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## DIABETES ASSOCIATED COMPLICATED DISORDERS AND ITS TREATMENT A REVIEW ARTICLE

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Article History	Abstract
Received on: 11-05-2023	Type 2 diabetes mellitus is increasingly prevalent in the worldwide and is associated with significant morbidity, mortality, and rising health care costs. Microvascular and, to a lesser extent, macrovascular complications are recognized to result from uncontrolled hyperglycemia. However, intensive therapy to achieve normal glucose levels is not without risk, as demonstrated by increased rates of hypoglycemia, weight gain, and all-cause mortality rates in the intensive treatment arm of the ACCORD trial. In addition, observational studies indicate that the presence of diabetes increases the risk of other comorbidities such as fracture and certain cancers, and treatment choice may affect risk. Thus, in an effort to maintain glucose control, the clinician encounters a complex interplay of primary disease management while simultaneously seeking to avoid complications associated with glucose lowering. The chronic nature of diabetes management, efficacy must be balanced against side effects to achieve a tolerable long-term regimen. The goal of this concept is to identify complications of non-insulin treatment of diabetes. The major classes of medication should be reviewed with special attention given to patient considerations, mechanism of action, effect on weight, and cardiovascular outcomes, and additional class-specific side effects including effects on bone. In addition, effects on $\beta$ -cell function are rectified. It is possible to identify diabetes mellitus risk years or decades in advance on the basis of numerous personal, historic, and laboratory measures and user-friendly clinical decision-support tool to estimate absolute risk for individuals. The patient families, communities, and health organizations should encourage healthy eating and physical activity and should focus the most intensive diabetes mellitus prevention efforts on those at highest risk for progression to diabetes mellitus.
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### Introduction

Diabetes and its complications are a major cause of morbidity and mortality in the United States and contribute substantially to health care costs. Although we have already seen an epidemic of diabetes in the United States over the past 2 decades, we can expect a continued rise in the incidence of diabetes as the population ages, a continued increase in adult obesity rates, and an increase in the population of minority groups that are at high risk for diabetes. In addition, rising childhood obesity rates and the increasing diagnosis of type 2 among children and young adults have become an increasingly serious health crisis, which will result in more people having

and managing diabetes for most of their lives [1-5]. Diabetes is widely recognized as an emerging epidemic that has a cumulative impact on almost every country, age group, and economy across the world. According to the International Diabetes Federation, in 2015, approximately 415 million people were suffering from diabetes worldwide, and this number is expected to exceed 640 million by the year 2040. It is estimated that half of patients with diabetes are unaware of their disease and are thus more prone to developing diabetic complications. However, the cost of dealing with diabetes can be unaffordable in terms of money spent and lives lost. In 2015, approximately 5.0 million deaths were attributed to diabetes, albeit in the same year, more than 12% of the global health expenditure was dedicated to coping with the disease and its complications.

Diabetes complications are common among patients with type 1 or type 2 diabetes but, at the same time, are responsible for significant morbidity and mortality. The chronic complications of diabetes are broadly divided into microvascular and macrovascular, with the former having much higher prevalence than the latter. Microvascular complications include

neuropathy, nephropathy, and retinopathy, while macrovascular complications consist of cardiovascular disease, stroke, and peripheral artery disease (PAD). Diabetic foot syndrome has been defined as the presence of foot ulcer associated with neuropathy, PAD, and infection, and it is a major cause of lower limb amputation. Finally, there are other complications of diabetes that cannot be included in the two aforementioned categories such as dental disease, reduced resistance to infections, and birth complications among women with gestational diabetes [6-9]. The present special issue has been devoted to showcase a broad spectrum of research and review papers addressing recent fundamental advances in our understanding of diabetic complications. It includes 12 articles in total, which cover 5 thematic areas: (a) epidemiology and pathogenesis of diabetic complications, (b) microvascular complications, (c) macrovascular complications, (d) miscellaneous complications, and (e) treatment options.

### Diagnosis of diabetes mellitus

Healthcare providers diagnose diabetes by checking glucose level in a blood test. Three tests can measure blood glucose level:

- **Fasting blood glucose test:** For this test, don't eat or drink anything except water (fast) for at least eight hours before the test. As food can greatly affect blood sugar, this test allows provider to see your baseline blood sugar.
- **Random blood glucose test:** Random" means that you can get this test at any time.
- **A1c:** This test, also called HbA1C or glycated hemoglobin test, provides average blood glucose level over the past two to three months.

### Pathophysiology of Diabetes mellitus

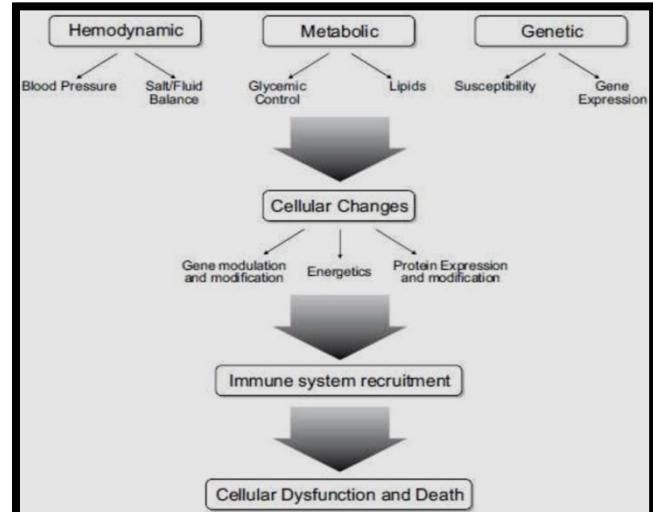
Diabetes mellitus is a group of chronic metabolic conditions, all of which are characterized by elevated blood glucose levels resulting from the body's inability to produce insulin or resistance to insulin action, or both [10-11].

This group of conditions can be subdivided into 4 clinically distinct types:

1. type 1, which results from autoimmune beta-cell destruction in the pancreas and is characterized by a complete lack of insulin production;
2. type 2, which develops when there is an abnormal increased resistance to the action of insulin and the body cannot produce enough insulin to overcome the resistance;
3. gestational diabetes, which is a form of glucose intolerance that affects some women during pregnancy; and
4. a group of other types of diabetes caused by specific genetic defects of beta-cell function or insulin action, diseases of the pancreas, or drugs or chemicals.

Type 1 diabetes accounts for 5% to 10% of all cases of diabetes. Its risk factors include autoimmune, genetic, and environmental factors. To date, there are no known ways to prevent type 1 diabetes. Type 2 diabetes accounts for 90% to 95% of all diagnosed diabetes cases. This form of diabetes generally begins as insulin resistance and, because the body is unable to produce enough insulin to address the resistance, the pancreas may reduce the production of insulin or eventually stop producing it. Minority women, women who are obese,

women with a family history of diabetes, and women who have had gestational diabetes in a previous pregnancy are at higher risk than other women for developing gestational diabetes. Strict glycemic control and management of women with gestational diabetes is necessary to prevent birth complications in the developing infant. Women who have had gestational diabetes have a 20% to 50% increased risk for developing type 2 diabetes later in life [12-16].



### Risk Factors

Although the pathogenesis of diabetes is complex, a number of factors that increase the risk for the disease have been identified. Risk factors for type 1 diabetes include family history, race (with whites at higher risk than other racial or ethnic groups), and certain viral infections during childhood. Risk factors for type 2 diabetes are more diverse; some are modifiable, and others are not. Non-modifiable risk factors for type 2 diabetes include age, race or ethnicity, family history (genetic predisposition), history of gestational diabetes, and low birth weight. Diabetes incidence and prevalence increases with age. In 2005, the Centers for Disease Control and Prevention reported that the prevalence of diabetes among people aged 20 years or older was 20.6 million (9.6% of the people in that age group), and the prevalence of diabetes increased with age (10.3 million people aged 60 years or older, or 20.9% of those in that age group, had diabetes).

African Americans are more likely to develop diabetes than whites. In addition, for Native Americans, the rates of diagnosed diabetes range from 5% to 50% in different tribes and population groups. Little difference exists by sex. Genetic factors also play a role, but nongenetic or lifestyle risk factors (such as diet and physical activity) appear to be the primary culprits. Modifiable or lifestyle risk factors include increased body mass index (BMI), physical inactivity, poor nutrition, hypertension, smoking, and alcohol use, among others. Increased BMI is consistently shown to be one of the strongest risk factors for development of diabetes. In addition, distribution of body fat,<sup>14</sup> and specifically an increased waist-to-hip ratio, increase a person's risk for diabetes. Consistent findings from various studies show that lower levels of physical activity increase a person's risk for diabetes. A recent review of 10 prospective cohort studies investigating moderate-intensity physical activity and diabetes provides evidence that people who achieve recommended levels of even moderate activity are

about 30% less likely to develop diabetes than their inactive counterparts. Total caloric intake, as well as specific components of diet such as refined carbohydrates and fats, have been linked to diabetes development. Moderate alcohol use may reduce the risk for developing diabetes, but smoking has been shown to be an independent risk factor for diabetes. Psychosocial factors such as depression, increased stress, lower social support, and poor mental health status also are associated with an increased risk for the development of diabetes [17-21]. Recently, adverse housing conditions were found to be independently associated with the development of self-reported diabetes, although the mechanism by which housing conditions exert their risk is still unknown.

### Mortality

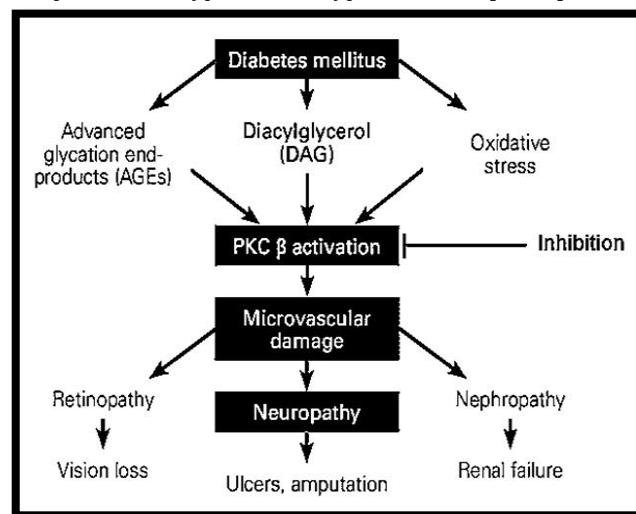
In 2002, diabetes was the sixth leading cause of death, with 73,249 death certificates listing diabetes as the underlying cause of death and an additional 224,092 death certificates listing diabetes as a contributing cause of death. Diabetes is likely to be underreported as a cause of death due to the many complications associated with diabetes that ultimately cause death. Overall, the risk of death among people with diabetes is almost twice that of people of similar age who do not have diabetes. Duration of diabetes also is an important determinant of mortality; younger age-of-onset groups (<45 years of age) have an increased risk of premature death. From death certificate data, it appears that age-adjusted death rates for African Americans and Hispanic Americans are similar to the rates of whites. There is general agreement about the distribution of causes of death in type 2 diabetes. Two thirds of people with diabetes die of heart disease and stroke. The risk for cardiovascular disease mortality is 2 to 4 times higher in people with diabetes than in people who do not have diabetes. There are several risk factors that increase the risk for dying in people with diabetes. In a large intervention trial, men with diabetes were more likely to die as a result of cardiovascular disease when they had the conventional risk factors of elevated serum cholesterol, elevated systolic blood pressure, and cigarette smoking. In recent studies, "tight control" of elevated blood pressure in type 2 diabetes reduced deaths related to diabetes by 32% compared with less tight control [22-29].

### Diabetic Complications

Diabetes can affect many different organ systems in the body and, over time, can lead to serious complications. Complications from diabetes can be classified as microvascular or macrovascular. Microvascular complications include nervous system damage (neuropathy), renal system damage (nephropathy) and eye damage (retinopathy).<sup>1</sup> Macrovascular complications include cardiovascular disease, stroke, and peripheral vascular disease. Peripheral vascular disease may lead to bruises or injuries that do not heal, gangrene, and, ultimately, amputation.

The data from the 1999–2004 NHANES indicate that the prevalence of microvascular complications chronic kidney disease (defined as microalbuminuria), foot problems (defined as foot/toe amputation, foot lesion, or numbness), and eye damage (defined as being told that diabetes had affected the eyes or had retinopathy) are much higher than the prevalence of macrovascular complications (heart attack, chest pain, coronary heart disease, congestive heart failure, and stroke).

Complications can be either episodic (eg, foot ulcers or infections) that can be treated and recur numerous times or progressive (eg, nephropathy), which usually begin relatively mildly, but over time result in further damage to the organ and greater loss of functionality that is generally irreversible. Other complications include dental disease, reduced resistance to infections such as influenza and pneumonia, and macrosomia and other birth complications among pregnant women with diabetes. Although the types of complications are similar for type 1 and type 2 diabetes patients, the frequency or timing of occurrence can vary. The types and prevalence of the most common diabetes complications are discussed further in more detail with specific attention to differences between complications of type 1 versus type 2 diabetes [30-33].



### Heart Disease and Stroke

Cardiovascular disease causes up to 65% of all deaths in people with diabetes [31]. Ischemic heart disease and stroke account for the greatest proportion of morbidity associated with diabetes. In addition, as described above, mortality rates due to heart disease are 2 to 4 times higher among people with diabetes compared with those without diabetes. People with diabetes also are 2 to 4 times more likely to develop stroke than people without diabetes. More than 70% of people with diabetes have high blood pressure or are being treated with medications for hypertension. The role of hyperglycemia in cardiovascular complications among persons with diabetes is not clear.

Risk factors for cardiovascular disease among people with diabetes are similar to those for people without diabetes and include hypertension, hypercholesterolemia, and smoking. It appears, however, that the presence of even one of these risk factors leads to poorer outcomes among people with diabetes compared with those without diabetes.<sup>28</sup> Data on trends in cardiovascular disease complications associated with diabetes are available from the 1950s to 2003 for different populations, and overall these data indicate that there have been large and significant decreases in the incidence of cardiovascular complications among people with diabetes over time. The greatest decreases appear to have occurred during the 1980s and 1990s and coincide with significant advances in medicines to control glycemic levels as well as medicines to control blood pressure and blood cholesterol levels.

### **Peripheral Arterial Disease**

Peripheral arterial disease (PAD, also referred to as peripheral vascular disease [PVD]), is caused by the narrowing of blood vessels that carry blood to the arms, legs, stomach, and kidneys. In people with diabetes, the risk for PAD is increased by age, duration of diabetes, and presence of neuropathy. Other factors associated with cardiovascular disease, such as C-reactive protein levels and homocysteine levels, also are associated with an increased risk for PAD. Peripheral arterial disease is characterized by 2 types of symptoms: intermittent claudication (or the intermittent pain, ache, or discomfort that may occur during exercise or walking but resolves with rest) and pain at rest (which is caused by ischemia in the limb, indicating inadequate blood flow to the affected limb). Data on PAD trends come from hospital discharge data from the National Center for Health Statistics and indicate that the hospital discharge rates for PAD as the primary diagnosis have decreased steadily since 1996. The age-adjusted hospital discharge rate for PAD peaked at 7.8 per 1,000 people with diabetes in 1996 and was down to 3.3 per 1,000 people with diabetes in 2003.

### **Retinopathy (Blindness)**

Diabetic retinopathy is the most common microvascular complication among people with diabetes and results in more than 10,000 new cases of blindness per year. In addition, retinopathy is associated with prolonged hyperglycemia, it is slow to develop, and there is some evidence that it can begin to develop as early as 7 years before clinical diagnosis of type 2 diabetes. The age-adjusted prevalence of visual impairment decreased from 23.7 per 100 people with diabetes in 1997 to approximately 17.7 per 100 people with diabetes in 2005. The prevalence of visual impairment among people with diabetes increases with age. In 2005, 27% of adults with diabetes who were 75 years of age or older reported some degree of visual impairment compared with 15% of adults with diabetes who were between 18 and 44 years of age. Throughout the period of 1997–2005, women with diabetes were more likely than men with diabetes to have visual impairment. Prevalence rates in women with diabetes have been falling throughout this time period, whereas rates in men with diabetes have stayed fairly constant since 2001. There appears to be no difference between racial groups in the prevalence of visual impairment during the period 1997–2005. Duration of diabetes is the most significant predictor of visual impairment among people with type 2 diabetes. As much as 90% of blindness due to retinopathy among people with diabetes may be preventable if detected and treated early. Annual dilated eye examinations are recommended for all patients with diabetes.

### **Nephropathy (Renal Disease)**

*Diabetic nephropathy* is defined as persistent proteinuria (more than 500 mg of protein or 300 mg of albumin per 24 hours) in patients without urinary tract infection or other diseases causing the proteinuria. In patients with type 1 diabetes, development of clinical nephropathy is a relatively late event; however, in patients with type 2 diabetes, diabetic proteinuria may be present at diagnosis.

The incidence of diabetic nephropathy in patients with type 2 diabetes is low during the first 10 to 15 years of diabetes duration, after which it increases rapidly to a maximum at

about 18 years of duration, and then declines. The actual onset of type 2 diabetes may precede its clinical diagnosis by many years, which may explain the high prevalence of nephropathy at diabetes diagnosis. In 2002, diabetes-related nephropathy accounted for 44% of new cases of end-stage renal disease (ESRD), and 153,730 people with ESRD due to diabetes had either received a kidney transplant or were on chronic dialysis treatment.

The etiology of diabetic nephropathy is poorly understood. Several risk factors are involved, some of which are modifiable and others are not. Metabolic regulation is one of the key modifiable risk factors for development of diabetic nephropathy. In people with either type 1 or type 2 diabetes, strict metabolic control leads to a significant reduction in the risk of developing microalbuminuria and the risk of progression to persistent proteinuria [43–45]. The impact of strict metabolic control on prognosis is most pronounced in patients with normal levels of albumin in the urine and patients with microalbuminuria. Increasing blood pressure and hypertension also are associated with an increased risk of progression of diabetic renal disease [46]. However, it is still unclear whether blood pressure at diabetic onset predicts later development of diabetic nephropathy. Other risk factors, including cigarette smoking, obesity, anemia, and genetic factors, also have been suggested.

People with type 2 diabetes and diabetic nephropathy are at increased risk for developing many other diabetic complications. The renal-retinal syndrome has been known for years and refers to the presence of both types of diseases at the same time. People with diabetes and nephropathy also are more likely to develop coronary heart disease and stroke compared with patients with diabetes without nephropathy. People with diabetes and nephropathy also are more likely to die from macrovascular disease, as described above. Overall, the incidence of nephropathy has declined in recent decades, due to improvements in the management of people with diabetes to promote tight control of glycemia as well as improved control of hypertension. For example, comparison of 4 cohorts of patients with type 1 diabetes whose disease was diagnosed between 1965 and 1984 showed that the cumulative incidence of diabetic nephropathy over the following 20 years were lowest in the most recently diagnosed cohorts.

### **Peripheral Neuropathy**

Diabetic peripheral neuropathy (DPN) is a common complication estimated to affect 30% to 50% of individuals with diabetes. The primary risk factor for DPN is hyperglycemia. Other independent risk factors include age, duration of disease, cigarette smoking, hypertension, elevated triglycerides, higher BMI, alcohol consumption, and taller height.

Chronic sensorimotor distal symmetric polyneuropathy is the most common form of DPN. Polyneuropathy can lead to sensory loss, muscle weakness, and pain. The typical presentation of polyneuropathy is a gradual onset of sensory impairment, including burning and numbness in the feet. The onset is so gradual that the disease may go undetected for years. Neuropathic pain may be severe when present; however, it is reported to occur in only 11% to 32% of individuals with polyneuropathy [34–39].

Diabetic peripheral neuropathy leads to a number of impairments and functional limitations. Individuals with DPN are at high risk for foot ulceration and subsequent lower-extremity amputation. In individuals with diabetes, the presence of DPN is associated with a greater number of health care visits per year and an inability to work due to physical limitations. Data from the National Center for Health Statistics indicate that the hospital discharge rates for DPN have steadily increased from 1996 to 2003. The age-adjusted hospital discharge rate for DPN increased from 4.7 per 1,000 people with diabetes in 1996 to 6.8 per 1,000 people with diabetes in 2003. Discharge rates were higher in men than in women and higher for people younger than 45 years of age compared with those who were 45 years of age and older.

#### **Lower-Extremity Amputations**

Nontraumatic lower-extremity amputations (LEAs) are a devastating complication of diabetes. As many as 15% of people with diabetes will have such amputations during their lifetime. People with diabetes are 10 to 20 times more likely to have LEAs than those without diabetes. People 65 years of age and older account for about 55% of patients with diabetes who had nontraumatic LEAs.

#### **Burden to the Health Care System**

According to the American Diabetes Association, the estimated costs associated with diabetes in the United States in 2002 totaled \$132 billion, with direct medical costs of \$92 billion and indirect costs (disability, loss in work productivity and premature mortality) of \$40 billion.<sup>75</sup> Given no additional increase in the prevalence of diabetes in the United States, these expenditures would be expected to reach approximately \$192 billion by 2020. Of the \$92 billion in direct costs for 2002, \$23 billion was due to health care events with a primary diagnosis of uncomplicated diabetes and an additional \$25 billion was for treatment of diabetes-related cardiovascular disease [40].

Approximately 40% of the total cost of diabetes in the United States is due directly to inpatient care for treatment of diabetes complications [77]. Several studies have estimated annual and cumulative economic costs of diabetes complications over time [78, 79]. These studies found that macrovascular disease (mainly cardiovascular events and stroke) accounted for as much as 85% of the costs of complications associated with diabetes and that these conditions are a significant determinant of costs at an earlier time during the course of the disease than microvascular complications. It is important to note, however, that relatively mild microvascular complications can become more serious over time and contribute significantly to morbidity and related costs in later years.

#### **Treatment for diabetic complications**

##### **Diabetes mellitus management**

Diabetes is a complex condition, so its management involves several strategies. In addition, diabetes affects everyone differently, so management plans are highly individualized.

##### **The four main aspects of managing diabetes include [41-42]**

- **Blood sugar monitoring:** Monitoring your blood sugar (glucose) is key to determining how well your current treatment plan is working. It gives you information on

how to manage your diabetes on a daily and sometimes even hourly basis.

- **Oral diabetes medications:** Oral diabetes medications (taken by mouth) help manage blood sugar levels in people who have diabetes but still produce some insulin mainly people with Type 2 diabetes and prediabetes. People with gestational diabetes may also need oral medication. There are several different types. Metformin is the most common.
- **Insulin:** People with Type 1 diabetes need to inject synthetic insulin to live and manage diabetes. Some people with Type 2 diabetes also require insulin. There are several different types of synthetic insulin. They each start to work at different speeds and last in the body for different lengths of time. The four main ways can take insulin include injectable insulin with a syringe (shot), insulin pens, insulin pumps and rapid-acting inhaled insulin.
- **Diet:** Meal planning and choosing a healthy diet for key aspects of diabetes management, as food greatly impacts blood sugar. If you take insulin, counting carbs in the food and drinks you consume is a large part of management. The amount of carbs eat determines how much insulin need at meals.
- **Exercise:** Physical activity increases insulin sensitivity (and helps reduce insulin resistance), so regular exercise is an important part of management for all people with diabetes.

##### **Insulin Sensitizers**

The 2 classes of drugs categorized as insulin sensitizers are biguanides (metformin) and thiazolidinediones (rosiglitazone and pioglitazone).

##### **Biguanides**

Metformin remains the primary drug within the class of biguanides in current use, and remains the preferred initial agent for T2DM based on a recent joint statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as well as the American Association of Clinical Endocrinologists (AACE).<sup>9-11</sup> Metformin was approved by the Food and Drug Administration (FDA) for use in the United States in 1994 for the treatment of T2DM in adults, with a pediatric indication for children older than 10 years. Concern about risk for lactic acidosis potentiated by decreased clearance of drug led to a black-box warning for use within specific populations including those with renal or hepatic impairment, acute congestive heart failure, sepsis, dehydration, and excessive alcohol intake. In addition, it is recommended that therapy be temporarily discontinued before the administration of intravascular radiocontrast agents or surgical procedures, because of the potential for dehydration and/or kidney injury.

##### **Thiazolidinediones**

Pioglitazone (Actos) and rosiglitazone (Avandia) are thiazolidinedione (TZD) drugs approved by the FDA for the treatment of T2DM. Caution is advised for use with CHF (New York Heart Association [NYHA] class I or II), and both drugs are contraindicated in advanced CHF (NYHA class III or IV). Despite demonstrated glycemic efficacy and improved insulin sensitivity, because of troublesome side effects including weight gain and fluid retention, the ADA consensus statement

favors metformin over TZD for first-line treatment of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) [41].

### **Secretagogues**

Sulfonylureas and meglitinides, lower glucose levels by stimulating insulin secretion.

### **Sulfonylureas**

Sulfonylureas are approved by the FDA for the treatment of T2DM in adults. In addition, clinical efficacy has been demonstrated in single-gene diabetes (HNF1A MODY) and permanent neonatal diabetes associated with the KCNJ11 and ABCC9 genes.<sup>62</sup> Because of the risk for hypoglycemia, sulfonylureas should be used with caution in elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency. In these patients the initial dosing, dose increments, and maintenance dosage should be conservative.

### **Meglitinides**

Meglitinide analogues, nateglinide (Starlix) and repaglinide (Prandin), are approved for the treatment of T2DM in adults. Caution is recommended for moderate to severe hepatic impairment, and dose adjustment is indicated for creatinine clearance of less than 20 to 40 mL/min for repaglinide.

### **$\alpha$ -Glucosidase Inhibitors**

The  $\alpha$ -glucosidase inhibitors (AGI), acarbose (Precose), miglitol (Glyset), and voglibose (Voglib), are indicated for treatment of adults with T2DM. The class is contraindicated in patients with cirrhosis, inflammatory bowel disease, colonic ulceration, intestinal obstruction, or predisposition to obstruction and diabetic ketoacidosis.

### **Glucagon-Like Peptide 1-Based Drugs**

Glucagon-like peptide 1 (GLP-1) is a gut hormone secreted in response to nutrient ingestion, which regulates postprandial glucose homeostasis. Once secreted into the circulation, GLP-1 is metabolized rapidly to inactive compounds by the action of ubiquitous enzyme dipeptidyl-peptidase 4 (DPP-4), leading to a plasma t<sub>1/2</sub> of 1 to 2 minutes.<sup>93</sup> Two classes of drugs in this category, GLP-1 receptor (GLP-1r) agonists and DPP-4 inhibitors, have been developed using strategies to bypass or block DPP-4 action, leading to compounds with half-lives longer than native GLP-1 or causing higher concentrations of native GLP-1 levels, respectively.

### **Amylin Analogues**

Pramlintide (Symlin) is indicated for adjunctive use in both T1DM and T2DM in patients already taking prandial insulin. It is contraindicated in patients with a confirmed diagnosis of gastroparesis and hypoglycemia unawareness, owing to the increased risk of hypoglycemia. Dose titration is recommended, and prandial insulin doses should be reduced by 50% at the onset of therapy to limit the risk of hypoglycaemia [43-47].

### **Sodium-Glucose Transporter Inhibitors**

Sodium-glucose transporter 2 (SGLT2) inhibitors are a novel class of antidiabetes agents that exert glucose lowering primarily through effects on renal glucose handling. Several drugs in this class are in various stages of clinical development; canagliflozin (Invokana) is the first agent in this class to achieve a recent FDA approval for the treatment of T2DM. Use is contraindicated in severe renal impairment (glomerular filtration rate [GFR] <30 mL/min) or severe liver disease, and

dose adjustment is advised for moderate renal impairment (GFR <45 mL/min).

### **Conclusion**

Diabetes is a condition that happens when your blood sugar (glucose) is too high. It develops when your pancreas doesn't make enough insulin or any at all, or when your body isn't responding to the effects of insulin properly. Diabetes affects people of all ages. Most forms of diabetes are chronic (lifelong), and all forms are manageable with medications and/or lifestyle changes. Early projections for the number of people with diagnosed diabetes in the United States in 2050 were calculated to be around 39 million. Since those calculations were done, however, the national incidence of diabetes has continued to increase from 2000 to 2004, and the mortality rate among people with diabetes has declined<sup>48-50</sup>. Therefore, new projections for the diabetes burden in 2050 were published in 2006. The number of people with diagnosed diabetes in the United States is expected to increase from 16.2 million in 2005 to 48.3 million in 2050. These new estimates clearly depend on a stable incidence rate for diabetes over time; even incremental increases in incidence will have a significant effect on the expected number of people with diagnosed diabetes in the future. In addition, these estimates assume no advances in prevention, treatments, or control of risk factors; no increases in life expectancy; and no discovery of a cure. Changes in any of these factors could substantially alter the projections for 2050. It is possible to identify DM2 risk years or decades in advance on the basis of numerous personal, historic, and laboratory measures, although there is not yet a robust, user-friendly clinical decision-support tool to estimate absolute risk for individuals. The individual families, communities, and health organizations should encourage healthy eating and physical activity and should focus the most intensive DM2 prevention efforts on those at highest risk for progression to diabetes mellitus.

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