Adv Ther (2025) 42:2659–2678
https://doi.org/10.1007/s12325-025-03185-9

REVIEW

Diabetes Mellitus and Associated Vascular Disease: Pathogenesis, Complications, and Evolving Treatments

Kazi Islam · Rahib Islam · Ivan Nguyen · Hassan Malik · Humza Pirzadah · Barsha Shrestha · Isabella B. Lentz · Sahar Shekoohi · Alan D. Kaye

Received: August 14, 2024 / Accepted: March 19, 2025 / Published online: April 19, 2025

ABSTRACT

Diabetes mellitus is a metabolic disorder, characterized by elevated blood sugar levels (hyperglycemia) and insulin dysregulation. This disease is associated with morbidity and mortality, including significant potential vascular complications. High levels of hyperglycemia lead to not only elevated levels of reactive oxygen species but also advanced glycation end products, which are detrimental to the vascular endothelium and reduce protective compounds such as nitric oxide and prostacyclin. This damage contributes to the development of both macrovascular and microvascular complications. The present investigation explores the pathophysiological mechanisms of diabetic vascular complications and evaluates current management strategies, including lifestyle modifications, pharmacological treatments, and emerging therapies. The review underscores the importance of ongoing progress in diabetes management and patient education to lead to optimal patient-health outcomes and quality of life for individuals with diabetes mellitus.

Keywords: Diabetes mellitus; Vascular complications; Hyperglycemia; Endothelial dysfunction; Pharmacological treatments

Key Summary Points

Diabetes mellitus is a metabolic disorder, characterized by elevated blood sugar levels (hyperglycemia) and insulin dysregulation.

Advancements in diabetes mellitus management and education are essential for leading to optimal patient outcomes and a better quality of life for individuals with highly prevalent systematic diseases.

K. Islam
Central State University, 1400 Brush Row Road, Wilberforce, OH 45384, USA

R. Islam · I. Nguyen · H. Malik · H. Pirzadah · B. Shrestha
LSU Health Sciences Center New Orleans School of Medicine, 1901 Gravier Street, New Orleans, LA 70112, USA

I. B. Lentz · S. Shekoohi (✉) · A. D. Kaye
Department of Anesthesiology, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA 71103, USA
e-mail: sahar.shekoohi@lsuhs.edu

A. D. Kaye
Department of Pharmacology, Toxicology, and Neurosciences, Louisiana State University Health Sciences Center Shreveport, Shreveport, LA 71103, USA

The present investigation explores the pathophysiological mechanisms of diabetic vascular complications and evaluates current management strategies, including lifestyle modifications, pharmacological treatments, and emerging therapies.

INTRODUCTION

Worldwide, diabetes mellitus is a chronic disease characterized by dysregulation of glucose metabolism and hyperglycemia. Type 1 diabetes mellitus is associated with insufficient insulin secretion in youths, while type 2 diabetes mellitus (T2DM), the focus of the present investigation, is often associated with insulin resistance in middle-aged and older adults. The combination of genetics, poor diet, and sedentary lifestyle are often the source of the development of T2DM [1].

Consequently, atherosclerosis from diabetes mellitus is one of the biggest contributors to early mortality and a multitude of morbidities [2]. Complications related to the vascular origin of T2DM come from being in a state of chronic hyperglycemia, which leads to enhanced levels of reactive oxygen species (ROS), enhanced levels of advanced glycosylation end products (AGE), and decreased levels of nitric oxide (NO) [3]. Furthermore, diabetic cardiovascular damage can be categorized as macrovascular complications, which include coronary artery disease, cerebrovascular disease, and peripheral vascular disease. Likewise, microvascular complications include retinopathy, nephropathy, and neuropathy [4]. It should be emphasized that diabetic retinopathy is one of the, if not most, leading cases of blindness among adults in their working age, and having diabetes is one of the strongest predictors of chronic kidney disease in the United States [5, 6]. Additionally, patients with diabetes mellitus have a 30 times higher risk of having an amputation in their lives compared to patients without diabetes [7]. Despite these morbidities and increased mortality, the prevalence of diabetes mellitus has only been rising in the United States [8].

In 2021, the Centers for Disease Control and Prevention (CDC) estimated that 11.6% of the United States population had diabetes mellitus, which totaled 38.4 million people [9]. In terms of global data, the prevalence of diabetes mellitus was estimated at 10.5%, and it is predicted that this number will increase to 12.5% over the next two decades. This means that, by 2045, there will be over half a billion people suffering from diabetes mellitus in the world [10]. As for the financial aspects, the economic burden of diabetes in the United States totaled about US$412.9 billion in the year 2022. Likewise, patients with diabetes mellitus have a total medical expenditure that is 2.6 times higher than patients without diabetes [11]. The total prevalence and cost of diabetes mellitus are astounding, and it demands an urgent need for developing more efficient management of the disease. Fixing the problem of diabetes mellitus in the overall community begins with preventative measures by identifying risk factors.

Racial differences present as a concerning risk factor in developing T2DM, for the prevalence in different races present as Hispanic/Latino (12.5%), Black (11.7%), and Asian (9.2%) compared to white (7.5%) [9]. These variations in the prevalence of diabetes mellitus can be linked to additional risk factors such as physical environment, socioeconomic status, food availability, genetics, and behavior [12–14]. Many of these risk factors extend beyond the scope of what healthcare and medicine can directly affect, but early screenings and patient education for populations at higher risk will allow for earlier detection and improved outcomes [13].

In the search for new therapeutics and management protocols for diabetes mellitus, it is vital to understand the pathophysiological mechanisms of the disease through its effects on the vasculature system. In this study, we examine the detrimental impacts of diabetes on blood vessels and investigate different strategies to counteract these effects.

This article is based on previously conducted studies and does not contain any new studies

with human participants or animals performed by any of the authors.

MECHANISM OF VASCULAR ENDOTHELIAL DAMAGE

Diabetes mellitus is a complex disease with various forms, primarily classified as type 1 diabetes (e.g., insulin-dependent) and T2DM (e.g., non-insulin-dependent). The International Diabetes Federation projects that, by 2045, one in eight adults will have diabetes mellitus, with more than 90% of these cases expected to be T2DM [10].

Diabetes mellitus disrupts endothelial function and metabolism, affecting various organs in the body. These disruptions primarily result from hyperglycemia and accumulate gradually over time. The vascular endothelium releases substances that promote vasodilation, such as prostacyclin I2, endothelium-derived hyperpolarizing factor, and NO, as well as vasoconstrictors like angiotensin II, thromboxane A2, and endothelin-1 [15]. In doing so, the endothelium plays a pivotal role in maintaining vascular health by coordinating a balance between vasodilation and vasoconstriction, prevention of blood clots, reducing inflammation, combating oxidation, and managing muscle cell growth [16].

When the endothelium becomes damaged, it can no longer maintain vascular homeostasis, leading to the onset of disease. Endothelial dysfunction is characterized by increased inactivation of NO and/or decreased NO production from the endothelium itself [17]. Diabetes is one of the many conditions that stem from the dysfunction of endothelial cells [18].

Persistent elevations in blood glucose levels create an environment conducive to oxidative stress and inflammation, which are the primary drivers of diabetes-associated complications. Oxidative stress is defined as a disparity between the ROS production and the anti-oxidant protection provided by the body, resulting in an accumulation of ROS that causes tissue damage all over. ROS can be described as small oxygen-derived molecules which possess at least one unpaired electron, enhancing their reactivity [19]. Examples of such include superoxide, hydroxyl, and hydrogen peroxide. These play significant roles regarding cell proliferation, differentiation, apoptosis, and necrosis. Low to intermediate levels maintain normal physiological functions and homeostasis, while excessive amounts are what are responsible for cell damage and dysfunction due to the activation of pro-inflammatory cytokines, resulting in subsequent inflammation that further promotes the production of ROS.

Endothelial function and oxidative stress are intertwined in their interaction [20]. Oxygen radicals (O_2·−) have a high affinity for directly neutralizing NO, reducing its availability. Moreover, the direct interaction between NO and O_2·− generates peroxynitrite, which can cause lipid peroxidation, protein tyrosine nitration, DNA damage, and cell death [17]. Peroxynitrite oxidizes tetrahydrobiopterin (BH4), a crucial cofactor for eNOS, into its inactive state, leading to decreased BH4 levels. When there are inadequate levels of BH4 available, eNOS uncouples to generate O_2− instead of NO. Thus, O_2·− is linked to the onset of endothelial dysfunction [17].

The pathways through which ROS production is heightened include the polyol, hexosamine, protein kinase C pathways, the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase family, and the build-up of advanced glycation end products (AGEs). Persistently elevated blood sugar levels activate these pathways, thereby increasing ROS production, which in turn contributes to premature morbidity and mortality [21]. As the disease process advances, the harmful effect of prolonged hyperglycemia provokes widespread organ damage, notably affecting the vascular system. Various vascular complications emerge, ranging from microvascular damage to the kidneys and eyes to macrovascular issues such as atherosclerosis and cardiovascular disease. These complications disrupt the body's normal functioning, diminishing the quality of life in all age groups [22].

A critical aspect of diabetic vascular complications is the phenomenon of 'metabolic memory,' which is defined as prior periods of hyperglycemia leading to long-lasting cellular

and molecular damage despite tight subsequent glycemic control. This is primarily due to the persistent accumulation of AGEs and ROS, which continue to impair endothelial function and exacerbate vascular complications even after normalizing glucose levels [23].

METABOLIC MEMORY: MECHANISMS AND IMPLICATIONS FOR DIABETES MANAGEMENT

Metabolic memory refers to the long-term effects of past periods of hyperglycemia on vascular tissues, even after glycemic control is achieved [24]. This phenomenon is primarily driven by the accumulation of AGEs, ROS, and persistent inflammation, which continue to damage the vascular endothelium [25]. The persistence of these molecular insults disrupts vascular repair processes and contributes to the progression of diabetes-related complications long after glucose levels return to normal [2].

One of the significant consequences of metabolic memory is altered reparative potency [26]. Prolonged oxidative stress and inflammation compromise the ability of endothelial cells to repair damaged tissues, reducing regenerative capacity in the vasculature [27]. This impaired repair can contribute to persistent endothelial dysfunction, which is central to both microvascular and macrovascular complications in diabetes [4].

Furthermore, metabolic memory exacerbates insulin resistance by promoting chronic activation of pro-inflammatory signaling pathways, increasing the production of ROS, and causing epigenetic changes that impair insulin signaling. Even with improved glycemic control, these molecular changes persist, perpetuating insulin resistance and hindering the body's ability to manage glucose effectively [28].

Adipocyte dysfunction is another critical aspect influenced by metabolic memory [29]. Prolonged hyperglycemia and oxidative stress lead to chronic inflammation in adipose tissue, altering the secretion of key adipokines, such as adiponectin and resistin, which regulate insulin sensitivity. This dysfunction further aggravates insulin resistance, contributing to the metabolic complications of diabetes [30].

Several antidiabetic drugs have shown promise in mitigating the effects of metabolic memory. For example, metformin has been shown to reduce ROS production and improve endothelial function, potentially enhancing reparative potency and improving insulin sensitivity [31]. Sodium-glucose co-transporter 2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists not only help control blood glucose levels but also exhibit anti-inflammatory and anti-oxidative effects, which can mitigate some of the long-term consequences of metabolic memory, including adipocyte dysfunction and insulin resistance [32].

Moreover, thiazolidinediones (e.g., pioglitazone) activate peroxisome proliferator–activated receptor (PPAR)-gamma pathways, reducing inflammation and improving endothelial repair. These agents may help restore some reparative capacity while also improving lipid metabolism and insulin sensitivity, countering the effects of metabolic memory on both vascular health and adipocyte function [33].

MACRO AND MICROVASCULAR COMPLICATIONS

Vascular complications are responsible for a major portion of the health burden associated with diabetes. They contribute to a multitude of morbidities and mortalities across millions of individuals [34]. Vascular complications are currently stratified into two different categories: macrovascular and microvascular. Macrovascular complications occurring as a result of atherosclerosis include many of the common vascular diseases, such as coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral vascular disease (PVD) [4]. Microvascular complications resulting from the thickening of the basement membrane include retinopathy, nephropathy, and neuropathy [4, 35]. The impact of risk factors is correlated with the individual risk factors. Pertinent risk factors include elevated blood

glucose, blood pressure, and cholesterol lipid levels [4, 35, 36]. Related to increased stress, the vascular endothelium experiences endothelial dysfunction characterized by increased inflammation and oxidative stress from reduced NO biosynthesis, endothelial–mesenchymal transition, senescence, and even cell death [4, 35, 36].

Hyperglycemia is the major systemic risk factor for diabetic microvascular complications. The duration of disease, the alteration of lipid metabolism, higher age, obesity, hypertension, and genetic factors also interplay in the vascular compromise [4, 35–39]. Dysfunction of cellular mechanisms like nonenzymatic glycation and the formation of AGEs, production of ROS, and multiple intracellular biochemical pathways (endoplasmic reticulum stress, the diacylglycerol–protein kinase C pathway, Src homology region 2 domain-containing phosphatase-1, Ras protein, and BK channel synthesis) are also main contributors to vascular complications [4, 35].

Hyperglycemia activates four main biochemical pathways which result in increased mitochondrial superoxide production, inhibiting glycolytic enzyme glyceraldehyde 3 phosphate dehydrogenase, thereby diverting upstream substrates from glycolysis and causing glucose overutilization. This shunt causes increased conversion of dihydroxyacetone phosphate to diacylglycerol and triose phosphates to methylglyoxal, the main intracellular AGEs [4, 35]. AGEs can interact with AGE receptors which promotes atherosclerotic formation by increasing inflammatory signals and upregulating inflammatory response elements. In addition, there is increased oxidative stress due to intracellular hyperglycemia, which accelerates the production of mitochondrial ROS through the NADPH oxidase family (upregulated in diabetic individuals) [4, 35]. This oxidative and inflammatory stress is a major contributor to endothelial dysfunction and is responsible for microvascular complications.

Diabetic neuropathy refers to disorders of the somatosensory or autonomic parts of the peripheral system. Diabetic somatosensory neuropathy is the most common cause of hospital admissions and lower-limb amputations among patients with diabetes. It is commonly associated with autonomic involvement and has a chronic and progressive course. Longer axons, like ones on lower limbs, are more vulnerable to nerve lesions induced by diabetes. The most important contributing factors are poor glycemic control, visceral obesity, diabetes duration, height, hypertension, age, and smoking [4, 35]. Diagnosis is made through quantitative bedside assessments and measurements, and patients present with "positive" sensory symptoms like burning, stabbing, or shooting pain [40]. On physical exam, physicians commonly use monofilament testing, vibration perception with a tuning fork, and temperature discrimination to assess the degree of sensory loss. Reflexes, mainly the ankle reflex, may be diminished or absent in patients with diabetic neuropathy [41].

There are also quantitative diagnostic tests, such as nerve conduction studies, which are often used to assess the speed of electrical conduction in peripheral nerves. Slowed conduction is an excellent indicator of diabetic neuropathy [42]. Electromyography can help evaluate the level of nerve damage and differentiate between different types of neuropathy [43]. In patients with suspected autonomic neuropathy, heart rate variability tests, blood pressure response to posture changes, and sweat function tests can provide valuable diagnostic information. Treatment is typically guided through lifestyle modifications and pharmacology aimed toward near-normoglycemic patients [44].

Diabetic nephropathy can be looked at as one of the primary causes of cases of chronic kidney disease worldwide. Its diagnosis is made through clinical investigation of worsening renal function and albuminuria [4, 35, 36, 45]. If not treated early, patients can progress to end-stage renal disease. It has also been reported that diabetic nephropathy can potentially exacerbate hypoglycemia due to reduced glucose production, excretion of antidiabetic drugs, and lowering overall food intake.

Diabetic retinopathy is one of the main causes of blindness and moderate visual impairment in adults worldwide [5]. Microaneurysm and microhemorrhages caused by capillary occlusion and increased vessel permeability are common causes of diabetic retinopathy. Patients present with "cotton-wool spots" that can be

seen as white-grayish areas with blurred margins [4, 35, 36, 45]. Diabetic retinopathy can lead to two major complications linked to a high risk of vision loss, which include: diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). In DME, microvascular complications involve the macula (a portion of the retina responsible for the vision of colors and details), causing severe functional impairment. In PDR, progressive retinal ischemia leads to the growth of new vessels, which may extend into the vitreous and iris. This leads to intraocular hemorrhage, fibrovascular proliferation, and retinal detachment [4, 35, 36, 45]. The most important contributing risk factors for all microvascular complications are poor glycemic control, visceral obesity, diabetes duration, height, hypertension, age, and smoking [4, 35–39, 45, 46].

CAD, peripheral artery disease (PAD), and CVD are increased 2–4-fold in patients with diabetes [37, 45]. The mortality with each disease is much worse in patients with diabetes. The hyperglycemic environment and the insulin resistance environment in patients with diabetes increase pro-atherogenic conditions by allowing plaque build-up and altering vascular tone and permeability [37, 45]. This allows inflammatory cells to transmigrate and lipid accumulation in the vessel wall. More than 60% of diabetes-related deaths are due to cardiovascular disease. CAD is characterized by reduced blood flow in the coronary arteries, which is easily compromised due to atherosclerotic plaque [37–39, 45, 46]. Patients with diabetes commonly experience heart attacks, otherwise known as myocardial infarctions (MI), most presenting within the first 10 years of disease status. PAD has a similar mechanism to coronary artery disease; however, the disease status differs in the anatomic location [37–39, 45, 46]. PAD is denoted as the vessels affected other than coronary or cerebrovascular vessels. Late signs of PAD are seen with claudication and limb ischemia. A common diabetes complication is the clinical presentation of PAD, known as diabetic foot [38, 39, 46]. The risks of amputation increase almost four times. Amputation can be evaded with timely and accurate intervention [38, 39, 46]. Cerebrovascular events are also due to atherosclerotic buildup and thrombo-embolic events associated with diabetes. Carotid disease, due to atherosclerotic plaque rupture, is a major complication in thrombo-embolic events leading to stroke. In addition, the narrowing of the carotids can reduce upstream blood flow to the Circle of Willis, leading to debilitating complications [38, 39, 46]. The vessel stress of diabetes can also result in aneurism rupture and hemorrhagic events, which has a myriad affect based off the anatomic location of the vascular compromise [38, 39, 46].

The concept of metabolic memory also plays a significant role in the progression of microvascular complications such as retinopathy and nephropathy. Studies have shown that early hyperglycemic events lead to sustained oxidative stress and vascular inflammation, increasing the risk of complications long after better glycemic control is achieved. This highlights the need for early and aggressive intervention in managing diabetes to mitigate these lasting effects [47].

MANAGEMENT AND TREATMENT OPTIONS

Exercise

Aerobic Exercise and Resistance Training

Exercise is essential in both the prevention and management of T2DM. Kirwan et al. showed in their study that aerobic exercise (anything from utilizing the Stairmaster, running outside or on the treadmill, engaging in mixed martial arts) had been shown to greatly improve levels of glucose control, sensitize insulin levels, and reduce causes of heart disease [48]. Furthermore, he demonstrated in his study that even moderate aerobic activity can significantly reduce glycated hemoglobin (HbA1c) levels, a glucose control marker over the long term [48]. Moreover, aerobic exercise improves cardiovascular fitness, which is crucial since individuals with diabetes are at a higher risk for cardiovascular diseases.

Resistance training with weights also greatly affects diabetes mellitus prevention and management. Resistance exercises, which include weightlifting, body-weight exercises, and resistance band workouts, help increase muscle mass. Enhanced muscle mass improves the body's

ability to use glucose, reducing blood sugar levels. Kirwan et al. note that resistance training enhances insulin sensitivity by multiplying the insulin receptors in muscle cells. Furthermore, combining aerobic and resistance training provides synergistic benefits, resulting in more effective glycemic control and overall metabolic health. This combination of training improves blood glucose levels, enhances lipid profiles, and reduces blood pressure, addressing multiple risk factors associated with diabetes [48].

As can be seen, exercise is a cornerstone of diabetes management, and additional studies have also shown the above points. A meta-analysis by Liu et al. [49] found that moderate-intensity aerobic exercise significantly reduced HbA1c levels in patients with T2DM by an average of 0.6% over a 12-week period. Francois and Little [50] conducted a review demonstrating that high-intensity interval training (HIIT) not only improved glycemic control but also led to reductions in cardiovascular risk markers in patients with diabetes. Colberg et al. [51], in their consensus report for the American Diabetes Association (ADA), recommend at least 150 min of moderate-to-vigorous intensity aerobic activity per week for adults with T2DM to improve glycemic control and cardiovascular fitness. These studies collectively reinforce the importance of exercise in diabetes management, showing that regular aerobic and resistance training improve glycemic control, reduce insulin resistance, and enhance cardiovascular outcomes. Moreover, incorporating a variety of exercise modalities ensures that patients can achieve therapeutic benefits even when time is limited.

High-Intensity Interval Training (HIIT)

HIIT is defined as high levels of energy-inducing movement or exercise divided up into intervals of time, separated by rest periods between groups. HIIT not only improves skeletal muscle oxidative capacity, glucose control, and insulin sensitivity but effectively leads to higher levels of fat loss over time [52]. The efficiency of HIIT lies in its ability to provide significant health benefits in a shorter duration compared to traditional exercise routines. Studies have shown that HIIT can significantly reduce HbA1c levels and improve cardiovascular fitness in individuals with diabetes, often with just a few weekly sessions [49].

The metabolic benefits of HIIT are attributed to its high intensity, which induces greater muscle adaptations and efficiently increases the body's ability to utilize glucose. Additionally, HIIT enhances mitochondrial function in muscle cells, further improving insulin sensitivity and glucose uptake [48]. This exercise modality is advantageous for individuals with limited time for exercise, as it offers substantial benefits in a time-efficient manner [50].

Intensity and Frequency of Aerobic Exercise for Therapeutic Effects

For aerobic exercise to provide therapeutic benefits in managing diabetes mellitus and its associated vascular complications, specific guidelines regarding intensity and frequency should be followed [51]. According to current recommendations from the ADA and other studies, the following guidelines are effective in improving glycemic control, cardiovascular health, and overall metabolic function [53].

Intensity Moderate-intensity aerobic exercise is recommended for most individuals with T2DM [54]. This typically involves activities that raise the heart rate to 50–70% of the individual's maximum heart rate (HRmax). Examples include walking in a fast and brisk form, cycling, or swimming [55]. Moderate-intensity activities should allow a person to carry on a conversation, but not do activities such as performing a speech, or even sing, during the activity [56]. For more advanced fitness levels, higher-intensity aerobic activities, raising the heart rate to 70–85% of HRmax, can provide additional cardiovascular and metabolic benefits [57].

Frequency To achieve therapeutic effects, it is recommended that individuals engage in aerobic exercise at least 3–5 days per week, with a minimum of 150 min of moderate-intensity aerobic activity spread throughout the week [58]. Ideally, exercise should be performed on most days, with at most two consecutive days without physical activity, as this can diminish the

benefits of exercise on insulin sensitivity and glycemic control [59].

Duration

Each session should last at least 30 min, but benefits can be observed with as little as 10-min bouts accumulated throughout the day to reach 150 min weekly. For those aiming for weight loss or additional cardiovascular benefits, increasing the duration to 300 min of moderate-intensity weekly exercise may be beneficial [60].

Exercise Mediated Mechanisms

Exercise improves glucose metabolism through various mechanisms. Yang et al. have described that one of the most well-established mechanisms is the increased expression and translocation of GLUT4 proteins to the cell membrane in skeletal muscle cells [61]. GLUT4 is a glucose transporter protein that facilitates glucose uptake into cells, and its activity is crucial for maintaining normal blood glucose levels. Exercise triggers insulin-dependent and insulin-independent pathways that enhance GLUT4 translocation, improving glucose uptake even in insulin-resistant conditions [61].

Moreover, exercise reduces systemic inflammation, a key contributor to insulin resistance. Chronic low-grade inflammation, often observed in individuals with diabetes, impairs insulin signaling pathways. Yang et al. discuss how regular physical activity lowers levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), and improves the anti-inflammatory profile of adipose tissue [61]. This reduction in inflammation enhances insulin sensitivity and overall metabolic health. Additionally, exercise boosts mitochondrial function and biogenesis in muscle cells, increasing glucose and lipid oxidation capacity, further supporting improved glycemic control [61].

Dietary Changes

Mediterranean Diet

The Mediterranean diet is regarded worldwide for its ability to effectively and efficiently manage and prevent T2DM mellitus due to its emphasis on a nutrient-rich profile that promotes overall metabolic health [62]. This diet integrates a high intake of fruits, vegetables, whole grains, nuts, and olive oil, which are fundamental in enhancing glycemic control and insulin sensitivity [63]. Studies highlight that the Mediterranean diet significantly improves insulin sensitivity by moderating glycemic load, thus reducing insulin demand and enhancing lipid profiles through its rich mono-unsaturated and omega-3 fatty acids content [64].

Adherence to this diet has been associated with a great number of benefits in diabetes management and prevention [65]. It has been shown to lead to reductions in HbA1c levels, a marker of long-term glucose management, and to lower the incidence of cardiovascular diseases commonly seen in patients with diabetes. The Mediterranean diet's effectiveness in reducing blood glucose levels and HbA1c is particularly significant, with reductions of 0.47% in HbA1c being reported, which is notable compared to other diets [66].

Moreover, the diet's low-glycemic-index foods slow down the absorption of sugar, avoiding spikes in blood glucose levels, which is essential for stable blood sugar management [67]. The fiber-rich components also play a critical role by reducing digestion speed and enhancing satiety, which aids in weight management—a key component of diabetes management [68].

Further research underscores the Mediterranean diet's role in improving cardiovascular outcomes. Meta-analyses have indicated a consistent reduction in the risk of heart diseases such as myocardial infarctions and stroke among those adhering to the diet, attributing this to the diet's balanced and diverse nutrient profile [69]. This comprehensive approach addresses glycemic control and targets associated metabolic conditions such as dyslipidemia and hypertension,

which are integral to comprehensive diabetes care [70].

Nutrient Timing and Composition

The timing and composition of meals are essential in managing and preventing diabetes. Eating a balanced diet focusing on low glycemic index foods, high fiber intake, and appropriate portion sizes can help effectively manage blood glucose levels [71]. Being able to eat meals at a consistent time helps to not only maintain steady blood sugar levels but also prevent any fluctuations that can lead to insulin resistance [72].

Including various nutrient-dense foods in the diet ensures that the body receives enough nutrients while minimizing excessive calorie intake [73]. For instance, incorporating lean proteins, healthy fats, and complex carbohydrates in each meal helps balance macronutrient intake and supports metabolic health [74]. Avoiding excessive carbohydrate intake in single meals can prevent postprandial hyperglycemia, which is critical for diabetes management [61]. Additionally, spreading carbohydrate intake throughout the day rather than consuming large amounts at once helps maintain stable blood glucose levels.

Intermittent fasting is an alternative dieting pattern that may assist in managing diabetes due in part to the fact that after a period of caloric intake restriction, serum insulin decreases and insulin sensitivity increases [75]. Since high insulin and/or a state of insulin resistance promote atherosclerosis, a reduction by means of intermittent fasting could reduce the rate of fatty plaque formation in coronary vasculature [76]. A review by Grajower and Horne found that intermittent fasting can reduce many negative mediators of diabetes, including inflammatory cytokines, adiponectin, and advanced glycation end products [77, 78]. The result of sustained intermittent fasting is, therefore, a potential increase in insulin sensitivity, providing patients with diabetes the opportunity to delay the onset of CVD complications.

Lifestyle Changes

Weight Management

Effective weight management is essential for diabetes prevention. Studies, such as those by Kirwan et al., demonstrate that losing 5–10% of body weight significantly enhances insulin sensitivity and reduces diabetes risk. This process involves dietary adjustments, regular exercise, and lifestyle changes. Lowering visceral fat, which is linked to insulin resistance, improves metabolic health, enhances lipid profiles, and lowers blood pressure, thereby reducing cardiovascular disease risks which are common in diabetes. Ongoing support and structured programs are crucial for sustainable weight management [48].

In addition to exercise, lifestyle modifications such as adopting a Mediterranean diet or engaging in nutrient timing strategies can help manage blood glucose levels and improve cardiovascular outcomes. A systematic review by Esposito et al. [79] demonstrated that adherence to a Mediterranean diet was associated with significant reductions in HbA1c and cardiovascular risk factors in patients with T2DM. Similarly, studies have shown that intermittent fasting may improve insulin sensitivity and reduce oxidative stress, further enhancing metabolic health [80].

Behavioral Modifications

Behavioral interventions are essential in creating sustainable lifestyle changes for diabetes prevention. Kirwan et al. noted that regular monitoring of blood glucose levels, stress management, and smoking cessation are vital components of diabetes prevention [48]. These interventions help individuals develop healthy habits and maintain long-term adherence to preventive measures.

Stress management techniques, e.g., mindfulness meditation, yoga, and cognitive–behavioral therapy, can reduce stress levels, which are known to negatively impact blood glucose control. Smoking cessation is particularly important, as smoking is a

significant risk factor for insulin resistance and cardiovascular diseases. Behavioral modifications also include setting realistic goals, tracking progress, and seeking social support from family, friends, and healthcare providers [48].

Education and Support Education about diabetes mellitus and lifestyle management, along with support from healthcare providers, family, and community, enhances adherence to preventive measures. Kirwan et al. stress that structured programs providing education on diet, exercise, and behavior modification effectively reduce the incidence of diabetes [48]. Educational programs about making healthier choices empower individuals with the knowledge and skills to make informed health decisions [81].

Educational interventions should focus on conditions that could arise from not adhering to a healthy lifestyle and cover various aspects of diabetes prevention [82, 83]. Additionally, personalized coaching and regular follow-up with healthcare providers ensure individuals receive tailored advice and ongoing motivation to adhere to preventive measures [48].

Drug Therapeutics

Microvascular Complications

The current literature recommends maintaining glycemic control with an HbA1c of 6.5% or lower [84] to reduce microvascular complications of diabetes. Studies have revealed that blood pressure control and statin therapy reduce microvascular complications such as retinopathy and neuropathy [85].

Fibrates were found to delay the onset of diabetic retinopathy [86]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have also been shown to decrease retinopathy progression significantly [87]. Vascular endothelial growth factor (VEGF) inhibitors, laser photocoagulation, and glucocorticoid therapies reduce angiogenesis and vessel leakage through anti-inflammatory actions [88, 89].

To prevent, delay onset, or reduce the progression of diabetic nephropathy, reducing blood pressure by means of reduced daily salt intake has been shown to slow the progression of diabetic nephropathy [90]. ACE inhibitors and ARBs are also effective anti-hypertensives used in managing diabetic nephropathy. It is important to avoid drugs that are nephrotoxic in these patients, including non-steroidal anti-inflammatory drugs and aminoglycosides [91].

Like with diabetic retinopathy and nephropathy, diabetic neuropathy is best managed with the maintenance of an adequately low glycemic index. To manage the pain commonly associated with diabetic neuropathy, several agents may be used, including tricyclic antidepressants, serotonin and norepinephrine re-uptake inhibitors, anti-epileptics, gabapentin, benzodiazepines, and opioids [92, 93]. Capsaicin and isosorbide dinitrate have also been reported as effective therapies for pain associated with diabetic neuropathy [94, 95].

Macrovascular Complications

The macrovascular complications of diabetes mellitus include CVD, stroke, and PVD. The mainstay of therapy for preventing these complications in patients with diabetes includes antihypertensives such as ACE inhibitors and ARBs, statins, aspirin, antiplatelets, and glycemic control agents [96]. If patients smoke, smoking cessation is also highly recommended, as smoking increases the risk for macrovascular diabetes complications by 2–4 times [97, 98].

Hypertension ultimately damages the endothelium of blood vessel walls, preventing endothelial cells from secreting vasodilatory and antithrombotic substances and causing pathologic alteration of vessel walls to promote atherosclerosis, leading to CVD, PVD, and stroke [99]. Antihypertensives such as ACE inhibitors and ARBs can, therefore, prevent these outcomes in patients with diabetes who also have hypertension. Statins function by reducing cholesterol synthesis and lipid deposition in the fatty plaques that define CVD, PVD, and stroke [100]. Aspirin and antiplatelets reduce blood clotting, which is an integral component of thrombogenesis following plaque rupture, leading to MI in patients with diabetes mellitus and CVD.

Glycemic control agents are the typical treatment for diabetes mellitus. These either reduce serum glucose directly (exogenous insulin, sulfonylureas) or increase insulin sensitivity (metformin, thiazolidinediones). Ultimately, reduced quantities of advanced glycation end products and reduced oxidative stress exist, which are believed to contribute to vasoconstriction, inflammation, and thrombosis in CVD, PVD, and stroke [101].

Given the potential long-term impacts of metabolic memory, early and aggressive management of blood glucose levels is crucial to minimizing the risk of vascular complications. Strategies that focus on achieving and maintaining near-normal glucose levels from the onset of diabetes have been shown to reduce the progression of both microvascular and macrovascular complications associated with metabolic memory [37].

Cost

Diabetes mellitus leads to various comorbidities and, therefore, poses a high burden of illness on the healthcare system. As of 2022, the total cost of diabetes in the US was $419 billion [11]. Patients with diabetes incur $19,736 of medical expenditures a year, with $12,022 being attributable to diabetes. Of this, 17% goes towards glycemic control medications. Patients with diabetes must spend, on average, 2.6 times more on medical costs than if they had not had diabetes [11].

One of the greatest contributors to diabetes burden of care is the cost of medications other than those for glycemic control [102]. ACE inhibitor/ARB therapy is not very costly, costing a mean of $6.74 and $2.52 for commercially insured and Medicare patients, respectively [103]. In 2019, the mean out-of-pocket cost for statins was $30, with a significant percentage of the cost covered by insurance [104].

Pharmacological Therapies

Therapies used to treat diabetes and CVD include SGLT2 inhibitors and GLP-1 agonists, such as empagliflozin and liraglutide. These medications have been shown to reduce cardiovascular mortality and all-cause mortality in patients with diabetes and CVD [105–107]. SGLT2 inhibitors inhibit glucose reuptake in the renal tubules, reducing serum glucose [108]. SGLT2 inhibitors are also the only known medication to reduce mortality rates in individuals experiencing heart failure with preserved ejection fraction [109]. GLP-1 agonists have also been shown to reduce adverse cardiovascular events in patients with diabetes by promoting myocardial glucose utilization, inhibiting apoptosis, and reducing oxidative stress [110]. SGLT2 inhibitors have been on the market since 2013 and GLP-1 agonists since 2005.

Research into new targets for drug therapy includes 11B hydroxysteroid dehydrogenase (11B-HSD), adiponectin, meteoric-like (Metrnl), pigment epithelium-derived factor (PEDF), Vaspin, and G-protein coupled estrogen receptor (GPER) [111]. Gene therapy is another potential diabetes treatment under study.

11B-HSD is a precursor to glucocorticoid (i.e. cortisol) synthesis [112]. Glucocorticoids are hormones known to cause increased serum glucose and a state of insulin resistance. By reducing the activity of 11B-HSD, researchers postulate that endogenous glucocorticoid production can be decreased, leading to improved insulin sensitivity and decreased serum glucose levels.

Adiponectin is a hormone produced by adipocytes [113]. It is decreased in diabetes and obesity, and this is believed to contribute to the state of insulin resistance found in diabetes and metabolic syndrome [114]. By maintaining adequate quantities of adiponectin in patients with diabetes, researchers believe insulin sensitivity can be increased.

Metrnl is a cytokine secreted by white adipose tissue that maintains glucose homeostasis and cardiovascular function, among other functions [115]. It is believed to exert its effects through the PPARγ pathway, thereby increasing insulin sensitivity [116]. The PPARγ pathway is also used by the thiazolidinedione drug class of diabetes medications, which function as agonists for PPARγ [117]. Metrnl has also been found to promote adipose tissue browning, improving glucose tolerance [118]. These effects of

Metrnl make it a promising candidate for future research.

PEDF, Vaspin, and GPER are other research targets that function at the insulin receptor substrate, kallikrein insulin degradation pathway, and estrogen signaling pathways, respectively [111]. All of these pathways ultimately increase insulin sensitivity or decrease serum glucose, making them potential targets for new therapy.

Gene therapy is another area of interest for managing diabetes. Patients can have a viral vector implanted in them that suppresses autoreactive T-cells from destroying insulin-producing cells in the Islets of Langerhans. This can increase endogenous insulin production in patients with diabetes whose disease is caused by autoimmune destruction [119].

Impact of Antidiabetic Agents on Cardiovascular Outcomes

Many antidiabetic agents not only improve glycemic control but also offer cardiovascular benefits, particularly in reducing the risk of major cardiovascular events such as MI, stroke, and heart failure [70]. The mechanisms underlying these CV outcomes vary depending on the drug class, but several agents show significant promise in improving long-term outcomes for patients with T2DM.

SGLT2 Inhibitors SGLT2 inhibitors, such as empagliflozin and canagliflozin, reduce cardiovascular risk through several mechanisms beyond glucose control [120]. By promoting glucosuria (increased glucose excretion through urine), these agents decrease blood pressure, body weight, and arterial stiffness [121]. Additionally, SGLT2 inhibitors reduce preload and afterload on the heart by improving diuresis and natriuresis, which results in lower cardiovascular stress, particularly in patients with heart failure. Studies have shown that these agents significantly reduce the risk of hospitalization for heart failure and cardiovascular mortality, even in patients without diabetes, highlighting their role in direct cardiovascular protection [122].

GLP-1 Receptor Agonists GLP-1 receptor agonists, such as liraglutide and semaglutide, have been shown to reduce major adverse cardiovascular events, including stroke, MI, and cardiovascular death [123]. The underlying mechanisms involve improvements in glycemic control and anti-inflammatory and anti-atherosclerotic effects [124]. GLP-1 agonists reduce inflammation by decreasing oxidative stress and modulating inflammatory cytokine production, thus reducing endothelial dysfunction and slowing the progression of atherosclerosis [125]. Furthermore, GLP-1 agonists improve lipid profiles by lowering triglycerides and increasing high-density lipoprotein cholesterol, contributing to better cardiovascular outcomes [126].

Metformin Metformin, one of the most commonly prescribed drugs for T2DM, has long been recognized for its cardiovascular benefits [127]. The drug improves insulin sensitivity, reduces hepatic glucose production, and lowers fasting blood glucose levels [128]. Beyond these effects, metformin also reduces oxidative stress and chronic inflammation, both of which are key drivers of cardiovascular complications in diabetes [129]. Metformin has been associated with a reduction in the incidence of cardiovascular events, especially in high-risk populations [130].

Thiazolidinediones (TZDs) Thiazolidinediones, such as pioglitazone, act as PPAR-gamma agonists, which help improve insulin sensitivity and have anti-inflammatory effects [131]. These agents lower the risk of cardiovascular events primarily through their ability to improve endothelial function, reduce inflammation, and slow the progression of atherosclerosis [132]. However, their use must be carefully monitored due to the potential risk of heart failure, as TZDs can cause fluid retention [133].

DPP-4 Inhibitors While dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin) primarily enhance incretin activity and improve glycemic control, their cardiovascular effects are generally neutral [134]. Unlike SGLT2 inhibitors and GLP-1 agonists, DPP-4 inhibitors do not significantly reduce the risk of major cardio-

vascular events, but they are considered safe in patients with established cardiovascular disease [135].

CONCLUSION

Diabetes mellitus presents a significant public health challenge, marked by early mortality and a broad spectrum of macrovascular and microvascular complications. The economic burden of managing diabetes in the United States is substantial, necessitating improved patient education and ongoing development of therapeutic strategies. This review highlights various lifestyle modifications, such as exercise and dietary changes, and discusses traditional pharmacological treatments, including SGLT-2 inhibitors, ACE inhibitors, and GLP-1 agonists. Additionally, emerging therapies targeting cytokine activation, adiponectin regulation, and other pathways show promise in enhancing insulin sensitivity and glucose control. Advancements in diabetes mellitus management and education are essential for leading to optimal patient outcomes and a better quality of life for individuals with highly prevalent systematic diseases.

Author Contribution. All authors listed have made a direct and intellectual contribution to the work. Study design and drafting of the manuscript and critical revision of the manuscript for important intellectual content: Kazi Islam, Rahib Islam, Ivan Nguyen, Hassan Malik, Humza Pirzadah, Barsha Shrestha, Isabella B. Lentz, Sahar Shekoohi and Alan D. Kaye.

Funding. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Alan D Kaye is an Editorial Board member of Advances in Therapy. Alan Kaye was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. All other authors (Kazi Islam, Rahib Islam, Ivan Nguyen, Hassan Malik, Humza Pirzadah, Barsha Shrestha, Isabella B. Lentz and Sahar Shekoohi) declare no conflict of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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