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Diabetic Comorbidities and its Molecular Mechanism

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Abstract: Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), is a complex metabolic disorder frequently accompanied by a wide array of comorbidities that significantly increase morbidity and mortality. These comorbidities encompass cardiovascular diseases (e.g., hypertension, atherosclerosis, stroke), renal dysfunction (diabetic nephropathy), hepatic disorders (non-alcoholic fatty liver disease), neurological complications (diabetic neuropathy and cognitive decline), and reproductive disturbances (male and female infertility). The shared pathophysiological mechanisms underlying these complications include chronic hyperglycemia, insulin resistance, oxidative stress, low-grade systemic inflammation, and advanced glycation end-product (AGE) formation. These factors contribute to endothelial dysfunction, mitochondrial impairment, and multiorgan cellular injury. Moreover, the presence of comorbidities further complicates glycemic control and worsens clinical outcomes, creating a vicious cycle of disease progression. Early detection and integrated management strategies targeting both hyperglycemia and comorbid conditions are essential for improving the quality of life and reducing the long-term burden of diabetes. This review aims to elucidate the major diabetic comorbidities, their underlying mechanisms, and the importance of comprehensive care in diabetic patients.

Keywords: *RAGE, AGE, PAD, TIDM, T2DM, PKC, IDF, TNF-α, IL-1β, and IL-6, CVD, AGE.*

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I. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both [1]. The condition is primarily categorized into type 1 diabetes mellitus (T1DM), which results from autoimmune destruction of pancreatic β-cells, and type 2 diabetes mellitus (T2DM), which is largely associated with insulin resistance and relative insulin deficiency [2]. Diabetes is a major global health concern due to its growing prevalence and the wide array of complications that affect multiple organ systems [3].

II. EPIDEMIOLOGY

As of 2021, approximately 537 million adults (20–79 years) worldwide were living with diabetes, and this number is projected to rise to 783 million by 2045 [4]. T2DM accounts for nearly 90–95% of all diabetes cases and is more prevalent in low- and middle-income countries due to urbanization, sedentary lifestyle, and unhealthy diets [5]. In India alone, over 77 million people are affected, placing the country among the top three globally in diabetes burden [6]. Alarmingly, nearly half of all adults with diabetes are undiagnosed, increasing the risk of complications and comorbidities [4].

- *Etiology*

The etiology of diabetes is multifactorial, involving both genetic and environmental factors. In T1DM, the primary cause is autoimmune-mediated destruction of insulin-producing β-cells of the pancreas, often triggered by environmental factors such as viral infections in genetically susceptible individuals [7]. Presence of autoantibodies such as GAD65, IA-2, and insulin autoantibodies support the autoimmune nature of T1DM [8].

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In T2DM, the development is predominantly due to insulin resistance in peripheral tissues (muscle, adipose tissue, and liver) and a progressive decline in pancreatic β-cell function [9]. Key risk factors include obesity, physical inactivity, family history, age over 45, and certain ethnicities [10]. Central obesity and elevated free fatty acids promote chronic inflammation and lipotoxicity, further impairing insulin signaling pathways [11].

Additionally, epigenetic modifications, gut microbiota alterations, and intrauterine exposures have been implicated in both the development and intergenerational transmission of diabetes risk [12].

- *Diabetic Neuropathy*

Diabetic neuropathy is a complex and debilitating complication of both type 1 and type 2 diabetes mellitus (DM), characterized by progressive nerve damage due to chronic hyperglycemia [13]. The mechanism of diabetic neuropathy is multifactorial and involves a cascade of metabolic and vascular insults to nerve tissues [13]. Prolonged hyperglycemia triggers several biochemical pathways that contribute to nerve damage. One primary mechanism is the polyol pathway activation, where excess glucose is converted into sorbitol by aldose reductase. Sorbitol accumulation within nerve cells leads to osmotic stress, reduced myo-inositol levels, and decreased Na^+/K^+-ATPase activity, impairing nerve conduction [13,14].

Another key contributor is the formation of advanced glycation end products (AGEs), which occur when glucose irreversibly binds to proteins, lipids, and nucleic acids. AGEs interact with their receptors (RAGE) on neuronal and endothelial cells, inducing oxidative stress and inflammation, and ultimately leading to axonal degeneration [13,14].

Oxidative stress plays a central role in diabetic neuropathy. Excess glucose enhances mitochondrial superoxide production, which in turn activates damaging pathways including nuclear factor-kappa B (NF-κB), leading to the upregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-6) [13]. These cytokines increase vascular permeability and damage the blood–nerve barrier, causing ischemia. Concurrently, protein kinase C (PKC) pathway activation—especially the β-isoform—contributes to reduced endothelial nitric oxide synthase (eNOS) activity and vasoconstriction, worsening microvascular blood flow to nerves. Additionally, hexosamine pathway flux affects transcription factors that alter expression of genes involved in extracellular matrix production, promoting fibrosis and nerve dysfunction [13,14].

From a structural perspective, diabetic neuropathy leads to demyelination, axonal atrophy, and loss of intraepidermal nerve fibers, especially in distal regions [14]. It predominantly affects sensory fibers, leading to numbness, tingling, and pain (termed "painful diabetic neuropathy"), though autonomic and motor fibers may also be impaired [13–15]. Sympathetic dysfunction can lead to cardiovascular autonomic neuropathy, while gastrointestinal or genitourinary systems can also be affected in autonomic neuropathy [14,15].

Statistically, diabetic neuropathy affects a substantial portion of the diabetic population. According to the International Diabetes Federation (IDF), approximately 30–50% of diabetic individuals will develop some form of neuropathy over their lifetime [13]. In a large epidemiological review by Pop-Busui et al., the prevalence of diabetic peripheral neuropathy (DPN) in type 2 diabetes ranged from 20% to over 50% depending on diagnostic criteria and population [13]. The UK Prospective Diabetes Study (UKPDS) further demonstrated that the risk of neuropathy increases with duration and severity of hyperglycemia [14]. Notably, in the U.S. NHANES 1999–2004, the estimated prevalence of peripheral neuropathy in diabetics aged over 40 was approximately 26.4% [15]. The Diabetes Control and Complications Trial (DCCT) also highlighted the importance of glycemic control in delaying onset and progression of neuropathy, with intensive insulin therapy reducing the risk by up to 60% in type 1 diabetes [16].

In conclusion, diabetic neuropathy is a multifactorial disorder involving hyperglycemia-induced metabolic dysregulation, oxidative stress, microvascular injury, and inflammation [13–16]. It represents a significant public health burden due to its high prevalence and its impact on quality of life, disability, and healthcare costs. Preventive strategies focused on tight glycemic control and emerging neuroprotective agents are essential for effective management [13,16].

- *Diabetic Nephropathy: Mechanism of Action and Statistical Data*

A progressive kidney disease due to long-standing diabetes is called diabetic nephropathy (DN). diabetes mellitus, and is one of the greatest microcirculatory problems and a probable cause of end-stage renal disease The number of (ESRD) globally [17]. It ensues in about 20-40 percent of diabetic patients. is more common in poorly glycemic follicle populations in type 1 and type 2 diabetics. high blood pressure [17,18]. Diabetic nephropathy has a complicated pathogenesis that is dependent on multiple factors. metabolic, and hemodynamic causes that result in glomerular and tubular suffering [17,19]. Glomerular hyperfiltration, resulting in the earliest aberration in diabetic nephropathy which is caused due to increased intraglomerular pressure. Hyperglycemia precipitates an excess formation of advanced glycation end stimulates protein kinase C (PKC), increases the flux of the polyol pathway, and these AGEs increase the flux of the polyol pathway. cause oxidative stress and inflammation [17,19]. These are molecular damages to glomerular endothelial cells, mesangial cells and podocytes. The thickening of the one of the key events is as follows. glomerular basement membrane and mesangial overgrowing as a result of extracellular expanded accumulation collagen and fibronectin and other matrix proteins. Transforming growth factor-beta (TGF-b 1), an essential profibrotic cytokine which is upregulated with

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hyperglycemia and promotes matrix synthesis and encourages renal fibrosis [17,19]. In the DN, the main role is played by podocyte injury and de-differentiation. The podocytes are essential Podocytes play a central role in podocytecris in sustaining the glomerular filtration barrier; in absence of such, proteinuria occurs, a characteristic of DN [18,19]. Chronic hyperglycemia would also activate the renin-angiotensin-aldosterone system. resulting it vasoconstriction, sodium retention, and to an even greater degree of higher - the system (RAAS), which leads to vasoconstriction, sodium retention, and an even greater increase in - levels. renal injury occurs due to pressure intraglomerular, and increases the rate of injury. Angiotensin II is a component of RAAS. has antioxidative properties, activates oxidative stress and inflammations, and triggers apoptosis of renal cells directly [17,19].

Inflammatory pathways contribute significantly to DN progression. Hyperglycemia stimulates the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as chemokines like MCP-1. These molecules recruit immune cells to the kidney, perpetuating local inflammation and promoting tubulointerstitial fibrosis [19]. Oxidative stress, via increased reactive oxygen species (ROS), exacerbates inflammation and endothelial dysfunction. Moreover, epigenetic modifications, including altered histone acetylation and microRNA expression, are now recognized as contributing factors in the chronic progression of DN by altering gene expression involved in fibrosis and inflammation [19].

Statistically, diabetic nephropathy affects approximately 30% of type 1 and 20–40% of type 2 diabetic patients globally [17]. According to the International Diabetes Federation (IDF), over 537 million adults were living with diabetes in 2021, and up to 40% of these may develop some degree of nephropathy [20]. In India, studies suggest that DN accounts for over 40% of chronic kidney disease (CKD) cases [17]. A meta-analysis by Thomas et al. (2015) reported that the global prevalence of microalbuminuria and macroalbuminuria among diabetics was 39% and 10%, respectively [17]. Additionally, the United States Renal Data System (USRDS, 2023) indicated that DN is the leading cause of ESRD in the U.S., accounting for 47% of new dialysis cases [21].

- *Diabetic Retinopathy: Mechanism of Action and Statistical Data*

Diabetic retinopathy (DR) is a shortage disease of diabetes mellitus, and the problems related to DR are still the leading cause of blindness. the commonest leading preventable cause of blindness amongst the working-world adults globally [22]. It is created as a result of: to persistent hyperglycemia, which initiates changes of the structure and functionality of the retina microvasculature. The DR has discernibly different stages: non-proliferative diabetic retinopathy Diabetic macular edema (DME), (NPDR) and proliferative diabetic retinopathy (PDR). because it is a complication that threatens vision at any following stage [22,23]. Pathophysiology of diabetic retinopathy Pathophysiological mechanism of diabetic retinopathy starts with long-term hyperglycemia causing the synthesis of the advanced glycation end products (AGEs), enhanced oxidative stress, and stimulation of destructive metabolic pathways e.g. the polyol and protein kinase c (PKC) The pathways [22,23]. These mechanisms are harmful to the retinal pericytes and endothelial cells- 0 the components of the capillary walls-causing the destruction of blood-retinal barrier (BRB). The loss of pericyte, a characteristic of early Dr, leads to damaged capillary walls leading to microaneurysms and capillary ooze [23]. The next significant key to DR entails the overexpression of vascular endothelial growth factor Angiogenic factors (VEGF) that are also induced by retinal hypoxia caused by capillary dropout and ischemia. VEGF cause neovascularization that is a feature of proliferative DR although these new vessels are weak and vulnerable to bleeding thus causing vitreous diversion and retinal separation. Also, VEGF elevates the vascular permeability, which promotes diabetic macular edema- the build-up of fluid in the eye center macula that affects clarity in the central vision [2224]. Chronic inflammation is as well a primary locomotive in the development of DR. The effect of hyperglycemia is to cause secretion of pro-inflammatory cytokines e.g. TNF-a, IL-1b, ICAM-1, which attract is directed to the retinal vessels via leukocytes. Adhesion of leukocytes to the endothelium also known as Leukostasis. Moreover, it injures capillaries and worsens ischemia and vascular overflows. Oxidative stress through production of reactive oxygen species (ROS) and increases the cellular damage and induces apoptotic destruction of the retinal neurons and glial cells in retinal pathways resulting to their neurodegeneration which in many cases precedes the retinal pathology manifestation. apparent vascular alterations [23]. Diabetic retinopathy has a huge statistical burden. International According to the International More than 537 million of the world population have diabetes, as reported by Diabetes Federation (IDF, 2021). about one-third of them are at risk of or have some of the diabetic retinopathy [24]. One great study, The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), however, demonstrated that once 20 had been reached, the changes varied little. After several years of diabetes almost every patient with type 1 diabetes and over 60 percent of type 2 diabetes Some retinopathy is developed by the patients [22]. Global Burden of Disease (GBD, 2020) study also proved DR as among the leading causes of sight impairment in individuals aged between 20 and 74 years [26]. In India, the prevalence of DR is varied and its rate is 18 to 30 percent among diabetes, where 6 10 percent suffer. end stages that are sight-threatening [25].

In conclusion, diabetic retinopathy is a multifactorial disease involving oxidative stress, inflammation, VEGF-mediated angiogenesis, and blood-retinal barrier breakdown, all stemming from chronic hyperglycemia [22–24]. Early detection through regular retinal screening and timely interventions—such as glycemic control, intravitreal anti-VEGF therapy, and laser photocoagulation—are crucial to prevent irreversible vision loss [23,25].

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- *Diabetic Foot Disease: Mechanism of Action and Pathophysiology*

Diabetic Foot Disease (DFD) is one of the most debilitating and costly complications of diabetes mellitus. It refers to a spectrum of conditions ranging from foot ulcers to infections and gangrene that often lead to amputation. The pathogenesis of DFD is multifactorial, primarily involving peripheral neuropathy, peripheral arterial disease (PAD), and impaired wound healing due to chronic hyperglycemia and immune dysfunction [27].

The initial event in diabetic foot disease is often peripheral neuropathy, which occurs in about 50% of diabetic patients. Hyperglycemia-induced metabolic changes, including increased polyol pathway flux, formation of advanced glycation end-products (AGEs), oxidative stress, and protein kinase C (PKC) activation, lead to microvascular damage and nerve injury [27]. Sensory neuropathy reduces pain sensation, allowing minor trauma (e.g., from tight shoes or sharp objects) to go unnoticed. Motor neuropathy causes muscle imbalances and foot deformities (e.g., claw toes), which increase pressure on certain foot areas. Autonomic neuropathy reduces sweat and oil production, resulting in dry, cracked skin prone to infection [27].

In parallel, peripheral arterial disease (PAD) - a macrovascular complication of diabetes—leads to reduced blood flow to the lower limbs. Hyperglycemia accelerates atherosclerosis, narrowing the arteries and decreasing oxygen and nutrient delivery to tissues. This ischemia impairs healing and makes tissues more susceptible to necrosis. The combination of ischemia and neuropathy significantly increases the risk of ulcer formation and poor wound healing [28].

Another crucial factor in DFD is immune dysfunction. Chronic hyperglycemia impairs neutrophil chemotaxis, phagocytosis, and microbial killing, weakening the host defense mechanism. As a result, even minor wounds can quickly become infected. Common pathogens include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and polymicrobial flora. If untreated, infections may spread to deeper tissues, bones (osteomyelitis), or cause systemic sepsis [28].

A typical sequence begins with unnoticed trauma or pressure injury in an insensate foot, which progresses to an ulcer. Due to PAD and poor immune response, the ulcer becomes infected, leading to tissue necrosis, abscess formation, and potentially gangrene. In severe cases, limb amputation becomes necessary. According to the International Diabetes Federation (IDF), one lower limb is lost to diabetes every 20 seconds globally. Studies report that up to 25% of diabetics may develop a foot ulcer in their lifetime, and among these, 15–20% require amputation [29].

Management of diabetic foot disease includes prevention through regular foot examinations, tight glycemic control, proper footwear, and patient education. Treatment involves debridement, infection control, off-loading, and in severe cases, revascularization or surgical intervention [30].

- *Diabetic Cardiovascular Disease (CVD): Mechanism of Action*

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in people with diabetes mellitus. Individuals with diabetes are 2–4 times more likely to develop CVD than those without diabetes [31]. The pathogenesis of CVD in diabetes is complex and involves endothelial dysfunction, chronic inflammation, atherosclerosis, dyslipidemia, and hypercoagulability, all driven by persistent hyperglycemia and insulin resistance.

The central mechanism starts with hyperglycemia-induced endothelial dysfunction, which is considered the initiating event in diabetic vascular complications. High glucose levels cause overproduction of reactive oxygen species (ROS) in the mitochondria, which impairs nitric oxide (NO) synthesis and bioavailability in endothelial cells. Nitric oxide is essential for vasodilation and maintaining vascular tone. Its deficiency leads to vasoconstriction, platelet aggregation, and leukocyte adhesion—key early steps in atherosclerosis [32].

Additionally, chronic hyperglycemia leads to the formation of advanced glycation end products (AGEs). AGEs bind to their receptor (RAGE) on vascular cells and macrophages, triggering the release of pro-inflammatory cytokines such as TNF-α, IL-6, and adhesion molecules like VCAM-1. This promotes a chronic inflammatory state within the vascular wall [33]. Inflammation recruits monocytes to the endothelium, where they differentiate into macrophages and ingest oxidized LDL cholesterol, forming foam cells—the hallmark of atherosclerotic plaque.

Insulin resistance, which is common in type 2 diabetes, further aggravates endothelial dysfunction and inflammation. It disrupts insulin signaling pathways, leading to reduced NO production and increased endothelin-1, a vasoconstrictor. Insulin resistance is also associated with dyslipidemia, characterized by elevated triglycerides, small dense LDL particles, and reduced HDL cholesterol—all of which are atherogenic and accelerate plaque formation [34].

Over time, atherosclerotic plaques in coronary arteries can rupture, triggering thrombosis due to platelet activation and hypercoagulable states. Diabetic patients have elevated levels of fibrinogen, PAI-1 (plasminogen activator inhibitor-1), and thromboxane A2, which promote clot formation and hinder fibrinolysis. These changes increase the risk of myocardial infarction, stroke, and sudden cardiac death [35].

Moreover, cardiac autonomic neuropathy (CAN)—a diabetes-related nerve complication—impairs heart rate variability and contributes to silent myocardial ischemia and arrhythmias. Chronic exposure to high glucose also causes diabetic cardiomyopathy, characterized by myocardial fibrosis,

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impaired diastolic function, and eventually, heart failure, even in the absence of coronary artery disease.

In conclusion, diabetic cardiovascular disease arises from a network of metabolic and vascular dysfunctions driven by chronic hyperglycemia and insulin resistance. The interplay of oxidative stress, endothelial damage, lipid abnormalities, inflammation, and coagulation disturbances culminates in atherosclerosis, ischemia, and cardiac dysfunction. Effective management includes glycemic control, blood pressure and lipid regulation, antiplatelet therapy, and lifestyle modification to reduce the cardiovascular burden in diabetic individuals.

- *Diabetic Cerebrovascular Disease (Stroke): Mechanism and Pathogenesis*

Cerebrovascular disease, particularly stroke, is a major macrovascular complication of diabetes mellitus and a leading cause of disability and death globally. Individuals with diabetes are 1.5 to 2 times more likely to experience a stroke than non-diabetics. Stroke in diabetic patients tends to occur earlier, with more severe neurological deficits, poorer outcomes, and a higher risk of recurrence. The mechanism by which diabetes increases stroke risk involves accelerated atherosclerosis, endothelial dysfunction, chronic inflammation, hypercoagulability, and small vessel disease[36].

Chronic hyperglycemia has been shown to add to vascular damage through oxidative stress and by the stimulation of other events. the generation of AGEs. The AGEs bind their receptors They (RAGE) stimulate endothelial cells and inflammatory cells and cause excessive reactive oxygen production species (ROS) and nuclear factor-kappa B (NF-κB). This causes endothelial Dysfunction, an important precedential event on the atherogenesis and cerebrovascular pathology [37].

An endothelial disfunction in the brain vessels limits the availability of nitric oxide (NO) leading to a deteriorated functionality. vasodilation, and facilitates the expression of ICAM-1 adhesion molecule, VCAM-1 adhesion molecule and so on. This enables both leukocyte binding and mobility into the blood vessel wall. This is part of the reason. inflammation and the development of plaque, which slims brain arteries and even worsens the exposure to risk. ischemic stroke [38).

Dyslipidemia, which is an abnormal level of triglycerides and small dense LDL, is also induced due to diabetes. cholesterol and low HDL. These abnormalities in lipids hasten atherosclerosis and hence cause: stenosis and occlusion of the cerebral vessels and particularly the large vessels - carotid and the middle seronergetic vessels Fowler [39] (cerebral arteries). Plaques can also burst, causing thrombosis and an acute ischemic stroke. Moreover, diabetes facilitates hypercoagulable state. High concentrates of plasminogen activator inhibitor-1 (PAI-1), fibrinogen and blood clotting factors catalyze poor fibrinolysis. increased clotting. Platelet hyperreactivity enhances more chances of thromboembolic stroke [40].

Furthermore, cardiac autonomic neuropathy in diabetics may result in arrhythmias, particularly atrial fibrillation, which increases the risk of cardioembolic stroke. Diabetics are also more prone to silent cerebral infarctions, which may go unnoticed but lead to progressive cognitive decline and functional impairment.

In conclusion, diabetes significantly increases the risk of both ischemic and hemorrhagic strokes through a complex interplay of metabolic and vascular abnormalities. These include oxidative stress, inflammation, endothelial dysfunction, atherogenesis, and altered coagulation. Effective prevention strategies include tight glycemic control, blood pressure and lipid management, antiplatelet therapy, and lifestyle modifications to reduce the burden of cerebrovascular disease in diabetic populations.

- *Diabetic Peripheral Artery Disease (PAD): Mechanism and Pathophysiology*

One of the serious, common complication of diabetes mellitus is peripheral artery disease (PAD). especially the type 2 diabetes. It entails gradual constrictions and closing of peripheral the arteries (in the lower limbs mostly) through the process of atherosclerosis that is quite considerably accelerated in Patients with diabetes [42]. PAD is linked with higher vulnerability of losing limbs, and heart diseases. deaths, and deaths. Diabetes leads to chronic hyperglycemia, which initiates a number of pathological processes that cause PAD. Endothelial dysfunction is among the key characteristics and its occurrence is mediated by oxidative stress and decreased nitric oxide (NO) availability [43]. Severe glucose tolerance leads to formation of oxidative damage of endothelial cells by producing reactive oxygen species (ROS), which diminish vasodilation [44]. Also, there are advanced glycation end products (AGEs) generated in a non- glycation of proteins and lipid substances by enzymatic activity that leads to vessel rigidity and inflammation responses [45]. AGEs also engage receptor of advanced glycation end products (RAGE), a cascade-signaling is triggered by it. of inflammatory transduction such as nuclear factor-kappa B (NF-κB) activation. increases the production of adhesion molecules (VCAM-1 ICAM-1) [46]. These molecules promote the binding maneuver of leukocyte to the endothelium and play an element in long-term vascular inflammation as well as development of atherosclerotic plaques [47]. PAD is worsened by insulin resistance that characterises type 2 diabetes. It affects lipids negatively metabolism thereby causing dyslipidemia; heightened triglycerides and small dense LDL. cholesterol, decreased high-density lipoproteins (HDL) and an increase in the number of particles. These anomalies advance infiltration of lipids into the proliferation of vascular wall and foam cell development which are major characteristics of atherogenesis [48]. Moreover, insulin resistance overrides the PI3K/Akt signaling which lowers the production of NO and increases vasoconstriction [49]. The hyperglycemia also plays a role in the proliferation and migration of the smooth muscle cells. inflammatory cytokines (e.g. IL-6, TNF-alpha), which

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propagate intimal thickening and also arterial remodeling [50]. Platelet aggregation is elevated and poor in diabetic people. fibrinolysis related to the hypercoagulable condition, which makes it vulnerable to thrombosis [51]. Clinically, diabetic PAD often presents as intermittent claudication, but it may be asymptomatic due to coexisting peripheral neuropathy, which blunts pain perception [52]. As the disease progresses, it can lead to critical limb ischemia (CLI), characterized by rest pain, non-healing ulcers, and gangrene. This condition is a major cause of non-traumatic lower limb amputations in diabetic patients [53].

Screening for PAD in diabetes includes the Ankle-Brachial Index (ABI), duplex ultrasonography, and in advanced cases, CT or MR angiography [54]. Early identification and management are crucial to prevent limb-threatening complications.

Management involves glycemic control, statins, antiplatelet therapy, and lifestyle changes such as smoking cessation and exercise. In severe cases, revascularization through angioplasty or bypass surgery may be needed [55].

In conclusion, diabetic PAD is a multifactorial vascular complication involving oxidative stress, endothelial dysfunction, inflammation, and metabolic derangements. Understanding its molecular and clinical mechanisms is vital for timely diagnosis and effective treatment.

- *Diabetic Hearing Impairment: Mechanisms and Evidence-Based Insight*

Diabetes mellitus (DM), particularly when chronic and poorly controlled, is associated with a wide range of complications, including sensorineural hearing loss (SNHL). Although often underrecognized, hearing impairment is now increasingly considered a microvascular complication of diabetes, similar to retinopathy, nephropathy, and neuropathy [56].

Hearing loss in diabetes is predominantly sensorineural, indicating damage to the cochlea (inner ear) or the auditory nerve pathways [57]. This impairment is usually bilateral, progressive, and most prominent in the high-frequency range, making early detection crucial [58].

The pathophysiology involves chronic hyperglycemia, which triggers several damaging mechanisms. One major contributor is microangiopathy, which leads to reduced blood supply to the cochlea due to thickening of capillary basement membranes in the stria vascularis and spiral ganglion [59]. These microvascular changes result in cochlear ischemia and hypoxia, leading to hair cell death and auditory dysfunction [60].

Another mechanism is oxidative stress, which arises due to excess production of reactive oxygen species (ROS) and impaired antioxidant defense in diabetes. ROS damage cellular components in the cochlea, including outer hair cells and neurons, thereby contributing to hearing loss [61]. Studies show increased oxidative markers in the cochlear tissues of diabetic animals [62].

Additionally, advanced glycation end-products (AGEs) accumulate in cochlear structures, disrupting collagen cross-linking and inducing inflammation via the RAGE receptor. This cascade leads to apoptosis of cochlear hair cells and spiral ganglion neurons, both critical for auditory transduction [63].

Neuropathy is another important mechanism. Diabetes-related auditory neuropathy affects the eighth cranial nerve (vestibulocochlear nerve) and its central connections, reducing the speed and synchrony of signal conduction, especially in noisy environments [64]. Brainstem auditory evoked potential (BAEP) studies in diabetic patients often show delayed wave latencies, supporting the role of central auditory dysfunction [165].

Furthermore, insulin resistance and impaired glucose metabolism in inner ear structures reduce energy supply needed for normal cochlear function. The stria vascularis, which maintains the endocochlear potential necessary for hearing, is particularly sensitive to metabolic changes [66].

Epidemiologically, several studies have linked diabetes with hearing loss. The National Health and Nutrition Examination Survey (NHANES) reported that adults with diabetes were twice as likely to have hearing impairment compared to non-diabetics [67]. Moreover, the severity and duration of diabetes correlate strongly with the degree of hearing loss [68].

Early screening using pure tone audiometry, otoacoustic emissions, and BAEP is advised, especially in long-standing or poorly controlled diabetes [69]. Preventive strategies include tight glycemic control, antioxidant therapy, and early auditory rehabilitation to minimize progression and enhance quality of life [70].

In summary, diabetic hearing loss is a multifactorial complication involving microangiopathy, oxidative stress, neuropathy, and AGE-induced inflammation. Awareness and early intervention can prevent irreversible auditory damage.

- *Diabetic Skin Conditions: Mechanisms and Clinical Manifestations*

Diabetes mellitus (DM) is a systemic metabolic disorder that not only affects internal organs but also manifests in the skin. Cutaneous complications are common in diabetic patients, with up to 30%–70% experiencing at least one skin disorder during the course of their disease [71]. These skin conditions range from infections to specific dermatoses that can serve as early indicators of diabetes.

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One of the most frequent diabetic skin manifestations is diabetic dermopathy, which presents as brown, atrophic, scar-like lesions usually on the shins. It is caused by microangiopathy, where chronic hyperglycemia damages the small blood vessels supplying the skin [72]. Histopathological studies show dermal collagen degeneration and capillary basement membrane thickening, akin to other diabetic microvascular complications [73].

Acanthosis nigricans is another notable skin change seen in diabetes, especially in those with insulin resistance. It appears as dark, velvety hyperpigmentation in intertriginous areas such as the neck and axillae. Hyperinsulinemia stimulates keratinocyte and fibroblast proliferation via the IGF-1 receptor pathway, resulting in the characteristic skin thickening [74].

Necrobiosis lipoidica diabeticorum (NLD) is a less common but more specific condition affecting about 0.3% of diabetics, often seen in young adults with type 1 diabetes. It presents as well-demarcated, yellow-brown plaques with central atrophy, mostly on the lower legs [75]. The pathogenesis involves immune complex deposition, altered collagen metabolism, and microangiopathy, leading to granulomatous inflammation [76].

Another concern is diabetic bullae (bullosis diabeticorum), which are spontaneous, non-inflammatory blisters appearing on the hands and feet. Although rare, these lesions are unique to diabetes and thought to result from basement membrane zone separation due to trauma or vascular compromise in neuropathic skin [77].

Skin infections, particularly bacterial (Staphylococcus aureus) and fungal (Candida species), are more common and severe in diabetics. Hyperglycemia impairs neutrophil function, reducing chemotaxis and phagocytosis, thus increasing susceptibility to infections [78]. Candidiasis frequently affects intertriginous areas and mucosal surfaces, while bacterial infections may present as boils, cellulitis, or carbuncles [79].

Pruritus (itching), a common but often underreported symptom, can arise from xerosis (dry skin), neuropathy, or poor glycemic control. Diabetes-related autonomic dysfunction reduces sweat gland function, leading to dry, itchy skin [80].

Additionally, wound healing is significantly impaired in diabetes due to reduced angiogenesis, collagen deposition, and fibroblast function. Chronic wounds, such as diabetic foot ulcers, are highly prevalent and often serve as portals for infection and subsequent limb amputation if not treated properly [81].

From a molecular perspective, chronic hyperglycemia promotes inflammatory cytokines (TNF-α, IL-6) and advanced glycation end products (AGEs), which damage skin tissues, alter keratinocyte behavior, and delay regeneration [82]. Insulin resistance and poor metabolic control exacerbate this by reducing nitric oxide production and blood flow to the skin [83].

In conclusion, diabetic skin conditions are diverse and often reflect the underlying vascular, metabolic, and immunological disturbances associated with chronic hyperglycemia. Early diagnosis and proper glycemic control are essential to manage and prevent these dermatologic complications.

- *Infections in Diabetes: Pathogenesis, Prevalence, and Clinical Relevance*

People with diabetes mellitus are at a significantly increased risk of various infections due to both immune dysregulation and the hyperglycemic environment, which promotes microbial growth and impairs host defenses [84]. This susceptibility affects not only common infections like urinary tract infections and pneumonia but also rare, life-threatening ones like mucormycosis.

Immune dysfunction in diabetes is multifactorial. Chronic hyperglycemia impairs neutrophil chemotaxis, phagocytosis, and intracellular killing—the first line of defense against pathogens [85]. Moreover, high glucose levels reduce the function of macrophages and impair complement fixation, leading to suboptimal clearance of infections [86].

A commonly encountered infection in diabetic individuals is the urinary tract infection (UTI). Diabetics are more prone to both asymptomatic bacteriuria and symptomatic UTIs, including complicated pyelonephritis and emphysematous cystitis. The increased glucose concentration in urine supports bacterial proliferation, particularly *Escherichia coli*, while autonomic neuropathy may cause incomplete bladder emptying, further increasing UTI risk [87]. A meta-analysis by Nitzan et al. (2015) confirmed that diabetic women have significantly higher rates of recurrent UTIs compared to non-diabetics [88].

Skin and soft tissue infections are also more prevalent. Conditions such as cellulitis, furunculosis, erysipelas, and intertrigo occur more frequently and often involve Staphylococcus aureus and Streptococcus species. The skin barrier is compromised due to neuropathy, microvascular disease, and poor wound healing, allowing easier microbial entry [89]. Diabetic foot infections are particularly concerning due to ischemia, neuropathy, and immune impairment, often resulting in chronic ulcers and amputations [90].

Another major concern is pneumonia, especially community-acquired and hospital-acquired types, which are more severe and carry higher mortality in diabetics. The impaired pulmonary immune defense and increased colonization of the upper respiratory tract by pathogens like *Streptococcus pneumoniae* and *Klebsiella pneumoniae* are important contributing factors [91]. A large cohort study found

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that diabetes increases the risk of pneumonia by over 1.5-fold, independent of other comorbidities [92].

A rare but serious infection associated with diabetes is mucormycosis, caused by fungi of the order *Mucorales*. It typically presents in diabetic ketoacidosis patients due to acidic pH and elevated iron levels, which favor fungal growth [93]. The rhinocerebral form is the most common in diabetes and is often fatal if not diagnosed early. The spores invade blood vessels and cause thrombosis and tissue necrosis, rapidly spreading to the brain and eyes [94].

Additionally, diabetics are more prone to fungal infections, especially Candida species, which cause oral candidiasis, vaginal infections, and intertriginous rashes. This is due to glucose-rich mucosal surfaces, reduced salivary antimicrobial peptides, and impaired T-cell-mediated immunity [95].

Infections in diabetes are not only more common but also more severe, leading to prolonged hospital stays and increased mortality. Tight glycemic control, vaccination (e.g., for influenza and pneumococcus), and early antimicrobial therapy are crucial in managing and preventing infections in diabetic individuals [96].

III. GASTROINTESTINAL AUTONOMIC NEUROPATHY IN DIABETES

Gastrointestinal Autonomic Neuropathy (GAN) is a serious and often underdiagnosed complication of long-standing diabetes mellitus, particularly in those with poor glycemic control. It results from damage to the autonomic nervous system, especially the vagus nerve, which regulates involuntary functions of the gastrointestinal (GI) tract. This dysfunction manifests as a wide range of GI symptoms such as gastroparesis, constipation, diarrhea, and fecal incontinence [97].

- *Pathophysiology*

Diabetes-induced chronic hyperglycemia leads to the formation of advanced glycation end products (AGEs), oxidative stress, and microvascular damage, which collectively impair autonomic nerves supplying the GI tract. The most severely affected nerves include parasympathetic (vagal) fibers, which modulate motility and secretory functions [98].

- *Gastroparesis*

Gastroparesis refers to delayed gastric emptying without mechanical obstruction, resulting from vagal nerve damage. The vagus normally coordinates the contraction of stomach muscles, ensuring timely delivery of chyme into the duodenum. In GAN, this coordination is lost, leading to symptoms such as early satiety, bloating, nausea, vomiting, and poor appetite [99]. Studies show that up to 50% of type 1 diabetics and a smaller proportion of type 2 diabetics may experience some degree of gastroparesis [100].

- *Constipation*

Constipation is a common manifestation of diabetic autonomic neuropathy due to delayed colonic transit time. Neuropathy affects the enteric nervous system and reduces the peristaltic efficiency of the colon. This leads to hard stools, straining, and infrequent bowel movements. Studies have shown that diabetic patients have a slower mean colonic transit time compared to non-diabetics [101].

- *Diarrhea*

Paradoxically, many patients also experience diabetic diarrhea, often characterized by nocturnal watery stools and urgency. This occurs due to denervation hypersensitivity, impaired small bowel motility, and sometimes bacterial overgrowth in the small intestine. These factors result in uncoordinated and rapid intestinal transit, causing diarrhea [102].

- *Fecal Incontinence*

Damage to the sacral parasympathetic nerves and internal anal sphincter innervation leads to reduced sphincter tone and impaired sensation, resulting in fecal incontinence. This condition is distressing and socially disabling, especially in elderly diabetics. Manometry studies confirm decreased anal resting pressure and abnormal rectoanal reflexes in affected individuals [103].

- *Management and Clinical Relevance*

Gastrointestinal autonomic neuropathy not only reduces quality of life but also interferes with oral medication absorption, leading to poor glycemic control and erratic blood glucose levels. Early diagnosis using gastric emptying studies, scintigraphy, or autonomic function testing, and treatment with prokinetics, dietary modifications, and neuromodulators is crucial [104].

- *Diabetic Non-Alcoholic Fatty Liver Disease (NAFLD):*

Non alcoholic fatty liver disease (NAFLD) refers to a continuum of diseases or liver disorders revealed by the feature of fatty accumulation. the presence of hepatic fat (>5 per cent hepatocytes) not attributable to a large intake of alcohol. In patients with diabetes mellitus especially type 2 diabetes mellitus (T2DM) -NAFLD much common because of the similarity in metabolic peculiarities like insulin resistance. dyslipidemia, and inflammatory processes which are chronic. In diabetic patients, NAFLD develops faster to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and hepatocellular carcinoma (HCC) [105]. Molecular Pathways of the Connection between diabetes and NAFLD 1. Insulin Resistance and Fatty Liver The refractory side of dysregulated insulin secretion: insulin resistance (IR) centers upon unusually abundant deposition of fat in the liver (hepatic steatosis) and/or fat inflammation (hepatic inflammatory fat) and/or fat-induced hepatic insulin resistance (IR) and/or generally unusual fat excess. the diabetic NAFLD pathogenesis. There is a defect in lipolysis suppression by insulin in IR states. adipose tissue resulting in the propagation of free fatty acid (FFA) circulation

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to the liver. This brings about the deposition of triglycerides in liver cells (hepatic steatosis) [106].

- Insulin resistance interferes with insulin mediated inhibition of gluconeogenesis and facilitates de novo an increase in lipogenesis (DNL) through stimulation of sterol regulatory element-binding protein-1c (SREBP- 1c) [107].
- De Novo Lipogenesis (DNL) An important aspect in NAFLD is that DNL is upregulated in NAFLD and especially inDNL. T2DM. Insulin activates the transcription factors Like SREBP-1c and carbohydrate lipogenic enzymes mediated by the responsive element-binding protein (ChREBP) that enhance expression enzymes such as fatty acid synthase (FASN) and the acquaintance-of-CoA carboxylase (ACC). to the enhanced lipid formation in hepatocytes [108].
- Mitochondrial Dysfunction and Oxidative Stress Excess FFAs entering the liver undergo β-oxidation in mitochondria, generating reactive oxygen species (ROS). In diabetes, mitochondrial dysfunction and ROS overproduction contribute to oxidative stress, lipid peroxidation, and hepatocyte injury—key events in progression from simple steatosis to NASH [109].
- Endoplasmic Reticulum (ER) Stress ER stress is increased in diabetic NAFLD due to lipid overload and misfolded protein accumulation. This activates the unfolded protein response (UPR), which exacerbates inflammation, insulin resistance, and apoptosis in hepatocytes [110].
- Inflammatory Signaling and Cytokines Chronic low-grade inflammation is characteristic of diabetes and NAFLD. Proinflammatory cytokines like TNF-α, IL-6, and MCP-1 activate nuclear factor kappa B (NF-κB) and c-Jun N-terminal kinase (JNK) pathways, promoting hepatocyte injury and fibrosis [111].
- Gut Microbiota and Metabolic Endotoxemia Altered gut microbiota in diabetic patients contributes to NAFLD via increased intestinal permeability and translocation of bacterial endotoxins like lipopolysaccharide (LPS). This activates hepatic Kupffer cells and promotes inflammation and fibrosis [112].

IV. CONCLUSION

Diabetes mellitus extends far beyond being a simple metabolic disorder; it is a complex, systemic condition that contributes to a wide range of comorbidities through intricate molecular interactions. Persistent hyperglycemia and insulin resistance trigger a cascade of harmful processes, including heightened oxidative stress, chronic low-grade inflammation, and mitochondrial dysfunction. These disturbances promote endothelial damage, accumulation of advanced glycation end products (AGEs), and activation of key molecular pathways such as NF-κB, MAPK, and PI3K/Akt. Together, these mechanisms play a central role in the development of cardiovascular complications, nephropathy, neuropathy, retinopathy, and reproductive health issues commonly associated with diabetes. Additionally, the interplay between adipokines, inflammatory cytokines, and the renin-angiotensin system further accelerates tissue injury and disease progression. A deeper understanding of these interconnected pathways is essential for creating more precise therapeutic approaches that address not only blood glucose control but also the prevention and management of diabetes-related complications.

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