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Micro and Macrovascular Complications in Diabetes Mellitus

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Abstract

Hyperglycaemia is the hallmark of diabetes mellitus. It is a complicated chronic metabolic disease. These problems, which have long-term detrimental effects on key organs, including the eyes, kidneys, heart, and brain, and increase patient mortality, can be categorized as either microvascular or macrovascular complications based on the various pathophysiological causes. The incidence and prevalence of diabetes mellitus have dramatically increased in recent years, making it a serious worldwide health concern. Furthermore, as more people embrace a Western diet and lifestyle, the incidence is predicted to keep rising. About one-third to one-half of diabetics suffer from organ and tissue damage as a result of the disease's strong correlation with both microvascular and macrovascular complications such as retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular). Vascular problems contribute significantly to diabetes mellitus (DM), globally accounting for 26.8% of cases. About 20% to 30% of diabetic patients experience macrovascular problems, which greatly increase the morbidity and death rate of type 2 diabetes. Patients with diabetes have significant increases in morbidity and a severe reduction in their quality of life due to microvascular problems. In this review, we will discuss both macrovascular and microvascular complications of diabetes mellitus, its mechanism, novel diagnostic tools, and treatment strategies in detail.

Keywords

Diabetes Mellitus, Retinopathy, Neuropathy, Nephropathy, Cardiovascular Disease

1. Introduction

Diabetes is a chronic condition brought on by either insufficient insulin production

by the pancreas or inefficient insulin utilization by the body. One hormone that controls blood sugar is insulin. Uncontrolled diabetes frequently results in hyperglycaemia, also known as elevated blood glucose or elevated blood sugar, which, over time, causes major harm to numerous bodily systems, particularly the blood vessels and neurons. [1] Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM) are the two primary subtypes of DM. T1DM and T2DM are both traditionally caused by impaired insulin production and/or action, respectively. T1DM presents in children or adolescents, while T2DM is thought to affect middle-aged and older adults who have prolonged hyperglycaemia due to poor lifestyle and dietary choices. [1] About one-third to one-half of diabetics suffer from organ and tissue damage as a result of the disease's strong correlation with both microvascular and macrovascular complications. [2] Anatomical, structural, and functional abnormalities that result in multiorgan dysfunction are among the vascular changes associated with diabetes. [3] Patients are more likely to experience a variety of vascular complications as their diabetes worsens; these consequences can be categorized as either microvascular or macrovascular, depending on the underlying pathophysiology. Numerous tissues, including those of the eye, heart, kidney, skin, and neurons, are affected pathologically and functionally by microvascular disorders. Depending on which tissues are impacted, these alterations are conventionally referred to as diabetic retinopathy (DR), nephropathy, peripheral neuropathy, and autonomic neuropathy, respectively. [4] Cardiovascular-disease (CVD), cerebrovascular disease (CeVD), and peripheral arterial disease (PAD) lesions are examples of macrovascular illnesses that impact big blood vessels like arteries and veins. About 20% to 30% of diabetic individuals experience these consequences, which greatly increase the morbidity and death rate of type 2 diabetes. [4] Activation of the polyol pathway, production of advanced glycation end products, initiation of flux through the hexosamine pathway, altered expression and action of growth factors, activation of the diacylglycerol/protein kinase C pathway, and the generation of reactive oxygen species (ROS) and oxidative stress are some of the classical hypotheses that have been put forth in recent decades to explain the process of developing microvascular complications. [5] [6] Furthermore, there have been some new proposals for novel mechanisms of diabetes microvascular problems. For example, the roles of long noncoding RNAs in mesangial cell proliferation and fibrosis, inflammatory processes, extracellular matrix accumulation in the glomeruli and tubular injury, aberrant neovascularization, and neuronal dysfunction are some of the possible mechanisms of long noncoding RNAs in the development of diabetic nephropathy (DN) and DR. [7] [8] Damage to the vascular endothelium is thought to be the primary pathogenic process underlying macrovascular problems. Additionally, poor platelet activity may raise the risk of thrombosis and the advancement of atherosclerosis, both of which are linked to the onset and progression of macrovascular problems associated with diabetes. [9] Through several pathogenetic pathways, hyperglycemia, obesity, insulin resistance, and other variables enhance the production of ROS, which in turn reduces NO

activity through their NO-inactivating impact. Because NO is essential for preserving endothelial cell function, obesity and insulin resistance cause endothelial dysfunction, which in turn causes atherosclerotic alterations because of decreased NO activity. [10]

2. Incidence and Prevalence

In 1990, 7% of adults aged 18 and over had diabetes; by 2022, that number had risen to 14%. [11] In 2022, over half (59%) of persons with diabetes who were 30 years of age or older did not take any medication for their condition. Low- and middle-income nations have the lowest rates of diabetes treatment coverage. [1] Diabetes was the direct cause of 1.6 million fatalities in 2021, and 47% of all diabetes-related deaths happened in people under 70. High blood glucose is responsible for about 11% of cardiovascular fatalities, and diabetes also contributed to another 530,000 deaths from kidney disease. [12] Diabetes-related deaths have been rising since 2000. In contrast, between 2000 and 2019, the likelihood of dying from diabetes between the ages of 30 and 70 fell by 20% worldwide. [1] Diabetes causes premature death and significantly shortens a person's lifespan. Diabetes was directly responsible for 1.6 million fatalities in 2016. Globally, an estimated 415 million individuals have diabetes, and by 2040, that number is expected to increase to 642 million. Particularly noticeable is the incidence of diabetes in middle- and low-income nations. With over 109 million diabetics, China leads the world in the number of cases, according to the International Diabetes Federation (IDF). India comes in second with 69 million, the United States with 29 million, Brazil with 14 million, and the Russian Federation with 12 million. [13]

In 2022, a study done by Suzanne V Arnold *et al.* [14] With a mean age of (56.9 ± 11.7) years, a duration of (5.7 ± 5.1) years, and a HbA1c of 8.4% ± 1.7%, 11,357 individuals with type 2 diabetes from 33 countries experienced a microvascular problem at enrollment (19.0%), most commonly neuropathy, and a macrovascular complication (13.2%), most commonly cardiovascular disease. 6.6% experienced an incident macrovascular complication, and 16.0% experienced an incident microvascular problem throughout the three-year follow-up period. 32.5% of patients experienced at least one microvascular complication, and 16.6% experienced at least one macrovascular complication at the conclusion of the three-year follow-up period. They said in the conclusion that patients with comparatively short durations of type 2 diabetes had a high 3-year incidence and prevalence of vascular problems, underscoring the necessity of early risk-factor adjustment.

A few US studies revealed a declining trend in T2DM complications over the past few decades, along with significant declines in older people's myocardial infarction (MI) and stroke. [15]-[17] Heart failure and peripheral artery disease were proposed as the most prevalent early cardiovascular symptoms in recent European investigations, which revealed a similar tendency. [18]-[20]

A study done by Jaejin An *et al.* 2021 [21] found 135,199 patients with T2D incidents. With a mean age of 58, 48% of the population was female. At the time

of T2D diagnosis, the prevalence of CVD was among the lowest at 3.3% (95% CI: 3.2% to 3.3%), while the greatest incidence of CKD was 12.3% (95% CI: 12.2% to 12.5%). Between 3.0 and 5.2 years was the median time to incidence of a T2D problem. The following conditions had high incidence rates (95% CI) of T2D complications: CVD (11.9, 95% CI: 11.7 to 12.2 per 1000 PY), CKD (21.2, 95% CI: 20.9 to 21.6 per 1000 PY), and peripheral neuropathy (26.9, 95% CI: 26.5 to 27.3 per 1000 PY). The 5-year incidence rates of T2D complications by diagnosis year showed a decreasing trend over time (p-value < 0.001). Higher incidence of CKD and CVD was linked to older age, non-Hispanic white race/ethnicity, sex, higher A1C, smoking, and hypertension.

3. Complications of Diabetes mellitus

There are two major complications of diabetes mellitus:

1) Microvascular Complications

2) Macrovascular Complications

3.1. Microvascular Complications

3.1.1. Diabetic Retinopathy

One of the main causes of visual impairment and blindness in diabetics is diabetic retinopathy (DR), a microvascular complication that can affect the peripheral retina, the macula, or both. [22]

1) Types of DR

DR can range in severity from non-proliferative and pre-proliferative to more severely proliferative DR, in which abnormal growth of new vessels occurs. [23] A vitreous haemorrhage or retinal detachment can cause total or partial vision loss, while retinal vessel leakage and ensuing macular oedema can cause central vision loss. [24] The prevalence of DR rises as diabetes is chronic. [25] Increased vascular permeability and capillary occlusion are two key findings in the retinal vasculature of non-proliferative diabetic retinopathy, which is the early stage of DR. Fundus photography can identify retinal diseases such as microaneurysms, haemorrhages, and hard exudates at this stage, even if the patients may not exhibit any symptoms. Proliferative DR is a more advanced stage of DR and is marked by neovascularization. During this stage, the patients may experience severe visual impairment when the new aberrant arteries flow into the vitreous (vitreous haemorrhage) or when tractional retinal detachment is present.

2) Etiology

Diabetic macular oedema is the most frequent cause of vision loss in DR patients. When the blood-retinal barrier (BRB) breaks down, fluid builds up in the macula both intra- and sub-retinally, causing swelling or thickening of the macula. [26]

In research involving individuals with both type 1 and type 2 diabetes, the majority of patients had some kind of DR after 30 years of diabetes, with more than half having proliferative DR. The highest prevalence of DR was found in those

with type 1 diabetes who were on insulin, and the lowest prevalence was found in those with type 2 diabetes who were diagnosed after the age of 30. [27] [28] About 10% of individuals with insulin resistance (prediabetes) have recently been found to have diabetic retinopathy, which has been linked to hypertension and a higher body mass index. [29] Pregnancy, renal disease, high homocysteine levels, tobacco usage, insulin treatment, abnormal blood lipid (*i.e.*, total cholesterol, low-density lipoprotein [LDL], and triglyceride) levels, and a younger age of onset were also linked to DR in other research. [30]

Visual image distortion and a reduction in visual acuity can result from DME, which can happen at any point during DR. [31]

In a study done by Wang *et al.* (2018) [31], 22 studies with a total of 10,427 newly diagnosed type 2 diabetics reported retinopathy. There were two studies from Oceania and Africa, but the majority of the research (n = 20) came from Asia. Studies have shown that Asia has the lowest and greatest prevalence of diabetic retinopathy, which ranges from 2% to 33%. The pooled prevalence of retinopathy, stratified by study region, was 11% (9% - 13%) in Asia, 13% (10% - 16%) in Africa, and 15% (8% - 25%) in Oceania (p-value = 0.469), indicating that regional variations did not explain the observed variability. [31]

Both the severity of hyperglycaemia and the presence of hypertension have been linked to the development of diabetic retinopathy (DR) in people with type 2 diabetes. According to Fong *et al.*, DR is responsible for about 10,000 new cases of blindness in the US. [32]

The relationship between DR and macrovascular problems has been the subject of numerous investigations. Researchers have examined retinal anomalies to uncover hints about the underlying pathophysiology of several cerebrovascular illnesses since the retinal microvasculature has embryologic and anatomical traits with cerebral circulation. [33] Retinopathy was linked to both the incidence of MI and cardiovascular disease (CVD) death in the World Health Organization Multinational Study of Vascular Disease in Diabetes. [34] Retinal microvascular abnormalities and widespread arteriolar constriction were linked to a higher risk of clinical stroke in the Atherosclerosis Risk in Communities study. [35]

3) Histologic Finding

The loss of pericytes is the first histological sign of DR. [36] Long, contractile cells called pericytes envelop the endothelial cells of tiny capillaries [37], helping to maintain capillary tone (dilatation and constriction), capillary development, and defense against ROS damage [38] [39] As a result, the loss of pericytes in DR would disrupt processes that shield capillaries from constant exposure to harmful chemicals (*i.e.*, normal homeostasis), capillary constriction (resulting in chronically dilated vessels), and new capillary production. Capillary basement membrane thickening [40], increased endothelial cell permeability, and the development of microaneurysms (*i.e.*, vessel wall weakness that causes the projection of a balloon-like sac) [41] are further microvascular alterations associated with DR.

4) Hyperglycemia and Retinal Microvasculopathy

It has long been known that DR is a microvascular condition. It is believed that hyperglycemia contributes significantly to the pathophysiology of retinal microvascular injury. Numerous metabolic processes, including the polyol route, the buildup of advanced glycation end products (AGEs), the protein kinase C (PKC) pathway, and the hexosamine pathway, have been linked to the vascular damage caused by hyperglycaemia [42].

Blood vessel dilatation and alterations in blood flow are the retinal blood vessels' initial reactions to hyperglycaemia. In diabetic patients, these alterations are thought to constitute a metabolic autoregulation that raises retinal metabolism [43]. Another characteristic of the early stages of DR is pericyte loss. Both in vitro and in vivo studies have demonstrated evidence of pericyte apoptosis induced by elevated hyperglycaemia [44] [45].

Loss of pericytes causes localized capillary wall outpouching since they are in charge of giving capillaries structural support. The earliest clinical indication of DR, microaneurysm development, is linked to this mechanism [46]. During the pathophysiology of DR, endothelial cell death and basement membrane thickening are also observed in addition to pericyte loss, and these factors together lead to the disruption of the BRB [47]. Moreover, capillary occlusion and ischemia are caused by a substantial loss of pericytes and endothelial cells. By activating hypoxia-inducible factor 1 (HIF-1), retinal ischemia/hypoxia causes VEGF to be upregulated [48]. Additional data indicated that the overexpression of VEGF is also triggered by the rise of phospholipase A2 (PLA2) in diabetics [49].

It is thought that VEGF, a major contributor to the development of PDR and DME, increases vascular permeability by causing tight junction proteins such as occludin and zonula occludens-1 (ZO-1) to become phosphorylated [50]. Furthermore, via activating mitogen-activated protein (MAP), VEGF, an angiogenic agent, stimulates the growth of endothelial cells [51]. Increased VEGF expression has been found in the vitreous of people with DME and proliferative DR, as well as in the retina of diabetic mice. [52] [53]

5) Molecular Mechanism of DR (Figure 1)

Numerous cellular pathways and possible molecular processes have been put up to explain the difficulties caused by diabetes. Increased polyol pathway flux, increased advanced glycation end-products (AGE) formation, abnormal signalling cascade activation, including the protein kinase C (PKC) pathway, increased oxidative stress, increased hexosamine pathway flux, and peripheral nerve damage are some of the most researched mechanisms in diabetic retinopathy. The pathophysiology of diabetic retinopathy is ultimately influenced by the upregulation of factors like insulin-like growth factor (IGF), stromal-derived factor-1 (SDF-1), vascular endothelial growth factor (VEGF), angiopoietins (Ang-2), tumor necrosis factor (TNF), and basic fibroblast growth factor-2 (bFGF) that are caused by increased oxidative stress, inflammation, and vascular occlusion. [54] [55] Numerous investigations have delineated the biochemical processes involved in the onset and advancement of diabetic retinopathy, yet no mechanism can be considered definitive.

Hyperglycemia, insulin resistance, a relative or complete lack of insulin action, and the emergence of diabetes-specific retinal disease are characteristics shared by all types of diabetes. [56] One of the main causes of vision impairment worldwide has been diabetic retinopathy. Pericyte loss, thickening of the basement membrane, microaneurysms, neovascularization, and disruption of the blood-retinal barrier are the fundamental characteristics of this illness. [57] Increased glucose flux via the polyol and hexosamine pathways, protein kinase C activation, and increased production of advanced glycation end products are molecular and metabolic processes linked to diabetic retinopathy. [58]

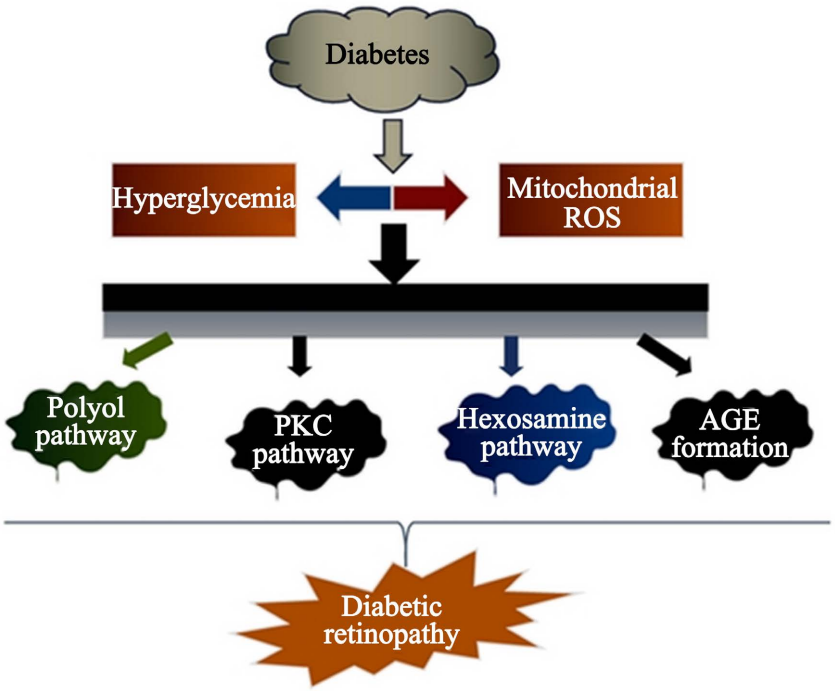

Figure 1. Four major mechanisms of DR.

3.1.2. Diabetic Nephropathy (Figure 2)

A dangerous and progressive adverse consequence of both type 1 and type 2 diabetes is diabetic nephropathy (DN). DN is the primary cause of end-stage renal disease (ESRD) [59] and usually begins as microalbuminuria, which develops into overt albuminuria (*i.e.*, elevated albumin levels in the urine, suggesting more severe renal dysfunction) and ultimately renal failure. [60] Proteinuria affects 5% - 20% of people with type 2 diabetes and 15% - 40% of people with type 1 diabetes. [61] The European Diabetes Prospective Complications Study found that among individuals with type 1 diabetes, the cumulative incidence of microalbuminuria over a 7.3-year period was 12.6%. [61] Nonetheless, a Danish 18-year follow-up research found that 33% of people with T1DM had the condition. [62] In a similar vein, T2DM patients in the UKPDS had an annual incidence of microalbuminuria of 2.0%, which rose to 25% ten years after diagnosis. [63] Native Americans, Asians, and African Americans were more likely than Caucasians to have diabetic

nephropathy. [61] According to CURES 45, microalbuminuria was 26.9% common in India, while overt diabetic nephropathy was 2.2%. [64]

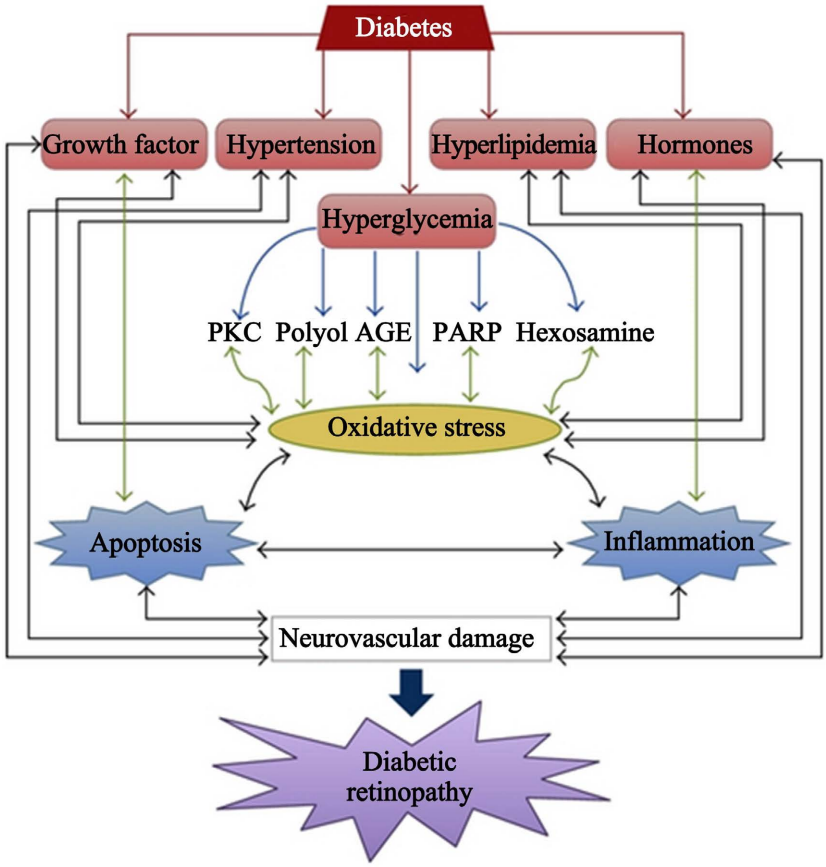

Figure 2. Hyperglycemia-induced biochemical alterations precipitated by mitochondria-driven oxidative stress leading to diabetic complications, including apoptosis, inflammation, and, ultimately, diabetic retinopathy.

1) Mechanism of Diabetic Nephropathy

The production of reactive oxygen species (ROS), the buildup of advanced glycation end product (AGE), and the activation of intracellular signaling molecules such as protein kinase C (PKC) are the pathogenic mechanisms that underlie diabetic nephropathy. [4] [65]

- In 2004-2005, Arora *et al.* [66] showed a substantial correlation between diabetic retinopathy and diabetic nephropathy in 50 newly diagnosed diabetic patients. Numerous investigations have also demonstrated a clear link between the existence of microalbuminuria and macrovascular problems. [67]
- In an observational study, Hägg *et al.* (2013) [68] found that 4083 patients with T1DM with 36,680 person-years of follow-up had a higher incidence of both cerebral haemorrhage and cerebral infarction in patients with severe diabetic nephropathy (SDR). It was discovered that SDR and nephropathy both independently raised the risk for every subtype of stroke.
- The Pittsburgh Epidemiology of Diabetes Complications study also confirmed

the higher incidence of stroke in diabetic nephropathy, showing that overt nephropathy increases the risk of ischemic stroke by 4.4 times (but not the risk of hemorrhagic stroke, likely because of the small sample size). Chinese patients have an increased incidence of cardiovascular events due to retinopathy and macroalbuminuria. [69]

3.1.3. Diabetic Neuropathy

Nearly half of people with diabetes have diabetic neuropathy, a potentially fatal condition that affects both peripheral and autonomic nerves. [70] The length of time and severity of hyperglycemia are closely correlated with the likelihood of developing diabetic neuropathy. Furthermore, some people may have hereditary characteristics that affect their likelihood of experiencing these issues. [67] Age, the duration of diabetes, tobacco use, dyslipidemia, hypertension (particularly diastolic), and poor glycemic management (*i.e.*, high glycation hemoglobin levels and reduced glucose tolerance) are risk factors for PN [71] [72] Increased height, cardiovascular disease (CVD), severe ketoacidosis (*i.e.*, elevated blood byproducts of fat metabolism), and microalbuminuria (*i.e.*, albumin in urine, indicating early renal dysfunction) are additional independent risk factors for PN. [73] Although this view is debatable, the pathophysiology of PN seems to be connected to both vascular and nonvascular metabolic processes, in contrast to that of DR. [74] [75]

1) Incidence and Prevalance

- Diabetic neuropathy is a very common illness that has a significant impact on patients by lowering quality of life (QOL), increasing falls, and generating discomfort. [76]
- In the United States, diabetic neuropathy and its complications cost about $10 billion a year. [77]
- Numerous research has evaluated the incidence and/or prevalence of neuropathy, albeit each study uses a different definition of the condition. Neuropathy prevalence estimates ranged from 1% to 4% in two population-based investigations that used door-to-door screening; 40% - 55% of these cases were related to diabetes. [78] [79] Similarly, after a neurologist's diagnostic work-up, diabetes was identified as the cause of neuropathy in more than half of the cases in another study. [80]
- With diabetes accounting for 32% of all cases, the incidence of neuropathy in the Netherlands [81] rises sharply with age, from <50 cases per 100,000 person-years in those under 50 to ~300 cases per 100,000 person-years in those over 75.
- Many epidemiological researches are limited to patients with either type 1 or type 2 diabetes, in addition to these studies assessing the incidence and prevalence of diabetic neuropathy in the general community. Compared to people with T1DM (2800 per 100,000 person-years), those with T2DM have a higher incidence of neuropathy (6100 per 100,000 person-years). [72] [73] [77]
- In contrast, neuropathy is equally common in people with T2DM (8% - 51%)

[74] [82] as it is in people with T1DM (11% - 50%). [83] [84] Crucially, 54% of patients with T1DM and 45% of those with T2DM develop neuropathy, making the prevalence considerably higher when silent neuropathy is taken into account. [82] There are likely a number of secondary causes for the increased occurrence of neuropathy in T2DM patients compared to those with T1DM or T2DM.

- With a similar prevalence in people with T2DM or T1DM, the increased incidence of neuropathy in T2DM patients is likely due to a variety of factors, such as variations in the underlying pathophysiology and the age at which diabetes first manifests.
- The length of the disease also affects the prevalence of diabetic neuropathy. In fact, after ten years of follow-up, the prevalence of diabetic neuropathy in T2DM patients rose from 8% to 42%. [84] In a group with very mild T2DM who maintained good metabolic control, individuals with newly diagnosed screen-detected T2DM [85] had a prevalence of diabetic neuropathy of 13% at the study entrance, with a cumulative incidence of 10% over the 13-year follow-up period.

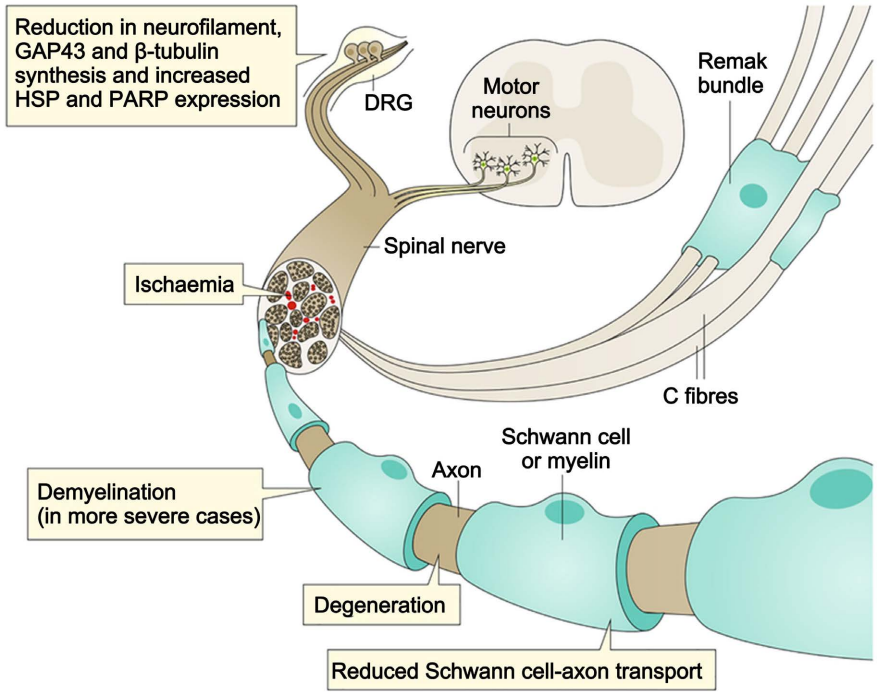

Figure 3. The peripheral nervous system and alterations in diabetic neuropathy.

2) The peripheral nervous system and alterations in diabetic neuropathy (Figure 3)

A distinct neurodegenerative condition of the peripheral nervous system, diabetic neuropathy primarily affects sensory and autonomic axons before affecting motor axons to a lesser degree. It's still unclear how diabetes mellitus affects sensory neurons. In progressive diabetic neuropathy, the perikarya (cell bodies) are

largely preserved while the terminal sensory axons in the periphery retract and "die back." Diabetic neuropathy is regarded as a length-dependent neuropathy because of its "stocking and glove" pattern of involvement, which shows damage to the longest sensory axons first, such as the loss of distal leg epidermal axons before loss in more proximal limbs. [86]

3.2. Macrovascular Complications

Cardiovascular disease (CVD), cerebrovascular disease (CeVD), and peripheral arterial disease (PAD) lesions are indications of macrovascular illnesses which affect big blood vessels like arteries and veins. [87] About 20% to 30% of diabetic individuals experience these consequences, which greatly increase the morbidity and death rate of type 2 diabetes. [88] [89]

3.2.1. Cardiovascular Disease (Figure 4)

More than 70% of deaths among people with type 2 diabetes are caused by CVD, making it the leading cause of death in this population. [90] It has been known for decades that diabetes raises the risk of cardiovascular disease. When classic CVD risk variables such as age, obesity, tobacco use, dyslipidaemia, and hypertension are taken into account, people with diabetes are four times more likely than people without diabetes to have a CVD episode. [4] [91] The symptoms of CAD, also called ischemic heart disease, coronary heart disease (CHD), atherosclerotic heart disease, and atherosclerotic CVD, include myocardial infarction (sometimes called a heart attack), unstable angina pectoris, and sudden cardiac death. [92] Approximately 32.2% of people with type 2 diabetes worldwide have CHD. [93] Furthermore, independent of a history of myocardial infarction, people with diabetes have a significantly higher 7-year risk of myocardial infarction than those without diabetes due to the strong association between diabetes mellitus and an increased risk of coronary artery disease (CAD). [94] [95] On the other hand, a meta-analysis of 13 trials with 45,108 patients revealed that those with diabetes who had never experienced a myocardial infarction were 43% less likely to experience any CHD events overall than those without diabetes who had experienced a myocardial infarction. [96] Genetic variation and epigenetic changes have been identified as risk factors for CAD problems in diabetic individuals by recent genome-wide investigations. [97] Based on ten years of genome-wide association studies, Jeanette Erdmann *et al.* made a list of 163 CAD risk loci. [98] These loci might be helpful in promoting preventative actions and better predicting the risk of CAD.

1) Mechanism (Figure 5)

The process of atherosclerosis, which causes the artery walls all over the body to narrow, is the primary pathogenic mechanism in macrovascular disease. It is believed that prolonged inflammation and damage to the arterial wall in the peripheral or coronary vascular system cause atherosclerosis. Oxidized lipids from LDL particles build up in the endothelium wall of arteries in reaction to inflammation and

endothelial damage. Angiotensin II might encourage these particles to oxidize. After entering the artery wall, monocytes develop into macrophages, which build up oxidized lipids to create foam cells. Following their formation, foam cells promote the growth of macrophages and draw in T-lymphocytes, which in turn cause the artery walls' smooth muscle to proliferate and collagen to accumulate. The process culminates in the development of an atherosclerotic lesion that is rich in lipids and has a fibrous cap. Acute vascular infarction results from the rupture of this lesion. [99]

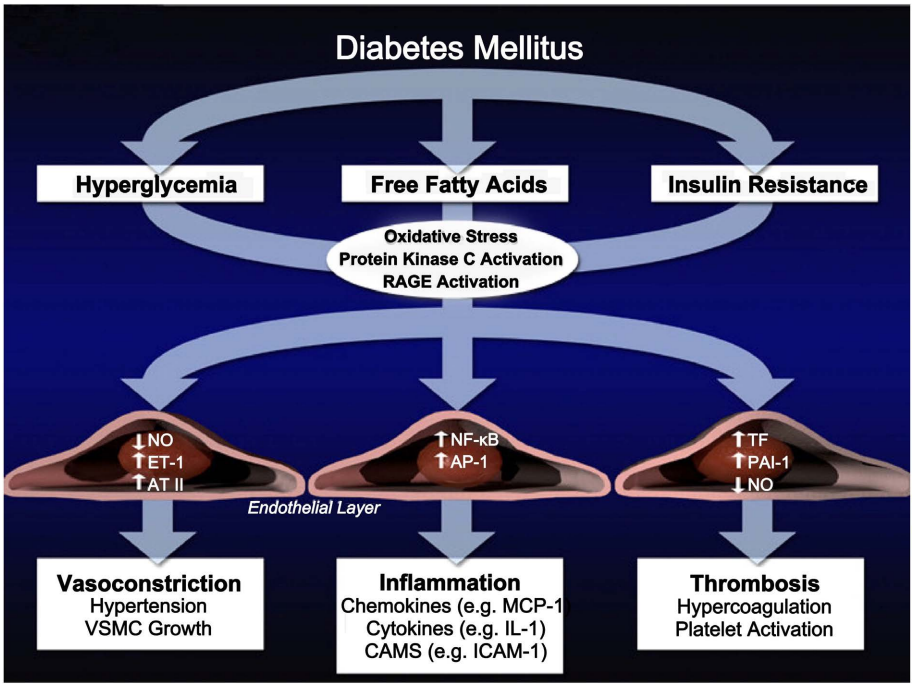

Figure 4. Diabetes mellitus and CVD.

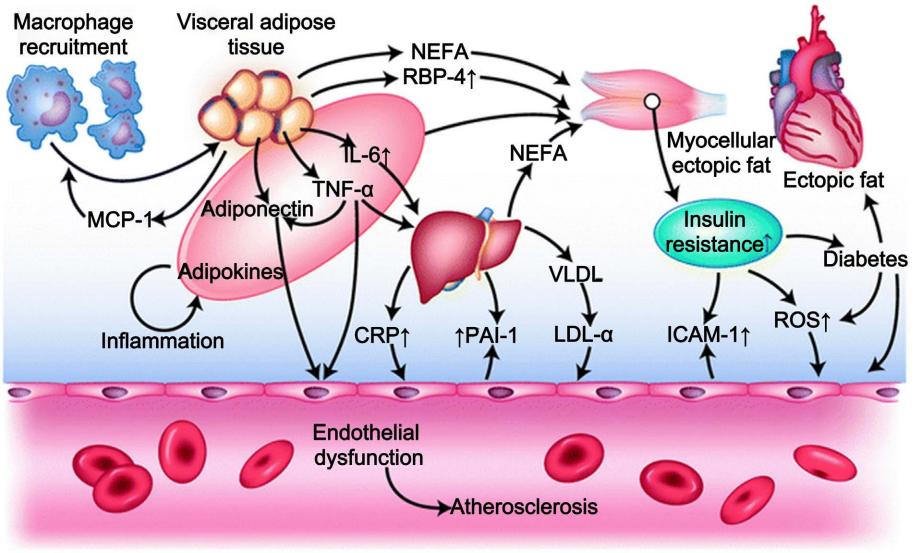

Figure 5. Mechanism of diabetic atherosclerosis.

Type 2 diabetes is strongly associated with hypercoagulability and enhanced platelet adhesion in addition to atheroma formation. Platelet aggregation may be encouraged by decreased nitric oxide production, elevated free radical creation in platelets, and changed calcium regulation. Patients with diabetes may also have impaired fibrinolysis due to elevated levels of plasminogen activator inhibitor type 1. In type 2 diabetes, the risk of arterial occlusion and cardiovascular events is probably further enhanced by the combination of elevated coagulability and impaired fibrinolysis. [100]

A person with diabetes has a higher chance of developing cardiovascular disease (CVD). The exact processes by which diabetes raises the risk of developing atherosclerotic plaque are not fully understood, although there is a strong correlation between the two. For those with type 1 or type 2 diabetes, cardiovascular disease (CVD) is the leading cause of death. [101] [102]

In actuality, the largest portion of health care costs for diabetics are related to CVD. [102] [103] Numerous investigations, starting with the Framingham research, have linked diabetes to coronary heart disease, one of the macrovascular consequences. [103] According to more recent research, individuals with diabetes have the same risk of myocardial infarction (MI) as non-diabetic patients who have previously experienced a MI. [104]

3.2.2. Cerebrovascular Disease (CeVD)

Around 20% to 40% of people with type 2 diabetes have CeVD, which is a major cause of death and severe morbidity globally. [97] CeVD includes a variety of conditions that affect the cerebral vessels and cerebral circulation, with stroke as one of its significant manifestations.

- In 2019, stroke killed 6.6 million people worldwide, with half of those deaths coming from ischemic stroke, 44% (2.9 million) from intracerebral hemorrhage, and 6% (0.4 million) from subarachnoid hemorrhage. [105]
- In addition, even though the total number of stroke-related deaths has been increasing, the age-standardized death rate has decreased by 14.7% over the 9-year period from 2010 to 2019 [105] [106]. An increased risk of stroke is linked to diabetes mellitus.
- A meta-analysis of 102 prospective trials with 698,782 participants found that the adjusted hazard ratio for ischemic stroke in people with type 2 diabetes was 2.27 (95% CI, 1.95 - 2.65) as opposed to people without the disease. [94]
- Furthermore, a study showed that compared to their male counterparts, female patients with type 2 diabetes are far more susceptible to stroke. [107] Numerous studies have shown that CeVD is linked to age, smoking, obesity, hypertension, high-density lipoprotein cholesterol, HbA1c, history of vascular disease, heart failure, and atrial fibrillation. [108] [109] In their evaluation of microalbuminuria in connection to CeVD, A. Rocco *et al.* concluded that, while further research is required, it may be predictive of stroke. [110]
- According to recent data, the microbiome is crucial for the development of

stroke. [83] Furthermore, a growing amount of research has looked at how genetic variants and epigenetic changes may affect the start of CeVD. [111] [112] PITX2 and ZFHX3, for instance, have been linked to atrial fibrillation and have been found to increase the risk of ischemic stroke in Caucasians. [113] [114] The discovery of more unique genetic variations linked to the risk of CeVD was made possible by the development of genome-wide association studies. [115]-[117]

3.2.3. Peripheral Artery Disease

PAD is another prevalent macrovascular consequence in diabetic patients, in addition to CAD and CeVD. The hallmark of peripheral vascular disease (PAD), commonly referred to as PVD, is atherosclerotic blockage in the lower limbs. Claudication, the most prevalent PAD symptom, is typified by cramping, pain, or discomfort in the lower leg, thigh, or buttock that goes away with rest. [118] An ankle-brachial index (ABI) cutoff value of 0.9 indicates arterial occlusion and is used to diagnose and grade the severity of PAD. However, compared to those without diabetes, ABI's sensitivity is lower in diabetic patients. Diabetes patients with high ABI values may have arterial occlusion, which could result in an underdiagnosis of PAD in this population. [119] [120]

PVD has become a major global health issue, impacting more than 200 million people globally. According to estimates, almost 8 million individuals in the US who are 40 years of age or older have low ABI levels (<0.9), and 25% of them have severe PAD (ABI < 0.7). [121] Increased mortality rates, a higher risk of lower extremity amputations, and enhanced rates of cardiovascular events are all substantially correlated with PAD. [122]

Compared to CAD or stroke, the risk of PAD is two to four times higher in people with diabetes mellitus. [123] [124] A number of risk factors, such as smoking, obesity, hypertension, hypercholesterolemia, and dyslipidemia, have been linked to the development of PVD in people with diabetes. [125] A cross-sectional study of 271 diabetic individuals revealed a strong correlation between PVD and obesity, smoking, high blood pressure, and high cholesterol. The length of diabetes, the severity of hyperglycemia, advancing age, male sex, elevated serum lipoprotein levels, insulin resistance, elevated serum fibrinogen levels, microalbuminuria, and elevated levels of intercellular adhesion molecules are additional factors that have been connected to an increased risk of PVD in people with diabetes. [126]

Diabetes-related PAD development and progression share similarities with other macrovascular complications, such as hemostasis-affecting factors, endothelial cell dysfunction, blood cell abnormalities, and vessel wall derangements caused by vascular inflammation. [127] It is noteworthy that several pathways significantly interact with one another. For instance, whereas elevated ROS can result in platelet and endothelial dysfunction, decreased NO generation can impact inflammation, endothelial function, and arteriogenesis. [122]

4. Risk Factors for Diabetic Vascular Complications (Figure 6)

Disease	Risk factors
Microvascular complications	
Diabetic retinopathy	Duration of diabetes, Hyperglycemia, Hypertension, Genetic factors, Nephropathy, Smoking, Dyslipidemia, BMI, Gut microbiome, NAFLD, lncRNAS
Diabetic nephropathy	Hyperglycemia,Hypertension, Genetic factors, Smoking, Dyslipidemia, Gut microbiome, Obesity, Race, Gender, Age, NAFLD, lncRNAS
Diabetic neuropathy	Duration of diabetes, Hyperglycemia, Hypertension, Genetic factors, Smoking, Age, higher levels of total and low-density lipoprotein cholesterol and triglycerides, higher body-mass index, higher von Willebrand factor levels, UAE rate, NAFLD
Macrovascular complications	
Cardiovascular disease	Hyperglycemia,Hypertension, Dyslipidemia Obesity, Diabetic nephropathy, Genetic factors, Age, NAFLD
Cerebrovascular disease	Hyperglycemia, Hypertension, Genetic factors, Smoking, Microbiota, Obesity, High-density lipoprotein cholesterol, history of vascular disease, Heart failure, Atrial fibrillation
Peripheral artery disease	Hyperglycemia, Obesity, Gender, Age, elevated serum lipoprotein levels, Insulin resistance, Elevated serum fibrinogen levels, Microalbuminuria, Increased levels of intercellular adhesion molecule

BMI = body mass index, LncRNAs = long noncoding RNAs, NAFLD = nonalcoholic fatty liver disease, UAE= urine albumin excretion.

Figure 6. Risk factors for diabetic vascular complications (Source: https://pmc.ncbi.nlm.nih.gov/articles/PMC10553000/).

5. Novel Diagnostic Tools and Therapeutic Approaches

Numerous molecular pathways that may impede ischemia, tissue damage, and vascular dysfunction have been discovered by novel studies. A well-known clinical test for diagnosing diabetes, assessing the risk of micro- and macrovascular complications, and managing the condition therapeutically is postprandial plasma glucose (PPG), which is often measured 1 - 2 hours after a big meal. [128]

1) The NHANES III study, which sought to determine whether projected PPG after 4 - 7.9 hours might be used to diagnose diabetes, involved a large number of patients that were studied by Dr. Yutang Wang and colleagues. To determine the anticipated PPG after 4 - 7.9, a multivariate prediction model taking into account 30 potential risk indicators was created. It showed a high diagnostic accuracy of 87.3%. The authors propose that PPG beyond 4 - 7.9 may be a viable diagnostic indication for diabetes since they believe this parameter is less affected by diet or other factors.

2) Hayden *et al.* and Fedulovs *et al.* offer fresh perspectives on the pathological alterations in diabetes and metabolic syndrome (MS). Fedulovs and colleagues, on the other hand, stratified the data based on MS status after doing a comparative examination of the LPS, LBP, EndoCAb IgM, EndoCAb IgG, and fecal calprotectin in T1D patients and controls for the first time. The authors support the necessity

of screening and treating MS in T1DM patients by demonstrating increased endotoxemia in these patients. The role of the perivascular unit, a novel concept created by Troili and colleagues [129], in the development of neuroinflammation, cerebrovascular disease, and neurodegeneration found in metabolic syndrome, obesity, and type 2 diabetes is thoroughly reviewed by Dr. Melvin R. Hayden and colleagues.

3) Based on the Developmental Origins of Health and Disease (DOHaD) theory, Dr. Ngema and Col. provide evidence in a narrative review that type 2 diabetes during pregnancy may affect fetal development and cause long-term impairment of hypothalamic-pituitary-adrenal (HPA) axis activity into adulthood.

4) An innovative non-invasive biomarker of advanced glycation end products is skin autofluorescence (SAF) [130]. The body's buildup of AGE is described by the level of SAF, which is linked to increased AGE formation, slower degradation, and renal clearance. According to a number of comparison studies, diabetic patients have greater SAF values than normal people, and skin autofluorescence increases even more in the presence of microvascular problems.

5) There are still a lot of issues to be worked out, though, because SAF values seem to be impacted by skin pigmentation and skin care product use; additional research with a greater number of individuals is required. In this regard, we applaud the study conducted on a sizable cohort of 885 T2DM patients by Dr. Reurean-Pintilei and Col. They discovered a correlation between SAF levels and cardiovascular risk, diabetic renal disease, and HbA1c. Particularly after controlling for age, gender, and HbA1c level, a cutoff value of 2.36 was linked to extremely high CV risk and might be helpful in choosing patients for revascularization operations.

6) An additional strategy by Dr. Hiroki Yamagami and Col. In order to compare the predictive power of SAF for the progression of diabetic kidney disease by urine albumin-to-creatinine ratio (uACR), a biomarker of glomerular injury, and urine liver-type fatty acid-binding protein (uLFABP)-to-creatinine ratio (uL-FABPCR), a biomarker of tubular injury, a one-year prospective study involving 350 Japanese individuals with type 2 diabetes was conducted. In individuals with type 2 diabetes, the authors discovered a correlation between SAF and uL-FABP but not uACR. This suggests that SAF may be a new predictor of the onset of diabetic tubular damage.

7) Inflammation, endothelium maturation, and angiogenesis all depend on angiopoietins and angiopoietin-like proteins [131] [132]. These have recently been studied for their possible involvement in the inflammatory and endothelial dysfunction processes seen in diabetic nephropathy. Circulating ANGPTL3, ANGPTL4, ANGPTL8, Ang1, and Ang2 were measured in the fasting plasma of T2DM patients with and without diabetic nephropathy by Dr. Eman Alshawaf *et al.* (in contribution 7). In a DN population, they discovered a strong correlation between Ang2 and ANGPTL8, indicating that they may serve as predictors of DN risk.

8) This work emphasizes the significance of Ang2 as an early indicator of tubular damage prior to the onset of clinical symptoms such as microalbuminuria, which is consistent with earlier experimental and clinical data about the effects of Ang2 expression on podocytes through paracrine signaling, resulting in glomerular EC destabilization and impaired filtration.

9) As possible predictive techniques, serum inflammatory indicators derived from basic complete blood cell counts were examined. When compared to normal patients, there is strong evidence that the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) rise in people with type 2 diabetes. These measurements are also strongly connected with the occurrence and severity of diabetic complications [132]-[134]. Systemic inflammation levels and persistent hyperglycemia were believed to be connected with these serum inflammatory indicators. However, because of the large range of means and cutoff values found in earlier research, putting those biomarkers into clinical practice remains difficult, and more data is still required.

10) Dr. Ana Dascalu *et al.*'s study revealed that none of the white cell inflammatory indicators showed statistically significant changes between the NDR and NPDR groups. Comparing the PDR group to the NDR and NPDR groups, however, revealed noticeably greater values for NLR, MLR, SII, and MPV. This finding might indicate that the advanced stage of DR linked to neovascularization has a higher amount of systemic inflammation. Serum inflammatory biomarkers may be influenced by a wide range of physiological and pathological circumstances, as well as age, sex, race, and ethnicity. However, when incorporated into thorough risk prediction models, serum inflammatory indicators may prove beneficial.

11) A new imagistic technique called optical coherence angiography (OCTA) provides useful information on macular arteries in a reproducible, non-invasive way. Using optical coherence tomography angiography (OCTA) and a 12-month follow-up, Dr. Irini Chatziralli and colleagues examined changes in the macular microvasculature in relation to functional changes in patients with proliferative diabetic retinopathy (PDR) receiving pan-retinal photocoagulation (PRP). The study found that while the foveal avascular zone (FAZ) area dramatically decreased and the FAZ became more circular, the foveal and parafoveal vessel density (VD) at the superficial capillary plexus (SCP) rose significantly at months 6 and 12 following PRP in comparison to baseline.

12) The improvement of the choroidal circulation at the macula could be explained by the PRP-induced inflammatory response and the shift of choroidal flow from destroyed peripheral capillaries to the macula [135] [136]. The BCVA of patients receiving laser treatment did not, however, improve, according to the authors.

13) An intriguing viewpoint on diabetic retinopathy as a neurodegenerative condition is provided by Dr. Tanasie *et al.* When the electrophysiological data of patients with and without DR are compared, the findings show that the neural retina is significantly dysfunctional in all phases of DR, and there are notable

variations in reaction latency between study groups.

14) The standard treatment for diabetic retinopathy linked to macular edema is currently intravitreal anti-VEGF. Nevertheless, a suboptimal response is observed in as many as 30% of patients, indicating the involvement of additional molecules in increasing capillary blockage and vascular permeability [137] [138]. An experimental investigation that attempts to examine the "in vitro" characteristics of a novel agent—the (transforming growth factor beta) TGFβ receptor inhibitor RepSox (RS)—is the significant contribution of Dr. Lietuvninkas and Col. The study's findings are promising because RS outperformed anti-VEGF medications in both preventing barrier relaxation and inducing the closure of the relaxed barrier caused by TNFα and VEGF. Because RS blocks several pathways, it may be a more effective treatment for diabetic macular Oedema.

6. Conclusion

One major factor contributing to elevated morbidity and decreased quality of life in diabetic patients is microvascular problems. However, people with diabetes, particularly those with type 2 diabetes, have a far higher mortality rate due to macrovascular illnesses. For diabetes and its related macrovascular and microvascular problems, hyperglycaemia, hypertension, hyperlipidaemia, diabetes duration, obesity, and smoking are common risk factors. Thus, strict control of blood pressure, cholesterol, and glucose levels, early diabetes detection and diagnosis, suitable exercise, and quitting smoking are all necessary for controlling diabetic vascular problems. Moreover, early management to halt development and enhance results depends on precise risk categorization of individuals with diabetic vascular problems and targeted screening for various consequences.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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