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The interplay between diabetes and atherosclerosis: A review of pathophysiological mechanisms

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Abstract

Atherosclerosis, characterized by lipid accumulation in arterial walls, is a leading cause of cardiovascular morbidity and mortality, with increased prevalence among individuals with diabetes mellitus. Diabetes is a chronic condition marked by persistently high blood glucose levels, a condition that can potentially result in long-term complications, including heart, blood vessel, eye, kidney, and nerve damage. Diabetes, marked by chronic hyperglycemia, contributes to atherogenesis through mechanisms including endothelial dysfunction, oxidative stress, formation of advanced glycation end-products (AGEs), and chronic inflammation. This study provides a synopsis of the predominant characteristics of diabetes that may potentially impact the atherogenic process, including oxidative stress, altered protein kinase signaling, and the role of select microRNAs and epigenetic modifications. This review comprehensively examines literature from 1969 to 2025, focusing on the molecular and cellular pathways linking diabetes to atherosclerosis. Effective glycemic control and management of associated risk factors remain pivotal in mitigating atherosclerotic progression in diabetic patients. Understanding these interconnected mechanisms is essential for developing targeted therapies to reduce cardiovascular complications associated with diabetes.

Keywords: Diabetes Mellitus; Coronary Artery Disease; Cardiovascular Disease; Atherosclerosis; Heart

Introduction

Atherosclerosis is a significant risk factor for cardiovascular diseases that impacts the arteries by causing the buildup of fatty plaques and narrowing of the blood vessels[1,2]. Atherosclerosis is a multifactorial inflammatory disease that ultimately results in atheroma formation. Even though atheroma plaque formation has its origins in childhood, the manifestations of this condition typically occur during middle age and after the age of 45. Atherosclerosis can result in cerebrovascular accidents (CVA) and myocardial infarctions (MI), contingent on the specific location of the vascular involvement. The significance of atherosclerotic plaque formation is further elucidated when considering that up to 80% of strokes are attributable to plaque and are ischemic[3]. Epidemiological research has shown a clear relationship between specific factors and atherosclerosis development, which are coronary artery disease (CAD) risk factors, including hypercholesterolemia, high blood pressure, and diabetes[4]. It is well established that oxidative stress, increased lipoproteins, age, hyperhomocysteinemia, inflammatory factors, genetics, smoking, cardiac ischemia, atherogenic diet, free radicals in the blood, and coronary artery disease (CAD) are all known factors in atherosclerosis[5,6]. Not exercising, increased blood clotting, alcohol consumption, obesity, and psychiatric disorders are also known potential factors in the extension of heart diseases. Atherosclerotic plaques are more rampant in the thoracic aorta and femoral arteries of patients with coronary artery disease. Consequently, the degree of obstruction of the aortic, carotid, and femoral arteries is of paramount importance in determining the severity of the condition[6,7]. Strokes are generally attributed to atherosclerosis in the carotid arteries.

Diabetes is a costly chronic disease and a significant predictor of atherosclerosis and stroke[8]. High glucose levels mainly affect tissues such as the liver, and the effects on the cells of the atherosclerotic lesion are caused by changing the signals of these tissues. An increase in intracellular glucose leads to excessive production of ROS. Additionally, hyperglycemia can activate proinflammatory responses by induction of protein kinase C and aldose reductase[9]. Also, high glucose levels lead to the formation of advanced glycation end-products. They seem to play a role in atherosclerosis expansion. Another function is LDL glycation, which can be considered an atherogenic change of LDL. AGE also inhibits reverse cholesterol transport by decreasing ABCG1 and ABCA1 expression, increasing vasoconstriction, and decreasing vasodilation and nitric oxide. Lastly, AGE promotes atherosclerotic lesions in diabetic patients[10–12]. Accumulation of intracellular ROS and advanced glycation end-products in hyperglycemic patients is one of the most prominent reasons for evaluating antioxidant remedies against diabetes and atherosclerosis[13].

Diabetes, or persistent hyperglycemia with elevated inflammatory markers, is present in the inner cells of the artery wall. In addition, ample amounts of fat cells in these conditions are faced with a disruption in the production of insulin[14]. Hyperglycemia is related to several genetic changes. These changes can affect the genetic sequence of vascular endothelial cells. Hyperglycemia induces epigenetic modifications in endothelium, which are associated with atherosclerosis development, thereby establishing a link between atherosclerosis and diabetes[15].

Individuals with diabetes are at a greater risk of developing carotid artery calcification than those without diabetes. In these groups, the frequency of calcification is significantly higher than in the group of non-afflicted patients. Furthermore, they are more susceptible to atherosclerosis[16]. Additionally, the data obtained from a total of patients with diabetes was analyzed in the group of four individuals. A group of individuals demonstrated bilateral calcification of the carotid arteries; calcification of the right carotid artery was observed in one group, while calcification of the left carotid artery also was observed in another group[17].

Diabetes mellitus represents approximately

90–95% of all forms of diabetes, and in developing countries, the population at risk of infection is the greatest. This phenomenon indicates that diabetes has become a significant public health concern in numerous countries[18]. One of the causes of mortality in diabetic patients is vascular accidents, which are largely attributable to the phenomenon of atherosclerosis. Hence, special attention is necessary regarding the relationship between diabetes and atherosclerosis[8]. The cardiovascular risk is multifaceted and involves two primary components: adequate control of blood glucose and the addressing of other contributing risk factors. The prevailing clinical practices prioritize the mitigation of risk factors, including hyperglycemia, hyperlipidemia, and hypertension. However, cardiovascular risk factors management cannot totally control development and progression of atherosclerosis in diabetes[19]. Furthermore, modifying atherosclerosis risk factors through patient education and follow-up can enhance the patient's quality of life[20]. Furthermore, plants with antioxidant activity have been shown to reduce the complications of both hyperglycemia and hyperlipidemia, indicating the possible interplay between them[21–23].

This study provides a synopsis of the predominant characteristics of diabetes that may potentially impact the atherogenic process. The investigation further explores the connection between atherosclerosis and diabetes mellitus, elucidating the potential mechanistic underpinnings of this relationship.

Methods

For this review, relevant articles published from 1961 to 2025 were collected from scientific databases, including Google Scholar, PubMed, SID, Web of Science, and Scopus. The terms diabetes, coronary heart disease, and atherosclerosis were used. Eligible articles were then reviewed.

Results

Aspects Relating to the Diabetes-Atherosclerosis Relationship

The leading cause of mortality in diabetic patients is coronary artery disease[24,25], and the rate is higher in women compared with diabetic male patients[26]. The factors involved in atherosclerosis and diabetes are presented below and summarised in Table 1. Their mechanistic aspects are also depicted in Figures 1 and 2.

Role of Nitric Oxide in Diabetes and Atherosclerosis

The process of accelerated atherosclerosis in diabetics is related to disruption of nitric oxide production. Nitric oxide causes the blood to properly flow into the vessels. Additionally, nitric oxide protects against the reaction of platelets and leukocytes with the blood vessel wall and subsequent intravascular damage. Nitric oxide also has immunomodulatory, anti-inflammatory, and antioxidant activities[27–29].

In diabetes, nitric oxide levels decrease, and as a result, the process of vasodilation is impaired. The accumulation of platelets also increases. It has been shown that under specific pathological conditions, such as high cholesterol, eNOS is impaired and that nitric oxide is produced in place of the nitrite proxy. In atherosclerosis, we see decreased eNOS expression[30].

The Role of LDL Lipoprotein in Diabetes and Atherosclerosis

The results of studies conducted on diabetic patients have demonstrated an elevated risk and accelerated progression of atherosclerosis[31]. According to research, atherosclerosis can develop at an earlier age in paediatric patients with type I diabetes. Moreover, dyslipidaemia, particularly increased LDL level, is a precipitating atherogenic factor in addition to hyperglycaemia and inflammatory responses[32]. The blood level of small, dense LDL in diabetic patients is a proven predictor of atherosclerosis progression[33]. LDL is an independent determinant of CVD. A moderate-intensity LDL for patients aged 40 to 75 years is important to evaluate their diabetes[34]. LDL easily penetrates the artery wall, oxidises, and causes atherosclerotic disease, which is most common in diabetics[35].

Table 1. Factors Involved in Diabetes-Atherosclerosis and the Expression of Mechanistic Aspects

Factor	Role in Diabetes	Mechanistic Contribution to Atherosclerosis	References
Advanced Glycation End Products (AGEs)	Formed through non-enzymatic glycation of proteins and lipids under hyperglycemic conditions. AGEs accumulate in various tissues and are elevated in diabetic patients	AGEs bind to their receptor (RAGE), triggering oxidative stress and inflammation. They promote crosslinking of collagen, leading to vascular stiffening, and enhance the oxidation of low-density lipoprotein (LDL), contributing to plaque formation.	(163-165)
RAGE (Receptor for AGEs)	A multi-ligand receptor that is upregulated in diabetic conditions. RAGE activation perpetuates chronic inflammation and cellular stress.	RAGE activation leads to the activation of nuclear factor kappa B (NF-κB), promoting the expression of pro-inflammatory genes. This contributes to endothelial dysfunction, vascular inflammation, and progression of atherosclerotic lesions.	(166-168)
	Hyperglycemia impairs endothelial nitric oxide (NO) production, reducing vasodilation and promoting a pro-thrombotic state	Endothelial dysfunction increases vascular permeability and facilitates the adhesion of monocytes and LDL to the endothelium, initiating atherogenesis. It also promotes vasoconstriction and thrombosis.	(169, 170)
Oxidative Stress	Elevated glucose levels increase the production of reactive oxygen species (ROS), overwhelming antioxidant defenses.	ROS oxidize LDL particles, which are then taken up by macrophages to form foam cells, a key component of atherosclerotic plaques. Oxidative stress also damages endothelial cells, exacerbating vascular injury.	(171, 172)
Epigenetic Modifications	Persistent hyperglycemia induces epigenetic changes, such as DNA methylation and histone modifications, leading to "metabolic memory."	These epigenetic alterations sustain the expression of pro-inflammatory and pro-atherogenic genes even after glycemic control is achieved, contributing to ongoing vascular damage.	(173, 174)
Inflammatory Cytokines	Diabetes is associated with increased levels of inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α).	These cytokines promote the recruitment of immune cells to the endothelium, enhancing inflammation and plaque instability in atherosclerosis	(175, 176)
Insulin Resistance	A hallmark of type 2 diabetes, leading to impaired glucose uptake and hyperinsulinemia.	Insulin resistance contributes to dyslipidemia and endothelial dysfunction, both of which are risk factors for atherosclerosis.	(177, 178)
Lipid Metabolism Disorders	Diabetes often leads to elevated triglycerides and decreased high-density lipoprotein (HDL) cholesterol levels.	Abnormal lipid profiles accelerate the formation of atherosclerotic plaques by increasing the availability of atherogenic lipoproteins.	(179, 180)

Table 1. Factors Involved in Diabetes-Atherosclerosis and the Expression of Mechanistic Aspects

Factor	Role in Diabetes	Mechanistic Contribution to Atherosclerosis	References
Monocyte/Macrophage Activation	Hyperglycemia and AGEs activate monocytes and macrophages, enhancing their inflammatory responses.	Activated macrophages ingest oxidized LDL, transforming into foam cells and contributing to plaque formation and progression.	(181, 182)
Genetic Factors	Certain genetic polymorphisms increase susceptibility to both diabetes and atherosclerosis.	Genetic variations can affect lipid metabolism, inflammatory responses, and endothelial function, thereby influencing the risk and progression of atherosclerosis in diabetic individuals.	(183, 184)

AGEs (Advanced glycation end-products), RAGE (Reseptor Advanced glycation end-products), LDL (High Density Lipoprotein), Nuclear factor kappa B (NF-κB), NO (Nitrogen Oxidative), ROS (Reactive Oxygen Species), inflammatory cytokines like interleukin-6 (IL-6), TNF-α (Tumor necrosis factor alpha),

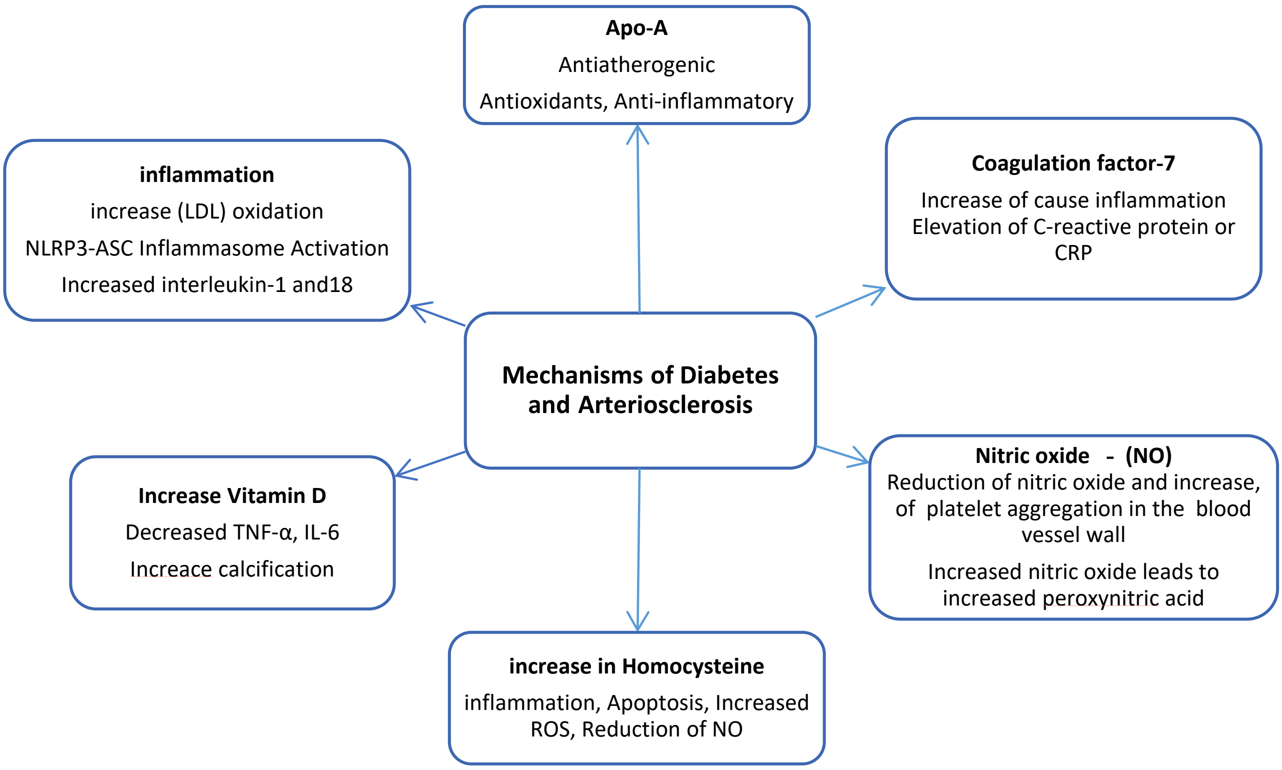

Figure 1. Association of Apo-A, Coagulation Factor-7, Nitric Oxide (NO), Vitamin D, Homocysteine, and Inflammation

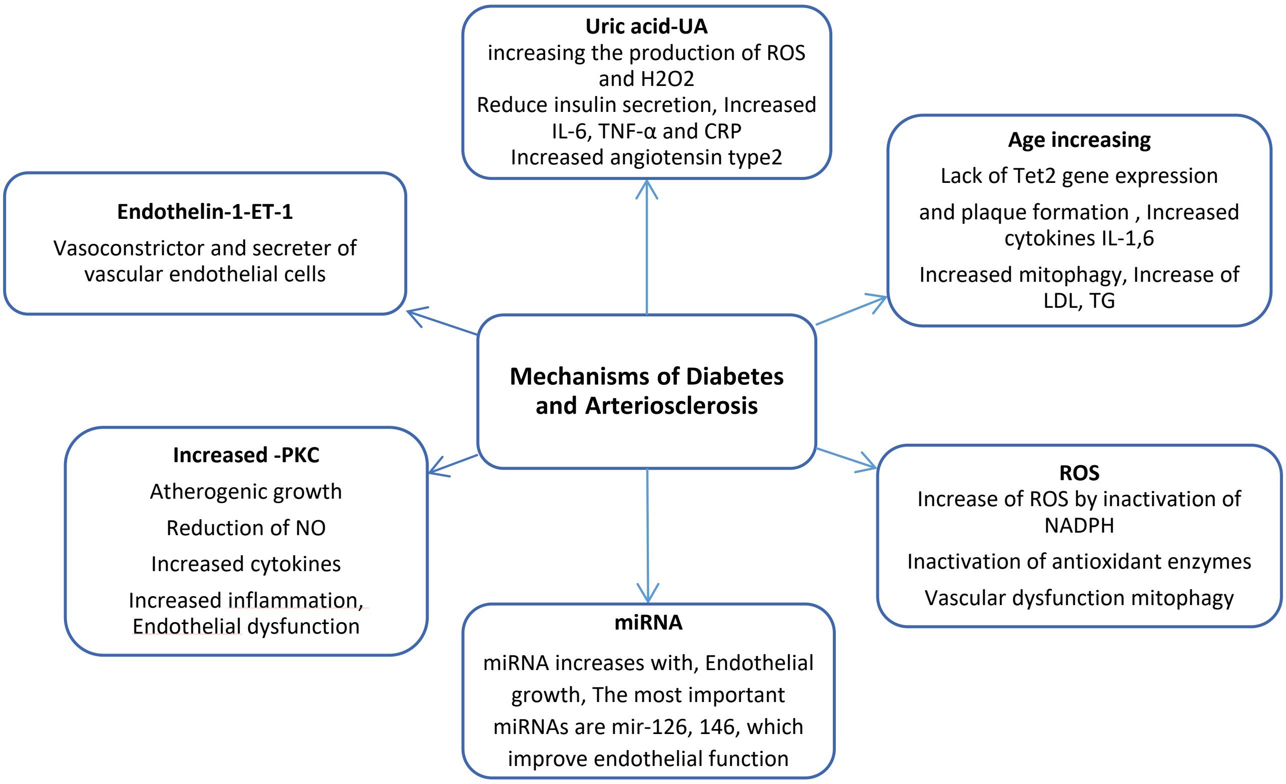

Figure 2. Association of Uric Acid (U), Age, ROS, miRNA, Endothelin-1 (ET-1), and Protein Kinase-C (PKC) with atherosclerosis and diabetes patients

The Role of Apolipoprotein A in Diabetes and Atherosclerosis

Apo A acts as an antioxidant component by increasing antioxidant activity and preventing oxidation. It is known for its anti-diabetic and anti-inflammatory activity that prevents LDL changes and lipoxygenase function. One study showed that Apo A reduces vascular lipids and macrophages and prevents atherosclerosis[36]. The concentrations of Apolipoprotein A-I and Apolipoprotein A-II have been demonstrated to increase beta-cell insulin secretion and decrease plasma glucose levels. It can be reasonably deduced that they may also have a protective role in T2DM, as well as reducing endothelial deposition and increasing HDL levels[37]. Apolipoprotein A-I, the primary protein constituent of high-density lipoproteins, has been demonstrated to possess anti-diabetic properties. It enhances insulin sensitivity and improves the function of pancreatic beta cells. Apolipoprotein A-I has also been shown to enhance insulin production and secretion in response to hyperglycaemia, indicating its therapeutic potential in diabetic patients[38].

The Role of Insulin Resistance in Diabetes and Atherosclerosis

In diabetics, the entire clotting process is disrupted. In patients with T2D, elevated blood glucose levels are caused by insulin resistance, and platelet adhesion to the vessel wall increases. This is because the function of insulin as a natural antagonist of platelets in the body is disrupted[39]. Insulin resistance has been demonstrated to diminish VLDL clearance. It is possible that this may have a lesser impact on the elevation of triglycerides in this particular condition. VLDL is metabolised to remnant lipoproteins and LDL, both of which are strongly associated with atherosclerosis. High LDL and low HDL levels are observed in insulin resistance. Additionally, higher levels of VLDL in diabetes can impair HDL metabolism[40].

The Role of C-Reactive Protein in Diabetes and Atherosclerosis

Fluctuations in blood glucose levels cause inflammatory responses in patients with T2D. These inflammatory responses are accompanied by elevated levels of CRP and cause vascular disease in diabetic patients, which is prominent in atherosclerosis[41]. Additionally, preliminary evidence indicates a potential correlation between CRP and lipids. CRP has the capacity to coagulate fat and lead to atherosclerosis[42]. The capacity for fat coagulation and interaction between CRP and cholesterol[43] is linked to the advancement of atherosclerosis. Furthermore, the binding of CRP to ox-LDL has been demonstrated in vivo in diabetic patients with atherosclerosis[44]. In a study conducted by Asgari et al., an elevation in CRP was observed in alloxan-induced diabetic rats relative to their untreated counterparts. Additionally, this study revealed that administration of cucurbita powder has potential benefits in treating dyslipidaemia and lowering CRP levels in rats[45]. Also, *Artocarpus lakoocha* leaf extract has shown a reduction in CRP and inflammation, as well as suppression of acetaminophen-induced hepatotoxicity[46].

The Role of Coagulation Factor 7 in Diabetes and Atherosclerosis

Studies show that factor 7, a clotting protein, is a major contributor to thrombosis. It is related to inflammatory parameters, as IL-6 and CRP in patients with hypercholesterolaemia are high and suggest a relationship in patients with atherosclerosis and diabetes[47]. Folsom and colleagues studied the long-term relationship between fibrinogen and factor 7 in 440 men and 550 women at risk for atherosclerotic disease. They reported that factor 7 in younger individuals, women, and patients who were overweight and diabetic, as well as in patients who had decreased plasma triacylglycerol, had a greater increase during hormone therapy. Based on the results of this long-term study, CVD risk factors were related to elevated plasma levels of fibrinogen and factor 7[48].

The Role of Endothelin-1 in Diabetes and Atherosclerosis

Endothelin factor 1 (ET1), which is a vasoconstrictor secreted by endothelial cells, vascular wall muscles, and inflammatory cells, is responsible for the dysfunction of the endothelium and small vessel disease. Endothelin factor 1 level is higher in diabetic patients compared to healthy individuals[49]. Carotid artery calcification is also more common in patients with T2D and atherosclerosis than in healthy individuals[17].

Endothelin-1 is a hallmark of endothelial dysfunction in diabetes, increasing vasoconstriction and decreasing nitric oxide production, which is crucial for vasodilation. The consequence of this imbalance is diminished blood flow, which in turn gives rise to microvascular complications including retinopathy, nephropathy, and neuropathy[49].

Homocysteine Role in Diabetes and Atherosclerosis

There is a relationship between coronary artery disease and hyperhomocysteinemia. Hyperhomocysteinemia and the formation of homocysteine impair nitric oxide production and increase oxidative stress. Reducing the level of homocysteine is likely to be another treatment goal for diabetes and atherosclerosis[50,51].

Elevated homocysteine levels have been demonstrated to induce an increase in insulin resistance and impairment of β-cell function, which in turn can contribute to the development of type 2 diabetes. This phenomenon is attributable to the presence of oxidative stress and inflammation, which are instigated by elevated levels of homocysteine[44]. Homocysteine has been demonstrated to exert a deleterious effect on endothelial cells by reducing nitric oxide levels and inducing oxidative stress and inflammatory response. These processes have been shown to play a role in the initiation and progression of atherosclerosis[45].

Inflammation Role in Atherosclerosis and Diabetes

Atherosclerosis is a major complication of diabetes. It involves various pathogenic factors including oxidative stress and endothelial dysfunction[52,53]. Hyperglycaemia and hyperlipidaemia are associated with rapid atherosclerosis development[54]. Glycaemia and dyslipidaemia may cause endothelial dysfunction[55]. In addition, in type 2 diabetes patients, oxidative stress is one of the main causes of insulin resistance. It may also increase low-density lipoprotein (LDL) oxidation. High levels of glucose and prolonged oxidative stress lead to the formation of Advanced Glycation End Products. AGEs play a crucial role in diabetes vascular complications through receptor interactions (RAGEs). Oxidative stress in the endothelium caused by hyperglycaemia is associated with diabetes complications, which can induce endothelial cell apoptosis, vascular inflammation, and the promotion of endothelial activation[30].

Diabetes enhances lipokinase and tumour necrosis factor (TNF) release from adipose tissues. IL-1β, one of the key inflammatory mediators in diabetes pathogenesis, usually promotes insulin resistance, disrupts islet cell function, and leads to cell apoptosis. Excessive expression of pro-inflammatory factors can lead to complications of diabetes[56]. NLRP3 inflammasome is associated with diabetes and its complications[57]. Blood glucose usually activates the NLRP3-ASC inflammasome, which activates caspase-1 and induces IL-18 and IL-1β secretion in monocyte cells[58]. Wang et al. showed that there was an association between NLRP3 gene polymorphism and type 2 diabetes[59]. NLRP3 and its downstream molecules are upregulated in diabetes and atherosclerosis[60]. NLRP3, IL-18, and IL-1β play crucial roles in atherosclerosis and are major atherosclerosis risk factors[61]. Ox-LDL also induces IL-1β macrophage secretion[62]. A high-fat diet or ox-LDL in endothelial cells induces ROS production, activating the NLRP3 inflammasome and secreting IL-1β. This occurs in patients with diabetes and atherosclerosis[63]. NLRP3 reduces the severity of atherosclerosis. In addition, acute hypercholesterolaemia can exacerbate endothelial dysfunction by NLRP3 inhibition[64].

In the inflammatory process, inflammatory protein complexes enhance inflammatory cytokine production and cell death when encountered with pathogenic and harmful stimuli. On the other hand, mitochondria play a role in the initiation and regulation of inflammation[65]. Inflammatory activators release cardiolipin and activate inflammation[66]. Inflammation is also associated with oxidative stress[67], which aggregates diabetes and atherosclerosis.

Vitamin D Deficiency in Atherosclerosis and Diabetes

Vitamin D deficiency leads to increased vascular cell adhesion molecules and selectins responsible for the creation of atherosclerotic plaques in these patients and in diabetics. However, supplementation reduces triglycerides, total cholesterol, and LDL, and increases HDL in affected patients[68].

The process of atherosclerosis starts at an earlier age in the presence of vitamin D deficiency[69]. Atherosclerosis, diabetes, and coronary heart disease are slightly more likely in individuals with adequate vitamin D[70].

Vitamin D can promote cardiovascular health through its immunomodulatory, anti-inflammatory, and antioxidant properties. More studies need to be done due to the increased rate of vitamin D deficiency and cardiovascular events worldwide, and the potential role of vitamin D in the process of atherosclerosis[71,72].

According to research, hypertension, dyslipidaemia, insulin resistance, and obesity are accompanied by vitamin D deficiency and can lead to atherosclerosis. Additionally, subclinical markers of atherosclerosis, such as increased carotid intima-media thickness and coronary artery calcification, are seen in vitamin D deficiency[73]. These findings suggest that vitamin D plays an important role in the pathogenesis of atherosclerosis[74]. On the other hand, vitamin D or plants containing this vitamin can suppress inflammatory mediators and improve management of diabetes and atherosclerosis[75,76].

Uric Acid Roles in Diabetes and Atherosclerosis

Increased production of reactive oxygen species leads to inflammation and elevation of uric acid (UA) and vascular disease[21]. By increasing the production of ROS such as H_2O_2, UA imposes pro-oxidant effects in vascular tissue and vascular damage, especially in diabetic and cardiac patients such as those with atherosclerosis[77]. Oxidative stress can also affect insulin gene expression and decrease insulin secretion[78].

Inflammation, by increasing uric acid (UA), expresses interleukin 6, interleukin 1β, CRP, and tumour necrosis factor α. Inflammation activation by UA results in insulin resistance[79]. Uric acid increases TNF-α levels and activates the classical inflammatory pathway[80].

Increased mitochondrial production caused by inflammation, hyperglycaemia, ROS, and endothelial dysfunction are chronic complication features of diabetes[81]. Renin–angiotensin–aldosterone activation leads to renin–angiotensin–aldosterone system (RAAS) activation through increased juxtaglomerular renin production[82]. UA-induced ROS increases angiotensin II, which causes the release of aldosterone and leads to the activation of the RAAS[77,83]. In diabetes, RAAS activation causes high intraglomerular pressure, vascular dysfunction, and inflammation, which in turn lead to cardiovascular diseases[84].

The Role of Age in Diabetes and Atherosclerosis

Age is a major factor in the development of diabetes and dyslipidaemia[85]. Patients with type 2 diabetes typically have low HDL, elevated TG, and increased levels of small and dense LDL[86]. With aging, TG metabolism changes, and its serum levels increase. This makes older individuals more susceptible to cardiovascular complications[87]. Recruitment of immune cells (T-cells and macrophages) and the activation and cytotoxicity of beta cells increase apoptosis or cell death in vascular cells associated with diabetes[88]. There is also a direct relationship between old age and the risk of atherosclerosis[89]. Understanding the mechanisms of morbidity and mortality associated with age in atherosclerotic and diabetic patients may improve treatment in these high-risk groups[90].

Several studies have linked Tet2 gene expression with atherosclerosis. Lower Tet2 gene expression is associated with larger atherosclerotic plaques[91]. In addition, a lack of Tet2 in macrophage cells derived from the bone marrow leads to increased secretion of inflammatory markers from smooth muscle cells. Aging also contributes to the manufacture of chemical absorbents, which increase the uptake of myeloid cells into the arterial wall and cause an increase in atherosclerosis. Vascular factors like the effect of age on vascular bioenergetics, mitophagy, and inflammation caused by mitochondrial dysfunction in blood vessels are examples that influence atherosclerosis[92]. MtDNA damage can cause inflammation, mitochondrial dysfunction, and apoptosis[93,94].

Vascular Endothelial Changes in Diabetes and Atherosclerosis

The function of the vascular endothelium is to represent a dynamic boundary between the circulation and the surrounding tissues. These single-layered endothelial cells may act as non-adhesive surfaces for leukocytes and platelets, producing crucial regulatory factors including nitric oxide and prostaglandins[95]. The accumulation of these substances on the endothelial cells is called plaque. Atherosclerotic plaque causes small vessel narrowing and blood flow obstruction. Also, the disintegration of plaques may cause blood clots[95–98]. Diabetes has been demonstrated to induce endothelial dysfunction, typified by impaired vasodilation, augmented oxidative stress, and enhanced inflammation. This impairment is attributable, at least in part, to decreased nitric oxide production and increased reactive oxygen species[99].

The Role of Oxidative Stress in Diabetes and Atherosclerosis

In diabetes, elevated glucose levels are known to trigger a surge in the production of reactive oxygen species, a phenomenon that arises through several mechanisms including glucose auto-oxidation and mitochondrial dysfunction[100]. ROS has been demonstrated to damage cellular components, disrupt insulin secretion, and contribute to beta cell dysfunction[101]. Additionally, oxidative stress can lead to endothelial damage and atherosclerosis progression in diabetic patients due to an imbalance between antioxidants and reactive oxygen species[102,103].

Adipose tissues are major sources of ROS. Visceral fat accumulation is upstream of ROS production[104]. Atherosclerosis and diabetes in metabolic syndrome are accompanied by increased reactive oxygen species production in adipose tissue, which has been associated with increased NADPH oxidase expression. This is also associated with the inactivation of catalase, an antioxidant enzyme. Studies done on obese mice showed that NADPH oxidase inhibitors can reduce reactive oxygen species production in adipose tissue. Moreover, several factors may reduce active fat ROS in obesity[105].

The Role of miRNA in diabetes and atherosclerosis

miR-126 and miR-146 have gained attention in atherosclerosis and diabetes; for example, they are important indicators of endothelial cell function[106]. MicroRNAs have been demonstrated to regulate endothelial function and inflammation, which are recognised as pivotal factors in the initiation and progression of atherosclerosis. For instance, microRNA-126 modulates the expression of pro-inflammatory cytokines and adhesion molecules[107]. A great diversity of miRNAs has been observed. For example, another important miRNA, miR-378a, plays a significant role in the homeostasis of hyperglycaemia and energy levels[108]. According to studies, miRNA-378a has a role in the expansion of atherosclerosis. Researchers showed that miRNA-378a targets SIRPα. As a result, it regulates macrophage phagocytosis and atherosclerosis progression[109].

The Role of Dnm3os in Diabetes and Atherosclerosis

The overexpression of DNM3OS in macrophages has been shown to result in enhanced inflammation, which is thought to occur as a consequence of alterations to global histone modifications, in addition to increased expression of immune response genes. This molecule has been demonstrated to interact with nucleolin and ILF-2, proteins that regulate chromatin structure, resulting in increased inflammatory gene expression[109]. Another non-coding RNA implicated in diabetes-related atherosclerosis is Dnm3os, the reverse strand of dynamin 3.

This RNA has been found in macrophages of both mice and human diabetic cases. Its overexpression leads to inflammation and enhanced macrophage phagocytosis, causing epigenetic chromatin modifications that further exacerbate the inflammatory response in diabetic patients with atherosclerosis[104].

The Role of Protein Kinase C in Diabetes and Atherosclerosis

Protein kinase C is an important kinase in the signalling pathway[110], and diacylglycerol is needed for its activation. The activation of abnormal glucose and lipid metabolism has been linked to altered vascular signalling, which contributes to diabetic complications. For the synthesis of diacylglycerol, increased glucose absorption by vascular cells is necessary. Increased activation of PKC may also trigger the oxidative stress response[111]. Diabetic animal models show increased vascular PKC activation. Enhanced PKC signalling has several atherogenic side effects[13]. It is well established that specific PKC isoforms are associated with various pathophysiological conditions, including oxidative stress, inflammation, endothelial dysfunction, and apoptosis of vascular smooth muscle cells[112].

Immunological and Molecular Aspects of Diabetes and Atherosclerosis

The process of diabetes and arteriosclerosis starts with a change in endothelial function and structure. They produce a variety of chemokines and cytokines, one of which is CXCL12, which causes inflammation. Also, chemokine receptors such as CXCR4 and ACKR3 have been considered good targets for atherosclerosis therapy[98]. From a structural standpoint, the endothelial glycocalyx is crucial as well. For instance, it has a notable impact on anticoagulant mechanisms. This structure, made up of proteoglycans and extracellular matrix components, can have its function diminished or impaired during the inflammatory process[113,114].

Arteries and veins can regulate their internal diameter through vasoconstriction and vasodilatation, which are controlled by the autonomic nervous system. These processes help regulate blood flow to downstream organs and body temperature. Blood vessels vary greatly in size, from 25 mm for the aorta to 8 µm for the capillaries. Vasoconstriction narrows blood vessels by smooth muscle contraction and is stimulated by vasoconstrictors such as prostaglandins, vasopressin, angiotensin, and epinephrine. Vasodilation, a similar process, is mediated by nitric oxide[115–117]. There is increasing evidence that reduced intercellular junctions lead to endothelial hyperpermeability[118].

MiRNAs have crucial roles in NO production and endothelial cell growth. For example, miR-217 is highly induced during endothelial cell aging[119]. This leads to decreased expression of Sirt1. NO activates endothelial synthase. eNOS produces NO and reduces atherosclerosis and diabetes[120].

Inflammatory innate immune signalling complexes are important modulators of the IL-1 cytokine family in atherosclerosis, contributing to the inflammatory response and promoting disease progression[121].

NLRP3 and NLRP1 are also major components of inflammation. These proteins are expressed in macrophage cells and lead to apoptosis and the formation of atherosclerotic plaques in patients. In addition, hypoxia can suppress mRNA expression in macrophages with activation of NLRP3. Activation of the NLRP3 inflammasome recruits and activates caspase-1, which in turn activates inflammatory mediators[122,123].

Adipocyte-like adiponectin can help increase plaque stability and reduce proliferation of smooth muscle cells in the endothelial wall, thereby reducing the progression of atherosclerosis[124–126]. Observations (AMP-dependent signalling pathway, AMPK, cyclooxygenase-2 dependent) support that adiponectin represses plaque growth. For example, cytokines such as TNF-α and IL-1 also activate monocytes and macrophages. Macrophages can modify LDL by the process of peroxidation; oxLDL has cytotoxic effects on endothelial and mesangial cells and causes central necrosis in the progenitors of atherosclerotic plaques. In addition, oxLDL promotes the release of cytokines produced by endothelial cells and contributes to plaque formation[127].

Discussion

This study assessed the relationship between diabetes and atherosclerosis, which is a predictor of coronary artery disease. It was stated that in diabetes and its mechanisms, due to the inflammatory process, lipid accumulation, platelet adhesion, nitric oxide reduction, and vasoconstriction, the process of atherosclerosis intensifies.

There are different mechanisms playing a role in the development of diabetes and atherosclerosis, which can be classified as preventable and non-preventable factors. Non-preventable factors include age, gender, and heredity. On the other hand, preventable factors include diet, regular exercise, smoking cessation, mental health, and controlling underlying diseases like hypertension[128,129].

Detection of atherosclerosis can be done through the assessment of total cholesterol, LDL, HDL, triglycerides, blood pressure, exercise testing, magnetic resonance imaging (MRA), or angiography. There are chemical and herbal treatments and antioxidants for managing atherosclerosis in diabetic patients[130,131].

Research conducted by Afridi in 2009 showed that the plasma chromium of type 2 diabetics was about 33% higher than that of controls. They reported this increase to be up to 50%. The amount of chromium in diabetics is higher than in healthy populations[132].

Diabetic smokers are twice as likely to develop atherosclerosis as non-diabetic smokers. The inhalation of hot cigarette smoke results in an increase in core body temperature. After that, the lungs lose their ability to undergo physiological exchange, and as a result, damage occurs to the thickness of the capillary intima. Considering that in diabetics, the capillary intima is already compromised, the damage caused by cigarette smoke doubles, accelerating the disease process. Research shows that capillary damage occurs two years earlier in diabetic smokers than in non-diabetic smokers[133].

Additionally, dyslipidaemia occurs through the disruption of vasodilation and the reduction of nitric oxide production, which is common in diabetics and also raises blood pressure. On the other hand, the reduction of blood lipids prolongs the presence and activity of NO in the endothelial wall, thereby promoting vasodilation. Studies by Chen YC et al. (2013) showed the role of fatty plaques in atherosclerosis and diabetes. ET-1 expression should be associated with endothelin secretion in these diseases[134].

The majority of prior research has suggested a relationship between hyperhomocysteine levels and type 2 diabetes. Moreover, a recent meta-analysis involving over 8,000 participants strongly supported this relationship[135]. Although another study on Mediterranean patients found no significant difference in homocysteine levels between diabetic and non-diabetic individuals[136], the study by Russo et al. revealed no significant difference in total homocysteine levels between diabetic and non-diabetic women[137], suggesting a potential gender effect on this relationship.

Furthermore, despite strong evidence supporting a causal link between homocysteine levels and the development of T2DM[135], it is believed that increased homocysteine levels lead to insulin resistance by reducing the secretory response to insulin, which is due to increased production of reactive oxygen species[138]. However, in diabetes, the liver accelerates glucocorticoid secretion, leading to increased homocysteine catabolism and a consequent decrease in plasma homocysteine levels[139].

Defective mitochondria trigger an immune response, especially in damaged cells, and release mitochondrial DAMPs, causing the release of inflammatory cytokines. Mitochondria can initiate and regulate NLRP3 and inflammation[65]. An NLRP3 activator releases cardiolipin, causing inflammation[66,140,141]. There is also a link between atherosclerosis and mtDNA[142–144]. Thus, the increase in intracellular lipid accumulation occurs in cytokine secretion[145]. Pro-inflammatory responses in macrophages are activated by the release of inflammatory cytokines through the stimulation of phagocytosis by LDL[146]. Atherosclerotic lesions in arterial walls may have a link to uncontrollable fat accumulation[147].

Defective mitophagy results in chronic inflammation. Thus, inflammation can model the development of atherosclerosis, which has been shown to stem from chronic inflammation caused by impaired mitophagy and modified LDL[148].

Studies conducted on the mechanism of vitamin D show that vitamin D decreases inflammatory cytokines in monocytes. By suppressing IL-6, it subsequently decreases the synthesis of acute-phase CRP, which can lead to atherosclerosis development[55,67]. A porcine study demonstrated that vitamin D increases nuclear factor κB activation, imposing anti-inflammatory activity[149].

Vitamin D deficiency leads to oxidative stress, increasing inflammation and atherosclerosis[68]. Vitamin D deficiency or supplementation has been associated with heart attack, stroke, and diabetes. Vitamin D deficiency increases CVD, hypertension, and diabetes risks. Unfortunately, the results regarding symptom relief in CVD are not clear and require more research[150,151].

Studies express the prospect of miRNA associated with diabetes, atherosclerosis, and heart disease. It is important to study miRNA signals rather than individual miRNA types[152].

Many miRNAs identified in humans are implicated in the pathogenesis of diabetes mellitus and microvascular complications[153]. miR-146 and miR-126 are mainly related to atherosclerosis[106].

The complexity of PKC-activated intracellular signalling pathways makes it important to recognise the precise atherogenic mechanisms[154]. Increased activation of PKCβ is associated with atherosclerosis development, and its inhibition decreases atherosclerotic lesions[155].

Regarding uric acid, research in the Japanese population has indicated that XO activity is an important CVD biomarker. Additionally, XO activity and the resultant production of uric acid and ROS can impact microcirculation, leading to tissue damage. This is also seen in the early stages of chronic kidney disease, as well as microartery dysfunction, hypertension, diabetes, and atherosclerosis[156,157].

Additionally, uric acid stimulates NADPH oxidase, which results in the reduction of nitric oxide and an increase in lipid oxidation[158]. Excessive production of reactive oxygen species also diminishes nitric oxide availability, while uric acid further restricts NO synthesis. Elevated ROS levels and activated NADPH oxidase contribute to mitochondrial damage, including reduced mitochondrial function and ATP production[159,160].

Research indicates a connection between age, diabetes, and arteriosclerosis, revealing that aging leads to increased aortic mitochondrial dysfunction. IL-6 is also associated with vascular mitochondrial dysfunction in a positive feedback loop in the aorta. These age-related changes aggravate vascular atherogenesis in acute hyperlipidaemic states[89]. Age and dyslipidaemia are associated with prediabetes and diabetes[85].

Endothelial glycocalyx has a role in endothelial function. For instance, it has a substantial impact on anticoagulant mechanisms. This structure, which consists of extracellular matrix and proteoglycan components, may experience diminished or lost functionality during the inflammatory process[113,114].

For vascular endothelial dysfunction associated with atherosclerosis, the main thing to consider is the activation of the endothelium. Molecular activation in the form of chemokine, cytokine, and adhesion molecule expression interacts with platelets, leukocytes, and other immune cells[161]. Increased ROS production induces endothelial dysfunction by activating pro-inflammatory and pro-thrombotic pathways, leading to protein, lipid, and nucleic acid oxidations. Mitochondrial DNA is particularly vulnerable to ROS, resulting in elevated ROS generation and apoptosis. Disruption of mitochondrial function accelerates atherosclerotic plaque development[162].

Conclusion

Atherosclerosis is caused by the production of atheromatous plaque in the vessel walls. Depending on the location of vessel involvement, it is associated with heart attack and stroke. Diabetes is one of the most common chronic diseases and a risk factor for atherosclerosis and stroke. One of the main causes of death in this disease is vascular accidents, which are essentially due to the phenomenon of atherosclerosis. This article presented current insights into the pathophysiological effects of atherosclerosis and diabetes, with an emphasis on endothelial dysfunction, aging, inflammatory factors, and the roles of miRNA, uric acid, ROS, nitric oxide, vitamin D, and elevated homocysteine. It summarised recent evidence on the interactions among these molecular and cellular components.

Limitations

The most important limitations of the study can be stated as follows: The studies referenced may be subject to publication bias, where positive findings are more likely to be published than negative or inconclusive results, potentially skewing the overall understanding of the topic. Regarding the mechanistic aspects, while the discussion touches on various mechanisms linking diabetes and atherosclerosis, it does not provide in-depth mechanistic studies or experimental data to substantiate these pathways. Hence, further studies are needed to provide deeper insights into the diabetes–atherosclerosis link.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: MS
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Data Analysis or Interpretation: AK, SJ
Manuscript Drafting: MD
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All authors have approved the final manuscript and are responsible for all aspects of the work.

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