



Diabetes and Cardiovascular–Microvascular Disease: Pathophysiology, Clinical Recognition, and Therapeutic Strategies-Updated Review.

Amani Khamash Hassan Asiri⁽¹⁾, Saad Mohammed Saad Al Mawwash⁽²⁾, Khalid Omar Mohammed Muhanna⁽³⁾, Abdullah Ibrahim Mrer⁽⁴⁾, Aisha Dahal Mahnashi⁽⁵⁾, Abdulhakim Aqeel Burayk Alotaibi⁽⁶⁾, Rajaa Abdulmonem Mohammed Fallatah⁽⁷⁾

(1)Alharajh General Hospital, Asir Health Cluster, Saudi Arabia

(2)King Salman Hospital, Riyadh First Health Cluster, Saudi Arabia

(3)Farasan General Hospital, Ministry of Health, Saudi Arabia

(4)Jazan General Hospital, Ministry of Health, Saudi Arabia

(5)Al-Laqiyah Health Center, Jazan, Ministry of Health, Saudi Arabia

(6)Hail University, Ministry of Education, Saudi Arabia

(7)King Fahd Hospital, Madinah, Ministry of Health, Saudi Arabia

Abstract

Background: Diabetes mellitus is a major global metabolic disorder associated with progressive vascular injury and substantial morbidity and mortality. Chronic hyperglycemia, oxidative stress, inflammation, endothelial dysfunction, and advanced glycation end products contribute to both microvascular and macrovascular complications. Early recognition and comprehensive management of modifiable risk factors are therefore essential for reducing long-term vascular burden.

Aim: This review aimed to summarize the mechanisms underlying diabetes-associated vascular injury and examine contemporary approaches to prevention and management, with emphasis on lifestyle modification, dietary strategies, pharmacological therapies, and cardiovascular risk reduction.

Methods: A narrative review of published literature addressing diabetes mellitus, endothelial dysfunction, metabolic memory, vascular complications, lifestyle interventions, dietary patterns, and pharmacological management was undertaken. Evidence concerning glycemic control, weight management, physical activity, Mediterranean dietary patterns, intermittent fasting, antihypertensive and lipid-lowering therapies, and newer glucose-lowering agents was synthesized.

Results: Persistent hyperglycemia promotes oxidative stress, inflammation, AGE formation, protein kinase C activation, and endothelial dysfunction, contributing to retinopathy, nephropathy, neuropathy, coronary disease, stroke, and peripheral vascular disease. Metabolic memory may sustain vascular injury despite subsequent improvement in glycemic control. Weight reduction, regular physical activity, Mediterranean dietary patterns, behavioral modification, and structured education support metabolic and cardiovascular risk reduction. Pharmacological management increasingly incorporates cardiovascular and renal outcomes. SGLT2 inhibitors and GLP-1 receptor agonists provide important cardiovascular benefits beyond glucose lowering, while metformin remains a foundational therapy. Blood-pressure and lipid management remain essential components of vascular risk reduction.

Conclusion: Prevention and treatment of diabetes-associated vascular disease require early, sustained, and multifactorial intervention integrating glycemic control, lifestyle modification, cardiovascular risk management, and individualized pharmacotherapy.

Keywords: Diabetes mellitus; vascular disease; endothelial dysfunction; microvascular complications; macrovascular complications; metabolic memory; cardiovascular disease; SGLT2 inhibitors; GLP-1 receptor agonists; lifestyle modification.

Introduction

Diabetes mellitus is a chronic metabolic disorder characterized by persistent disturbances in glucose homeostasis and hyperglycemia. Type 1 diabetes mellitus results primarily from autoimmune destruction of pancreatic β -cells and an absolute deficiency of insulin, whereas type 2 diabetes mellitus (T2DM) develops mainly through insulin resistance combined with progressive impairment of insulin secretion. Although T2DM occurs frequently in middle-aged and older adults, its incidence is increasing among younger populations. Genetic

susceptibility interacts with modifiable factors such as unhealthy dietary patterns, excess body weight, physical inactivity, and sedentary behavior to promote the development and progression of T2DM [1]. The increasing prevalence of T2DM has created a major challenge for healthcare systems because prolonged hyperglycemia affects multiple organs and contributes to substantial morbidity, mortality, and healthcare expenditure. Vascular disease represents one of the major consequences of diabetes and is a major contributor to premature mortality among affected individuals [2]. Persistent hyperglycemia induces

several interrelated molecular and cellular abnormalities within the vascular system. These include increased production of reactive oxygen species (ROS), accumulation of advanced glycation end products (AGEs), activation of inflammatory pathways, endothelial dysfunction, and reduced bioavailability of nitric oxide (NO) [3]. These processes impair vascular homeostasis and promote oxidative stress, inflammation, endothelial injury, vascular smooth-muscle dysfunction, and atherosclerotic plaque development. Consequently, diabetes increases the risk of both macrovascular and microvascular disease. Macrovascular complications include coronary artery disease, cerebrovascular disease, and peripheral arterial disease, whereas microvascular complications include diabetic retinopathy, diabetic kidney disease, and diabetic neuropathy [4].

The clinical consequences of diabetic vascular injury can be severe. Diabetic retinopathy remains a major cause of vision impairment and blindness among working-age adults, while diabetes represents an important risk factor for chronic kidney disease [5,6]. Peripheral vascular disease, neuropathy, impaired wound healing, and infection also contribute to diabetic foot complications and lower-extremity amputation. Individuals with diabetes have been reported to have a substantially higher lifetime risk of amputation than individuals without diabetes [7]. These complications can lead to loss of functional independence, reduced quality of life, prolonged hospitalization, and increased healthcare utilization. Despite advances in prevention and treatment, the growing prevalence of diabetes continues to increase the population burden of vascular disease [8]. The epidemiological burden of diabetes further emphasizes the need for effective prevention and management. In 2021, the Centers for Disease Control and Prevention estimated that 38.4 million people in the United States had diabetes, representing approximately 11.6% of the population [9]. Globally, diabetes affected an estimated 10.5% of adults, and the number of affected individuals is expected to increase substantially during the coming decades [10]. This increase will place additional pressure on healthcare systems because diabetes requires long-term monitoring, pharmacological treatment, complication screening, and management of associated cardiovascular, renal, neurological, and ophthalmic conditions. In the United States, the economic burden of diagnosed diabetes was estimated at approximately US\$412.9 billion in 2022, while medical expenditure among people with diabetes was substantially higher than among those without diabetes [11].

Diabetes prevalence also varies across population groups. In the United States, reported prevalence differs among Hispanic or Latino, Black, Asian, and White populations [9]. These differences reflect the interaction of genetic susceptibility with social, environmental, behavioral, and economic

factors. Food availability, socioeconomic conditions, physical environment, healthcare access, health literacy, and opportunities for physical activity can influence diabetes risk and disease outcomes [12–14]. Because several determinants operate outside the direct control of healthcare professionals, prevention requires coordinated interventions involving patient education, population screening, lifestyle modification, primary care, and targeted management of individuals at increased risk. Understanding the relationship between diabetes and vascular injury is essential for healthcare professionals because vascular complications develop through interconnected metabolic, inflammatory, oxidative, and endothelial mechanisms. Early identification of cardiovascular and microvascular risk factors can support timely intervention and reduce preventable complications. Contemporary diabetes management therefore extends beyond glycemic control and includes blood pressure management, lipid management, weight management, smoking cessation, renal protection, cardiovascular risk reduction, regular screening for microvascular complications, and individualized pharmacological therapy. Emerging therapeutic approaches have further expanded the capacity to reduce cardiovascular and renal outcomes in selected patients with T2DM. Accordingly, this review examines the relationship between diabetes mellitus and vascular disease, with emphasis on the pathophysiological mechanisms responsible for vascular injury, major macrovascular and microvascular complications, associated risk factors, prevention strategies, and evolving therapeutic approaches. Understanding these mechanisms can support healthcare professionals in recognizing vascular complications at an early stage and applying an integrated approach to diabetes management. This article is based on previously published evidence and does not involve new studies involving human participants or animals conducted by the authors.

Mechanism of Vascular Endothelial Damage

Diabetes mellitus is a metabolic disorder characterized by chronic disturbances in glucose regulation and persistent hyperglycemia. Type 1 diabetes mellitus results mainly from pancreatic β -cell destruction and an absolute deficiency of insulin, whereas type 2 diabetes mellitus (T2DM) is primarily associated with insulin resistance and progressive impairment of insulin secretion. The global burden of diabetes continues to increase, with the International Diabetes Federation projecting that approximately one in eight adults could be living with diabetes by 2045, with T2DM accounting for more than 90% of cases [10]. This increasing prevalence has major implications for vascular health because prolonged exposure to hyperglycemia promotes endothelial dysfunction, oxidative stress, inflammation, thrombosis, and atherosclerosis. The vascular endothelium represents a key interface between circulating blood and the vessel wall and therefore has a central role in maintaining vascular homeostasis.

Under physiological conditions, endothelial cells regulate vascular tone through the coordinated release of vasodilator and vasoconstrictor mediators. Important vasodilators include nitric oxide (NO), prostacyclin I₂, and endothelium-derived hyperpolarizing factors, whereas vasoconstrictors include angiotensin II, thromboxane A₂, and endothelin-1 [15]. This balance allows the endothelium to regulate blood flow and vascular resistance while also limiting platelet activation, leukocyte adhesion, inflammation, oxidative injury, and abnormal vascular smooth-muscle proliferation [16]. Endothelial cells also contribute to the maintenance of an antithrombotic surface and regulate interactions between circulating blood cells and the vascular wall. Diabetes disrupts these functions through several interconnected metabolic pathways. The resulting endothelial dysfunction represents an early event in diabetic vascular disease and can precede clinically apparent cardiovascular complications.

A central feature of diabetic endothelial injury is impaired NO signaling. Endothelial NO synthase (eNOS) normally generates NO, which promotes vasodilation and exerts anti-inflammatory, antiplatelet, and antiproliferative effects. In diabetes, endothelial NO bioavailability decreases because NO production becomes impaired while its degradation increases [17]. Chronic hyperglycemia promotes the generation of reactive oxygen species (ROS), particularly superoxide anion (O₂^{•−}). Superoxide reacts rapidly with NO, reducing its availability and producing peroxynitrite. This reaction creates a cycle in which oxidative stress further reduces NO-dependent vascular protection [17,20]. Consequently, vessels become more prone to vasoconstriction, leukocyte adhesion, platelet activation, inflammation, and vascular remodeling. Peroxynitrite represents an important mediator of oxidative endothelial injury. It can promote lipid peroxidation, protein modification, DNA damage, and cellular dysfunction [17]. Peroxynitrite also oxidizes tetrahydrobiopterin (BH₄), an essential cofactor required for normal eNOS activity. When BH₄ availability decreases, eNOS can become uncoupled. Instead of generating NO, uncoupled eNOS produces additional superoxide. This process further increases oxidative stress and creates a self-perpetuating mechanism of endothelial dysfunction [17]. Thus, the relationship between hyperglycemia, ROS production, impaired NO signaling, and eNOS dysfunction is central to the development of diabetic vascular injury.

Oxidative stress develops when ROS generation exceeds the capacity of endogenous antioxidant systems to neutralize them. ROS include superoxide, hydroxyl radicals, and hydrogen peroxide. At controlled concentrations, ROS participate in normal cellular signaling, proliferation,

differentiation, and programmed cell death. Persistent overproduction, however, can damage lipids, proteins, DNA, and cellular membranes [19]. In diabetes, hyperglycemia activates several metabolic pathways that increase ROS generation. These include the polyol pathway, hexosamine pathway, protein kinase C pathway, NADPH oxidase activity, and pathways associated with the formation and accumulation of advanced glycation end products (AGEs) [21]. Mitochondrial dysfunction can also contribute to excessive ROS production under conditions of sustained metabolic stress. AGE formation represents another important mechanism linking chronic hyperglycemia with vascular damage. AGEs form through nonenzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids. Their accumulation can alter the structural and functional properties of vascular proteins. AGEs also interact with specific cellular receptors, particularly the receptor for advanced glycation end products, activating intracellular signaling pathways that promote oxidative stress and inflammation. These processes increase endothelial activation and contribute to vascular stiffness, impaired vasodilation, leukocyte recruitment, and atherosclerotic progression [18,21]. AGE accumulation therefore provides a mechanism through which prolonged hyperglycemia produces structural and functional changes in the vascular wall.

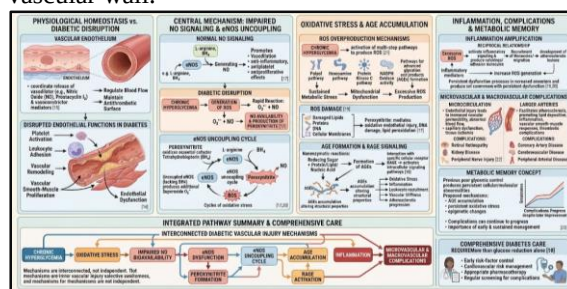


Figure-1: Mechanism of Vascular Damage.

Inflammation further amplifies diabetic endothelial damage. Excess ROS can activate inflammatory signaling pathways and increase the production of pro-inflammatory cytokines and adhesion molecules. Activated endothelial cells become more capable of recruiting circulating leukocytes to the vascular wall. Monocyte adhesion and migration into the intima contribute to the development of atherosclerotic lesions. In parallel, inflammatory mediators can increase ROS generation, creating a reciprocal relationship between oxidative stress and inflammation [18,20]. This interaction helps explain why endothelial dysfunction can persist and progress even when individual metabolic abnormalities fluctuate over time. Diabetes-associated endothelial dysfunction affects both microvascular and macrovascular beds. In the microcirculation, endothelial injury contributes to increased vascular permeability, abnormal blood flow regulation,

capillary dysfunction, and tissue ischemia. These changes contribute to diabetic retinopathy, diabetic kidney disease, and peripheral nerve injury. In larger arteries, endothelial dysfunction facilitates atherosclerosis by promoting lipid deposition, inflammation, vascular smooth-muscle responses, and thrombotic complications. Consequently, the same metabolic processes can contribute to coronary artery disease, cerebrovascular disease, and peripheral arterial disease [22]. The clinical expression depends on the vascular bed affected and the duration and severity of metabolic injury.

An important concept in diabetic vascular disease is metabolic memory. Previous periods of poor glycemic control can produce persistent cellular and molecular abnormalities that remain after subsequent improvement in glucose levels. Accumulation of AGEs, persistent oxidative stress, epigenetic changes, and other long-lasting cellular alterations have been proposed as mechanisms underlying this phenomenon [23]. Metabolic memory may therefore help explain why vascular complications can continue to progress despite later improvements in glycemic control. This concept reinforces the importance of early and sustained management of hyperglycemia rather than relying only on treatment after vascular complications become clinically evident. Overall, diabetic endothelial damage results from the interaction of hyperglycemia, oxidative stress, impaired NO signaling, AGE accumulation, inflammation, and abnormal vascular signaling. These mechanisms are interconnected rather than independent. Hyperglycemia activates metabolic pathways that increase ROS and AGE formation, oxidative stress reduces NO bioavailability and disrupts eNOS function, and endothelial dysfunction promotes inflammation and atherosclerotic processes. Over time, these changes contribute to both microvascular and macrovascular complications. Understanding these mechanisms provides an important foundation for healthcare professionals because prevention and treatment of diabetic vascular disease require more than glucose reduction alone. Early risk-factor control, cardiovascular risk management, appropriate pharmacotherapy, and regular screening for vascular complications are important components of comprehensive diabetes care.

Metabolic Memory: Mechanisms and Implications for Diabetes Management

Metabolic memory refers to the persistence of cellular and molecular abnormalities induced by previous periods of hyperglycemia, even after subsequent improvement in glycemic control [24]. This phenomenon provides one explanation for the continued progression of diabetic vascular complications despite later achievement of improved glucose levels. Prolonged hyperglycemia initiates a series of biochemical changes involving oxidative stress, advanced glycation end products (AGEs), inflammation, mitochondrial dysfunction, and

epigenetic alterations. Some of these changes can persist after glucose concentrations return toward the target range, allowing vascular injury to continue [24,25]. Metabolic memory therefore emphasizes the importance of early glycemic control and prevention of prolonged hyperglycemia rather than relying only on treatment after complications have developed. AGE accumulation represents an important mechanism underlying metabolic memory. Chronic hyperglycemia promotes the formation of AGEs, which can modify proteins and other cellular structures and activate the receptor for advanced glycation end products. This interaction stimulates oxidative and inflammatory signaling and contributes to endothelial dysfunction, vascular stiffness, and impaired tissue function [25]. Increased ROS production further amplifies cellular injury by damaging lipids, proteins, and DNA. Persistent oxidative stress can also interfere with normal endothelial signaling and reduce nitric oxide bioavailability. Together, these processes maintain an adverse vascular environment after glycemic improvement. Metabolic memory also affects vascular repair. Healthy endothelial cells can respond to vascular injury through mechanisms involving cellular proliferation, migration, and regeneration. Persistent oxidative stress and inflammation can impair these processes and reduce endothelial reparative capacity [26,27]. Reduced repair contributes to sustained endothelial dysfunction and may facilitate the development and progression of both microvascular and macrovascular complications [4]. This mechanism is particularly relevant to diabetes because endothelial injury occurs across multiple vascular beds, including the retina, kidneys, peripheral nerves, and cardiovascular system.

The effects of metabolic memory are not restricted to the vascular system. Persistent inflammatory and oxidative pathways may also contribute to insulin resistance. Chronic inflammation within adipose tissue can interfere with insulin signaling and promote further metabolic dysfunction [28]. Adipose tissue dysfunction can alter the production of adipokines involved in glucose and lipid regulation. Changes in mediators such as adiponectin and resistin may contribute to impaired insulin sensitivity and systemic inflammation [29,30]. Consequently, a cycle can develop in which metabolic dysfunction promotes inflammation and oxidative stress, while these processes further impair insulin action. Epigenetic mechanisms may also contribute to the persistence of metabolic memory. Hyperglycemia can produce changes in gene regulation that remain after glucose concentrations improve. These changes can influence inflammatory pathways, oxidative stress responses, endothelial function, and cellular repair. Such mechanisms provide a potential explanation for the prolonged biological effects of previous hyperglycemic exposure. However, metabolic memory is a complex process involving multiple

interacting mechanisms rather than a single molecular pathway [26]. The concept has important implications for diabetes management. Achieving glycemic control remains a central objective, but the potential persistence of vascular injury reinforces the importance of achieving appropriate control early in the course of diabetes. Preventing prolonged exposure to hyperglycemia may reduce the molecular changes that contribute to later complications. Management should therefore address multiple cardiovascular and metabolic risk factors rather than focusing exclusively on glycated hemoglobin.

Several antidiabetic therapies may influence pathways associated with metabolic memory in addition to lowering blood glucose. Metformin has been associated with effects on oxidative stress, endothelial function, and vascular biology, although its role in directly reversing established metabolic memory remains an area of investigation [31]. Sodium-glucose cotransporter 2 (SGLT2) inhibitors provide glucose-lowering effects and have demonstrated cardiovascular and renal benefits in selected patients with T2DM. Their biological effects may involve changes in inflammation, oxidative stress, hemodynamics, and metabolic signaling [32]. Glucagon-like peptide-1 receptor agonists also provide glucose-lowering and weight-related effects and have demonstrated cardiovascular benefits in appropriate patient populations. These effects may involve pathways beyond glycemic control. Thiazolidinediones, including pioglitazone, activate peroxisome proliferator-activated receptor- γ and improve insulin sensitivity. Their effects on adipose tissue metabolism and inflammatory signaling may influence mechanisms involved in insulin resistance and vascular dysfunction [33]. However, treatment selection should consider the patient's cardiovascular, renal, metabolic, and other clinical characteristics, together with the established benefits and adverse-effect profiles of each therapeutic class. Metabolic memory also supports the importance of comprehensive cardiovascular risk reduction. Blood pressure control, lipid management, smoking cessation, weight management, physical activity, dietary modification, and appropriate antidiabetic therapy can address several pathways that contribute to vascular disease. Regular screening for retinopathy, kidney disease, neuropathy, and cardiovascular risk allows complications to be detected before substantial functional damage occurs. Overall, metabolic memory demonstrates that the consequences of hyperglycemia may persist beyond the period of elevated glucose itself. AGEs, ROS, chronic inflammation, impaired endothelial repair, adipose tissue dysfunction, and epigenetic changes may contribute to this persistence [24–30]. For healthcare professionals, this concept reinforces the importance of early diagnosis, sustained glycemic control, and comprehensive risk-factor

management. Current evidence also supports consideration of therapies that provide cardiovascular and renal benefits beyond glucose reduction. Further research is required to clarify the molecular basis of metabolic memory and to determine whether targeted interventions can reverse established cellular changes and reduce long-term vascular complications.

Macrovascular and Microvascular Complications

Vascular complications account for a major proportion of diabetes-related morbidity and mortality and can affect almost every organ system. They are broadly classified into macrovascular and microvascular complications. Macrovascular disease results mainly from accelerated atherosclerosis and includes coronary artery disease (CAD), cerebrovascular disease, and peripheral artery disease (PAD). Microvascular disease is associated with abnormalities of small vessels, including basement membrane thickening, endothelial dysfunction, capillary occlusion, and increased vascular permeability. The major clinical manifestations are diabetic retinopathy, diabetic kidney disease, and diabetic neuropathy [34,35]. The development and progression of these complications are influenced by hyperglycemia, hypertension, dyslipidemia, obesity, smoking, age, diabetes duration, and genetic susceptibility [4,35–39]. Persistent hyperglycemia represents a central driver of diabetic vascular injury. Excess intracellular glucose promotes nonenzymatic glycation and the formation of advanced glycation end products (AGEs), increases reactive oxygen species (ROS), and activates several intracellular pathways associated with vascular dysfunction. These include the polyol pathway, protein kinase C signaling, hexosamine metabolism, and pathways involving endoplasmic reticulum stress and altered cellular signaling [4,35]. Hyperglycemia also increases mitochondrial superoxide production. Excess superoxide disrupts glycolytic metabolism and diverts glucose-derived substrates toward the formation of diacylglycerol, methylglyoxal, and other compounds involved in AGE formation. AGEs interact with their cellular receptors and activate inflammatory and oxidative pathways, promoting endothelial dysfunction and vascular remodeling [4,35]. Increased ROS production further reduces nitric oxide availability and promotes inflammation, endothelial senescence, and vascular cell injury [4,35,36].

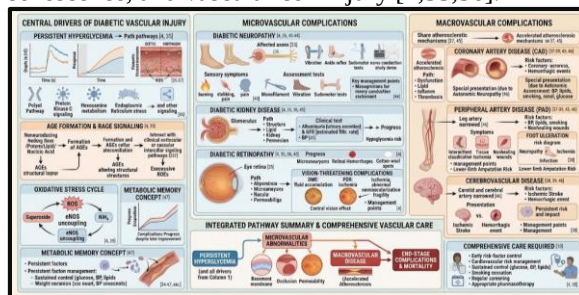


Figure-2: Macrovascular and Microvascular complications of diabetes.

Microvascular Complications

Diabetic neuropathy is a common microvascular complication involving the somatosensory and autonomic nervous systems. Distal symmetrical polyneuropathy is particularly common and preferentially affects longer axons, making the feet and lower limbs vulnerable to sensory loss and injury. Risk increases with poor glycemic control, longer diabetes duration, obesity, hypertension, smoking, age, and greater height [4,35]. Patients may develop burning, stabbing, shooting, or electric-like pain, numbness, and altered temperature or vibration perception [40]. Clinical assessment includes monofilament testing, vibration testing with a tuning fork, temperature discrimination, and assessment of ankle reflexes [41]. Nerve conduction studies can demonstrate reduced conduction velocity and provide objective evidence of peripheral nerve dysfunction [42]. Electromyography may assist in characterizing nerve involvement and excluding other causes of neuropathy [43]. Autonomic neuropathy can be evaluated through heart-rate variability, postural blood-pressure responses, and tests of sudomotor function. Management includes sustained glycemic control, lifestyle modification, foot protection, and pharmacological treatment of neuropathic symptoms [44]. Diabetic kidney disease is another major microvascular complication and an important cause of chronic kidney disease. Persistent hyperglycemia promotes glomerular endothelial dysfunction, oxidative stress, inflammation, and structural changes within the glomerulus. Clinically, assessment focuses on urinary albumin excretion and estimated glomerular filtration rate, together with evaluation of blood pressure and other renal risk factors [4,35,36,45]. Progressive disease can lead to substantial loss of renal function and end-stage kidney disease. Renal impairment also affects diabetes management because reduced renal glucose production and altered clearance of some antidiabetic medications can increase the risk of hypoglycemia. Early detection and management of albuminuria, blood pressure, glycemia, and cardiovascular risk are therefore important components of care. Diabetic retinopathy is a major cause of visual impairment and blindness among adults [5]. Chronic hyperglycemia damages retinal microvasculature through endothelial dysfunction, capillary occlusion, increased permeability, and retinal ischemia. Microaneurysms, retinal hemorrhages, and cotton-wool spots can occur as the disease progresses [4,35,36,45]. Two major vision-threatening complications are diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR). DME results from fluid accumulation involving the macula and can impair central and detailed vision. PDR develops when retinal ischemia stimulates abnormal neovascularization. Fragile new vessels can extend into the vitreous and contribute to

vitreous hemorrhage, fibrovascular proliferation, and retinal detachment [4,35,36,45]. Glycemic control, blood pressure management, regular retinal screening, and timely ophthalmological treatment are central to reducing vision loss.

Macrovascular Complications

Diabetes substantially increases the risk of CAD, PAD, and cerebrovascular disease. These conditions share atherosclerotic mechanisms involving endothelial dysfunction, lipid accumulation, inflammation, vascular remodeling, and thrombosis. Diabetes and insulin resistance promote a pro-atherogenic environment by altering vascular tone and permeability and facilitating the recruitment of inflammatory cells into the arterial wall [37,45]. Cardiovascular disease accounts for a large proportion of deaths among people with diabetes, making cardiovascular risk reduction a central component of diabetes management. CAD develops when atherosclerotic plaque reduces coronary blood flow. Diabetes increases the risk of myocardial infarction and other ischemic cardiovascular events [37–39,45,46]. Clinical presentation may differ between individuals, particularly when autonomic neuropathy alters pain perception. Therefore, cardiovascular risk assessment should form part of routine diabetes care, with attention to blood pressure, lipid levels, smoking status, renal function, glycemic control, and other established risk factors. PAD results from atherosclerotic narrowing of arteries supplying the lower extremities. Patients may develop intermittent claudication, reduced peripheral perfusion, rest pain, tissue ischemia, and nonhealing wounds [37–39,45,46]. Diabetes-related neuropathy can further increase the risk of unnoticed trauma and foot ulceration. The combination of neuropathy, ischemia, infection, and impaired wound healing can result in diabetic foot complications and increase the risk of lower-limb amputation. Early identification of peripheral vascular disease, regular foot examination, appropriate wound care, infection management, and timely vascular assessment can reduce the risk of severe limb complications [38,39,46]. Cerebrovascular disease is also strongly associated with diabetes. Atherosclerotic plaque affecting the carotid and cerebral circulation can reduce cerebral perfusion or contribute to thromboembolic events. Plaque rupture and thrombosis can result in ischemic stroke, while vascular structural abnormalities may also contribute to hemorrhagic events [38,39,46]. Stroke can produce substantial neurological disability and mortality, emphasizing the importance of cardiovascular risk-factor management in people with diabetes. Metabolic memory may further contribute to the progression of diabetic vascular complications. Previous exposure to hyperglycemia can produce persistent oxidative stress, AGE accumulation, inflammatory signaling, and endothelial dysfunction even after subsequent improvement in glycemic control [47]. This effect has particular relevance to

retinopathy and kidney disease and supports early intervention after diabetes diagnosis. Sustained control of glucose, blood pressure, and lipids, combined with smoking cessation, weight management, regular screening, and appropriate pharmacological therapy, is therefore important for reducing both microvascular and macrovascular complications.

Management and Treatment Options

Exercise is a core component of type 2 diabetes mellitus (T2DM) prevention and management. Regular physical activity improves glycemic control, insulin sensitivity, cardiovascular fitness, lipid metabolism, and blood pressure while supporting weight management. Aerobic activities such as brisk walking, running, cycling, swimming, and structured exercise programs can improve glucose regulation and reduce cardiovascular risk [48]. A meta-analysis by Liu et al. reported that moderate-intensity aerobic exercise reduced glycated hemoglobin (HbA1c) by approximately 0.6% over 12 weeks in individuals with T2DM [49]. These effects are clinically relevant because even modest reductions in HbA1c can contribute to improved metabolic control. Resistance training provides complementary benefits. Weightlifting, resistance-band exercises, and body-weight exercises increase or preserve skeletal muscle mass, which provides an important site for glucose disposal. Increased muscle mass and improved muscular insulin sensitivity enhance glucose uptake and can reduce blood glucose concentrations. Resistance training can also improve body composition, lipid profiles, and physical function. Combining aerobic and resistance exercise can therefore address several metabolic and cardiovascular risk factors simultaneously [48]. High-intensity interval training (HIIT) involves repeated periods of high-intensity exercise separated by recovery intervals. HIIT can improve insulin sensitivity, skeletal muscle oxidative capacity, mitochondrial function, and cardiovascular fitness [50,52]. It may also reduce HbA1c and provide metabolic benefits within a shorter exercise period than some traditional continuous exercise programs [49]. However, exercise intensity should be individualized according to physical capacity, comorbidities, age, treatment regimen, and cardiovascular status.

Exercise Intensity, Frequency, and Duration

Current recommendations support at least 150 minutes of moderate-to-vigorous aerobic activity each week for most adults with T2DM [51,53]. Moderate-intensity activity generally corresponds to approximately 50–70% of maximum heart rate and includes brisk walking, cycling, and swimming [54,55]. At this intensity, a person can usually talk but cannot comfortably sing during exercise [56]. Individuals with adequate fitness may undertake higher-intensity activity, generally corresponding to

approximately 70–85% of maximum heart rate, when appropriate [57]. Aerobic activity should generally be distributed across at least 3–5 days per week, with no more than two consecutive inactive days because prolonged inactivity can reduce the effects of exercise on insulin sensitivity and glucose regulation [58,59]. Sessions of approximately 30 minutes are practical for many individuals, although shorter bouts can be accumulated throughout the day to achieve the weekly target. Individuals seeking additional benefits related to weight management or cardiovascular fitness may benefit from progressively increasing activity toward approximately 300 minutes per week when appropriate [60].

Mechanisms of Exercise-Mediated Metabolic Benefits

Exercise improves glucose metabolism through several complementary mechanisms. One major mechanism involves increased expression and translocation of glucose transporter type 4 (GLUT4) to the skeletal muscle cell membrane. GLUT4 facilitates glucose entry into muscle cells, and exercise activates both insulin-dependent and insulin-independent pathways that increase GLUT4 translocation [61]. This mechanism allows skeletal muscle to increase glucose uptake even when insulin sensitivity is impaired. Regular physical activity also reduces chronic systemic inflammation, which contributes to insulin resistance. Exercise can influence inflammatory signaling and reduce the activity of pathways associated with pro-inflammatory mediators such as tumor necrosis factor- α and interleukin-6 [61]. These changes can improve insulin signaling and metabolic function. In addition, exercise promotes mitochondrial biogenesis and improves mitochondrial oxidative capacity in skeletal muscle, increasing the ability to oxidize glucose and fatty acids [61]. Overall, aerobic exercise, resistance training, and appropriately selected HIIT provide complementary approaches to T2DM management. A structured exercise program should be individualized and integrated with dietary management, pharmacological therapy, weight management, and cardiovascular risk reduction. Regular physical activity can therefore target both hyperglycemia and the vascular risk factors that contribute to diabetes-related complications.

Dietary Changes

The Mediterranean diet is widely recognized as an effective dietary approach for the prevention and management of type 2 diabetes mellitus (T2DM) because of its nutrient-dense composition and favorable effects on metabolic health [62]. It emphasizes fruits, vegetables, whole grains, legumes, nuts, olive oil, and other minimally processed foods, providing substantial fiber, monounsaturated fatty acids, and omega-3 fatty acids [63]. These components may improve insulin sensitivity, reduce glycemic load, and support healthier lipid profiles [64]. Adherence to

the Mediterranean diet has been associated with improved glycemic control and reduced cardiovascular risk in individuals with diabetes [65]. Studies have demonstrated reductions in HbA1c, with one analysis reporting an approximately 0.47% reduction compared with other dietary approaches [66]. The emphasis on low-glycemic-index foods limits rapid glucose absorption and postprandial glucose excursions [67]. Dietary fiber further delays gastric emptying and carbohydrate absorption, increases satiety, and supports weight management, which is particularly important in T2DM [68]. The cardiovascular benefits of the Mediterranean diet are also clinically relevant. Meta-analyses have reported lower risks of cardiovascular events, including myocardial infarction and stroke, among individuals adhering to Mediterranean dietary patterns [69]. These benefits may reflect improvements in glycemic control, dyslipidemia, blood pressure, inflammation, and endothelial function. Consequently, the Mediterranean diet addresses several interconnected metabolic and vascular risk factors and can be integrated into comprehensive diabetes management [70].

Nutrient Timing and Composition

Meal timing and macronutrient composition are important components of dietary diabetes management. Dietary patterns emphasizing low-glycemic-index carbohydrates, adequate fiber, appropriate portion sizes, lean protein, and unsaturated fats can help maintain more stable blood glucose concentrations [71]. Consistent meal timing may also reduce substantial fluctuations in glucose and insulin concentrations, although dietary recommendations should be individualized according to treatment regimen, physical activity, and patient preferences [72]. Including a variety of nutrient-dense foods helps meet nutritional requirements without excessive energy intake [73]. Combining complex carbohydrates with lean protein and healthy fats can moderate postprandial glucose responses and improve satiety [74]. Conversely, consuming large amounts of carbohydrate during a single meal may contribute to postprandial hyperglycemia. Distributing carbohydrate intake more evenly throughout the day may therefore support improved glycemic stability, particularly in patients receiving glucose-lowering medications [61].

Intermittent Fasting

Intermittent fasting has emerged as an alternative dietary pattern that may improve metabolic health in selected individuals with diabetes. Periods of caloric restriction can reduce circulating insulin concentrations and may enhance insulin sensitivity [75]. Because hyperinsulinemia and insulin resistance are associated with cardiometabolic risk, improvements in these parameters could potentially contribute to vascular protection [76]. Evidence also suggests that intermittent fasting may influence inflammatory pathways and other mediators involved

in diabetic complications. Reviews have reported potential reductions in inflammatory cytokines, advanced glycation end products, and alterations in adipokine signaling, including adiponectin [77,78]. These effects may improve insulin sensitivity and metabolic regulation and could contribute to reducing long-term cardiovascular risk. However, intermittent fasting should be individualized, particularly in patients receiving insulin or glucose-lowering therapies, because meal restriction may increase the risk of hypoglycemia and requires appropriate clinical monitoring.

Lifestyle Changes

Effective weight management is a cornerstone of diabetes prevention and management. Evidence indicates that a reduction of approximately 5–10% of body weight can improve insulin sensitivity and reduce metabolic risk, particularly among individuals with overweight or obesity [48]. Sustainable weight reduction is best achieved through a combination of dietary modification, regular physical activity, and behavioral interventions. Reduction of visceral adiposity is particularly important because excess visceral fat is strongly associated with insulin resistance, dyslipidemia, hypertension, and systemic inflammation. Consequently, weight loss can improve glycemic control and cardiometabolic risk factors while reducing the likelihood of cardiovascular complications. Lifestyle interventions should be individualized according to metabolic status, dietary preferences, physical capacity, and social circumstances. Dietary patterns such as the Mediterranean diet can complement physical activity by improving glucose regulation and cardiovascular risk profiles [79]. Intermittent fasting has also been investigated as an alternative dietary strategy, with evidence suggesting potential improvements in insulin sensitivity and reductions in oxidative stress in selected individuals [80]. However, dietary approaches should be appropriately supervised in patients receiving glucose-lowering medications because changes in meal timing or caloric intake may alter the risk of hypoglycemia.

Behavioral Modifications

Behavioral modification is essential for translating lifestyle recommendations into sustained changes in daily practice. Regular monitoring of glycemic status, appropriate stress management, smoking cessation, adequate sleep, and maintenance of physical activity are important components of diabetes prevention and long-term metabolic health [48]. Behavioral strategies should focus on establishing realistic and measurable goals rather than relying on short-term dietary or exercise changes. Chronic psychological stress may adversely affect glucose regulation through neuroendocrine and behavioral pathways. Stress-management approaches, including mindfulness-based interventions, yoga, relaxation techniques, and cognitive-behavioral

therapy, may support improved psychological well-being and facilitate adherence to healthy behaviors. Smoking cessation is particularly important because tobacco exposure is associated with insulin resistance, endothelial dysfunction, and increased cardiovascular risk. Patients should also be encouraged to monitor progress, identify barriers to adherence, and obtain support from family members, peers, and healthcare professionals [48].

Education and Support

Diabetes education and continuing support are fundamental to successful lifestyle modification. Structured programs that provide practical education on nutrition, physical activity, weight management, and behavioral strategies can improve self-management and contribute to diabetes prevention [48]. Health education also strengthens health literacy by enabling individuals to understand risk factors, recognize the consequences of unhealthy behaviors, and make informed decisions regarding diet, physical activity, medication adherence, and preventive care [81]. Educational interventions should address both immediate and long-term consequences of inadequate lifestyle adherence. Relevant topics include obesity, physical inactivity, unhealthy dietary patterns, smoking, cardiovascular risk, hyperglycemia, and diabetes-related complications [82]. Evidence also indicates that targeted health education can improve diabetes-related knowledge, attitudes, self-care practices, and glycemic control among individuals with T2DM [83]. Personalized coaching and regular follow-up can further improve the sustainability of lifestyle interventions. Healthcare professionals should assess individual barriers, establish achievable goals, provide feedback, and modify recommendations according to clinical progress [48]. Family and community support can reinforce these behaviors and reduce the likelihood of relapse. Thus, effective diabetes prevention requires an integrated approach combining weight management, behavioral modification, patient education, and continuous professional support.

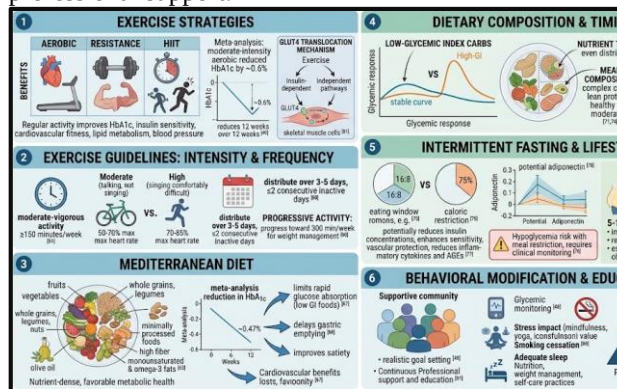


Figure-3: Lifestyle management of diabetes mellitus. Drug Therapeutics

Pharmacological management of diabetes aims not only to achieve adequate glycemic control but

also to prevent or delay microvascular and macrovascular complications. Maintaining HbA1c at approximately 6.5% or lower, when clinically appropriate, can reduce microvascular risk [84]. Blood pressure control and lipid-lowering therapy are also important in reducing vascular complications [85]. Fibrates may delay diabetic retinopathy progression [86], while ACE inhibitors and angiotensin receptor blockers (ARBs) can reduce retinopathy progression and are particularly important in patients with diabetic kidney disease and hypertension [87]. Retinopathy may additionally require vascular endothelial growth factor (VEGF) inhibitors, laser photocoagulation, or corticosteroid-based treatments to reduce vascular leakage, inflammation, and pathological angiogenesis [88,89]. Prevention of diabetic nephropathy requires optimization of blood pressure, dietary sodium intake, glycemic control, and renal protection [90]. ACE inhibitors and ARBs remain important therapies, whereas potentially nephrotoxic medications, including nonsteroidal anti-inflammatory drugs and aminoglycosides, should be avoided when possible [91]. Diabetic neuropathy is managed primarily through sustained glycemic control and symptom-directed treatment. Neuropathic pain may be treated with antidepressants, anticonvulsants such as gabapentin, topical capsaicin, and other analgesic approaches according to clinical circumstances [92–95]. Macrovascular complications, including coronary cardiovascular disease, stroke, and peripheral vascular disease, require multifactorial risk reduction. Common pharmacological strategies include antihypertensive agents, statins, antiplatelet therapy when indicated, and glucose-lowering medications [96]. Smoking cessation is particularly important because smoking substantially increases cardiovascular risk in diabetes [97,98]. ACE inhibitors and ARBs reduce vascular risk through blood-pressure control and additional vascular effects, whereas statins reduce atherogenic lipid concentrations and plaque progression [99,100]. Antiplatelet therapy can reduce thrombotic events in appropriately selected patients.

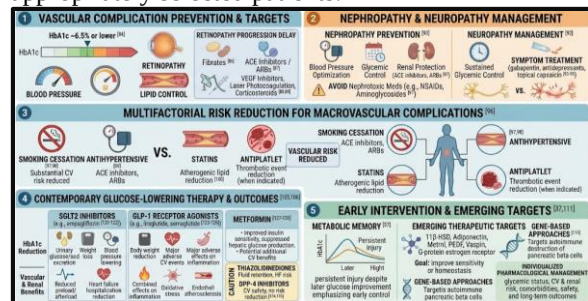


Figure-4: Drug therapy for management and control of diabetes mellitus.

Contemporary glucose-lowering therapy increasingly emphasizes cardiovascular and renal outcomes in addition to HbA1c reduction. SGLT2 inhibitors, including empagliflozin and canagliflozin,

promote urinary glucose and sodium excretion, lowering blood pressure, body weight, and cardiac preload and afterload. They substantially reduce hospitalization for heart failure and provide cardiovascular and renal benefits [105,106,120–122]. GLP-1 receptor agonists, including liraglutide and semaglutide, reduce major adverse cardiovascular events through combined effects on glycemic control, body weight, inflammation, oxidative stress, endothelial function, and atherosclerosis [123–126]. Metformin improves insulin sensitivity and suppresses hepatic glucose production and may provide additional cardiovascular benefits through reductions in oxidative stress and inflammation [127–130]. Other agents require individualized consideration. Thiazolidinediones such as pioglitazone improve insulin sensitivity through PPAR- γ activation but may cause fluid retention and increase heart-failure risk [131–133]. DPP-4 inhibitors generally provide cardiovascular safety without demonstrating the cardiovascular risk reduction observed with SGLT2 inhibitors and GLP-1 receptor agonists [134,135]. Early and sustained glycemic control remains important because metabolic memory may perpetuate vascular injury despite subsequent improvement in glucose levels [37]. Emerging therapeutic targets include 11 β -hydroxysteroid dehydrogenase, adiponectin, Metrnl, pigment epithelium-derived factor, vaspin, and G-protein-coupled estrogen receptor pathways, which may improve insulin sensitivity or glucose homeostasis [111–118]. Gene-based approaches targeting autoimmune destruction of pancreatic β -cells are also under investigation [119]. Collectively, pharmacological management should be individualized according to glycemic status, cardiovascular and renal risk, comorbidities, treatment safety, and long-term vascular outcomes.

Conclusion:

Diabetes mellitus is closely associated with progressive vascular injury driven by chronic hyperglycemia, oxidative stress, inflammation, advanced glycation, and endothelial dysfunction. These mechanisms contribute to microvascular complications, including retinopathy, nephropathy, and neuropathy, as well as macrovascular disease involving the coronary, cerebral, and peripheral circulation. Metabolic memory further emphasizes the importance of achieving effective glycemic control early and maintaining it over time. Prevention and management should therefore extend beyond glucose reduction and incorporate weight management, regular physical activity, healthy dietary patterns, smoking cessation, blood-pressure control, lipid management, and structured patient education. Contemporary pharmacological therapy increasingly prioritizes cardiovascular and renal protection. SGLT2 inhibitors and GLP-1 receptor agonists have demonstrated benefits extending beyond glycemic control, while established therapies such as metformin, statins, ACE inhibitors, and ARBs remain

important according to individual clinical indications. An integrated, patient-centered approach involving healthcare professionals is essential to reduce vascular complications, improve quality of life, and limit the substantial clinical and economic burden associated with diabetes.

References:

1. Sapra A, Bhandari P. Diabetes. In: StatPearls. Treasure Island: StatPearls Publishing; 2024. <https://www.ncbi.nlm.nih.gov/books/NBK560927/>.
2. Rask-Madsen C, King GL. Vascular complications of diabetes: mechanisms of injury and protective factors. *Cell Metab.* 2013;17:20–33. <https://doi.org/10.1016/j.cmet.2012.11.012>.
3. Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. *Eur Heart J.* 2013;34:2436–43. <https://doi.org/10.1093/eurheartj/ehi149>.
4. Yang D-R, Wang M-Y, Zhang C-L, Wang Y. Endothelial dysfunction in vascular complications of diabetes: a comprehensive review of mechanisms and implications. *Front Endocrinol.* 2024. <https://doi.org/10.3389/fendo.2024.1359255>.
5. Kropp M, Golubnitschaja O, Mazurakova A, Koklesova L, Sargheini N, Vo T-TKS, de Clerck E, Polivka J, Potuznik P, Polivka J, et al. Diabetic retinopathy as the leading cause of blindness and early predictor of cascading complications-risks and mitigation. *EPMA J.* 2023;14:21–42. <https://doi.org/10.1007/s13167-023-00314-8>.
6. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl.* 2011;2022(12):7–11. <https://doi.org/10.1016/j.kisu.2021.11.003>.
7. Molina CS, Faulk JB. Lower extremity amputation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. <https://www.ncbi.nlm.nih.gov/books/NBK546594/>.
8. Fang L, Sheng H, Tan Y, Zhang Q. Prevalence of diabetes in the USA from the perspective of demographic characteristics, physical indicators and living habits based on NHANES 2009–2018. *Front Endocrinol (Lausanne).* 2023;14:1088882. <https://doi.org/10.3389/fendo.2023.1088882>.
9. CDC National Diabetes Statistics Report. <https://www.cdc.gov/diabetes/php/data-research/index.html>. Accessed 30 May 2024.
10. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, Stein C, Basit A, Chan JCN, Mbanya JC, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022;183: 109119. <https://doi.org/10.1016/j.diabres.2021.109119>.
11. Parker ED, Lin J, Mahoney T, Ume N, Yang G, Gabbay RA, ElSayed NA, Bannuru RR.

- Economic costs of diabetes in the US in 2022. *Diabetes Care*. 2024;47:26–43. <https://doi.org/10.2337/dci23-0085>.
12. Bancks MP, Kershaw K, Carson AP, Gordon-Larsen P, Schreiner PJ, Carnethon MR. Association of modifiable risk factors in young adulthood with racial disparity in incident type 2 diabetes during middle adulthood. *JAMA*. 2017;318:2457–65. <https://doi.org/10.1001/jama.2017.19546>.
 13. US Preventive Services Task Force. Screening for prediabetes and type 2 diabetes: US preventive services task force recommendation statement. *JAMA*. 2021;326:736–43. <https://doi.org/10.1001/jama.2021.12531>.
 14. Hill-Briggs F, Adler NE, Berkowitz SA, Chin MH, Gary-Webb TL, Navas-Acien A, Thornton PL, Haire-Joshu D. Social determinants of health and diabetes: a scientific review. *Diabetes Care*. 2021;44:258–79. <https://doi.org/10.2337/dci20-0053>.
 15. Epstein FH, Vane JR, Änggård EE, Botting RM. Regulatory functions of the vascular endothelium. *N Engl J Med*. 1990;323:27–36. <https://doi.org/10.1056/NEJM199007053230106>.
 16. Xu S, Ilyas I, Little PJ, Li H, Kamato D, Zheng X, Luo S, Li Z, Liu P, Han J, et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond: from mechanism to pharmacotherapies. *Pharmacol Rev*. 2021;73:924–67. <https://doi.org/10.1124/pharmrev.120.000096>.
 17. Maruhashi T, Higashi Y. Pathophysiological association between diabetes mellitus and endothelial dysfunction. *Antioxidants*. 2021;10:1306. <https://doi.org/10.3390/antiox10081306>.
 18. Yuan T, Yang T, Chen H, Fu D, Hu Y, Wang J, Yuan Q, Yu H, Xu W, Xie X. New insights into oxidative stress and inflammation during diabetes mellitus-accelerated atherosclerosis. *Redox Biol*. 2019;20:247–60. <https://doi.org/10.1016/j.redox.2018.09.025>.
 19. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol*. 2023;97:2499–574. <https://doi.org/10.1007/s00204-023-03562-9>.
 20. Förstermann U, Xia N, Li H. Roles of vascular oxidative stress and nitric oxide in the pathogenesis of atherosclerosis. *Circ Res*. 2017;120:713–35. <https://doi.org/10.1161/CIRCRESAHA.116.309326>.
 21. Charlton A, Garzarella J, Jandeleit-Dahm KAM, Jha JC. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. *Biology*. 2020;10:18. <https://doi.org/10.3390/biology10010018>.
 22. Zakir M, Ahuja N, Surksa MA, Sachdev R, Kalariya Y, Nasir M, Kashif M, Shahzeen F, Tayyab A, Khan MSM, et al. Cardiovascular complications of diabetes: from microvascular to macrovascular pathways. *Cureus*. 2023;15:e45835. <https://doi.org/10.7759/cureus.45835>.
 23. Berezin A. Metabolic memory phenomenon in diabetes mellitus: Achieving and perspectives. *Diabetes Metab Syndr*. 2016;10(2 Suppl 1):S176–S183. <https://doi.org/10.1016/j.dsx.2016.03.016>.
 24. Bianchi C, Miccoli R, Del Prato S. Hyperglycemia and vascular metabolic memory: truth or fiction?. *Curr Diab Rep*. 2013;13(3):403–410. <https://doi.org/10.1007/s11892-013-0371-2>.
 25. Khalid M, Petroianu G, Adem A. Advanced glycation end products and diabetes mellitus: mechanisms and perspectives. *Biomolecules*. 2022;12:542. <https://doi.org/10.3390/biom12040542>.
 26. Dong H, Sun Y, Nie L, Cui A, Zhao P, Leung WK, Wang Q. Metabolic memory: mechanisms and diseases. *Signal Transduct Target Ther*. 2024;9:38. <https://doi.org/10.1038/s41392-024-01755-x>.
 27. Higashi Y. Roles of oxidative stress and inflammation in vascular endothelial dysfunction-related disease. *Antioxidants (Basel)*. 2022;11:1958. <https://doi.org/10.3390/antiox11101958>.
 28. Zatterale F, Longo M, Naderi J, Raciti GA, Desiderio A, Miele C, Beguinot F. Chronic adipose tissue inflammation linking obesity to insulin resistance and type 2 diabetes. *Front Physiol*. 2020;10:1607. <https://doi.org/10.3389/fphys.2019.01607>.
 29. Farruggia MC, Small DM. Effects of adiposity and metabolic dysfunction on cognition: a review. *Physiol Behav*. 2019;208: 112578. <https://doi.org/10.1016/j.physbeh.2019.112578>.
 30. Feijóo-Bandín S, Aragón-Herrera A, Moraña-Fernández S, Anido-Varela L, Tarazón E, Roselló-Lletí E, Portolés M, Moscoso I, Gualillo O, González-Juanatey JR, et al. Adipokines and inflammation: focus on cardiovascular diseases. *Int J Mol Sci*. 2020;21:7711. <https://doi.org/10.3390/ijms21207711>.
 31. Triggie CR, Marei I, Ye K, Ding H, Anderson TJ, Hollenberg MD, Hill MA. Repurposing metformin for vascular disease. *Curr Med Chem*. 2023;30:3955–78. <https://doi.org/10.2174/0929867329666220729154615>.
 32. Youssef ME, Yahya G, Popoviciu MS, Cavalu S, Abd-Eldayem MA, Saber S. Unlocking the full

- potential of SGLT2 inhibitors: expanding applications beyond glycemic control. *Int J Mol Sci*. 2023;24:6039. <https://doi.org/10.3390/ijms24076039>.
33. Duszka K, Gregor A, Guillou H, König J, Wahli W. Peroxisome proliferator-activated receptors and caloric restriction—common pathways affecting metabolism, health, and longevity. *Cells*. 2020;9:1708. <https://doi.org/10.3390/cells9071708>.
 34. Yachmaneni A, Jajoo S, Mahakalkar C, Kshirsagar S, Dhole S. A comprehensive review of the vascular consequences of diabetes in the lower extremities: current approaches to management and evaluation of clinical outcomes. *Cureus*. 2023;15:e47525. <https://doi.org/10.7759/cureus.47525>.
 35. Ziegler D, Porta M, Papanas N, Mota M, Jermendy G, Beltramo E, Mazzeo A, Caccioppo A, Striglia E, Serhiyenko V, et al. The role of biofactors in diabetic microvascular complications. *Curr Diabetes Rev*. 2022;18: e250821195830. <https://doi.org/10.2174/1871527320666210825112240>.
 36. Crasto W, Patel V, Davies MJ, Khunti K. Prevention of microvascular complications of diabetes. *Endocrinol Metab Clin North Am*. 2021;50:431–55. <https://doi.org/10.1016/j.ecl.2021.05.005>.
 37. Li Y, Liu Y, Liu S, Gao M, Wang W, Chen K, Huang L, Liu Y. Diabetic vascular diseases: molecular mechanisms and therapeutic strategies. *Signal Transduct Target Ther*. 2023;8:152. <https://doi.org/10.1038/s41392-023-01400-z>.
 38. Paul S, Ali A, Katare R. Molecular complexities underlying the vascular complications of diabetes mellitus—a comprehensive review. *J Diabetes Complications*. 2020;34: 107613. <https://doi.org/10.1016/j.jdiacomp.2020.107613>.
 39. Schalkwijk CG, Stehouwer CDA. Vascular complications in diabetes mellitus: the role of endothelial dysfunction. *Clin Sci (Lond)*. 2005;109:143–59. <https://doi.org/10.1042/CS20050025>.
 40. Atmaca A, Ketenci A, Sahin I, Sengun IS, Oner RI, Erdem Tilki H, Adas M, Soyleli H, Demir T. Expert opinion on screening, diagnosis and management of diabetic peripheral neuropathy: a multidisciplinary approach. *Front Endocrinol (Lausanne)*. 2024;15:1380929. <https://doi.org/10.3389/fendo.2024.1380929>.
 41. Yang Z, Zhang Y, Chen R, Huang Y, Ji L, Sun F, Hong T, Zhan S. Simple tests to screen for diabetic peripheral neuropathy. *Cochrane Database Syst Rev*. 2018;2018:CD010975. <https://doi.org/10.1002/14651858.CD010975.pub2>.
 42. Novello BJ, Pobre T. Electrodiagnostic evaluation of peripheral neuropathy. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. <https://www.ncbi.nlm.nih.gov/books/NBK563169/>.
 43. Bains S, Rocha Cabrero F. Electrodiagnostic evaluation of ulnar neuropathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. <https://www.ncbi.nlm.nih.gov/books/NBK564408/>.
 44. Serhiyenko VA, Serhiyenko AA. Cardiac autonomic neuropathy: risk factors, diagnosis and treatment. *World J Diabetes*. 2018;9:1–24. <https://doi.org/10.4239/wjd.v9.i1.1>.
 45. Mota RI, Morgan SE, Bahnson EM. Diabetic vasculopathy: macro and microvascular injury. *Curr Pathobiol Rep*. 2020;8:1–14. <https://doi.org/10.1007/s40139-020-00205-x>.
 46. Wei J, Tian J, Tang C, Fang X, Miao R, Wu H, Wang X, Tong X. The influence of different types of diabetes on vascular complications. *J Diabetes Res*. 2022;2022:3448618. <https://doi.org/10.1155/2022/3448618>.
 47. Testa R, Bonfigli AR, Prattichizzo F, La Sala L, De Nigris V, Ceriello A. The, “metabolic memory” theory and the early treatment of hyperglycemia in prevention of diabetic complications. *Nutrients*. 2017;9:437. <https://doi.org/10.3390/nu9050437>.
 48. Kirwan JP, Sacks J, Nieuwoudt S. The essential role of exercise in the management of type 2 diabetes. *CCJM*. 2017;84:S15–21. <https://doi.org/10.3949/ccjm.84.s1.03>.
 49. Liu J, Zhu L, Li P, Li N, Xu Y. Effectiveness of high-intensity interval training on glycemic control and cardiorespiratory fitness in patients with type 2 diabetes: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2019;31:575–93. <https://doi.org/10.1007/s40520-018-1012-z>.
 50. Francois ME, Little JP. Effectiveness and safety of high-intensity interval training in patients with type 2 diabetes. *Diabetes Spectr*. 2015;28:39–44. <https://doi.org/10.2337/diaspect.28.1.39>.
 51. Colberg SR, Sigal RJ, Yardley JE, Riddell MC, Dunstan DW, Dempsey PC, Horton ES, Castorino K, Tate DF. Physical activity/exercise and diabetes: a position statement of the American Diabetes Association. *Diabetes Care*. 2016;39:2065–79. <https://doi.org/10.2337/dc16-1728>.
 52. Atakan MM, Li Y, Koşar ŞN, Turnagöl HH, Yan X. Evidence-based effects of high-intensity interval training on exercise capacity and health: a review with historical perspective. *Int J Environ Res Public Health*. 2021;18:7201. <https://doi.org/10.3390/ijerph18137201>.
 53. Kirwan JP, Sacks J, Nieuwoudt S. The essential role of exercise in the management of type 2 diabetes. *Cleve Clin J Med*. 2017;84:S15–21. <https://doi.org/10.3949/ccjm.84.s1.03>.

54. Kanaley JA, Colberg SR, Corcoran MH, Malin SK, Rodriguez NR, Crespo CJ, Kirwan JP, Zierath JR. Exercise/physical activity in individuals with type 2 diabetes: a consensus statement from the American College of Sports Medicine. *Med Sci Sports Exerc.* 2022;54:353–68. <https://doi.org/10.1249/MSS.0000000000002800>.
55. What Is Moderate to Vigorous Exercise Intensity? PMC. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8493117/>. Accessed 3 Oct 2024.
56. Jones M, Bright P, Hansen L, Ihnatsenka O, Carek PJ. Promoting physical activity in a primary care practice: overcoming the barriers. *Am J Lifestyle Med.* 2019;15:158–64. <https://doi.org/10.1177/1559827619867693>.
57. Ito S. High-intensity interval training for health benefits and care of cardiac diseases—the key to an efficient exercise protocol. *World J Cardiol.* 2019;11:171–88. <https://doi.org/10.4330/wjc.v11.i7.171>.
58. Yang YJ. An overview of current physical activity recommendations in primary care. *Korean J Fam Med.* 2019;40:135–42. <https://doi.org/10.4082/kjfm.19.0038>.
59. Syeda USA, Battillo D, Visaria A, Malin SK. The importance of exercise for glycemic control in type 2 diabetes. *Am J Med Open.* 2023;9: 100031. <https://doi.org/10.1016/j.ajmo.2023.100031>.
60. Qiu Y, Fernández-García B, Lehmann HI, Li G, Kroemer G, López-Otín C, Xiao J. Exercise sustains the hallmarks of health. *J Sport Health Sci.* 2023;12:8–35. <https://doi.org/10.1016/j.jshs.2022.10.003>.
61. Yang D, Yang Y, Li Y, Han R. Physical exercise as therapy for type 2 diabetes mellitus: from mechanism to orientation. *Ann Nutr Metab.* 2019;74:313–21. <https://doi.org/10.1159/000500110>.
62. Derrick SA, Nguyen ST, Marthens JR, Dambacher LL, Sikalidis AK, Reaves SK. A Mediterranean-style diet improves the parameters for the management and prevention of type 2 diabetes mellitus. *Medicina (Kaunas).* 2023;59:1882. <https://doi.org/10.3390/medicina59101882>.
63. Khemayanto H, Shi B. Role of Mediterranean diet in prevention and management of type 2 diabetes. *Chin Med J (Engl).* 2014;127(20):3651–3656.
64. Mirabelli M, Chiefari E, Arcidiacono B, Corigliano DM, Brunetti FS, Maggisano V, Russo D, Foti DP, Brunetti A. Mediterranean diet nutrients to turn the tide against insulin resistance and related diseases. *Nutrients.* 2020;12:1066. <https://doi.org/10.3390/nu12041066>.
65. Sarsangi P, Salehi-Abargouei A, Ebrahimpour-Koujan S, Esmailzadeh A. Association between adherence to the Mediterranean diet and risk of type 2 diabetes: an updated systematic review and dose-response meta-analysis of prospective cohort studies. *Adv Nutr.* 2022;13:1787–98. <https://doi.org/10.1093/advances/nmac046>.
66. Milenkovic T, Bozhinovska N, Macut D, Bjekic-Macut J, Rahelic D, Velija Asimi Z, Burekovic A. Mediterranean diet and type 2 diabetes mellitus: a perpetual inspiration for the scientific world. A review. *Nutrients.* 2021;13:1307. <https://doi.org/10.3390/nu13041307>.
67. Sabarathinam S. A glycemic diet improves the understanding of glycemic control in diabetes patients during their follow-up. *Future Sci OA.* 2023;9:FSO843. <https://doi.org/10.2144/fsoa-2022-0058>.
68. Lattimer JM, Haub MD. Effects of dietary fiber and its components on metabolic health. *Nutrients.* 2010;2:1266–89. <https://doi.org/10.3390/nu2121266>.
69. Cai Z, Wang L, Zhang B, Zhu A. Mediterranean diet for cardiovascular disease: an evidence mapping study. *Public Health Nutr.* 2024;27:e118. <https://doi.org/10.1017/S1368980024000776>.
70. Jyotsna F, Ahmed A, Kumar K, Kaur P, Chaudhary MH, Kumar S, Khan E, Khanam B, Shah SU, Varrassi G, et al. Exploring the complex connection between diabetes and cardiovascular disease: analyzing approaches to mitigate cardiovascular risk in patients with diabetes. *Cureus.* 2023;15:e43882. <https://doi.org/10.7759/cureus.43882>.
71. Reynolds A, Mitri J. Dietary advice for individuals with diabetes. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, de Herder WW, Dhatariya K, Dungan K, Hofland J, Kalra S, Kaltsas G, Kapoor N, Koch C, Kopp P, Korbonits M, Kovacs CS, Kuohung W, Laferrère B, Levy M, McGee EA, McLachlan R, New M, Purnell J, Sahay R, Shah AS, Singer F, Sperling MA, Stratakis CA, Trencle DL, Wilson DP, editors. *Endotext.* South Dartmouth: MDText.com, Inc.; 2000.
72. Associations between timing and duration of eating and glucose metabolism: a nationally representative study in the US-PMC. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9919634/>. Accessed 6 Aug 2024.
73. Troesch B, Biesalski HK, Bos R, Buskens E, Calder PC, Saris WHM, Spieldenner J, Verkade HJ, Weber P, Eggersdorfer M. Increased intake of foods with high nutrient density can help to break the intergenerational cycle of malnutrition and obesity. *Nutrients.* 2015;7:6016–37. <https://doi.org/10.3390/nu7075266>.
74. Carreiro AL, Dhillon J, Gordon S, Jacobs AG, Higgins KA, McArthur BM, Redan BW, Rivera

- RL, Schmidt LR, Mattes RD. The macronutrients, appetite and energy intake. *Annu Rev Nutr.* 2016;36:73–103. <https://doi.org/10.1146/annurev-nutr-121415-112624>.
75. Klempel MC, Kroeger CM, Bhutani S, Trepanowski JF, Varady KA. Intermittent fasting combined with calorie restriction is effective for weight loss and cardio-protection in obese women. *Nutr J.* 2012;11:98. <https://doi.org/10.1186/1475-2891-11-98>.
 76. Breen DM, Giacca A. Effects of insulin on the vasculature. *Curr Vasc Pharmacol.* 2011;9:321–32. <https://doi.org/10.2174/157016111795495558>.
 77. Grajower MM, Horne BD. Clinical management of intermittent fasting in patients with diabetes mellitus. *Nutrients.* 2019;11:873. <https://doi.org/10.3390/nu11040873>.
 78. Golbidi S, Daiber A, Korac B, Li H, Essop MF, Laher I. Health benefits of fasting and caloric restriction. *Curr Diab Rep.* 2017;17:123. <https://doi.org/10.1007/s11892-017-0951-7>.
 79. Esposito K, Maiorino MI, Ceriello A, Giugliano D. Prevention and control of type 2 diabetes by Mediterranean diet: a systematic review. *Diabetes Res Clin Pract.* 2010;89(2):97–102. <https://doi.org/10.1016/j.diabres.2010.04.019>.
 80. Vasim I, Majeed CN, DeBoer MD. Intermittent fasting and metabolic health. *Nutrients.* 2022;14:631. <https://doi.org/10.3390/nu14030631>.
 81. Auld ME, Allen MP, Hampton C, Montes JH, Sherry C, Mickalide AD, Logan RA, Alvarado-Little W, Parson K. Health literacy and health education in schools: collaboration for action. *NAM Perspect.* 2020. <https://doi.org/10.31478/202007b>.
 82. Galaviz KI, Narayan KVM, Lobelo F, Weber MB. Lifestyle and the prevention of type 2 diabetes: a status report. *Am J Lifestyle Med.* 2015;12:4–20. <https://doi.org/10.1177/1559827615619159>.
 83. Chawla SPS, Kaur S, Bharti A, Garg R, Kaur M, Soin D, Ghosh A, Pal R. Impact of health education on knowledge, attitude, practices and glycemic control in type 2 diabetes mellitus. *J Family Med Prim Care.* 2019;8:261–8. https://doi.org/10.4103/jfmprc.jfmprc_228_18.
 84. Khalil H. Diabetes microvascular complications—a clinical update. *Diabetes Metab Syndr.* 2017;11(Suppl 1):S133–9. <https://doi.org/10.1016/j.dsx.2016.12.022>.
 85. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ.* 1998;317:703–13.
 86. ACCORD Study Group, ACCORD Eye Study Group, Chew EY, Ambrosius WT, Davis MD, Danis RP, Gangaputra S, Greven CM, Hubbard L, Esser BA, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N Engl J Med.* 2010;363:233–44. <https://doi.org/10.1056/NEJMoa1001288>.
 87. Wang B, Wang F, Zhang Y, Zhao S-H, Zhao W-J, Yan S-L, Wang Y-G. Effects of RAS inhibitors on diabetic retinopathy: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2015;3:263–74. [https://doi.org/10.1016/S2213-8587\(14\)70256-6](https://doi.org/10.1016/S2213-8587(14)70256-6).
 88. Abbate M, Cravedi P, Iliev I, Remuzzi G, Ruggenenti P. Prevention and treatment of diabetic retinopathy: evidence from clinical trials and perspectives. *Curr Diabetes Rev.* 2011;7:190–200. <https://doi.org/10.2174/157339911795843168>.
 89. Zhang X, Wang N, Schachat AP, Bao S, Gillies MC. Glucocorticoids: structure, signaling and molecular mechanisms in the treatment of diabetic retinopathy and diabetic macular edema. *Curr Mol Med.* 2014;14:376–84. <https://doi.org/10.2174/1566524014666140128114414>.
 90. Suckling RJ, He FJ, Macgregor GA. Altered dietary salt intake for preventing and treating diabetic kidney disease. *Cochrane Database Syst Rev.* 2010. <https://doi.org/10.1002/14651858.CD006763.pub2>.
 91. Fineberg D, Jandeleit-Dahm KAM, Cooper ME. Diabetic nephropathy: diagnosis and treatment. *Nat Rev Endocrinol.* 2013;9:713–23. <https://doi.org/10.1038/nrendo.2013.184>.
 92. Khalil H. Painful diabetic neuropathy management. *Int J Evid Based Healthc.* 2013;11:77–9. <https://doi.org/10.1111/1744-1609.12010>.
 93. Cohen K, Shinkazh N, Frank J, Israel I, Fellner C. Pharmacological treatment of diabetic peripheral neuropathy. *P T.* 2015;40:372–88.
 94. van Nooten F, Treur M, Pantiri K, Stoker M, Charokopou M. Capsaicin 8% patch versus oral neuropathic pain medications for the treatment of painful diabetic peripheral neuropathy: a systematic literature review and network meta-analysis. *Clin Ther.* 2017;39:787–803.e18. <https://doi.org/10.1016/j.clinthera.2017.02.010>.
 95. Spallone V. Management of painful diabetic neuropathy: guideline guidance or jungle? *Curr Diab Rep.* 2012;12:403–13. <https://doi.org/10.1007/s11892-012-0287-2>.
 96. Beckman JA, Creager MA. Vascular complications of diabetes. *Circ Res.* 2016;118:1771–85. <https://doi.org/10.1161/CIRCRESAHA.115.306884>.
 97. Lu JT, Creager MA. The relationship of cigarette smoking to peripheral arterial disease. *Rev Cardiovasc Med.* 2004;5:189–93.

98. Conen D, Everett BM, Kurth T, Creager MA, Buring JE, Ridker PM, Pradhan AD. Smoking, smoking cessation and risk of symptomatic peripheral artery disease in women: a prospective study. *Ann Intern Med.* 2011;154:719–26. <https://doi.org/10.1059/0003-4819-154-11-201106070-00003>.
99. Haller H. Hypertension, the endothelium and the pathogenesis of chronic vascular disease. *Kidney Blood Press Res.* 1996;19:166–71. <https://doi.org/10.1159/000174066>.
100. Ludwig S, Shen GX. Statins for diabetic cardiovascular complications. *Curr Vasc Pharmacol.* 2006;4:245–51. <https://doi.org/10.2174/15701610677698388>.
101. Davidson JA, Parkin CG. Is hyperglycemia a causal factor in cardiovascular disease? Does proving this relationship really matter? *Yes Diabetes Care.* 2009;32(Suppl 2):S331–333. <https://doi.org/10.2337/dc09-S333>.
102. Shore S, Basu T, Kamdar N, Brady P, Birati E, Hummel SL, Chopra V, Nallamotheu BK. Use and out-of-pocket cost of sacubitril-valsartan in patients with heart failure. *J Am Heart Assoc.* 2022;11: e023950. <https://doi.org/10.1161/JAHA.121.023950>.
103. Matyori A, Brown CP, Ali A, Sherbeny F. Statins utilization trends and expenditures in the US before and after the implementation of the 2013 ACC/AHA guidelines. *Saudi Pharm J.* 2023;31:795–800. <https://doi.org/10.1016/j.jsps.2023.04.002>.
104. The role of newer anti-diabetic drugs in cardiovascular disease. <https://www.acc.org/latest-in-cardiology/articles/2018/05/22/16/59/http%3a%2f%2fwww.acc.org%2flatest-in-cardiology%2farticles%2f2018%2f05%2f22%2f16%2f59%2fthe-role-of-newer-anti-diabetic-drugs-in-cv-disease>.
105. Neal B, Perkovic V, Matthews DR. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med.* 2017;377:2099. <https://doi.org/10.1056/NEJMc1712572>.
106. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2016;375:311–22. <https://doi.org/10.1056/NEJMoA1603827>.
107. Kalra S. Sodium glucose co-transporter-2 (SGLT2) inhibitors: a review of their basic and clinical pharmacology. *Diabetes Ther.* 2014;5:355–66. <https://doi.org/10.1007/s13300-014-0089-4>.
108. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner-La Rocca H-P, Choi D-J, Chopra V, Chuquiere-Valenzuela E, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med.* 2021;385:1451–61. <https://doi.org/10.1056/NEJMoA2107038>.
109. Ferhatbegović L, Mršić D, Macić-Džanković A. The benefits of GLP1 receptors in cardiovascular diseases. *Front Clin Diabetes Healthc.* 2023;4:1293926. <https://doi.org/10.3389/fcdhc.2023.1293926>.
110. Dhankhar S, Chauhan S, Mehta DK, Nitika, Saini K, Saini M, Das R, Gupta S, Gautam V. Novel targets for potential therapeutic use in diabetes mellitus. *Diabetol Metab Syndr.* 2023;15:17. <https://doi.org/10.1186/s13098-023-00983-5>.
111. Chapman K, Holmes M, Seckl J. 11 β -Hydroxysteroid dehydrogenases: intracellular gate-keepers of tissue glucocorticoid action. *Physiol Rev.* 2013;93:1139–206. <https://doi.org/10.1152/physrev.00020.2012>.
112. Hug C, Lodish HF. Diabetes, obesity, and Acrp30/adiponectin. *Biotechniques.* 2002;33:654. <https://doi.org/10.2144/02333dd01>.
113. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, et al. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat Med.* 2001;7:941–6. <https://doi.org/10.1038/90984>.
114. Li Z-Y, Song J, Zheng S-L, Fan M-B, Guan Y-F, Qu Y, Xu J, Wang P, Miao C-Y. Adipocyte Metn1 antagonizes insulin resistance through PPAR γ signaling. *Diabetes.* 2015;64:4011–22. <https://doi.org/10.2337/db15-0274>.
115. Li Z, Gao Z, Sun T, Zhang S, Yang S, Zheng M, Shen H. Meteorin-like/Metn1, a novel secreted protein implicated in inflammation, immunology, and metabolism: a comprehensive review of preclinical and clinical studies. *Front Immunol.* 2023;14:1098570. <https://doi.org/10.3389/fimmu.2023.1098570>.
116. Chiarelli F, Di Marzio D. Peroxisome proliferator-activated receptor-gamma agonists and diabetes: current evidence and future perspectives. *Vasc Health Risk Manag.* 2008;4:297–304. <https://doi.org/10.2147/vhrm.s993>.
117. Rao RR, Long JZ, White JP, Svensson KJ, Lou J, Lokurkar I, Jedrychowski MP, Ruas JL, Wrann CD, Lo JC, et al. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. *Cell.* 2014;157:1279–91. <https://doi.org/10.1016/j.cell.2014.03.065>.
118. Garcia-Beltran C, Navarro-Gascon A, López-Bermejo A, Quesada-López T, de Zegher F, Ibáñez L, Villarroya F. Meteorin-like levels are associated with active brown adipose tissue in early infancy. *Front Endocrinol (Lausanne).*

2023;14:1136245.

<https://doi.org/10.3389/fendo.2023.1136245>.

Wong MS, Hawthorne WJ, Manolios N.
Gene therapy in diabetes. *Self Nonself*. 2010;1:165–
75. <https://doi.org/10.4161/self.1.3.12643>..