The Review Of
DIABETIC
STUDIES OPEN ACCESS

The Role Of Oxidative Stress And Inflammation In The Pathogenesis Of Hypertension

Asmaa Abdalhadi Hisham Abdalbaset[1], Mohammed A. Abdo[1*], Reem Salem Saleem Al-Saadi[2], Ahmad Mahmood Baker Saleh[3], Abdulrahman Ali Aljohani[4], Sowade Mohammed Al Ahmady[4], Eidah Saleh Alsehli[4], Manal Nughaymish Musaad Aljohani[4], Saeed Mahdi Assaf Alqarni[5], Fahda Abdullah Aljuaid[6], Osama Abdullbaset Najjar[7], Abed Abduallah Al Sufiani[8], Abduljalil Saleh Abdullah Alahmadi[9], Waleed Mohammed Shuwayt Alharbi[9], Abdulwahab Awwad Alsharif[10], Rola mahmoud Aljohani[11]

[1]King Abdulaziz Hospital, Makkah Healthcare Cluster, Ministry of Health, Saudi Arabia
[2]Secret Visitor, Al-Madinah Health Cluster, Ministry of Health, Madinah 42325, Saudi Arabia
[3]Riyadh First Health Cluster, Ministry of Health, Riyadh 11622, Saudi Arabia
[4]Al-Awali Health Care Centre in Madinah, Qurban, Madinah 42316, Saudi Arabia
[5]Alsalmah & Alzaryah Health Center, Asir Health Complex, Aseer Province, Abha 67542, Saudi Arabia
[6]Erada And Mental Health Complex -Taif, Taif 26513, Saudi Arabia
[7]Ohud General Hospital-Madinah, As Salam-7118, Medina 42354, Saudi Arabia
[8]Taif Branch of The Ministry of Health, Taif, Saudi Arabia
[9]Supply Chain, Madinah Health Cluster, Ministry of Health, Madinah 42325, Saudi Arabia
[10]King Fahd Hospital Madinah, Ministry of Health, Madinah-42351, Saudi Arabia
[11]Maternity and Children Hospital-Madinah, King Salman Bin Abdulaziz Medical City, Madinah 42319, Saudi Arabia
[*]Corresponding author: Mohammed A. Abdo

Abstract
Hypertension is a leading global risk factor for cardiovascular disease, contributing significantly to morbidity and mortality worldwide. While traditional mechanisms such as the renin–angiotensin–aldosterone system, sympathetic nervous system activation, and renal dysfunction are well recognized, increasing evidence highlights oxidative stress and inflammation as key contributors to the pathogenesis of hypertension. Oxidative stress results from an imbalance between the generation of reactive oxygen species and antioxidant defense mechanisms, leading to reduced nitric oxide bioavailability, endothelial dysfunction, vascular remodeling, and arterial stiffness. Concurrently, chronic low-grade inflammation characterized by immune cell activation and elevated levels of pro-inflammatory cytokines, including tumor necrosis factor-α, interleukin-6, and interleukin-17, further exacerbates vascular injury and blood pressure elevation. These processes are closely interconnected, forming a self-amplifying cycle in which oxidative stress promotes inflammation and inflammatory pathways enhance reactive oxygen species production. This interaction plays a central role in the initiation, maintenance, and progression of hypertension and its associated target-organ damage. Understanding the molecular and cellular mechanisms underlying the oxidative stress–inflammation axis provides valuable insights into disease development and highlights potential therapeutic targets. Interventions targeting these pathways, including renin–angiotensin–aldosterone system inhibitors, antioxidants, anti-inflammatory agents, and lifestyle modifications, may offer improved strategies for hypertension prevention and management. This review summarizes current evidence on the role of oxidative stress and inflammation in hypertension and discusses their clinical and therapeutic implications.

Keywords Hypertension; Oxidative Stress; Inflammation; Reactive Oxygen Species; Endothelial Dysfunction; Vascular Remodeling; Immune Activation.

Introduction

Hypertension is a common health issue in the world, which is a major risk factor in cardiovascular disease, among every four adults, approximately ten million people die every year due to hypertension worldwide (1). Being directly connected to the changes in modern lifestyle and the aging of the population, this condition increased many times since 1990, reaching 1.3 billion in 2019 (2). Although the global average systolic blood pressure has been slightly decreasing since the 1980s, mostly in high-

income nations, there is a worrying trend of the low- and middle-income nations especially the countries in South Asia (1). This epidemiological pattern highlights the multi-billion factors in international burden of hypertension that include genetic inclinations, environmental influences, and socioeconomic determinants. Alongside these demographic and lifestyle factors, underlying molecular processes also play a key role in the etiology of hypertension, and oxidative stress and inflammation present themselves as key paradigms of unification (3,4). All these interrelated biological processes play a role in vascular dysfunction, structural remodeling, and eventually, persistent increase of blood pressure that is typical of the disease (5,6).

The etiology of hypertension is elusive, especially the exact mechanism but some factors have been observed as causes and they include genetic predispositions, sedentary lifestyle and diets like high content of salt have been known to be causes (7). Besides, a significant share of disability-adjusted life years in the world is caused by chronic non-communicable illnesses, which are often related to hypertension (2). The complex genetic, lifestyle, and molecular interaction underlines the need to have an in-depth understanding of hypertension in order to create effective preventive and therapeutic interventions (8). The close connection between inflammation and hypertension is one of the most important areas of study, in which it is examined whether inflammation is a causative or rather an effect of high blood pressure (9). However, recent studies are also giving growing attention to the value of inflammation as a separate cause of hypertension development, which is mediated by different numbers of pathways such as endothelial dysfunction and stiffening of arteries (2). To deepen this correlation, there is a substantial amount of evidence indicating that a close association exists between hypertension and an increase in oxidative stress in the vascular system, but the timing of this relationship, is it a cause or an effect, is still a topic under investigation (10). However, the majority of studies reflect that systemic inflammation and oxidative stress play a vital role in the pathogenesis of hypertension via the following processes endothelial dysfunction, vascular remodeling, and arterial stiffness (11). The complexity of this multiple creates a need to explore these pathways in-depth in order to come up with specific therapeutic interventions. In particular, the vascular health triad, which includes inflammation, reactive oxygen species, and endothelial dysfunction, is important in the regulation of blood pressure (12). Unregulated functioning of these elements may cause impaired vascularity and elevated peripheral resistance, which are symptomatic of hypertension (13,14).

Defining Hypertension

Epidemiology, clinical significance and new diagnostic recommendations. The disease is highly common with dire health repercussions and therefore the importance of understanding more of the underlying pathophysiology and developing effective management interventions on hypertension cannot be underrated. The key to that undertaking is the realization that it is the derailment of most of the neural, renal, hormonal, and vascular mechanisms, particularly, the loss of balance in the actions of vasoactive factors secreted by endothelium (15). The recent evidence identifies the long-term inflammation as a pivotal factor in the hypertension pathogenesis as actively promoting the increase of blood pressure, vascular inflammation, and microvascular remodeling (14). Oxidative stress and endothelial dysfunction and arterial stiffness are some of the pathological conditions brought about by these inflammatory reactions towards the onset and progression of hypertension (15,16). The consequence of this dysregulation, which entails the decrease in the synthesis of nitric oxide and the rise in the synthesis of endothelin-1 entails encouragement of oxidative strain and low-grade inflammation, which causes the endothelial dysfunction and heightened vasoconstrictor action (15). The existence of advanced glycation end products increases this inflammatory condition and interacts with their respective receptors and results in intracellular signal pathways that maintain endothelial malfunction and oxidative stress (17).

Conventional Pathogenic Mechanisms

Renin-angiotensin-aldosterone, sympathetic nervous, and vascular dysfunction. These recognized mechanisms, although central, are also being recognized to be synergistically interacting with oxidative stress and inflammation to produce a more detailed model of the multifactorial etiology of hypertension (18). One study also reports that T-cell activity, which is a component of the immune system, is a cause of hypertension (10). In addition, the renin-angiotensin-aldosterone system, which is a major regulator

of blood pressure, has a major contribution to hypertension development that is mainly contributed by angiotensin II (19,20). An example is the Angiotensin II that enhances the generation of reactive oxygen species and cellular attraction of inflammatory cells thus aggravating the inflammatory cascade (21).

Emerging Concepts

The increased acceptance of oxidative stress and inflammation as major catalysts. The complexity of their interaction causes damage to the endothelium, remodeling of the vascular system, and prolonged hypertension (20). As an example, more endothelin-1 production, a potent vasoconstrictor, is observed in arteries that are aging and developing atherosclerotic changes, further resulting in the arteries becoming hard and developing isolated systolic hypertension (15). This process is also closely associated with dysfunction of endothelium, since the loss of the potential to produce vasodilators such as nitric oxide and the excessive production of vasoconstrictors such as endothelin-1 are also among the factors contributing to the effect of vascular stiffness and high blood pressure (15). The presence of such dysfunction is a contributing factor to essential hypertension by various mechanisms such as an altered endothelium-dependent relaxation of the arteries and structural alteration of the arteries (22). The complexity of this relationship highlights the role of the endothelium as an important mediator in the pathophysiology of hypertension and is a integration of both an inflammatory and oxidative stress pathway**.**

Oxidative Stress in High Blood Pressure

The process of oxidative stress where generation of reactive oxygen species is disproportionate to antioxidant defense systems is gaining momentum as a determinant in the dysfunction of hypertension onset and development (23,24). Such disproportion causes augmented oxidative harm to cell constituents and especially to the vasculature that causes endothelial dysfunction and vascular remodeling (25). In particular, the overproduction of oxygen free radicals that is frequently aggravated by the malfunction of mitochondria and the build-up of glycosylation end products overwhelms the endogenous antioxidant system, resulting in extensive cellular damage of renal and vascular tissues (26). Activating RHO/ROCK, hexosamine, polyol, advanced glycation end products and protein kinase C pathways, hyperglycemia greatly increases the production of reactive oxygen species, which in turn enhances the activity of MAPK, JAK signal transducers and activators of transcription, and NFkB which play a significant role in the development of inflammation and fibrosis (21,27).

Reactive Oxygen Species in Hypertension

The NADPH oxidases of vascular smooth muscle cells, endothelial cells and immune cells. Additional noteworthy causes comprise xanthine oxidase, decoupled endothelial nitric oxide synthase (eNOS) and mitochondrion dysfunction (28). In this case, mitochondrial dysfunction and especially its involvement in diabetes-related oxidative stress and kidney inflammation is a very important issue in the production of an excess of reactive oxygen species (26). Electron transport chain and mitochondrial dysfunction. All of these pathways lead to an increase in the level of oxidative stress that further degrades the bioavailability of nitric oxide, hence, facilitating vasoconstriction and further worsening endothelial dysfunction (17). The result of this imbalance is an impaired nitric oxide-mediated vasodilation which is a characteristic of endothelial dysfunction seen in a number of cardiovascular diseases such as hypertension (10,27).

Uncoupled endothelial nitric oxide synthase (eNOS). This dissociation reduces the bioavailability of nitric oxide, instead producing superoxide, which further causes endothelial dysfunction spreading oxidative stress (14). Xanthine oxidase, myeloperoxidase and other enzymatic sources. Angiotensin II also increased the production of reactive oxygen species, including superoxide, by the activation of membrane-bound NADH or NADPH oxidase in hypertension (29). This is worsened by hyperglycemia which causes the overexpression and hyperactivity of several NADPH oxidases such as NOX1, NOX2, NOX4, and NOX5 resulting in an increased level of reactive oxygen species (21). The complexity of the interplay between hyperglycemia and these enzymatic sources is a major cause of chronic oxidative stress that is evident in hypertensive condition. On the other hand, reduced antioxidant defense systems are also factors that drive the pathogenesis of hypertension (30).

TABLE 1: Sources of Oxidative Stress and Their Effects in Hypertension.

Source of Reactive Oxygen Species	Cellular Location	Mechanism of Action	Contribution to Hypertension	References
NADPH oxidases (NOX1, NOX2, NOX4, NOX5)	Endothelial cells, vascular smooth muscle cells, immune cells	Excess superoxide production leading to nitric oxide inactivation	Endothelial dysfunction, vasoconstriction, vascular remodeling	[4, 41]
Uncoupled endothelial nitric oxide synthase (eNOS)	Endothelium	Reduced nitric oxide synthesis and increased superoxide generation	Impaired vasodilation and increased peripheral resistance	[34, 35]
Mitochondrial dysfunction	Vascular and renal cells	Electron transport chain–derived ROS overproduction	Vascular injury and arterial stiffness	[36]
Xanthine oxidase	Endothelium and plasma	ROS generation during purine metabolism	Oxidative vascular damage	[38]
Reduced antioxidant defenses	Systemic	Decreased SOD, catalase, and glutathione peroxidase activity	Sustained oxidative stress	[25, 30]

Mechanisms of Oxidative Damage

Lipid peroxidation, protein alkylation, and damage to DNA. These oxidative changes undermine cellular integrity and cellular work resulting in increased cellular senescence and apoptosis in the cardiovascular tissues (31). Dysfunction of endothelial and bioavailability of nitric oxide. Oxidative stress, by producing superoxide anion, reacts with nitric oxide giving peroxynitrite which in turn reacts with tetrahydrobiopterin, an essential cofactor of endothelial nitric oxide synthase (eNOS), to uncouple eNOS, thereby lowering NO generation (32,33). The process does not only diminish the supply of the essential vasodilator nitric oxide, but also actively increases the production of reactive oxygen species, which contributes to the vicious circle of oxidative stress and vascular injury (34,35). Subsequent dysfunctional endothelium also leads to a compromised glomerular filtration rate and vascular inflammation, which is another typical antecedent to thrombosis (33). Subsequently, the production of peroxynitrite, a very potent reactive nitrogen species, further oxidizes biomolecules such as glutathione and tetrahydrobiopterin available, which further propagates devastating oxidative stress and triggers cellular pathways, such as the AGE-RAGE pathway and NFkB expression (17). It is this rampant oxidative injury that causes great cellular damage which in turn encourages inflammation and fibrosis of the cardiovascular system thus contributing to the formation and progression of hypertension (36).

Antioxidant Defense Systems

Enzymatic antioxidants (e.g. Superoxide Dismutase, Catalase, Glutathione Peroxidase). These are superoxide dismutase and catalase and glutathione peroxidase in which they all collaborate to counteract reactive oxygen species and provide redox homeostasis (25). Specifically, superoxide dismutase serves a key role in the antioxidant activity regarding converting superoxide radicals to hydrogen peroxide and molecular oxygen (37).

Non-enzyme antioxidants (e.g. Glutathione, Vitamin C, Vitamin E). These include an extensive list of molecules, including vitamins (e.g., vitamin C, vitamin E), minerals (e.g., selenium, zinc), and other phytochemicals, which either have a direct scavenging action of free radicals or indirectly facilitate the activity of enzymatic antioxidants (7). Disregard or inadequacy of these systems in hypertension. The oxidative burden has been further increased by the reduced activity of enzyme antioxidants including superoxide dismutase and glutathione peroxidase which have been reported as reduced in hypertensive states (30,38). This lack is usually enhanced by decreased concentrations of non-enzymatic antioxidants such as lycopene, ascorbate, and b-carotene in hypertensive patients that reduce the total ability to neutralize oxidative stress (7). These disparities between pro-oxidants and antioxidants cause not only disturbances of redox signals, but also cause post-translational alterations of the proteins, which result into massive cellular and tissue damage (4). The subsequent oxidative stress is a decisive element in the pathogenesis of hypertension which avails endothelial dysfunction, inflammation and augmentation of vascular contractility that culminates into cardiovascular tissue remodelling (39). This chronic oxidative stress results in a vicious cycle, so further production of ROS further degrades antioxidant defenses, and an environment that supports the further development of hypertension and related complications is created (40,41).

TABLE 2: Inflammatory Mediators and Immune Cells Involved in Hypertension.

Inflammatory Component	Primary Source	Pathophysiological Role	Impact on Blood Pressure	References
Tumor necrosis factor-α (TNF-α)	Macrophages, T lymphocytes	Activation of NF-κB and endothelial dysfunction	Increased vascular resistance	[3, 14]
Interleukin-6 (IL-6)	Immune and endothelial cells	Induction of acute-phase response and vascular inflammation	Sustained hypertension	[49]
Interleukin-17 (IL-17)	Th17 cells	Promotion of ROS generation and vascular injury	Elevated blood pressure	[47, 54]
Macrophages	Vascular and renal tissues	Cytokine and ROS release	Vascular remodeling	[9, 53]
T lymphocytes	Kidney and vasculature	Immune-mediated vascular dysfunction	Development of hypertension	[10, 51]

Hypertension Inflammation

Inflammation is since considered an essential pathophysiological factor in the pathogenesis and pathophysiology of hypertension, which is closely connected with oxidative stress and endothelial dysfunction (30). This persistent inflammatory condition facilitates the process of vascular remodeling and enhances the increase in blood pressure by using a number of immune cell-mediated mechanisms (14). In particular, immune cells activation and following pro-inflammatory cytokines release are the factors which contribute to vascular damage and dysfunction in hypertensive conditions (38). As an example, the ratio between the pro- and antioxidant factors directly affects the formation of cardiovascular conditions, such as arterial hypertension by activating systemic inflammation (25,42). This is the self-perpetuating cycle of reactive oxygen species and inflammation where ROS may stimulate the pathways of inflammation and where inflammatory mediators can stimulate the production of new ROS and so on, and this cycle perpetuates the pathogenesis of hypertension (43).

Cellular participants in Hypertensive Inflammation

Dendritic and T cells, T cells, macrophages, and dendritic cell infiltration and activation in vascular tissues and kidneys. Macrophages, T-cells, and dendritic cells are specifically involved, which release a range of inflammatory mediators, which play a role in vascular remodelling and dysfunction (12). In particular, activated T lymphocytes, as well as classic activated macrophages and neutrophils, release pro-inflammatory cytokines, including interferon-gamma and interleukin-17,

which cause oxidative stress and dysfunction of endothelium thereby worsening hypertension (14). This inflammatory environment also stimulates nuclear factor kappa-light-chain-enhancer of activated B cells which is one of the prominent transcription factors that promote a large number of pro-inflammatory genes and thereby, this contributes to the further enhancement of the inflammatory environment (12,26,44).

Sources of inflammatory mediators Resident vascular cells (endothelial cells, smooth muscle cells). When provoked by a high blood pressure and oxidative stress, endothelial, vascular smooth muscle, and fibroblasts are capable of release cytokines and chemokines, thereby enhancing the local inflammatory response in the vasculature (45). The resulting complex cumulative interaction involving such cellular interactions sustains inflammation of the vascular system in addition to facilitating structural and functional alterations that are characteristic of hypertension through the regulation of vascular tone and the facilitation of fibrosis (46).Some of the key inflammatory mediators that mediate the pathogenesis of hypertension include tumor necrosis factor-alpha, transforming growth factor-beta, and other interleukins (17). Regulatory T cells and alternatively activated macrophages, on the other hand, can play a protective role, which highlights the finer details of role of immune interference in hypertensive conditions (14). This complex immune response which involves both the innate and adaptive responses is a part of the inflammatory landscape in general which leads to pathological changes experienced in hypertension (47).

Key Inflammatory Mediators

Pro-inflammatory cytokines (e.g., TNF-α IL-6 IL-1). These cytokines play a significant role in the coordination of the inflammatory reaction, vasoconstriction, and endothelial dysfunction by stimulating signaling pathways such as NF-kB, which increases the expression of adhesion molecules and chemokines (21). It is important to note that, IL-1b also causes the expression of inducible oxidase synthase and cyclooxygenase type 2, as well as production of downstream inflammatory mediators, whereas TNF-a augments inflammation by promoting cell growth and proliferation and increasing MHC class I and II molecules (48). The other important pro-inflammatory cytokine is interleukin-6, which directly activates the synthesis of acute-phase proteins in the liver and is part of the overall inflammatory cascade due to the generation of secondary cytokine signatures (49, 50). Chemokines (e.g., MCP-1, RANTES), adhesion molecules (e.g., VCAM-1, ICAM-1). Those molecules support recruiting and extravasation of immune cells into vascular tissues fuelling the process of inflammation and causing the vascular remodeling and damage that can be noted in hypertension (51).

Acute-phase proteins (e.g. C-reactive protein). The hypertensive individuals have also increased acute-phase proteins, including C-reactive protein, which are markers and mediators of inflammation and are also indicators of the systemic inflammatory burden and an added contributor to vascular injury (49, 52). T helper 17 cells secrete inflammatory cytokines (interleukin-17) and interferon-g that have an important effector role in hypertension, which can raise blood pressure and cause damage to end-organs (47). Also, the occurrence of T cells and monocytes/macrophages in the kidneys and blood vessels of hypertensive individuals also points to the fact that these cells also generate powerful cytokine that affects the work of the kidneys and vascularity (53).

Involved Signaling Pathways

NF-k B pathway and its stimulation by ROS and other stimuli. This route plays a significant role in triggering the expression of a wide range of pro-inflammatory genes, such as cytokine, chemokine, and adhesion molecule genes, increasing the level of the inflammatory response in hypertension (14). Activation of IL-6/JAK/STAT3 pathway also plays a crucial role in the pathogenesis of hypertension by the AngII (54). The stress hormones can also be dysregulated which can further increase this inflammatory condition by modifying the release patterns of the cytokines produced by the immune cells with predisposition to pro-inflammatory cytokines instead of anti-inflammatory cytokines (55).

Pyroptosis and activation of inflammasomes. The specific one is the NLRP3 inflammasome, which is a multiprotein complex specifically involved in hypertension, which results in the protein cleavage of pro-inflammatory cytokines, e.g., IL-1b and IL-18, and finally in pyroptosis, an extremely inflammatory form of programmed cell death (47). MAPK pathways. ERK, JNK, and p38 are also involved in the transduction of inflammatory signals, cellular response to stress, and vascular remodeling and endothelial dysfunction in hypertensive states involving the mitogen-activated protein kinase pathways. Moreover, NLR family pyrin domain containing 3-mediated inflammasome activation is a part of the inflammatory cascades that take place in diabetes, and it connects oxidative stress and end-products of advanced glycation to stimulating mesangial cells and triggering chronic kidney disease development (21). Th17 cells, macrophages, dendritic cells, and natural killer cells also produce another cytokine, IL-17, which is also implicated in hypertension and vascular dysfunction (possibly via its action on NOS3 phosphorylation and nitric oxide synthesis in endothelial cells) (54). A hyperstimulation of the NOX4, e.g. results in the burst of superoxide that harms the glomerular cells, causing diabetic nephropathy and vascular side effects through the enhancement of pro-inflammatory cytokines, NFkB, and adhesion molecules (17). This chain of action highlights the direct involvement of oxidative stress in the pathogenesis of inflammatory microenvironment of cardiometabolic diseases as a contributor of both systemic and local vascular damage (26, 56).

In that regard, angiotensin II has a strong effect on vascular inflammation and oxidative stress through the activation of NADH/NADPH oxidase and the stimulation of multiple signaling molecules such as Rho/Rho kinase and the protein kinase C that result in endothelial dysfunction and vascular damage (57). Furthermore, renin per se has the capability of stimulating the mitogen-activated protein kinase signalling pathway, and angiotensin II stimulates fibrosis directly by enhancing transforming growth factors production, vascular endothelial growth factor, and cell adhesion molecules (21). Moreover, hyperglycemia-induced end-products of advanced glycation and their interplay with receptors on the kidneys promote the inflammation and fibrosis process through stimulating various intracellular signaling cascades, such as transforming growth factor-b and protein kinase C (26). It is the result of such a complex interaction that causes renal interstitial fibrosis, sclerosis of the arteries, and structural damage to the kidney (17, 26). Kidney is an active, mitochondria-rich organ that is especially vulnerable to oxidative stress-dependent hyperglycemia and may increase the rate of chronic kidney disease, a complication of hypertension and other ailments in late stages (17, 58). There is a vicious cycle between oxidative stress and chronic microinflammation that preserves and further enhances kidney damage and chronic kidney disease progression (59). This makes the management of hyperglycemia a key risk factor of diabetic nephropathy, which directly damages the endothelial cells and podocytes of the renal vascular directly by causing a number of molecular and cellular malfunctions (26). Increased oxidative markers are seen in diabetes and strategies to address the resulting oxidative stress and chronic inflammation would be an effective method of treating diabetic nephropathy (26, 60).

TABLE 3: Therapeutic Targets Addressing Oxidative Stress and Inflammation in Hypertension.

Therapeutic Strategy	Target Pathway	Mechanism of Action	Potential Clinical Benefit	References
RAAS inhibitors (ACEIs, ARBs)	Angiotensin II signaling	Reduction of ROS generation and inflammatory signaling	Improved endothelial function	[15, 57]
Antioxidants (Tempol, N-acetylcysteine)	Reactive oxygen species	Direct scavenging of free radicals	Reduced oxidative stress	[25, 38]
Nrf2 activators	Antioxidant response element	Upregulation of endogenous antioxidant enzymes	Vascular protection	[17, 101]

Anti-inflammatory agents	NF-κB and cytokines	Suppression of inflammatory signaling pathways	Reduced vascular damage	[14, 99]
Lifestyle interventions	Metabolic and inflammatory pathways	Reduction of systemic oxidative stress and inflammation	Blood pressure control	[39, 102]

Interaction between Oxidative Stress and Inflammation

Oxidative stress, which can be defined as a disproportion between reactive oxygen species production and antioxidant responses, is a direct promoter of inflammation, and an important factor in the development of chronic kidney disease (59). This intensification of the oxidative stress can be observed at the early renal failure stages, which stimulates the activity of podocytes destruction, proteinuria, and tubulointerstitial fibrosis (59). This is further enhanced by hyperglycemia that intensifies the synthesis of advanced glycation end-products and their binding with receptor of advanced glycation end-products which results in an intensification of oxidative stress and activation of several pro-inflammatory signaling pathways that further promote renal injury (28,61). In particular, hyperglycemia triggers intracellular reactive oxygen species in mesangial and tubular epithelial cells and this stimulates the release of cytokines like IL-6 and TNF-a that also leads to the glomerular and tubular damage in the diabetic kidney (62).

Vicious Cycle

Mechanism of generation of oxidative stress and of exacerbation of oxidative stress by inflammation with respect to hypertension. Such bidirectional interaction plays a critical role in hypertension whereby oxidative stress that can be provoked by NADPH oxidase activation leads to the activation of inflammatory reactions, with inflammatory reactions further inducing the production of reactive oxygen species leading to a vicious cycle that perpetuates vascular damage (17,63). The constant hyperglycemia caused by diabetes is a major cause of this cycle that favors excessive production of reactive oxygen species and resultant mitochondrial damage to increase oxidative stress (17). It is this chronic exposure to high glucose levels that stimulate pathways like the polyol and hexosamine pathways, polyol and hexosamine increases protein kinase C activity, and converges on the production of reactive oxygen species in renal cells (64). In addition, the metabolic imbalances resulting in this trigger collateral pathways, such as polyol and sorbitol pathways that cause biochemical disorders of primary renal tissues and the alteration of their functions irreversibly (28). Moreover, chronic inflammation and oxidative stress are also major pathophysiological factors that cause nephropathy, which is a major reason of dialysis in diabetic patients around the world (65).

Endothelial Dysfunction

The oxidative stress-induced NO inactivation and inflammation as the central factors in the process of endothelial damage, causing vasoconstriction and vascular remodelling. This complex pathological interaction eventually leads to structural and functional renal degradation, which leads to end-stage renal disease (66,67). One of the main pathways through which oxidative stress can contribute to the development of CKD is by causing young renal failure through intracellular and extracellular generation of oxygen-derived radicals and the subsequent inflammatory reaction, where the free radical molecules react with the nephron components resulting in the loss of membrane integrity and damaged DNA (68).

Vascular Remodeling

Role in hypertrophy, fibrosis, and stiffening of blood vessels which are caused by oxidative stress and inflammation. Hyperglycemia as a characteristic of diabetes directly causes this vascular remodeling, damaging endothelial cells, disrupting vascular tone, and making them more permeable, thus increasing inflammation and oxidative stress (26). Also, saturation of glycolysis by high glucose condition diverts glucose to the other metabolic pathways, including polyol and sorbitol pathways, which overactivity also leads to a high level of metabolic imbalance and also an additional cause of biochemical disorders in the renal tissues (28).

Renal Dysfunction

Effect on renal hemodynamics and tubular activity which contributes to salt and water retention. This renal hemodynamic derangement is only augmented by the escalation of activity of the sympathetic nervous system that enhances vasoconstriction and worsens fluid retention hence increasing the rate at which kidney damage develops (69). In addition, the nephron is in persistent hypoxia, which is a result of reduced oxygenation and an overload of SGLT2 channels, worsening the renal dysfunction and further increasing oxidative stress (21). This creates a vicious cycle in which the problem of mitochondrial dysfunction generates more superoxides, which is directly associated with oxidative stress and causes additional renal damage (28). However, with time, hyperglycemia and the secondary impact on oxidative stress and inflammation eventually result in a widespread renal fibrosis, which is a principal pathological characteristic of diabetic kidney disease (21). It is not yet well understood how all these factors interact to produce tissue-specific damage (17). These complex interactions can only be understood to design specific therapeutic approaches to counter the development of diabetic nephropathy and cardiovascular complications that accompany it (5). As an example, peroxisome proliferator-activated receptor-gamma coactivator-1a (PGC-1a), one of the controllers of the mitochondrial biogenesis, has its expression changed in diabetic kidney disease, which leads to mitochondrial dysfunction (21). This impairment is presented in the form of the inability to produce ATP and the elevation of reactive oxygen species, which exacerbates the oxidative stress levels of renal cells.

Consequences and Damage to Target Organs

The chronic hyperglycemia which is the hallmark of diabetes not only triggers but also sustains the activation of a series of biochemical pathways that result in extensive destruction of various organ systems with the kidneys being the most susceptible (70). This hypersensitivity can be explained by the complexity of the microvasculature and intense metabolic activity of the kidney that makes it acutely sensitive to the metabolic mal-adaptation and oxidative stress caused by chronic hyperglycemia (71). The complexity of the relationship between hemodynamic and metabolic processes, which are often impaired in diabetes, is relevant in the onset and development of nephropathy (65). Particularly, a glomerulus that plays a key role in filtration is severely damaged because of the increased intraglomerular pressure and accumulation of end products of advanced glycation, contributing to proteinuria and a renal functional deterioration (17,26). It is a gradual deterioration of the glomerular filtration barrier which is sometimes called the podocyte centrality which emphasizes that it is the specialized podocytes that are susceptible to apoptosis which eventually causes glomerular permeability and the development of diabetic kidney disease (28). Heart failure, fibrosis, diastolic failure, and cardiac hypertrophy. This effect is not limited to the heart but it involves the rest of the cardiovascular system, which puts diabetic patients at a high risk of atherosclerosis, myocardial infarction, and stroke (26).

Moreover, macrovascular complications associated with diabetes are significant contributors to cardiovascular disease, which is the leading cause of death in people with the type 2 diabetes (27).

Peripheral and autonomic neuropathies, which result in sensory loss, pain, and dysfunction of an organ. The condition of diabetic neuropathy also includes the destruction of the autonomic nervous system that results in dysfunction of cardiovascular reflexes, gastrointestinal motor activity, and bladder problems (27). Furthermore, the complex metabolic disturbances that are presented by diabetic patients, i.e., insulin resistance and dyslipidemias, cause the neurohormonal activation to an even greater working order, undermining the fragile equilibrium between the metabolic, cardiac, and renal systems (72). These systemic effects explain the extensive impact of uncontrolled diabetes on multiple physiological systems that trigger a cascade of complications that cumulatively reduce the quality of life of patients and increase healthcare burdens (73,74). Microvascular abnormalities and ischemic alterations also result in ocular complications such as diabetic retinopathy and optic neuropathy, which causes impairment of vision (75). These are conditions, which are accompanied by diabetic nephropathy and peripheral neuropathy, which are categorized as micro-vascular complications, largely compromising the small blood vessels (76,77).

Glomerulosclerosis, tubulointerstitial fibrosis and development of chronic kidney disease. This is due to the changes in the microvasculature that lead to local ischemia and morphological and functional impairment of different tissues (72). In particular, one microvascular complication, diabetic nephropathy, can be defined by fibrosis in the kidney, and it is the most frequent cause of end-stage renal disease (78). In addition, panvascular diseases that involve the whole vascular system such as atherosclerosis, cardiovascular diseases and cerebrovascular disorders are prone in diabetes patients mainly because of the changes in vascular wall structure and they also affect the functioning (26). These extensive vascular pathologies have played a role in the high rate of morbidity and mortality that is witnessed in diabetic populations (77,79). A combination of all these complications imposes a significant burden on healthcare systems and requires all-encompassing measures in terms of early detection, prevention, and management (78-80). Having acknowledged the systemic nature of diabetes, it is essential to treat the patient holistically going beyond the glycemic control plainly and the multifaceted complications of chronic hyperglycemia (77,80).
Cerebral accident, dysfunction of blood-brain barrier and cognitive deficiency. These neurobiological effects usually present in the form of a faster cognitive and more susceptible stroke, which remains a highly significant repercussion of diabetes on the integrity of the central nervous system. The retina is also damaged due to diabetes, and this is known as diabetic retinopathy, which may cause loss of vision (74). The most common microvascular complications include retinopathy nephropathy and neuropathy, which are the leading causes of blindness, end-stage renal disease, and amputation of lower extremities, respectively (81-83).

These microvascular defects are usually accompanied by structural impairment of the endoneurial blood circulation and oxygen levels, which result in nerve fiber loss of the peripheral nerves, and in some cases, the optic nerve (75). Besides, the neuropoietic cytokines, including interleukin-1 and TNF-alpha, accumulate and worsen nerve damage by slowing nerve conduction and supporting the inflammation in the nervous system (75). All these microvascular and macrovascular complications, which are caused by chronic hyperglycemia, result in a high level of morbidity and mortality in patients with diabetes, which is why there is an urgent need to develop multifaceted therapeutic management (27,80). Macrovascular complications also caused by chronic hyperglycemia include atherosclerosis, a key cause of cardiovascular, cerebrovascular and peripheral artery diseases (84). These ailments are often based on persistent inflammation and endothelial malfunction, which are complicated by the persistent metabolic imbalances of diabetes (27). The extensive nature of persistent hyperglycemia, consequently, creates the extremely important connection between the persistence of high glucose and the broad spectrum of microvascular and macrovascular complications that can be seen in diabetics (85-87).

Clinical Implications and Future Research

The complexity of diabetes pathology that requires a multifaceted approach to treatment, not the simple glycemic regulation, but the treatment of the underlying molecular processes (27,88). This is coupled with coming up with interventions that focus on the neurodegenerative alterations in the retina, as they tend to be the first changes to have been affected in vascular disease and may be irreversible with chronic hyperglycemia (89). Moreover, the therapeutic approach should also be involved to lessen the effect of high levels of neuropoietic cytokines and ischemia that play important roles in neuropathy development and nerve fiber degeneration (75). These approaches may include the involvement of the abnormal metabolic pathways, where hyperglycemia out of control is associated with the increased activity of enzymes that have a role in the metabolic processes causing diabetic complications and therefore these enzymes can serve as a potential therapeutic target (90). To illustrate, sirtuins have been identified to be possible candidates as a therapeutic approach to diabetic nephropathy and retinopathy upon activation (17).

Recognizing valid biomarkers of oxidative stress and inflammation to detect hypertension early in the disease. Also, attention to the advanced glycation end products, the polyol pathway, which contribute to the damaging of cells, provides additional opportunities to confront therapeutic interventions to avoid microvascular and macrovascular complications (87,91). The proposed holistic solution is to break the vicious cycle where the hyperglycemia over time induces harmful biochemical pathways that result in the various complications witnessed among patients with diabetes (92). The current studies have found a number of essential processes through which hyperglycemia triggers diabetic complications that include polyol pathway, hexosamine pathway, protein kinase C activation, and the presence of advanced glycation products endogenous (28,90). The overall pattern of these pathways leads to metabolic abnormalities and biochemical malfunctions in major tissues that trigger irreversible functional and structural alterations of diabetic nephropathy and other complications (28).

The possibility of treating disease progression and patient outcomes in different complications of diabetes with these complex molecular pathways using novel therapeutic agents has great potential (26,27,93). Such specific interventions could involve the generation of certain agents, such as BH4 supplement, or artemisinin that have shown their potential in the alleviation of diabetic complications through the handling of essential molecular phenomena such as nitric oxide impairment or TGFb overexpression (17). Additionally, the implementation of the strategies to avoid the simultaneous appearance of several complications of diabetes are also important in enhancing patient care and overall patient outcomes (80). Targeting Oxidative Stress:Antioxidant treatment (e.g., N-acetylcysteine, Tempol, polyphenols). Since surplus production of oxygen free radicals and the antioxidant system imbalance are major contributors to the development of intracellular oxidative stress, therapeutic strategies to reestablish balance to the antioxidant system, including Nrf2 activators or direct ROS scavengers, has significant potential in preventing the damage of cells in diabetic patients (17,26). A combination of modulating these pathways together with the approaches that target the advanced glycation end products and protein kinase C activity can offer a multi-pronged intervention that aims at offering an effective approach to manage the complex pathophysiology of diabetes (94-96). Moreover, it is also important to realize that all these different pathways eventually lead to hyperglycemia-induced oxidative stress which implies that an even more efficient way to prevent complications of diabetes is to use novel single-agent antioxidant treatments, other than the conventional scavengers (97).

Methods to improve native antioxidants systems. In this respect, special attention should be paid to approaches that enhance the expression of Nrf2 or employ powerful antioxidant biomolecules that can eliminate reactive oxygen species and stimulate the expression of Nrf2 (17). The oxidative-inflammatory network that is induced by chronic hyperglycemia further mounts the numerous interconnected pathogenic pathways such as the polyol pathway, hexosamine pathway, protein kinase C signaling, and the advanced glycation end products/receptor of advanced glycation end products axis, all of which play a role in the development of diabetic complications (95). Thus, oxidative stress, mitochondrial quality, and the regulation of inflammation and mesenchymal activation should be targeted as therapeutic interventions to deliver desirable outcomes in preclinical settings (78, 98). In particular, the vicious cycle between inflammation and vascular damage associated with the diabetic kidney disease can be interrupted with the help of strategies that prevent the nicotinamide adenine dinucleotide phosphate oxidases and reduce the consequential formation of reactive oxygen species (21).

Targeting Inflammation

Anti-inflammatory agents. Since oxidative stress and inflammation have been known to interact synergistically, anti-inflammatory treatments that can target the production of reactive oxygen species, possibly by inhibiting the NADPH oxidases activity, may be synergistically useful in the treatment of diabetic complications (26, 64). It has been noted that inflammatory mediators play a crucial role in diabetic kidney disease, and such targets as NLRP3 inflammasome inhibitors, NF-kB pathway modulators, and biologic agents targeting IL-6, IL-1b, and TNF-a are promising and have the potential to reduce disease progression (99). These anti-inflammatory methods in combination with antioxidant methods that support endogenous antioxidant defenses such as Nrf2 can provide a combination of therapeutic approaches to the complex pathology of diabetic complications (17, 100).

Immunomodulatory approaches. Other areas of intervention are emphasized by the fact that advanced glycation end products bind receptors, like RAGE, on renal endothelial cells and trigger the activation of pro-oxidative and pro-inflammatory pathways including NADPH oxidase, MAPK, and NF-kB (26). Since hyperglycemia triggers pro-inflammatory products and activates various pathways, which induce a pro-oxidant condition with dysfunctional antioxidant mechanisms, intervention in the inflammatory pathways directly or indirectly as a result of antioxidant strategies is essential in reducing the changes in the renal filtration unit (101). Lifestyle Interventions: Diet (e.g., DASH diet, Mediterranean diet), exercise, and their impact on oxidative stress and inflammation. Since the long-term hyperglycemia is a major causative factor in the progression of diabetic nephropathy, effective glycemic regulation by means of lifestyle changes, such as diet and exercise, can greatly decrease the prevalence of diabetic microvascular and macroangiopathic complications (28).

Moreover, specific dietary interventions and exercise can have a direct effect on systemic inflammation and oxidative stress and thus provide renoprotective effects in diabetic kidney disease (102). Such non-pharmacological measures are used in conjunction with pharmacological intervention options to decrease the load of renal cells and, possibly, reverse the initial damage stages due to the decreased systemic load of inflammation and oxidative stress (26, 28). In particular, the engagement of the Nrf2 signaling pathway which may be stimulated by different mechanisms such as the inhibition of Keap1 and the up-regulation of Nrf2 expression is a potential treatment option that could be used to alleviate oxidative stress caused by hyperglycemia in renal podocytes (17). In addition, diet, age, and lifestyle have many complex interactions that result in nephropathy in diabetic individuals, and other factors such as obesity play significant roles in causation, and hence the need to adopt multidisciplinary management strategies (103).

These measures including tight glycemic regulation and hypertension control using such agents as ACE inhibitors or angiotensin receptor blockers are essential in reducing the progression of diabetic renal disease at its initial stages (104). Synergistic Strategies: The use of anti-hypertensive and anti-oxidant/anti-inflammatory interventions. Since renin-angiotensin-aldosterone system is known to have a strong role in the pathogenesis of diabetic nephropathy, incorporating of RAAS blockers with antioxidant and antiphlogammatory drugs is a sound approach to a multifaceted approach to the treatment of this condition (26). This dual strategy is able to reach numerous pathways that cause kidney damage such as oxidative stress, inflammation, and fibrosis, and thus provides better renoprotection than single therapy (105). An example is rapamycin, which is a mTOR inhibitor that has been proven effective in animal models as it reduces the progression of DKD but has yet to be used in humans because of its side effects (21). These issues must offer a broad outline of your paper. In addition, regulating the KEAP1/Nrf2/ARE pathway has also become a potential approach to up-regulation of antioxidant genes and alleviation of oxidative stress, which is one of the major sources of kidney damage in diabetic nephropathy (101, 106).
This approach makes use of the natural defense mechanism of the body to fight the excess of reactive oxygen species that are common with diabetes (107). In addition, natural products that stimulate Nrf2 signaling and suppress the NF-kB system have provided a promise in preclinical research by improving the antioxidant defense mechanism and suppressing inflammatory events and fibrosis (106).

Moreover, the complexity of the relationships between hyperglycemia and oxidative stress suggests the challenge of effective intervention, but also offers varied opportunities to reduce pathological consequences through targeting master transcription factors, i.e. NFkB, Nrf2 or FoxO (17). Although the modern treatment methods only slow down the disease development of diabetic nephropathy, Nrf2 pathway still serves as a central focus of innovative therapies designed to stop or reverse the disease progression (108).

Conclusion

Oxidative stress and inflammation play critical and interconnected roles in the development and progression of hypertension. Excessive production of reactive oxygen species disrupts redox

homeostasis, reduces nitric oxide bioavailability, and promotes endothelial dysfunction, vascular remodeling, and arterial stiffness. Simultaneously, chronic low-grade inflammation, driven by immune cell activation and pro-inflammatory cytokines, further amplifies vascular damage and contributes to sustained elevation of blood pressure. The bidirectional interaction between oxidative stress and inflammation establishes a self-perpetuating cycle that accelerates target-organ injury and increases cardiovascular risk. Recognition of this oxidative–inflammatory axis extends the traditional understanding of hypertension beyond hemodynamic mechanisms and highlights novel molecular pathways involved in disease pathogenesis. Therapeutic strategies targeting oxidative stress and inflammatory pathways, including renin–angiotensin–aldosterone system inhibitors, antioxidants, anti-inflammatory agents, and lifestyle interventions, show promise in improving vascular function and blood pressure control. Future research should focus on identifying reliable biomarkers and developing targeted therapies to disrupt this pathogenic cycle, which may lead to more effective prevention and management strategies for hypertension.

Conflict of Interest
The authors declare they don't have any conflict of interest.

Author contributions
The first author wrote the first draft of the paper, which was supervised by a cross-responding author. Each author contributed to the manuscript's writing, gathered information, edited it, made tables, and received approval to submit it to a journal for publication.

Acknowledgement
The authors thank numerous resources for their open access publications, including DOAJ, Google Scholar, PubMed, Cochrane Library, BMJ Clinical Evidence, Embase, and Medline.

Ethical Approval
Not Applicable

References

1. Prabhakaran D, Jeemon P, Ghosh S, Shivashankar R, Ajay VS, Kondal D, et al. Prevalence and incidence of hypertension: Results from a representative cohort of over 16,000 adults in three cities of South Asia. 2017.
2. Zhang M, Xia X, Wang Q, Pan Y, Zhang GY, Wang Z. Application of machine learning algorithms in predicting new onset hypertension: a study based on the China Health and Nutrition Survey. Environ Health Prev Med. 2025;30:3. doi:10.1265/ehpm.24-00270
3. Aboukhater D, Morad B, Nasrallah N, Nasser SA, Sahebkar A, Kobeissy F, et al. Inflammation and hypertension: Underlying mechanisms and emerging understandings. J Cell Physiol. 2023;238(6):1148. doi:10.1002/jcp.31019
4. Touyz RM, Rios FJ, Alves-Lopes R, Neves KB, Camargo LL, Montezano AC. Oxidative Stress: A Unifying Paradigm in Hypertension. Can J Cardiol. 2020;36(5):659. doi:10.1016/j.cjca.2020.02.081
5. Ravarotto V, Bertoldi G, Stefanelli LF, Nalesso F, Calò LA. Pathomechanism of oxidative stress in cardiovascularrenal remodeling and therapeutic strategies. Kidney Res Clin Pract. 2022;41(5):533. doi:10.23876/j.krcp.22.069
6. Khullar M, Mittal A. Introductory Chapter: Hypertension – A Perspective. In: IntechOpen eBooks. IntechOpen; 2022. doi:10.5772/intechopen.106880
7. Rao AV, Ray MR, Rao LG. LYCOPENE. 2006.
8. Lee J, Son D, Kwon Y. Association between oxidative balance score and new-onset hypertension in adults: A community-based prospective cohort study. Front Nutr. 2022;9:1066159. doi:10.3389/fnut.2022.1066159
9. Barrows IR, Ramezani A, Raj DS. Inflammation, Immunity, and Oxidative Stress in Hypertension—Partners in Crime? Adv Chronic Kidney Dis. 2019;26(2):122. doi:10.1053/j.ackd.2019.03.001

10. Das D, Shruthi NR, Banerjee A, Jothimani G, Duttaroy AK, Pathak S. Endothelial dysfunction, platelet hyperactivity, hypertension, and the metabolic syndrome: molecular insights and combating strategies. Front Nutr. 2023;10:1221438. doi:10.3389/fnut.2023.1221438
11. Gökaslan S, Gökaslan ÇÖ, Çelik S. The role of endothelial dysfunction and inflammation in young-onset hypertension. Ital J Med. 2020;14(3):151. doi:10.4081/itjm.2020.1272
12. Ranadive SM, Dillon GA, Mascone SE, Alexander LM. Vascular Health Triad in Humans With Hypertension—Not the Usual Suspects. Front Physiol. 2021;12:746278. doi:10.3389/fphys.2021.746278
13. Hamza SM, Dyck JRB. Systemic and renal oxidative stress in the pathogenesis of hypertension: modulation of long-term control of arterial blood pressure by resveratrol. Front Physiol. 2014;5:292. doi:10.3389/fphys.2014.00292
14. Zhang Z, Zhao L, Zhou X, Meng X, Zhou X. Role of inflammation, immunity, and oxidative stress in hypertension: New insights and potential therapeutic targets. Front Immunol. 2023;13:1098725. doi:10.3389/fimmu.2022.1098725
15. Kostov K. The Causal Relationship between Endothelin-1 and Hypertension: Focusing on Endothelial Dysfunction, Arterial Stiffness, Vascular Remodeling, and Blood Pressure Regulation. Life (Basel). 2021;11(9):986. doi:10.3390/life11090986
16. Shrivastava AK, Singh HV, Raizada A, Singh SK. C-reactive protein, inflammation and coronary heart disease. Egypt Heart J. 2014;67(2):89. doi:10.1016/j.ehj.2014.11.005
17. González P, Lozano P, Ros G, Solano F. Hyperglycemia and Oxidative Stress: An Integral, Updated and Critical Overview of Their Metabolic Interconnections. Int J Mol Sci. 2023;24(11):9352. doi:10.3390/ijms24119352
18. Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, et al. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. Signal Transduct Target Ther. 2023;8(1). doi:10.1038/s41392-023-01430-7
19. Kim H. Arterial stiffness and hypertension. Clin Hypertens. 2023;29(1). doi:10.1186/s40885-023-00258-1
20. Liu W, Hou C, Wang H, Du H, Dai X, Jiang Y, et al. The role of oxidative stress in modulating mortality risk across the hypertension control cascade. Front Cardiovasc Med. 2025;12:1621911. doi:10.3389/fcvm.2025.1621911
21. Qaz M, Sawaf H, Ismail J, Qazi H, Vachharajani TJ. Pathophysiology of Diabetic Kidney Disease. EMJ Nephrol. 2022;102. doi:10.33590/emjnephrol/22-00060
22. Köpp W. Pathogenesis of (smoking-related) non-communicable diseases—Evidence for a common underlying pathophysiological pattern. Front Physiol. 2022;13:1037750. doi:10.3389/fphys.2022.1037750
23. Oliveira MG de, Nadruz W, Mónica FZ. Endothelial and vascular smooth muscle dysfunction in hypertension. Biochem Pharmacol. 2022;205:115263. doi:10.1016/j.bcp.2022.115263
24. Ji W, Zhang Y, Cheng Y, Wang Y, Zhou Y. Development and validation of prediction models for hypertension risks: A cross-sectional study based on 4,287,407 participants. 2022.
25. Amponsah-Offeh M, Diaba-Nuhoho P, Speier S, Morawietz H. Oxidative Stress, Antioxidants and Hypertension. Antioxidants (Basel). 2023;12(2):281. doi:10.3390/antiox12020281
26. Zhang X, Zhang J, Ren Y, Sun R, Zhai X. Unveiling the pathogenesis and therapeutic approaches for diabetic nephropathy: insights from panvascular diseases. Front Endocrinol (Lausanne). 2024;15:1368481. doi:10.3389/fendo.2024.1368481
27. Cade WT. Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Phys Ther. 2008;88(11):1322. doi:10.2522/ptj.20080008
28. Wu T, Ding L, Andoh V, Zhang J, Chen L. The Mechanism of Hyperglycemia-Induced Renal Cell Injury in Diabetic Nephropathy Disease: An Update. Life (Basel). 2023;13(2):539. doi:10.3390/life13020539
29. Ohara M, Kohata Y, Nagaike H, Koshibu M, Gima H, Hiromura M, et al. Association of glucose and blood pressure variability on oxidative stress in patients with type 2 diabetes mellitus and hypertension: a cross-sectional study. Diabetol Metab Syndr. 2019;11(1). doi:10.1186/s13098-019-0425-y

30. Arendshorst WJ, Vendrov AE, Kumar N, Ganesh SK, Madamanchi NR. Oxidative Stress in Kidney Injury and Hypertension. Carolina Digital Repository (University of North Carolina at Chapel Hill). 2024. doi:10.17615/t8rz-0458
31. Su MP, Nizamutdinov D, Liu H, Huang JH. Recent Mechanisms of Neurodegeneration and Photobiomodulation in the Context of Alzheimer's Disease. Int J Mol Sci. 2023;24(11):9272. doi:10.3390/ijms24119272
32. Panda P, Verma HK, Lakkakula S, Merchant N, Kadir F, Rehman S, et al. Biomarkers of Oxidative Stress Tethered to Cardiovascular Diseases. Oxid Med Cell Longev. 2022;2022:9154295. doi:10.1155/2022/9154295
33. Scioli MG, Storti G, D'Amico F, Guzmán RR, Centofanti F, Doldo E, et al. Oxidative Stress and New Pathogenetic Mechanisms in Endothelial Dysfunction: Potential Diagnostic Biomarkers and Therapeutic Targets. J Clin Med. 2020;9(6):1995. doi:10.3390/jcm9061995
34. Bayraktutan U. Reactive Oxygen Species, Nitric Oxide and Hypertensive Endothelial Dysfunction. Curr Hypertens Rev. 2005;1(3):201. doi:10.2174/157340205774574568
35. Schiffrin EL. Oxidative Stress, Nitric Oxide Synthase, and Superoxide Dismutase. Hypertension. 2007;51:31. doi:10.1161/hypertensionaha.107.103226
36. Camargo LL, Rios FJ, Montezano AC, Touyz RM. Reactive oxygen species in hypertension. Nat Rev Cardiol. 2024;22(1):20. doi:10.1038/s41569-024-01062-6
37. Okorie N, Obeagu EI, Nnamani AD, Ude UA, Agada UN, Ihuoma A, et al. Histopathological Effect of Emzolyn Codein Cough Syrup on Lungs and Its Oxidative Stress Biomarkers. J Pharm Res Int. 2021;228. doi:10.9734/jpri/2021/v33i49b33359
38. Rodrigo R, González J, Paoletto F. The role of oxidative stress in the pathophysiology of hypertension. Hypertens Res. 2011;34(4):431. doi:10.1038/hr.2010.264
39. Krzemińska J, Wronka M, Młynarska E, Franczyk B, Rysz J. Arterial Hypertension—Oxidative Stress and Inflammation. Antioxidants (Basel). 2022;11(1):172. doi:10.3390/antiox11010172
40. Alam R, Ahsan H, Khan S. The Role of Malondialdehyde (MDA) and Ferric Reducing Antioxidant Power (FRAP) in Patients with Hypertension. Mol Cell Biomed Sci. 2023;7(2):58. doi:10.21705/mcbs.v7i2.288
41. Griendling KK, Camargo LL, Rios FJ, Alves-Lopes R, Montezano AC, Touyz RM. Oxidative Stress and Hypertension. Circ Res. 2021;128(7):993. doi:10.1161/circresaha.121.318063
42. Kaczmarek A, Sieradocha K, Dotka M, Jedlikowska W, Strzyżewska N, Krasińska B, et al. Oxidatively modified protein products and lipid peroxidation products in hypertensive patients. Arter Hypertens. 2023;27(3):133. doi:10.5603/ah.95806
43. Caminiti R, Carresi C, Mollace R, Macrì R, Scarano F, Oppedisano F, et al. The potential effect of natural antioxidants on endothelial dysfunction associated with arterial hypertension. Front Cardiovasc Med. 2024;11:1345218. doi:10.3389/fcvm.2024.1345218
44. Gnebga V, Tengue K, Djagadou Ka, Sewa E, Sabi Ka. Aspects Epidemiologiques Cliniques, Paracliniques, Etiologiques, Therapeutiques Et Evolutifs Des Nephropathies Obstructives Au Chu-So I. 2024.
45. Sadik MI. Immune System and Inflammation in Hypertension. In: IntechOpen eBooks. IntechOpen; 2022. doi:10.5772/intechopen.105203
46. Handra CM, Gurzu IL, Chirilă M, Ghiţă I. Silicosis: New Challenges from an Old Inflammatory and Fibrotic Disease. Front Biosci (Landmark Ed). 2023;28(5):96. doi:10.31083/j.fbl2805096
47. Guzik TJ, Nosalski R, Maffia P, Drummond GR. Immune and inflammatory mechanisms in hypertension. Nat Rev Cardiol. 2024;21(6):396. doi:10.1038/s41569-023-00964-1
48. DeWitt JC, Germolec DR, Shipkowski KA, Frawley RP, Evans E. Markers of Inflammation. 2018.
49. Mantovani A, Garlanda C. Humoral Innate Immunity and Acute-Phase Proteins. N Engl J Med. 2023;388(5):439. doi:10.1056/nejmra2206346
50. Petersen HH, Nielsen JP, Heegaard PMH. Application of acute phase protein measurements in veterinary clinical chemistry. Vet Res. 2004;35(2):163. doi:10.1051/vetres:2004002
51. Leibowitz A, Schiffrin EL. Immune Mechanisms in Hypertension. Curr Hypertens Rep. 2011;13(6):465. doi:10.1007/s11906-011-0224-9
52. Gruys E, Toussaint MJM, Niewold T, Koopmans SJ. Acute phase reaction and acute phase proteins. J Zhejiang Univ Sci B. 2005;6(11):1045. doi:10.1631/jzus.2005.b1045

53. Hao X, Liu Y, Hailaiti D, Gong Y, Zhang X, Yue B nan, et al. Mechanisms of inflammation modulation by different immune cells in hypertensive nephropathy. Front Immunol. 2024;15:1333170. doi:10.3389/fimmu.2024.1333170
54. Miguel CD, Rudemiller NP, Abais JM, Mattson DL. Inflammation and Hypertension: New Understandings and Potential Therapeutic Targets. Curr Hypertens Rep. 2014;17(1). doi:10.1007/s11906-014-0507-z
55. Pickering TG. Stress, Inflammation, and Hypertension. J Clin Hypertens (Greenwich). 2007;9(7):567. doi:10.1111/j.1524-6175.2007.06301.x
56. Liu M, Chen R, Zheng Z, Xu S, Hou C, Ding Y, et al. Mechanisms of inflammatory microenvironment formation in cardiometabolic diseases: molecular and cellular perspectives. Front Cardiovasc Med. 2025;11:1529903. doi:10.3389/fcvm.2024.1529903
57. Cheung BMY, Li C. Diabetes and Hypertension: Is There a Common Metabolic Pathway? Curr Atheroscler Rep. 2012;14(2):160. doi:10.1007/s11883-012-0227-2
58. Sharma A, Tate M, Mathew G, Vince JE, Ritchie RH, Haan JB de. Oxidative Stress and NLRP3-Inflammasome Activity as Significant Drivers of Diabetic Cardiovascular Complications: Therapeutic Implications. Front Physiol. 2018;9:114. doi:10.3389/fphys.2018.00114
59. Duni A, Liakopoulos V, Roumeliotis S, Peschos D, Dounousi E. Oxidative Stress in the Pathogenesis and Evolution of Chronic Kidney Disease: Untangling Ariadne's Thread. Int J Mol Sci. 2019;20(15):3711. doi:10.3390/ijms20153711
60. Sedeek M, Callera GE, Montezano AC, Gutsol A, Heitz F, Szyndralewiez C, et al. Critical role of Nox4-based NADPH oxidase in glucose-induced oxidative stress in the kidney: implications in type 2 diabetic nephropathy. AJP Renal Physiol. 2010;299(6). doi:10.1152/ajprenal.00028.2010
61. Thallas-Bonke V, Jandeleit-Dahm K, Cooper ME. Nox-4 and progressive kidney disease. Curr Opin Nephrol Hypertens. 2014;24(1):74. doi:10.1097/mnh.0000000000000082
62. Kafle D, Islam N, Aryal B, Adhikary P, Singh N. Inflammation and Oxidative Stress via Persistent Hyperglycemia in Progression of Diabetic Nephropathy in Type 2 Diabetes Mellitus. J Chitwan Med Coll. 2013;3(1):1. doi:10.3126/jcmc.v3i1.8456
63. Pellegrino D, Russa DL, Marrone A. Oxidative Imbalance and Kidney Damage: New Study Perspectives from Animal Models to Hospitalized Patients. Antioxidants (Basel). 2019;8(12):594. doi:10.3390/antiox8120594
64. Charlton A, Garzarella J, Jandeleit-Dahm K, Jha JC. Oxidative Stress and Inflammation in Renal and Cardiovascular Complications of Diabetes. Biology (Basel). 2020;10(1):18. doi:10.3390/biology10010018
65. Zahra S, Saleem MK, Ejaz KF, Akbar A, Jadoon SK, Hussain S, et al. Prevalence of nephropathy among diabetic patients in North American region: A systematic review and meta-analysis. Medicine (Baltimore). 2024;103(38). doi:10.1097/md.0000000000039759
66. Jin Q, Liu T, Qiao Y, Liu D, Yang L, Mao H, et al. Oxidative stress and inflammation in diabetic nephropathy: role of polyphenols. Front Immunol. 2023;14:1185317. doi:10.3389/fimmu.2023.1185317
67. Wang N, Zhang C. Oxidative Stress: A Culprit in the Progression of Diabetic Kidney Disease. Antioxidants (Basel). 2024;13(4):455. doi:10.3390/antiox13040455
68. Cassano V, Pelaia C, Armentaro G, Miceli S, Tallarico V, Perini DD, et al. New potential biomarkers for early chronic kidney disease diagnosis in patients with different glucose tolerance status. Front Endocrinol (Lausanne). 2023;14:1206336. doi:10.3389/fendo.2023.1206336
69. Dobrek Ł. Oxidative stress mechanisms as potential therapeutic targets in chronic kidney disease. Med Stud. 2022;38(2):163. doi:10.5114/ms.2022.117714
70. Srivastava M, Rai B. Molecular Mechanisms of Pathways in Diabetic Nephropathy Development in Patients with T2DM -A Review. Int J Appl Biol Pharm Technol. 2021;12(4). doi:10.26502/ijabpt.202107
71. Sridhar VS, Limonte CP, Groop P, Heerspink HJL, Pratley RE, Rossing P, et al. Chronic kidney disease in type 1 diabetes: translation of novel type 2 diabetes therapeutics to individuals with type 1 diabetes. Diabetologia. 2023;67(1):3. doi:10.1007/s00125-023-06015-1
72. Usman M, Khan MS, Butler J. The Interplay Between Diabetes, Cardiovascular Disease, and Kidney Disease. ADA Clin Compendia. 2021;2021(1):13. doi:10.2337/db20211-13

73. Mugo EM, Nzuma R, Tade OO, Epia GO, Funmilayo OG, Anyibama B. Nutritional interventions to manage diabetes complications associated with foodborne diseases: A comprehensive review. World J Adv Res Rev. 2024;23(1):2724. doi:10.30574/wjarr.2024.23.1.2274
74. Yameny A. Diabetes Mellitus Overview 2024. J Biosci Appl Res. 2024;10(3):641. doi:10.21608/jbaar.2024.382794
75. Saadoun A, Rajab M, Yousef H. Electroretinogram and Visual Evoked Potentials in Patients with Type ll Diabetes Mellitus. Am J Biomed Life Sci. 2020;8(6):212. doi:10.11648/j.ajbls.20200806.14
76. Lu Y, Wang W, Liu J, Xie M, Liu Q, Li S. Vascular complications of diabetes: A narrative review. Medicine (Baltimore). 2023;102(40). doi:10.1097/md.0000000000035285
77. Iwasaki H, Yagyu H, Shimano H. A Comprehensive Analysis of Diabetic Complications and Advances in Management Strategies. J Atheroscler Thromb. 2025;32(5):550. doi:10.5551/jat.65551
78. Srivastava SP. Editorial: Current understanding of complications associated with diabetes. Front Clin Diabetes Healthc. 2023;4:1338656. doi:10.3389/fcdhc.2023.1338656
79. Mohammed SH, Muhammed HJ, Shetty T, Shanavas S. Micro and Macrovascular Complications in Diabetes Mellitus. Yangtze Med. 2025;9(1):96. doi:10.4236/ym.2025.91009
80. Ebrahimi M, Ahmadieh H, Kanavi MR, Safi S, Parsa S, Advani S, et al. Shared signaling pathways and comprehensive therapeutic approaches among diabetes complications. Front Med. 2025;11:1497750. doi:10.3389/fmed.2024.1497750
81. WINEGRAD AI, Toole J, Taggart G, Sheldon W, Lukens FDW. DIABETES AND ITS COMPLICATIONS. Med J Aust. 1932;1(4):136. doi:10.5694/j.1326-5377.1932.tb42301.x
82. Chen M, Pu L, Gan Y, Wang X, Kong L, Guo M, et al. The association between variability of risk factors and complications in type 2 diabetes mellitus: a retrospective study. Sci Rep. 2024;14(1). doi:10.1038/s41598-024-56777-w
83. Ziegler D, Porta M, Παπάνας N, Moţa M, Jermendy G, Beltramo E, et al. The Role of Biofactors in Diabetic Microvascular Complications. Curr Diabetes Rev. 2021;18(4). doi:10.2174/1871527320666210825112240
84. Kaur M, Misra S, Swarnkar P, Patel P, Kurmi BD, Gupta GD, et al. Understanding the role of hyperglycemia and the molecular mechanism associated with diabetic neuropathy and possible therapeutic strategies. Biochem Pharmacol. 2023;215:115723. doi:10.1016/j.bcp.2023.115723
85. Ha K. Transglutaminase 2 in diabetes mellitus: Unraveling its multifaceted role and therapeutic implications for vascular complications. Theranostics. 2024;14(6):2329. doi:10.7150/thno.95742
86. Cojić M, Klisić A, Sahmanovic A, Petrović N, Kocić G. Cluster analysis of patient characteristics, treatment modalities, renal impairments, and inflammatory markers in diabetes mellitus. Sci Rep. 2024;14(1). doi:10.1038/s41598-024-56451-1
87. Yapışlar H, Gürler EB. Management of Microcomplications of Diabetes Mellitus: Challenges, Current Trends, and Future Perspectives in Treatment. Biomedicines. 2024;12(9):1958. doi:10.3390/biomedicines12091958
88. Islam KN, Islam RK, Nguyen ID, Malik H, Pirzadah H, Shrestha B, et al. Diabetes Mellitus and Associated Vascular Disease: Pathogenesis, Complications, and Evolving Treatments. Adv Ther. 2025. doi:10.1007/s12325-025-03185-9
89. Haddad M. Mécanismes des lésions nerveuses périphériques lors du développement du diabète : rôle de la voie cytochrome P450. Munich Personal RePEc Archive (Ludwig Maximilian University of Munich); 2021. Available from: http://www.theses.fr/2021STRAJ007/document
90. Ohiagu FO, Chikezie PC, Chikezie CM. Pathophysiology of diabetes mellitus complications: Metabolic events and control. Biomed Res Ther. 2021;8(3):4243. doi:10.15419/bmrat.v8i3.663
91. Russell N, Cooper ME. 50 years forward: mechanisms of hyperglycaemia-driven diabetic complications. Diabetologia. 2015;58(8):1708. doi:10.1007/s00125-015-3600-1
92. Yamagishi S, Imaizumi T. Diabetic Vascular Complications: Pathophysiology, Biochemical Basis and Potential Therapeutic Strategy. Curr Pharm Des. 2005;11(18):2279. doi:10.2174/1381612054367300
93. Laddha AP, Oza MJ, Kulkarni YA. Editorial: Molecular aspects of natural products in diabetic complications. Front Endocrinol (Lausanne). 2024;15:1431775. doi:10.3389/fendo.2024.1431775
94. Giacco F, Brownlee M. Oxidative Stress and Diabetic Complications. Circ Res. 2010;107(9):1058. doi:10.1161/circresaha.110.223545

95. Liu J, Li K, Yi Z, Saqirile, Wang C, Yang R. Oxidative–Inflammatory Crosstalk and Multi-Target Natural Agents: Decoding Diabetic Vascular Complications. Curr Issues Mol Biol. 2025;47(8):614. doi:10.3390/cimb47080614
96. Iacobini C, Vitale M, Pesce C, Pugliese G, Menini S. Diabetic Complications and Oxidative Stress: A 20-Year Voyage Back in Time and Back to the Future. Antioxidants (Basel). 2021;10(5):727. doi:10.3390/antiox10050727
97. Reusch JEB. Diabetes, microvascular complications, and cardiovascular complications: what is it about glucose? J Clin Invest. 2003;112:986. doi:10.1172/jci19902
98. McCarty MF, DiNicolantonio JJ, O'Keefe JH. Nutraceutical Prevention of Diabetic Complications—Focus on Dicarbonyl and Oxidative Stress. Curr Issues Mol Biol. 2022;44(9):4314. doi:10.3390/cimb44090297
99. Zhang H, Wang K, Zhao H, Qin B, Cai X, Wu M, et al. Diabetic kidney disease: from pathogenesis to multimodal therapy–current evidence and future directions. Front Med. 2025;12:1631053. doi:10.3389/fmed.2025.1631053
100. Lushchak VI, Gospodaryov DV. Oxidative Stress and Diseases. In: InTech eBooks. 2012. doi:10.5772/2535
101. Tănase DM, Gosav EM, Anton MI, Floria M, Isac PNS, Hurjui LL, et al. Oxidative Stress and NRF2/KEAP1/ARE Pathway in Diabetic Kidney Disease (DKD): New Perspectives. Biomolecules. 2022;12(9):1227. doi:10.3390/biom12091227
102. Valle-Velázquez E, Zambrano-Vásquez OR, Cortés-Camacho F, Sánchez-Lozada LG, Guevara-Balcázar G, Osorio-Alonso H. Naringenin – a potential nephroprotective agent for diabetic kidney disease: A comprehensive review of scientific evidence. Biomol Biomed. 2024;24(6):1441. doi:10.17305/bb.2024.10511
103. Mima A. Inflammation and Oxidative Stress in Diabetic Nephropathy: New Insights on Its Inhibition as New Therapeutic Targets. J Diabetes Res. 2013;2013:248563. doi:10.1155/2013/248563
104. Sahakyan G, Véjux A, Sahakyan N. The Role of Oxidative Stress-Mediated Inflammation in the Development of T2DM-Induced Diabetic Nephropathy: Possible Preventive Action of Tannins and Other Oligomeric Polyphenols. Molecules. 2022;27(24):9035. doi:10.3390/molecules27249035
105. Rahayu I, Arfian N, Kustanti CY, Wahyuningsih MSH. The effectiveness of antioxidant agents in delaying progression of diabetic nephropathy: A systematic review of randomized controlled trials. Bioimpacts. 2024. doi:10.34172/bi.30129
106. Al-Waili N, Al-Waili H, Al-Waili T, Salom K. Natural antioxidants in the treatment and prevention of diabetic nephropathy; a potential approach that warrants clinical trials. Redox Rep. 2017;22(3):99. doi:10.1080/13510002.2017.1297885
107. Abdo S. Reactive Oxygen Species and Nuclear Factor Erythroid 2-Related Factor 2 Activation in Diabetic Nephropathy: A Hidden Target. J Diabetes Metab. 2015;6(6). doi:10.4172/2155-6156.1000547
108. Shahzad K, Bock F, Al-Dabet MM, Gadi I, Nazir S, Wang H, et al. Stabilization of endogenous Nrf2 by minocycline protects against Nlrp3-inflammasome induced diabetic nephropathy. Sci Rep. 2016;6(1):34228. doi:10.1038/srep34228