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# The Impact of Diabetes and Hypertension on Cardiovascular Disease A Review

A. Vasanth[1]*, M. Vishnupriya [1], N. Vishva[1], R. Rajapandi [2] And S. Gopikrishnan [3]

*1 Doctor of pharmacy, Arulmigu Kalasalingam College of Pharmacy, Viruthunagar, Tamilnadu, India - 626126.*

*2 Department of Pharmaceutical Chemistry, Arulmigu Kalasalingam College of Pharmacy, Viruthunagar, Tamilnadu, India – 626126.*

*3 Department of Pharmacology, Arulmigu Kalasalingam College of Pharmacy, Viruthunagar, Tamilnadu, India – 626126.*

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**ABSTRACT**:
It is common for type 2 diabetes and hypertension to coexist. Those with diabetes experience hypertension twice as often as those without diabetes. People with hypertension typically exhibit signs of insulin resistance and have a higher risk of developing diabetes when compared to people with normal blood pressure. Hypertension increases the risk of cardiovascular disease, which is the primary illness and cause of death among diabetics. The strong correlation between diabetes and hypertension is due to shared risk factors like endothelial dysfunction, vascular inflammation, arterial remodeling, atherosclerosis, dyslipidemia, and obesity. Both illnesses share similar cardiovascular complications, particularly microvascular and macrovascular disorders. Activation of the immune system, oxidative stress, inflammation, and the renin-angiotensin-aldosterone system are a few examples of common pathways that may be involved in the connection between diabetes and hypertension. This article thoroughly explains the pathophysiology of the vascular issues caused by diabetes and hypertension. It also highlights numerous vascular pathways involved in diabetes and hypertension, such as advanced glycation end products, oxidative stress, inflammation, the immune system, and microRNAs.

**KEYWORDS:**type 2 diabetes mellitus, hypertension, cardiovascular disease, vascular complications.

## I. INTRODUCTION

The prevalence of type 2 diabetes (T2DM) is rising on a global scale. Obesity, sedentary lifestyles, and excessive calorie diets are largely responsible for this. By 2040, the number of T2DM cases could rise from 415 million to 642 million.[1] In addition, the prevalence of hypertension (HTN) is even more widespread, with an estimated 1.39 billion cases worldwide.[2]

Cardiovascular disease (CVD) susceptibility is increased by both hypertension and diabetes mellitus. The coexistence of HTN and T2DM in the same person is not a random occurrence. Their shared pathophysiology, particularly in relation to obesity and insulin resistance, is the basis of this association. An investigation revealed that 52.5% of people with type 2 diabetes also had hypertension.[3] By affecting the metabolism of carbohydrates, proteins, and lipids, insulin is essential for preserving the body's glucose homeostasis. However, the liver, muscles, and adipose tissues are primarily impacted by insulin resistance, which results in a decreased sensitivity to the effects of insulin. While insulin's capacity to control sodium retention in the distal tubule is still preserved, this resistance specifically affects the metabolism of glucose and lipids.[4,5] The body reacts to a decrease in insulin-mediated glucose disposal by compensatorily increasing insulin secretion in order to maintain glucose homeostasis. Glucose intolerance, however, can result if the endocrine pancreas does not adequately respond. However, in obese individuals, a supranormal response from beta cells can delay the onset of T2DM.[6] In recent years, the importance of adipose tissue in these associations has been increasingly recognized in recent times.[7]

Both the microvascular (small arteries and capillaries) and macrovascular (large arteries) systems are impacted by complications related to T2DM. Diabetes' two main risk factors, chronic hyperglycemia, and insulin resistance, are closely

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linked to the emergence of vascular complications. These factors influence the onset of complications through a number of mechanisms, including oxidative stress, inflammation, increased production of advanced glycation end products (AGEs), and activation of the receptor for advanced glycation end products (RAGE) via the AGE-RAGE axis.[8] HTN contributes to vascular injury and dysfunction, making it a recognized important risk factor for vascular complications linked to diabetes (see Fig. 1). In this review, we put particular focus on examining how T2DM and hypertension interact to cause cardiovascular disease.

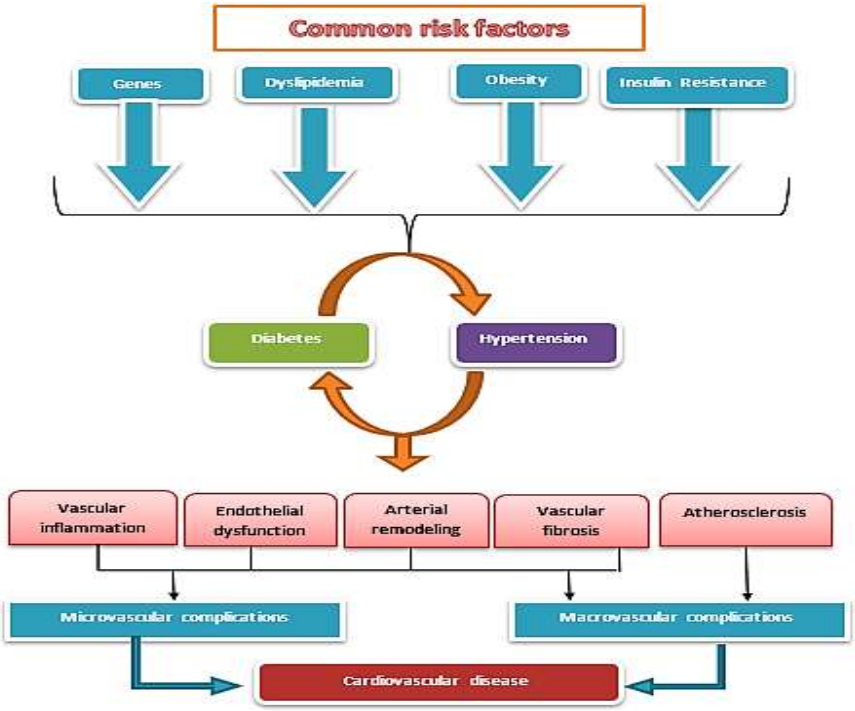


Figure 1. Diabetes and hypertension together increase the risk of susceptibility to cardiovascular disease through several vascular mechanisms. Shared risk factors play both conditions play a significant role in the development of atherosclerosis, vascular inflammation, endothelial dysfunction, and structural remodeling. These factors collectively contribute to the onset of macrovascular and microvascular diseases. Importantly, in cases where diabetes and hypertension coexist, the damage to blood vessels and the impairment of endothelial function are further intensified.

## II. MACROVASCULAR COMPLICATIONS:

### Clinical features

Macrovascular complications, involving larger arteries, encompass a complex inflammatory process that can result in Peripheral artery disease, myocardial infarction, and stroke. The main pathological process linked to macrovascular disease is atherosclerosis. Diabetes causes atherosclerosis to develop more quickly, which causes vascular lesions to appear more frequently.[9] The risk of CVD is doubled in people with T2DM, which is comparable to the risk posed by a prior myocardial infarction.[10,11]Patients with T2DM experience unfavorable outcomes following acute coronary syndrome, and heart failure, and exhibit higher rates of myocardial infarction.[12] At the prediabetes stage, the risk of CVD starts to increase in correlation between impaired glucose tolerance and insulin resistance.[13] The development of microvascular complications and CVD is significantly influenced by hyperglycemia, which also serves as the hallmark of T2DM. However, compared to hypertension, dyslipidemia, and, regrettably, smoking, which are more common in many populations, hyperglycemia is thought to be a relatively weaker modifiable risk factor in people with established T2DM.[14,15]

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**Pathophysiological features**

Several years before the onset of T2DM, insulin resistance can be identified. Obesity, especially central obesity, is frequently linked to it. However, lean people with high blood pressure can also have insulin resistance.[16] In cases of calorie excess, adipocytes in obese individuals, regardless of their location in subcutaneous or visceral areas, experience an enlargement known as hypertrophy. Visceral adipocytes, specifically, have a higher tendency to undergo cellular death as they expand, resulting in the infiltration of macrophages into their stromal vascular fraction.[17]

The presence of "crown-like structures," which are formed by macrophages surrounding deceased adipocytes, serves as a histological indication of the production of cytokines like interleukin-6 (IL-6), inducible nitric oxide synthase, and tumor necrosis factor-alpha (TNF-α).[18] By linking these observed changes to the emergence of insulin resistance, a pathophysiological link between metabolic and vascular diseases has been made.[19]

Adipocyte enlargement is linked to increased triglyceride storage, higher rates of lipolysis, and an atherogenic lipid profile in addition to the proinflammatory changes. This lipid profile is characterized by elevated levels of very low-density lipoprotein cholesterol, small, dense low-density lipoprotein cholesterol, high levels of triglycerides, triglyceride-rich remnants, and apolipoprotein B. Additionally, low levels of high-density lipoprotein cholesterol are frequently present in conjunction with these lipid abnormalities. Furthermore, this lipid profile is associated with elevated levels of nonesterified fatty acids (NEFAs) in circulation, decreased levels of adiponectin, increased leptin production, and activation of oxidative stress pathways in vascular endothelial cells.[7]

Obesity and insulin resistance have pro-inflammatory and metabolic effects that lead to endothelial dysfunction, which is essential for the onset and development of atherosclerosis. People with prediabetes and people with hypertension have both been found to have this dysfunction.[20] Not only can first-degree relatives of people with T2DM show signs of endothelial dysfunction, but so can otherwise healthy people who have insulin resistance.[21,22] Disruptions in the complex balance between vasoconstrictors (like endothelin and angiotensin II) and vasodilators (like nitric oxide and prostacyclin) characterize endothelial dysfunction. Proatherogenic and antiatherogenic factors, procoagulant and anticoagulant factors, and growth-promoting and growth-inhibiting factors are also affected.[23,24] Evidence supports the idea that impaired endothelium-dependent vasodilation can worsen or cause insulin resistance by preventing glucose, the necessary substrate, from reaching important target tissues.[25]

In addition to these functional modifications, the endothelial and smooth muscle cells of the vascular wall simultaneously experience low-grade inflammation. This inflammatory response aids in cell apoptosis, remodeling, hypertrophy, and proliferation.[26] This inflammatory process consequently accelerates the imbalance between the proteins that make up the arterial wall scaffolding, elastin, and collagen, which are essential for preserving vascular compliance. This imbalance aids in the development of hypertension-related "vascular aging," a condition.[27,28,29,30] Vascular stiffening, resulting from this process, leads to an elevation in arterial pulse pressure and intensified pulsatile shear stress. These elements accelerate the development of vascular disease and exacerbate endothelial dysfunction.[31]

## III. MICROVASCULAR COMPLICATIONS:

**Clinical features**

In diabetic patients, nephropathy, retinopathy, and neuropathy are the main causes of morbidity and mortality. primarily arising from microvascular complications. About 16.10% of people with confirmed T2DM in India have diabetic retinopathy.[32] Globally, diabetic retinopathy is accountable for approximately 10,000 cases of blindness annually.[33,34] About 40% of T2DM patients have diabetic nephropathy.[35] Diabetic peripheral neuropathy (DPN) affects 18.8 to 61.9% of T2DM patients in India.[36] The clinical and histological characteristics of the microvascular complications linked to particular organs are unique. The frequency of these complications, however, rises with the duration of hyperglycemia and is primarily influenced by cellular reactions that take place after hyperglycemia. These outcomes include polyol accumulation (due to hexokinase pathway saturation and elevated aldose reductase activity), AGE-induced damage, increased vascular permeability, and oxidative stress.[8]

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Controlled

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Evaluation, a long-term follow-up of the ADVANCE trial cohort, has confirmed that having microvascular complications increases the risk of cardiovascular complications in people with T2DM.[37] Furthermore, having both hypertension and retinopathy is a major risk factor for the development of nephropathy. Angiotensin II receptor blockers have been shown to be effective in treating nephropathy and may also be able to slow the progression of retinopathy, which provides evidence in favor of their use in the management of hypertension.[38]

**Pathophysiological Features**

Differentiating characteristics of diabetic microangiopathy include thickening of the capillary basement membrane, increased endothelial permeability, and diminished functionality of both endothelial and vascular smooth muscle cells. Hyperglycemia, which initiates damaging pathways and activates the polyol pathway, oxidative stress, proinflammatory transcription factors, and immune responses, is the main cause of these changes. Similar processes are also brought on by hypertension.[39]

## IV. THE EFFECTS OF HTN AND THE MECHANISMS BEHIND VASCULAR COMPLICATIONS IN T2DM

The next sections discuss the several connected pathways that contribute to the emergence of vascular problems. (Fig. 2)

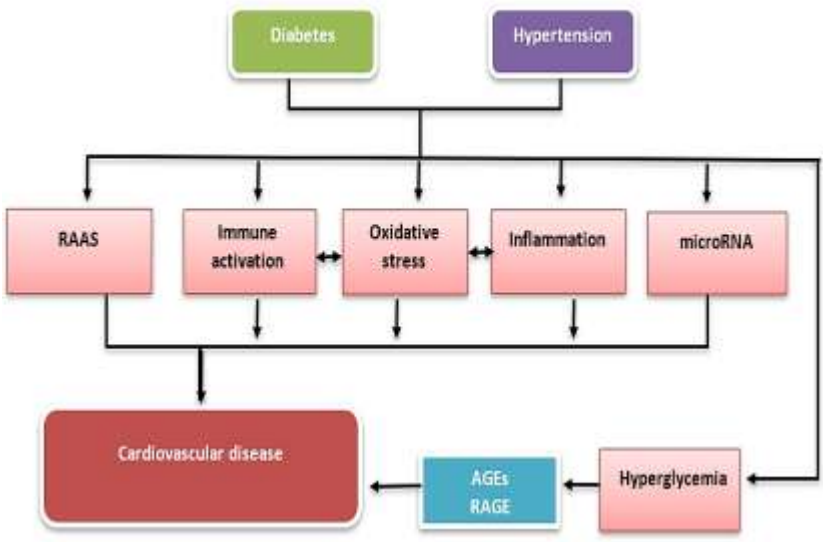


Figure 2. Both diabetes and hypertension advance vascular disease through a number of different mechanisms. These comprise inflammation and the activation of immune cells, both of which are impacted by oxidative stress. Advanced glycation end products (AGEs), the renin-angiotensin-aldosterone system (RAAS), and the binding of ligands to the AGEs receptor (RAGE) are other components of this complex process.

**Oxidative stress and NADPH oxidase**

Oxidative stress is a key factor in the harmful effects of elevated glucose levels in diabetes. In blood vessels, hyperglycemia increases the production of reactive oxygen species (ROS) and leads to the accumulation of oxidative by-products in lipids, proteins, and nucleic acids.[26] NADPH oxidases (NOX) and dysfunctional endothelial nitric oxide synthase are the main causes of increased ROS in the vasculature in people with T2DM.40,[41] Through their interactions with DNA, these ROS molecules cause inflammation, fibrosis, and vascular damage by activating a number of redox-sensitive signaling pathways. The elevated levels of oxidative stress associated with diabetes and hypertension lead to an increase in oxidative protein modification, which damages cells and impairs vascular function. The redox-sensitive protein kinase C, polyol, and hexosamine pathways are also stimulated by hyperglycemia, and they help to cause oxidative

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stress, endoplasmic reticulum stress, mitochondrial dysfunction, and eventual cellular damage.[42] Nitric oxide is a vital vasodilator, and oxidative stress decreases its availability, leading to endothelial dysfunction.

Activation of the pro-oxidant renin-angiotensin system increased mitochondrial respiration stimulated by glucose, endoplasmic reticulum stress, decreased vascular antioxidant capacity, decreased activity of the key antioxidant transcription factor nuclear factor-erythroid 2-related factor (Nrf-2), and activation of particular isoforms of the enzyme Nox are just a few of the mechanisms by which diabetes causes oxidative stress.[43] The activation of Nox isoforms is one of these mechanisms which is significant. Human blood vessels have four known types. Nox comes in five different isoforms: Nox1, Nox2, Nox4, and Nox5. Nox enzymes' production of ROS has a significant impact on the redox-sensitive signaling systems in vascular cells. Among the pathways involved are protein tyrosine phosphatases (PTPs), transcription factors, calcium channels, ion transporters, and proinflammatory genes.44 In people with diabetes and hypertension, the presence of oxidative stress—defined by high levels of ROS—contributes to vascular inflammation, fibrosis, and damage. The use of Nox inhibitors, ROS scavengers, or a combination of the two can slow these processes down. Notably, our study using Nox1-deficient mice on an ApoE-/- background that were induced to develop diabetes by streptozotocin injection demonstrated that Nox1 appears to play a critical role in the development of atherosclerosis in diabetics.[45] Nox4 has been identified to play a function in renal damage in diabetic mice models. The harmful effects associated with Nox4 can be mitigated by using Nox1/4 inhibitors and by utilizing mice that lack Nox4.[46,47] Additionally, Nox5 may also contribute to vascular injury and nephropathy associated with diabetes. In a study, it was discovered that diabetic nephropathy patients' kidneys expressed more Nox5 than normal. Additionally, in transgenic mice expressing human Nox5, hyperglycemia made kidney damage worse, especially in podocytes.[48] Similar outcomes were also observed in mice that specifically expressed human Nox5 in vascular smooth muscle cells.[49] A recent clinical trial using GKT137831, a Nox1/4 inhibitor, did not show improvement in renal function among patients with diabetic nephropathy, despite strong experimental data supporting the Renoprotective effects of Nox4 inhibition in diabetes.[50] Since there are no Nox5 inhibitors on the market, it is unclear if targeting Nox5 would result in better clinical outcomes.

**Immune system and inflammation**

Numerous experimental findings demonstrate the relationships between inflammatory response, immunological function, metabolic disorder, high blood pressure, and cardiovascular disease. [51] These connections touch on a variety of immune metabolisms, including the crucial role of the tricarboxylic cycle and the regulation of vascular inflammation by sphingosine-1-phosphate.[51,52] According to clinical studies, type 2 diabetes is associated with higher total leukocyte counts, particularly neutrophils and lymphocytes, which are correlated with insulin sensitivity.[53] Adipose tissue inflammation plays a role in mediating these changes to some extent.[54] It has been demonstrated that the development of targeted cardiovascular therapies for metabolic dysfunction benefits from the use of inflammatory biomarkers.[55] Genetic studies and clinical trials that have shown the preventive advantages of immune-targeted therapy as well as the anti-inflammatory properties of traditional anti-diabetes medications have further strengthened the link between inflammation and T2DM.[56] TNF-alpha, interferon-gamma, IL-1beta, and IL-12, for example, can modify insulin release in the pancreas and alter peripheral tissues' sensitivity to insulin.[57,58,59,60] Increased immune cell infiltration in target tissues is associated with increased glucotoxicity and lipotoxicity, which contributes to cardiovascular disease and organ damage brought on by diabetes.[60,61] involves the onset of metabolic cardiomyopathy.[62,63] Inflammation is an important regulator of metabolic and diabetic CVD.

**Clinical evidence**.

Clinical evidence suggests that immune factors play a role in T2DM and its associated cardiovascular Disorders. Immune-targeted medications, such as anti-TNF drugs, used to treat illnesses such as rheumatoid arthritis and autoimmune disorders, have shown potential in avoiding insulin resistance and lowering cardiovascular risk.[56,72] The risk of developing diabetes, obesity, and insulin sensitivity decreases over time, according to a meta-analysis of the research on anti-TNF medications.[73] Although severe infections were noted as a side effect, a different trial using canakinumab to target IL-1b showed a reduction in cardiovascular events in patients recovering from a heart attack.[74] The IL-1b

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blockade may increase insulin sensitivity, based on the available data. These results point to the potential benefits of immune-modulating and anti-inflammatory drugs in the management of T2DM and its complications, possibly via direct effects that prevent blood vessel damage. The idea of immunometabolism has emerged, emphasizing how metabolic changes in tissues are connected. There are many variables to take into account, including inflammation and immune cells' metabolic state.[27,48] A transition between phosphorylation with oxygen and glycolysis under anaerobic conditions is a distinguishing characteristic of macrophages and T cells.[29,51] Understanding the onset of T2DM and its effects requires understanding the interaction of vascular inflammation and oxidative stress between adipose tissue and the vasculature.

Genetic evidence. The immune system's genes have not been strongly associated with insulin resistance or type 2 diabetes, according to genome-wide association studies (GWAS). there are significant links between immune-related loci and numerous metabolic characteristics.[75] By combining metabochip approaches with GWAS, researchers have identified the role of key immunometabolic genes in T2DM. These genes include those associated with JNK signaling pathways, regulators of nuclear factor kappa B (NF-kB), like MAP3K1, as well as MACROD1. NRF3 and interferon-g receptor genes are two other inflammasome activators that have been linked to T2DM.[73,76] Genes like MAEA and ST6GAL1 that are involved in macrophage function and antigen presentation have been found by recent large-scale GWAS in T2DM. Additionally, T2DM has been linked to genes involved in T-cell signaling, including CMIP and PTPRJ. These results emphasize the potential involvement of immune-related genes in the initiation and development of T2DM.[75,77] The direct impact of single-gene variability is still constrained, and it is crucial to understand that GWAS techniques have limitations in that they can only account for a very small portion of the heritability of complex characteristics.[78]

**Anti-inflammatory features of diabetestherapy.**

Weight loss and the use of medications like metformin, statins, pioglitazone, and insulin have both traditionally been used to improve metabolic health and have demonstrated anti-inflammatory effects. For instance, studies have shown that metformin can reduce C-reactive protein levels by about 13%. Additionally, a study has demonstrated that metformin has a unique anti-inflammatory mechanism that modifies macrophage polarization, particularly the M1/M2 phenotype, thereby reducing low-grade inflammation related to obesity. Adenosine monophosphate-activated protein kinase (AMPK) is stimulated by metformin. maybe responsible for this impact. AMPK and its counterpart, 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR), were discovered to affect the actions stated above, with larger effects identified when compared to metformin.[79] Recent research has also shown that salicylates have anti-inflammatory properties, including suppressing NF-kB. In animal and human models, these medicines have shown promise in avoiding diabetes and reducing insulin resistance.[80,81] It has been shown that other medications, such as glicazide, troglitazone, and N-acetylcysteine, reduce the markers of inflammation in diabetic nephropathy and retinopathy.[82]

Epigenetics is emerging as an additional pathway that might alter inflammation and immuno-metabolism in diabetes, in addition to medication-based therapies.[51] It has been demonstrated that histone deacetylase (HDAC) inhibitors, such as givinostat (formerly known as ITF2357), suppress NF-kB by acetylating the p65 subunit, hence delaying the onset of diabetes.[83,84] Activation of sirtuin1, a protein involved in inflammation, metabolism, and aging, has additionally shown anti-inflammatory properties when used to treat diabetes.[85]

**The AGE-RAGE relationship:**

The irreversible posttranslational modifications to proteins and nucleic acids caused by interactions between amino groups on proteins and sugars are known as AGEs. As AGEs accumulate in the extracellular matrix of blood vessels and damage the vascular system in diabetes, hyperglycemia speeds up their production.64 AGE stimulation increases the production of reactive oxygen species (ROS). AGEs can also cause immunological reactions and exhibit antigenic properties.[64] Methylglyoxal, a byproduct of glycolysis, is another substance that builds up in tissues and causes vascular damage in diabetes.[65]

The two main types of cell surface receptors that AGEs interact with are scavenger receptors, which remove and destroy AGEs, and

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Receptors for AGEs RAGE, which cause specific cellular signaling responses upon binding AGEs. RAGE, a member of the immunoglobulin family, has the capacity to bind to a wide variety of ligands in AGEs. Some of the ligands that can bind to RAGE include high mobility group protein B1, S100 calcium-binding proteins, beta-amyloid protein, and amphotericin. Numerous pathological processes connected to inflammation and disease depend on the interaction between RAGE and these ligands. TGF-beta, NF-kB, MAPK, and Nox signaling pathways are all activated by the interactions of AGEs and RAGE. Vascular adhesion molecule 1, E-selectin, vascular endothelial growth factor, and proinflammatory cytokines (IL-1beta, IL-6, and TNF-alpha) are all produced as a result of this stimulation.66 Diabetes leads to the activation of these signaling pathways in vascular smooth muscle cells, which causes vascular fibrosis, calcification, inflammation, and vascular damage. These mechanisms contribute to the development of diabetic nephropathy, retinopathy, neuropathy, and atherosclerotic cardiovascular disease.[67] These consequences are made worse by the presence of hypertension, which also significantly speeds up the onset of vasculopathy.[68] Diabetes patients have higher levels of AGEs and soluble AGE receptors (sRAGE) in their tissues and blood, which are indicators of cardiovascular problems and overall mortality. Therefore, measuring AGEs and sRAGE levels in the urine and plasma may be useful in identifying vascular complications in diabetics.[69]

A potential treatment approach for lowering or preventing CVD in diabetics involves the AGE-RAGE pathway. Numerous significant clinical trials have looked at alagebrium (ALT-711) including DIAMOND (NCT00043836), SAPPHIRE (NCT00045981), SILVER (NCT00045994), SPECTRA (NCT00089713), BREAK-DHF-I (NCT00662116), and BENEFICIAL (NCT00516646). There aren't many published results from these studies, though. Nevertheless, small-scale clinical studies have shown that algebrium improves cardiovascular function in people with diabetes and hypertension.[70] These studies discovered that algebrium therapy increased vascular compliance, decreased aortic stiffness, and improved endothelial function.[71]

**Diabetes, MIRNAs, and Vascular Disorders**

MiRNAs are a diverse class of non-coding RNAs that have been connected to the development of diabetic vascular disorders and T2DM, among other disease processes. They are essential for regulating the expression of genes. There have been discovered miRNAs specific to pancreatic beta cells, such as miR-375, miR-200, miR-124a, miR-9, miR-96, miR-7a, miR-30d, miR-7a2, miR-184, and let-7.[86] These micro RNAs have an impact on glucose tolerance, insulin secretion, and pancreatic function. Notably, distinct miRNA profiles have been found in individuals with prediabetes, diabetes, and diabetes and vascular issues, suggesting that miRNAs may be practical biomarkers. Diabetes-related cardiovascular issues are associated with elevated levels of miR-501, miR-223, miR-320, miR-504, and miR-1, while miR-373, miR-16, and miR-133 levels are decreased.[87] However, it is not clear whether these modifications in miRNA expression are merely a side effect of the illness or if they actively contribute to the emergence of vascular diseases associated with diabetes.

## V. CONCLUSION

Diabetes has been linked to a higher risk of cardiovascular disease, which is made worse by hypertension. Inflammation, oxidative stress, and fibrosis are the root causes of these conditions, and they all play a role in the progression of the microvascular and macrovascular complications of diabetes. These same pathways contribute to vascular remodeling and dysfunction in hypertension. In order to minimize the detrimental effects of diabetes on both microvascular and macrovascular complications, effective comorbidity management, particularly hypertension, and implementation of techniques to improve vascular health becomes essential.

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