in tears. Patient K apologizes to Dr. G for the outburst and states that he has not been sleeping well. When asked how often this was happening, Patient K states only a few times a month.

Over the next 18 months, Patient K and his wife continue to attend his scheduled appoints without fail. The tension in the couple's relationship continues, but Dr. G feels that he should not pry.

However, at the next visit Dr. G notes that Patient K is more withdrawn than usual and is avoiding all eye contact with Mrs. K as she sits on a stool in the corner of the room rather than in the seat next to the patient, as she usually does. Furthermore, Mrs. K is not engaging in any of the comforting gestures he has come to expect from her (e.g., rubbing Patient K's back and hand).

Dr. G reviews Patient K's medical record and notes a weight gain of 20 pounds and an increase in his HbA_{1c} (from 8.0% to 9.2%). Even more tension and perceived friction is evident between the patient and his wife. When Dr. G asks about Patient K's activities, the only response is a shrug from the patient's shoulders and a roll of the eyes from Mrs. K. Dr. G can no longer ignore these behaviors. He has known the couple for more than 20 years and has noted a dramatic change just in the last two years. He closes Patient K's chart and tells the couple what he has been witnessing.

Both the patient and his wife begin to cry. Patient K states that it is a personal problem they are handling, and he is uncomfortable talking about it. Dr. G asks Mrs. K to have a seat in the waiting room. After the wife has left the room, Dr. G asks for details, reassuring Patient K that everything they discuss will be confidential and that he will not be judged. Eventually, Patient K confides that he has been a poor husband and does not know how to make his wife happy. Dr. G asks if either of them is seeing other people. Patient K responds that he is not, and while he does not think Mrs. K is, he would not blame her if she was. He also states that he is not "a real man." Dr. G presses the patient regarding what has made him feel this way. After several moments, Patient K admits that he has been unable to achieve an erection for the last 20 months, despite a previously healthy sex life and continuing to find his wife attractive.

Dr. G assures the patient that many men experience erectile dysfunction and that, with treatment, he should be able to experience a healthy sex life with his wife once again. Dr. G and Patient K discuss the many treatment options available, addressing benefits and potential drawbacks of each. In addition, Dr. G emphasizes the importance of lifestyle changes in improving sexual functioning, encouraging the patient once again to quit smoking and lose weight. Due to Patient K's reluctance to add another medication to his regimen, he decides to try a vacuum pump device. The patient and his wife meet with an educator for information regarding safe application of the device and conditions requiring healthcare provider notification. Although the couple is initially timid and appears embarrassed, the educator puts them at ease and the education session progresses. Patient and Mrs. K are encouraged to go home and practice.

After six months, Patient K returns to Dr. G's office with his wife. Unfortunately, even with significant practice, the couple remains unable to achieve a fulfilling sex life. Dr. G assesses the patient's testosterone level to determine if this is a contributing factor. The result is 205 pg/mL (normal range: 44–244 pg/mL), effectively ruling out a hormonal etiology. Although the vacuum pump device allows for a functional sexual relationship, they miss the spontaneity they once enjoyed. As a result, Patient K expresses interest in investigating the available pharmacologic options.

Following an in-depth discussion of each agent, Patient K ultimately decides to utilize sildenafil. Dr. G provides the couple with education regarding the drug interactions and possible adverse effects, taking time to answer any questions and to emphasize the continued importance of lifestyle interventions. At the end of the visit, Patient K and his wife feel comfortable with the new arrangement and commit to calling if any further questions arise or if adverse effects are experienced.

In six months, Patient K returns to his primary care provider for follow-up. When Dr. G enters the examination room, he is met by a more confident appearing patient. He is calm, at ease, and sitting with a relaxed smile on his face. Patient K tells Dr. G that his relationship with Mrs. K is improving, and they have been able to engage in sexual activity regularly. In addition, Patient K has lost 25 pounds and has cut back on his smoking. His HbA_{1c} level is normal on medications, and he seems very happy.

CASE STUDY 2

Patient N is a postmenopausal Latina woman, 59 years of age. She has a history of depression (2 years), fibromyalgia (11 years), diabetes (12 years), hypertension (3 years), osteoarthritis (6 years), and hypercholesterolemia (6 years). She has two adult children, both born by cesarean delivery. Her past surgical history is positive for bilateral knee replacement (nine years ago), cholecystectomy (20 years ago), and appendectomy (47 years ago). She has a family history of diabetes, cardiovascular disease, hypertension, stroke, and prostate and breast cancer.

Patient N uses alcohol (beer, wine, and liquor) occasionally and socially, consuming approximately three drinks per week or less. She has no history of tobacco use. Her diet consists primarily of convenience foods due to a lack of desire to cook and availability of the items. She has gained 20 pounds over the past year, and she denies engaging in any form of exercise.

At her routine gynecologic visit, Patient N is free of initial complaints. Although she has a strong professional relationship with her gynecologist, Patient N presents with a flat affect and withdrawn behavior. Dr. J questions the patient regarding her disposition, but she dismisses the behavior as "nothing." Dr. J continues to pursue the cause of the mood change and inquires regarding Patient N's relationship with her husband of 37 years. Patient N begins crying and states that she has been separated from her husband for the past five months, a fact that is all her own fault.

Dr. J comforts Patient N and asks her to describe what happened. At first, the patient is reluctant to discuss the problems, but Dr. J reassures Patient N that many couples experience problems and it is nothing to be ashamed of. He lets the patient know that he would like to help her. While continuing crying, Patient N claims she is no longer desirable to her husband. She admits to a noticeable change in her attitude toward sexual intimacy, pain with intercourse, and vaginal dryness, all of which have occurred gradually over the past six years. Patient N states that she still loves her husband and finds him attractive, but no longer knows how to demonstrate that love.

Dr. J assures the patient that this is a common complaint for many women, especially those who are postmenopausal and/or diabetic. Dr. J tells Patient N that when women progress through menopause, their estrogen levels decrease, and estrogen plays an important role in sexual health and desire in women. Furthermore, Dr. J educates the patient regarding the neuropathic aspect of diabetes and sexual function.

Initially, Dr. J advises Patient N to exercise and adopt a healthier diet to promote better glycemic management and weight loss. Patient N agrees to try this approach and to contact her primary care provider for assistance. Dr. J also encourages her to inquire about possible adjustment of her depression medication during this period in her life, which the patient also agrees to.

Patient N feels encouraged to talk with her husband regarding their situation and determine if the relationship was something they wanted to salvage or dissolve. Although she believes she already knows the answer and is confident to take the first step, she is unsure of what to say. Dr. J encourages the patient to engage in a frank conversation regarding what she is going through and determine if her husband is willing to attend counseling.

Patient N returns for a follow-up visit in six months, and Dr. J notes a slightly brighter affect to the patient's demeanor. Dr. J evaluates Patient N's progress and finds that she and her husband are meeting with a therapist to attempt to overcome their issues. During therapy, Mr. N stated that he felt responsible for Patient N's lack of sexual desire. Although Patient N and her husband have started to work past some of their issues, pain with intercourse and persistent vaginal dryness continue to be problems. Dr. J suggests utilizing an over-the-counter, silicone- or water-based lubricant. He cautions the couple to avoid oil-based products and to be cautious with application due to the potential risk for falls. Enhancing the sensual experience (through erotic massage or viewing erotic materials) is also suggested.

Patient N continues to follow-up with Dr. J for the next six months and reports progression in her sexual relationship with her husband. She states that while things are not perfect, she and her husband are committed to finding their optimal comfort level with each other.

CONCLUSION

Unfortunately, sexual dysfunction is common among individuals living with diabetes. The greatest defenses are controlling blood glucose, addressing cardiac risk factors, establishing a healthy blood pressure level, and maintaining an open and honest relationship [6]. However, in many cases, more intensive intervention, in the form of psychotherapy, pharmacotherapy, or surgery, may be necessary. The most important points for healthcare providers are to ensure that patients feel comfortable and secure in discussing sexual issues and to provide clear and accurate information regarding diabetes, sexual functioning, and available treatment options.

FACULTY BIOGRAPHY

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 1000 hours of education to diabetes patients, Ms. Thompson earned her certification as a diabetes educator in 2003. Since 2006, Ms. Thompson has been the Director of Diabetes Healthways at Munroe Regional Medical Center in Ocala, Florida. As the director of the diabetes center, Ms. Thompson is responsible for the hospital diabetes clinicians, hospital wound care clinicians, and out-patient education program. 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 26 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 see 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.

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