The Role of Oxidative Stress and Inflammation in Hypertension: Mechanisms, Therapeutic Targets, and Future Directions

Nader Hamdan Hamoud Aloufi[1], Mohmmed Masad Ghali Almutairi[1*], Enas Ibrahim Ali Dandini[1], Alahmadi Naif Muqaybil S[1], Maher Oudah Suleiman Alqayidi[1], Merfat Mohammed O Taha[1], Rayid Marzouq Aljohani[2], Fayez Mohsen Tawhari[3], Eiadah Awad Ealtaqtaqi[4], Omar Hamid Alsobhi[5], Mohammed Salman Almuzaini[5], Hussain Saleh Aljoheni[5], Bander Jumah Aloufi[5], Abdullah Mousa Essa Alahmadi[5], Ahmed Suwayyid Almalki[6]

[1]Prince Sultan Armed Forces Hospital in Madinah, Aldifa, Madinah -42375, Saudi Arabia
[2]Albad General Hospital, Al Bad' 49814, Tabuk, Saudi Arabia
[3]Al-Mithnab General Hospital, Prince Faisal Ibn Bandar St, Alrayyan Al Sharqy, Al Mithnab-56526, Al-Qassim, Saudi Arabia
[4]Ashwaq general hospital, Ashwaq 49444, Tabuk, 8756, Saudi Arabia
[5]Regional Blood Bank, 2981 Khalid Ibn Al Walid Rd, Madinah 42351, Saudi Arabia
[6]Al Qara General Hospital, Albaha health cluster, Al Bahah Province, Alqari, BCJA4158, Saudi Arabia
Email: m_s1425@hotmail.com

Abstract

Hypertension is a multifactorial condition characterized by elevated blood pressure, where oxidative stress and inflammation play central roles. This article explores the intricate relationship between these two processes, detailing how they contribute to endothelial dysfunction, vascular remodeling, and renal impairment, all of which exacerbate hypertension. The renin-angiotensin system (RAS) and sympathetic nervous system (SNS) also interact with oxidative stress and inflammation, promoting vasoconstriction and sodium retention. Current therapeutic strategies targeting oxidative stress and inflammation, including antioxidants, anti-inflammatory compounds, and dietary interventions, show promise in managing hypertension. Future directions include investigating molecular pathways like Nrf2 and NF-κB, which may provide new therapeutic targets for reducing inflammation and oxidative stress.

Keywords: Hypertension, Oxidative stress, Inflammation, Endothelial dysfunction, Renin-angiotensin system, Antioxidants, Nrf2 and NF-κB.

1. Introduction

Hypertension, a condition characterized by elevated blood pressure, is increasingly recognized as a multifactorial disease where inflammation and oxidative stress play pivotal roles in its development and progression. The interplay between these two biological processes is complex and involves various signaling pathways and molecular mechanisms that contribute to vascular dysfunction, renal impairment, and ultimately, sustained hypertension. Oxidative stress is defined as an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage. In the context of hypertension, oxidative stress is primarily driven by factors such as angiotensin II, aldosterone, and various cytokines, which stimulate the activity of enzymes like NADPH oxidases and uncoupled nitric oxide synthase.

These enzymes generate ROS that contribute to vascular dysfunction by promoting vasoconstriction and sodium retention in the kidneys, thereby exacerbating hypertension (Tangvarasittichai et al., 2016). The production of ROS can lead to endothelial dysfunction, characterized by reduced nitric oxide availability, which is crucial for maintaining vascular tone and health (Somers et al., 2000). Inflammation, on the other hand, is characterized by the activation of immune responses that can lead to tissue damage and further exacerbate oxidative stress. In hypertensive patients, inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are often elevated, indicating a chronic inflammatory state that contributes to vascular remodeling and increased peripheral resistance (Wang et al., 2022). The relationship between inflammation and oxidative stress is bidirectional; inflammation can enhance oxidative stress through the activation of inflammatory cells that produce ROS, while oxidative stress can activate inflammatory pathways, creating a vicious cycle that perpetuates hypertension (Javkhedkar et al., 2015).

The role of the renal system in hypertension is particularly significant, as the kidneys are central to blood pressure regulation. Studies have shown that oxidative stress and inflammation within the renal interstitium can lead to renal damage and dysfunction, which in turn contributes to the development of hypertension (Tangvarasittichai et al., 2016). For instance, the activation of intrarenal angiotensin II has been shown to promote both oxidative stress and inflammation, leading to increased vascular resistance and reduced natriuresis, thereby raising blood pressure (Javkhedkar et al., 2015). Furthermore, interventions aimed at reducing oxidative stress, such as the administration of antioxidants like resveratrol, have demonstrated efficacy in lowering blood pressure and reducing renal inflammation in hypertensive models (Javkhedkar et al., 2015). Dietary factors, particularly salt intake, also play a crucial role in modulating oxidative stress and inflammation in hypertension.

High salt diets have been shown to elicit oxidative stress and inflammation in the hypothalamic paraventricular nucleus, a critical area for blood pressure regulation (Su et al., 2022). This suggests that dietary sodium can exacerbate hypertension through mechanisms involving both oxidative stress and inflammatory pathways. The Na+/K+-ATPase has been implicated in this process, as its dysfunction can lead to increased ROS production, further contributing to the

hypertensive state (Su et al., 2022). Moreover, the therapeutic implications of managing oxidative stress and inflammation in hypertension are significant. Continuous positive airway pressure (CPAP) therapy in patients with obstructive sleep apnea has been shown to reduce both inflammatory mediators and oxidative stress, leading to improvements in blood pressure control (Wang et al., 2022). This highlights the potential for targeting oxidative stress and inflammation as therapeutic strategies in managing hypertension. In summary, the development and progression of hypertension are intricately linked to the processes of inflammation and oxidative stress.

The interplay between these two mechanisms leads to vascular dysfunction, renal impairment, and sustained increases in blood pressure. Understanding these relationships is crucial for developing effective therapeutic strategies aimed at mitigating hypertension and its associated complications. The current understanding of how inflammatory processes influence hypertension pathophysiology has evolved significantly, revealing a complex interplay between immune responses, oxidative stress, and vascular function. Inflammation is increasingly recognized as a critical contributor to the development and progression of hypertension, with various inflammatory mediators playing pivotal roles in altering vascular homeostasis and renal function. One of the primary inflammatory mediators implicated in hypertension is tumor necrosis factor-alpha (TNF-α). Elevated levels of TNF-α have been observed in hypertensive patients, and its expression is significantly increased in peripheral blood monocytes upon pro-inflammatory stimulation (Yang et al., 2022).

This cytokine contributes to endothelial dysfunction by promoting oxidative stress and vascular inflammation, leading to increased vascular resistance and blood pressure. The relationship between TNF-α and hypertension highlights the importance of inflammatory pathways in the disease's pathophysiology, as these pathways can lead to structural and functional changes in the vasculature, ultimately resulting in sustained hypertension. Moreover, the accumulation of myeloid-derived suppressor cells (MDSCs) in hypertensive states has been shown to regulate blood pressure through their effects on renal inflammation (Shah et al., 2015). In models of hypertension induced by angiotensin II (Ang II) or L-NAME, there is a marked increase in renal CD45+ inflammatory cells, indicating a robust inflammatory response in the kidneys. This renal inflammation is not merely a consequence of hypertension but rather a contributing factor that exacerbates the condition.

The infiltration of inflammatory cells into the renal interstitium can lead to renal damage, impaired sodium excretion, and increased blood pressure, thereby establishing a feedback loop that perpetuates hypertension. Oxidative stress is another critical component that interacts with inflammatory processes in hypertension. The generation of reactive oxygen species (ROS) can activate inflammatory pathways, further enhancing the inflammatory response (Zhang et al., 2021). For instance, studies have demonstrated that Ang II can induce oxidative stress in endothelial cells, leading to DNA damage and endothelial dysfunction (Zhang et al., 2021). This oxidative damage is compounded by the inflammatory milieu, creating a vicious cycle where inflammation leads to oxidative stress, which in turn exacerbates inflammation. The interplay between oxidative stress and inflammation is particularly evident in conditions such as

pregnancy-induced hypertension, where elevated oxidative stress markers have been linked to endothelial damage and increased blood pressure (Shah et al., 2019).

The role of microRNAs in modulating inflammation and hypertension is also gaining attention. For example, circulating microRNA-505 has been identified as a potential biomarker for hypertension-associated endothelial dysfunction and inflammation (Yang et al., 2022). This microRNA may influence the expression of inflammatory mediators, thereby contributing to the pathophysiological changes observed in hypertensive patients. The identification of such biomarkers can provide insights into the underlying mechanisms of hypertension and may offer new therapeutic targets for intervention. Furthermore, maternal factors such as exposure to environmental toxins and dietary influences can program hypertension in offspring through mechanisms involving oxidative stress and inflammation.

Research has shown that maternal exposure to bisphenol A, combined with a high-fat diet, can lead to programmed hypertension in male rat offspring, mediated by oxidative stress and renal dysfunction (Hsu et al., 2019). This highlights the importance of early-life exposures in shaping the inflammatory and oxidative stress responses that contribute to hypertension later in life. In conclusion, the current understanding of hypertension pathophysiology emphasizes the significant role of inflammatory processes in its development and progression. The interplay between inflammatory mediators, oxidative stress, and vascular dysfunction creates a complex network that perpetuates hypertension. Ongoing research into these mechanisms will be crucial for developing targeted therapies aimed at mitigating the inflammatory and oxidative stress components of hypertension, ultimately improving patient outcomes.

2. Inflammation and Hypertension Mechanisms

The roles of immune cells and cytokines in vascular dysfunction related to hypertension have garnered significant attention in recent years, revealing a complex interplay between the immune system and the cardiovascular system. This relationship is characterized by the activation of various immune cells, the release of pro-inflammatory cytokines, and the subsequent effects on vascular function and blood pressure regulation. One of the key players in this process is the innate immune system, particularly macrophages and dendritic cells, which infiltrate the kidneys in hypertensive states. Studies have shown that the activation of these innate immune cells is associated with increased blood pressure in experimental models of hypertension (Sims et al., 2022).

The infiltration of pro-inflammatory innate immune cells into the renal interstitium leads to the secretion of cytokines that can impair renal sodium handling and contribute to kidney dysfunction, thereby propagating hypertension (Sims et al., 2022). This renal inflammation is a hallmark of hypertension and is characterized by an increase in the number of inflammatory cells, including CD45+ leukocytes, which are indicative of an ongoing immune response (Shah et al., 2015). Cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) play crucial roles in mediating the inflammatory response in hypertension. TNF-α, in particular, has been shown to promote oxidative stress and endothelial dysfunction, leading to increased vascular resistance and elevated blood pressure (McMaster et al., 2015). The activation of microglial cells, which are specialized macrophages in the brain, further exacerbates this process

by enhancing sympathetic outflow, thereby contributing to sustained elevations in blood pressure (McMaster et al., 2015).

Elevated levels of these cytokines in the circulation have been associated with the severity of hypertension, indicating their potential as biomarkers for disease progression. Additionally, the role of adaptive immunity, particularly T cells, has been increasingly recognized in the context of hypertension. Immunosenescent CD8+ T cells, which exhibit pro-inflammatory and cytotoxic properties, have been found to be elevated in hypertensive patients (Youn et al., 2013). These T cells can contribute to vascular inflammation through the release of granzyme B and other inflammatory mediators, which may damage endothelial cells and promote vascular dysfunction (Youn et al., 2013). The presence of these activated T cells in the circulation suggests a link between immune activation and the pathophysiology of hypertension. B cells also play a significant role in hypertension through their production of antibodies and cytokines. Research has indicated that plasma cell depletion can attenuate hypertension in models of autoimmune disease, suggesting that B cells contribute to the inflammatory milieu that drives hypertension (Taylor et al., 2018).

The mechanisms by which B cells influence hypertension may involve antigen presentation to T cells and the production of autoantibodies that exacerbate vascular inflammation (Taylor et al., 2018). This highlights the multifaceted role of B cells in the pathogenesis of hypertension. The interplay between immune cells and cytokines in hypertension is further complicated by the presence of myeloid-derived suppressor cells (MDSCs), which can accumulate in hypertensive states and modulate immune responses (Shah et al., 2015). These cells have been shown to regulate blood pressure by influencing the activity of other immune cells and cytokine production, thereby affecting vascular function and blood pressure regulation (Shah et al., 2015). The presence of MDSCs in the renal tissue of hypertensive models underscores the importance of the immune microenvironment in the pathophysiology of hypertension. In summary, immune cells and cytokines play critical roles in the vascular dysfunction associated with hypertension.

The activation of innate and adaptive immune cells, along with the release of pro-inflammatory cytokines, contributes to renal inflammation, endothelial dysfunction, and ultimately, elevated blood pressure. Understanding these immune-mediated mechanisms is essential for developing targeted therapies aimed at mitigating hypertension and its associated complications. The contribution of specific cytokines, particularly tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), to blood pressure elevation in hypertensive patients is a subject of extensive research. Both cytokines are integral to the inflammatory processes that underlie the pathophysiology of hypertension, influencing vascular function, renal sodium handling, and overall cardiovascular health. TNF-α is a pro-inflammatory cytokine that has been shown to play a significant role in the development of hypertension. Elevated levels of TNF-α are associated with increased vascular resistance and endothelial dysfunction, which are critical components of hypertension (Chamarthi et al., 2011).

TNF-α contributes to the pathogenesis of hypertension by promoting oxidative stress and reducing nitric oxide (NO) bioavailability, leading to impaired vasodilation and increased vascular tone (Zhang et al., 2016). In models of angiotensin II (Ang II)-induced hypertension, TNF-α has been shown to exacerbate blood pressure elevation by limiting renal NO generation,

which is essential for maintaining normal blood pressure (Zhang et al., 2016). This reduction in NO availability enhances sodium reabsorption in the nephron, further contributing to hypertension through increased blood volume and vascular resistance. IL-6, another key cytokine, has been implicated in the inflammatory response associated with hypertension. Increased levels of IL-6 have been observed in hypertensive patients and are correlated with elevated blood pressure (Meléndez et al., 2010). IL-6 acts as a potent growth factor for smooth muscle cells and fibroblasts, promoting vascular remodeling and hypertrophy, which can lead to increased vascular stiffness and resistance (Pellicelli et al., 2010). The relationship between IL-6 and blood pressure is complex; while it is associated with hypertension, the exact mechanisms by which IL-6 influences blood pressure regulation are still being elucidated.

Some studies suggest that IL-6 may enhance the renin-angiotensin system (RAS) activity, further contributing to hypertension through increased angiotensin II levels (Chamarthi et al., 2011). This interaction between IL-6 and the RAS underscores the multifaceted role of cytokines in the regulation of blood pressure. The interplay between TNF-α and IL-6 in the context of hypertension is also noteworthy. Both cytokines can activate inflammatory pathways that lead to vascular dysfunction. For instance, TNF-α can stimulate the production of IL-6, creating a feedback loop that perpetuates inflammation and vascular damage (Ensminger et al., 2022). This synergistic effect can exacerbate the hypertensive state by promoting further endothelial dysfunction and increasing vascular resistance. Additionally, the presence of these cytokines in the circulation can serve as biomarkers for the severity of hypertension and its associated complications, such as heart failure and renal impairment (Meléndez et al., 2010). In summary, TNF-α and IL-6 are critical mediators of the inflammatory processes that contribute to blood pressure elevation in hypertensive patients. Their roles in promoting oxidative stress, reducing NO availability, and enhancing vascular remodeling highlight the importance of targeting these cytokines in the management of hypertension. Understanding the specific mechanisms by which these cytokines influence blood pressure regulation can lead to the development of novel therapeutic strategies aimed at mitigating the inflammatory components of hypertension.

The interplay between inflammation, the renin-angiotensin-aldosterone system (RAAS), and the sympathetic nervous system (SNS) is crucial in understanding the pathophysiology of hypertension. Evidence suggests that pro-inflammatory cytokines significantly influence both the RAAS and the SNS, contributing to the elevation of blood pressure in hypertensive patients. Pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) have been shown to interact with the RAAS, enhancing its activity. For instance, TNF-α can stimulate the production of angiotensin II, a potent vasoconstrictor that plays a pivotal role in increasing blood pressure (Akhmedov & Sharipov, 2023). This interaction is particularly relevant in the context of salt-sensitive hypertension, where cytokines can modulate the expression of RAAS-related genes in immune cells, thereby influencing blood pressure regulation (Ertuğlu et al., 2023).

The activation of the RAAS leads to vasoconstriction, increased sodium retention, and subsequent fluid overload, all of which contribute to hypertension (Terry et al., 2010). Moreover, the sympathetic nervous system is intricately linked to the inflammatory response. The SNS not only regulates vascular tone and heart rate but also has been implicated in the

release of pro-inflammatory cytokines. Studies have shown that sympathetic nerve activity can stimulate the production of TNF-α and IL-6, creating a feedback loop that exacerbates hypertension (Akhmedov & Sharipov, 2023). This suggests that the SNS may serve as both a mediator and a target of inflammatory processes in hypertension. In fact, targeted sympathetic ablation has been shown to reverse genetic salt-sensitive hypertension, highlighting the importance of sympathetic activity in the pathogenesis of hypertension (Foss et al., 2013). The relationship between the RAAS and the SNS is further complicated by the role of immune cells. Myeloid cells have been identified as key players in the regulation of the RAAS, particularly in the context of salt-sensitive hypertension. Research indicates that dietary sodium intake can dynamically regulate the expression of RAAS-related genes in these immune cells, linking dietary factors to immune-mediated hypertension (Ertuğlu et al., 2023).

This suggests that inflammation within the RAAS can be modulated by external factors, such as sodium intake, which may influence blood pressure regulation. Additionally, maternal factors such as gestational hypertension have been shown to program hypertension in offspring, potentially through mechanisms involving the RAAS and SNS. Studies have demonstrated that offspring of mothers with gestational hypertension exhibit increased sympathetic activity and elevated aldosterone levels, suggesting that prenatal exposure to high blood pressure can sensitize the RAAS and SNS in later life (Xue et al., 2017). This highlights the long-term implications of inflammatory processes in hypertension, as early-life exposures can predispose individuals to elevated blood pressure through alterations in these regulatory systems. In summary, the evidence linking inflammation in the RAAS and SNS to hypertension is robust. Pro-inflammatory cytokines enhance RAAS activity and stimulate sympathetic nerve activity, creating a vicious cycle that perpetuates hypertension. The involvement of immune cells in regulating these systems further underscores the complexity of hypertension's pathophysiology. Understanding these interactions is essential for developing targeted therapeutic strategies aimed at mitigating hypertension and its associated complications.

3. Oxidative Stress and Hypertension Mechanisms

Oxidative stress is a significant contributor to the pathophysiology of hypertension, with various sources and mechanisms implicated in its development and progression. The primary sources of oxidative stress in hypertensive patients include increased production of reactive oxygen species (ROS) from various cellular processes, particularly those associated with the renin-angiotensin-aldosterone system (RAAS), the sympathetic nervous system (SNS), and metabolic disturbances. One of the key sources of oxidative stress in hypertension is the activation of the RAAS. Angiotensin II (Ang II), a potent vasoconstrictor, not only raises blood pressure directly but also stimulates the production of ROS through the activation of NADPH oxidase in vascular smooth muscle cells and endothelial cells (Govender & Nadar, 2015).

This increased oxidative stress leads to a reduction in nitric oxide (NO) bioavailability, which is crucial for maintaining vascular tone and promoting vasodilation. The scavenging of NO by superoxide anions ($O2^-$) results in impaired vasodilation and increased vascular resistance, contributing to elevated blood pressure (Govender & Nadar, 2015). Furthermore, Ang II-induced oxidative stress can promote inflammation and vascular remodeling, further exacerbating hypertension (Govender & Nadar, 2015). The sympathetic nervous system is

another significant contributor to oxidative stress in hypertensive patients. Increased sympathetic activity can lead to elevated levels of catecholamines, which stimulate ROS production in various tissues, including the heart and vasculature (Somers et al., 2000). This sympathetic activation not only raises blood pressure through vasoconstriction but also enhances oxidative stress, creating a feedback loop that perpetuates hypertension. Studies have shown that interventions aimed at reducing sympathetic activity can decrease oxidative stress markers and improve blood pressure control (Murri et al., 2011). Metabolic disturbances, particularly those associated with obesity and insulin resistance, also play a crucial role in the generation of oxidative stress in hypertensive patients.

Adipose tissue, especially in obese individuals, can produce pro-inflammatory cytokines and free fatty acids that contribute to oxidative stress (Kumar et al., 2012). These metabolic factors can activate the RAAS and SNS, leading to further increases in blood pressure. For instance, the presence of excess free fatty acids can stimulate the production of ROS in endothelial cells, impairing NO signaling and promoting vasoconstriction (Kumar et al., 2012). Chronic renal failure is another condition closely linked to oxidative stress and hypertension. In patients undergoing peritoneal dialysis, oxidative stress markers such as malondialdehyde and myeloperoxidase are elevated, indicating increased oxidative damage (Demirci et al., 2011). The kidneys play a critical role in blood pressure regulation, and oxidative stress can lead to renal dysfunction, further exacerbating hypertension. Antihypertensive medications, such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), have been shown to reduce oxidative stress and improve renal function, highlighting the importance of managing oxidative stress in hypertensive patients (Demirci et al., 2011).

In summary, the primary sources of oxidative stress in hypertensive patients include the activation of the RAAS, increased sympathetic nervous system activity, and metabolic disturbances associated with obesity and chronic renal failure. These sources contribute to hypertension through mechanisms involving reduced NO bioavailability, increased vascular resistance, and renal dysfunction. Understanding these pathways is essential for developing targeted therapeutic strategies aimed at mitigating oxidative stress and improving blood pressure control.

Oxidative stress is a critical factor in the development of endothelial dysfunction, particularly in the context of hypertension. The mechanisms by which oxidative stress leads to endothelial dysfunction involve the production of reactive oxygen species (ROS), the depletion of nitric oxide (NO), and the activation of various signaling pathways that promote vascular inflammation and remodeling. One of the primary sources of oxidative stress in hypertensive patients is the overactivity of the renin-angiotensin-aldosterone system (RAAS), particularly through the action of angiotensin II (Ang II). Ang II stimulates the production of ROS, primarily through the activation of NADPH oxidase in vascular smooth muscle cells and endothelial cells (Carlström et al., 2010). This increased ROS production leads to a reduction in NO bioavailability, which is essential for maintaining endothelial function and vascular homeostasis. The scavenging of NO by superoxide anions ($O2^-$) results in impaired vasodilation, increased vascular tone, and ultimately, elevated blood pressure (Carlström et al., 2010).

The relationship between oxidative stress and NO deficiency is particularly evident in the context of microvascular remodeling, where ROS contribute to structural changes in the vasculature that further exacerbate hypertension (Carlström et al., 2010). In addition to the RAAS, other factors contribute to oxidative stress and endothelial dysfunction in hypertension. For instance, systemic inflammation, often characterized by elevated levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), can enhance oxidative stress (Mathis et al., 2012). These cytokines can stimulate the production of ROS and activate inflammatory pathways that lead to endothelial injury. The resultant endothelial dysfunction is characterized by a reduced ability to produce NO, increased expression of adhesion molecules, and enhanced vascular permeability, all of which contribute to the pathogenesis of hypertension (Mathis et al., 2012). Furthermore, oxidative stress can directly affect the function of endothelial cells. Increased levels of ROS can lead to the activation of signaling pathways that promote apoptosis and senescence in endothelial cells, further impairing their function (Ekun et al., 2020).

This dysfunction is associated with a decrease in the production of vasodilators and an increase in the production of vasoconstrictors, leading to a net increase in vascular resistance and blood pressure (Ekun et al., 2020). The link between oxidative stress and endothelial dysfunction is also supported by studies showing that antioxidant therapies can improve endothelial function and reduce blood pressure in hypertensive patients (Tousoulis et al., 2010). The role of oxidative stress in hypertension is further underscored by its impact on renal function. In hypertensive patients, oxidative stress can lead to renal microvascular dysfunction, characterized by increased renal vascular resistance and impaired sodium handling (Mathis et al., 2012).

This renal dysfunction can contribute to the overall hypertensive state by promoting fluid retention and increasing blood volume. The interplay between oxidative stress, renal function, and endothelial dysfunction highlights the multifaceted nature of hypertension and the importance of targeting oxidative stress in its management. In summary, oxidative stress leads to endothelial dysfunction in hypertension through mechanisms involving increased ROS production, decreased NO bioavailability, and the activation of inflammatory pathways. The interplay between these factors contributes to vascular remodeling, increased vascular resistance, and impaired renal function, ultimately resulting in sustained hypertension. Understanding these mechanisms is crucial for developing effective therapeutic strategies aimed at mitigating oxidative stress and improving endothelial function in hypertensive patients.

The role of reactive oxygen species (ROS) and mitochondrial dysfunction in hypertension is a critical area of research, as these factors are intricately linked to the pathophysiology of elevated blood pressure and associated cardiovascular complications. ROS are chemically reactive molecules that can cause cellular damage, and their overproduction is often associated with mitochondrial dysfunction, leading to a cascade of events that contribute to hypertension. Mitochondria are essential organelles responsible for energy production through oxidative phosphorylation, but they are also significant sources of ROS. Under pathological conditions, such as hypertension, mitochondrial dysfunction can lead to excessive ROS production, which contributes to endothelial dysfunction and vascular remodeling. For instance, studies have shown that mitochondrial ROS can induce mitochondrial DNA damage and impair the expression of

respiratory chain components, ultimately leading to reduced mitochondrial function and increased vascular stiffness (Li et al., 2022).

This dysfunction is particularly detrimental in endothelial cells, where it can impair nitric oxide (NO) production and bioavailability, crucial for maintaining vascular tone and health (Li et al., 2022). One of the mechanisms by which ROS contribute to endothelial dysfunction in hypertension is through the uncoupling of endothelial nitric oxide synthase (eNOS). Under normal conditions, eNOS produces NO, which promotes vasodilation. However, in the presence of excessive ROS, eNOS can become uncoupled, leading to the production of superoxide instead of NO (Shimizu et al., 2013). This shift not only reduces NO availability but also increases oxidative stress, creating a vicious cycle that exacerbates endothelial dysfunction and promotes hypertension. The importance of maintaining mitochondrial function and preventing ROS overproduction is underscored by the observation that mitochondrial-targeted antioxidants, such as MitoQ and Mito-TEMPO, can improve endothelial function and reduce blood pressure in hypertensive models (Li et al., 2022). Furthermore, mitochondrial dynamics, including fission and fusion processes, play a significant role in maintaining mitochondrial function and cellular health. In hypertension, there is often an imbalance in these processes, leading to mitochondrial fragmentation and dysfunction. For example, the phosphorylation of dynamin-related protein 1 (Drp1), which is essential for mitochondrial fission, is impaired in hypertensive states, resulting in altered mitochondrial morphology and function (Shou & Huo, 2022). This dysfunction can further contribute to oxidative stress and endothelial injury, perpetuating the cycle of hypertension.

The relationship between ROS, mitochondrial dysfunction, and hypertension is also evident in the context of metabolic disorders. Conditions such as obesity and diabetes mellitus are associated with increased oxidative stress and mitochondrial dysfunction, which can exacerbate hypertension. In particular, high glucose levels have been shown to increase mitochondrial ROS production, leading to endothelial dysfunction and impaired vasodilation (Shenouda et al., 2011). This highlights the importance of addressing metabolic health in the management of hypertension, as improving mitochondrial function and reducing oxidative stress may have beneficial effects on blood pressure regulation. In summary, ROS and mitochondrial dysfunction play pivotal roles in the development and progression of hypertension. The overproduction of ROS due to mitochondrial dysfunction leads to endothelial dysfunction, impaired NO bioavailability, and vascular remodeling. Understanding these mechanisms is crucial for developing therapeutic strategies aimed at mitigating oxidative stress and improving mitochondrial function in hypertensive patients.

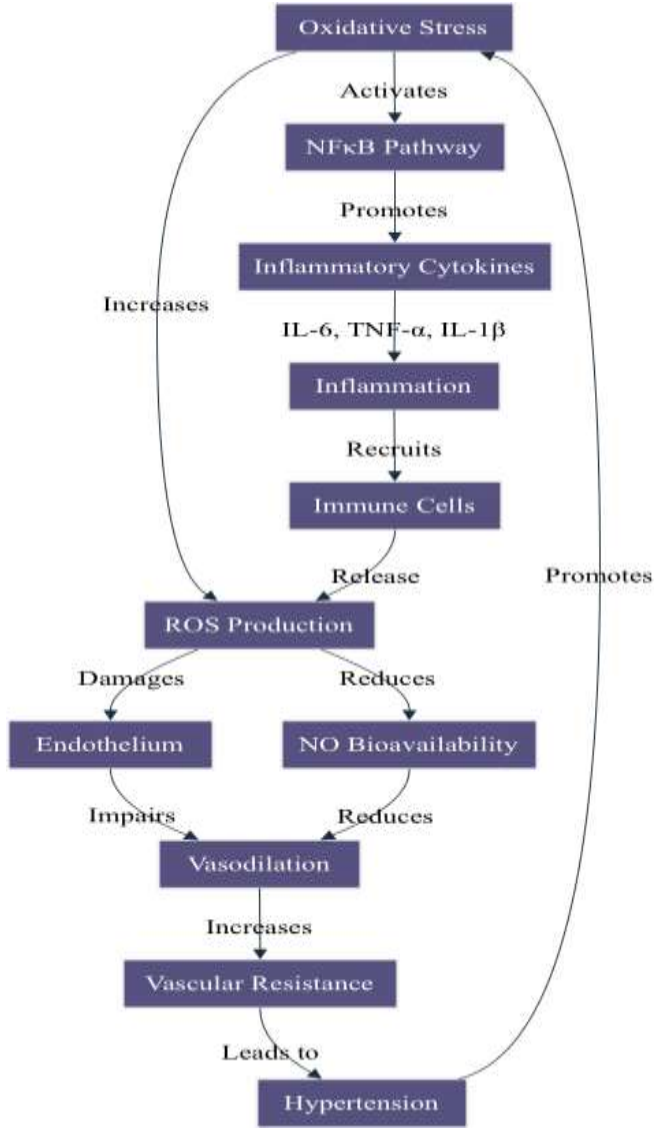

Figure 1. This diagram illustrates the complex interactions between oxidative stress and inflammation in the development of hypertension. Oxidative stress activates the NF-κB pathway, which promotes the release of inflammatory cytokines (e.g., IL-6, TNF-α, IL-1β). These cytokines lead to further inflammation and immune cell recruitment, resulting in increased ROS (Reactive Oxygen Species) production. Elevated ROS damages the endothelium and reduces nitric oxide (NO) bioavailability, impairing vasodilation and increasing vascular resistance. Together, these processes contribute to the onset and progression of hypertension.

4. Interaction of Inflammation and Oxidative Stress

The interaction between inflammation and oxidative stress is a critical factor in the exacerbation of hypertension. This relationship is characterized by a complex interplay where oxidative stress not only contributes to inflammatory processes but also enhances the effects of inflammation, creating a vicious cycle that perpetuates elevated blood pressure. One of the primary mechanisms through which oxidative stress contributes to hypertension is through the production of reactive oxygen species (ROS). In hypertensive patients, elevated levels of ROS can lead to endothelial dysfunction by reducing the bioavailability of nitric oxide (NO), a key vasodilator. This reduction in NO availability results in impaired vasodilation and increased vascular resistance, which are hallmarks of hypertension Tangvarasittichai et al. (2016). The presence of ROS can also activate various signaling pathways that promote inflammation, further exacerbating the hypertensive state. For instance, oxidative stress can stimulate the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which contribute to vascular inflammation and remodeling (Zhang et al., 2023).

The relationship between oxidative stress and inflammation is particularly evident in the context of the renin-angiotensin-aldosterone system (RAAS). Angiotensin II (Ang II) is a potent vasoconstrictor that not only raises blood pressure but also induces oxidative stress and inflammation. Studies have shown that Ang II can activate NADPH oxidase, leading to increased ROS production, which in turn promotes inflammation through the activation of nuclear factor kappa B (NF-κB) and other inflammatory pathways (Javkhedkar et al., 2015). This interaction creates a feedback loop where oxidative stress enhances the inflammatory response, leading to further activation of the RAAS and perpetuation of hypertension. Moreover, the infiltration of immune cells into the renal interstitial has been shown to play a significant role in the development of hypertension. Inflammatory cells, such as macrophages and T cells, produce ROS and pro-inflammatory cytokines that contribute to renal damage and impaired sodium handling, further exacerbating hypertension (Franco et al., 2013). The presence of these immune cells in the kidneys is associated with reduced pressure natriuresis, a critical mechanism for regulating blood pressure.

The generation of ROS during inflammation can impair the renal vasodilatory response, leading to increased blood pressure and sodium retention (Franco et al., 2013). Additionally, dietary factors such as high salt intake can exacerbate oxidative stress and inflammation in hypertensive patients. High salt diets have been shown to activate the sympathetic nervous system and promote oxidative stress in the hypothalamic paraventricular nucleus, leading to increased blood pressure (Su et al., 2022). The interaction between sodium intake, oxidative stress, and inflammation underscores the importance of dietary management in hypertension. In summary, the interaction between inflammation and oxidative stress plays a crucial role in exacerbating hypertension. The production of ROS leads to endothelial dysfunction, activation of inflammatory pathways, and renal impairment, all of which contribute to elevated blood pressure. Understanding these mechanisms is essential for developing targeted therapeutic strategies aimed at mitigating oxidative stress and inflammation in hypertensive patients.

The interplay between inflammation and oxidative stress in hypertension has prompted extensive research into potential molecular targets that could disrupt this detrimental cycle. Several promising targets have emerged, focusing on various pathways and mechanisms that contribute to the pathophysiology of hypertension. One of the key molecular targets being investigated is the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Nrf2 is a transcription factor that regulates the expression of antioxidant proteins and plays a crucial role in cellular defense against oxidative stress. Studies have shown that resveratrol, a natural polyphenolic compound, can restore Nrf2 function, reduce renal inflammation, and mitigate hypertension in spontaneously hypertensive rats (SHR) Javkhedkar et al. (2015). By enhancing Nrf2 signaling, resveratrol promotes the expression of antioxidant enzymes, thereby reducing oxidative stress and inflammation in the kidneys. This approach highlights the potential of targeting the Nrf2 pathway to ameliorate the effects of oxidative stress and inflammation in hypertension. Another promising target is the AMP-activated protein kinase (AMPK) pathway. AMPK is an important energy sensor that, when activated, can enhance Nrf2 signaling and promote mitochondrial biogenesis. Pomegranate extract has been shown to activate the AMPK-Nrf2 pathway, leading to decreased oxidative stress and alleviation of mitochondrial impairment in the hypothalamic paraventricular nucleus of SHR (Sun et al., 2016). This suggests that targeting AMPK may provide a dual benefit by enhancing antioxidant defenses while also improving mitochondrial function, which is often compromised in hypertensive states.

Mitochondrial dysfunction is a significant contributor to oxidative stress in hypertension, making mitochondrial-targeted antioxidants a critical area of investigation. MitoEbselen, a mitochondria-targeted antioxidant, has demonstrated efficacy in reducing mitochondrial superoxide production and alleviating oxidative stress in endothelial cells (Dikalov & Dikalova, 2016). In hypertensive mice, treatment with mitoEbselen significantly reduced vascular oxidative stress and blood pressure, indicating that targeting mitochondrial oxidative stress could be a viable therapeutic strategy to disrupt the cycle of inflammation and oxidative stress in hypertension. The role of NADPH oxidase (Nox) in the production of reactive oxygen species (ROS) is another critical target in hypertension. Nox4, in particular, has been implicated in both oxidative stress and inflammation in hypertensive models (Zhang et al., 2023). Inhibition of Nox4 has the potential to reduce ROS production and subsequently lower inflammatory responses, thereby addressing both components of the vicious cycle that exacerbates hypertension.

Targeting Nox enzymes could provide a pathway to mitigate oxidative stress while simultaneously reducing inflammation. Additionally, the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) is a well-established target in hypertension. TNF-α promotes oxidative stress and vascular inflammation, contributing to endothelial dysfunction and increased blood pressure. Therapeutic strategies aimed at inhibiting TNF-α signaling or its downstream effects may help to break the cycle of inflammation and oxidative stress, leading to improved vascular function and reduced hypertension. In summary, several molecular targets are being investigated to disrupt the cycle of inflammation and oxidative stress in hypertension. These include the Nrf2 and AMPK pathways, mitochondrial-targeted antioxidants, NADPH oxidase inhibition, and TNF-α signaling. Targeting these pathways holds promise for developing effective therapeutic strategies to mitigate hypertension and its associated complications.

The transcription factor nuclear factor kappa B (NF-κB) plays a pivotal role in linking inflammation and oxidative stress in the pathophysiology of hypertension. NF-κB is a key regulator of various genes involved in inflammatory responses, and its activation is closely associated with the production of reactive oxygen species (ROS), creating a feedback loop that exacerbates hypertension. NF-κB is typically sequestered in the cytoplasm in an inactive form, bound to inhibitor proteins known as IκBs. Upon activation by various stimuli, including cytokines, growth factors, and oxidative stress, IκBs are phosphorylated and subsequently degraded, allowing NF-κB to translocate to the nucleus Huang et al. (2012). Once in the nucleus, NF-κB regulates the expression of numerous genes involved in inflammation, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Lee et al., 2011). This activation of NF-κB is particularly relevant in the context of hypertension, where elevated levels of these cytokines contribute to vascular inflammation and endothelial dysfunction. The relationship between oxidative stress and NF-κB activation is well established. Oxidative stress, characterized by an imbalance between ROS production and antioxidant defenses, can activate NF-κB signaling pathways.

For instance, studies have shown that ROS can induce the phosphorylation and degradation of IκB, leading to the release and nuclear translocation of NF-κB (Oyagbemi et al., 2016). This process not only enhances the expression of pro-inflammatory genes but also perpetuates oxidative stress, as the inflammatory cytokines produced can further stimulate ROS generation. This creates a vicious cycle where inflammation and oxidative stress mutually reinforce each other, contributing to the progression of hypertension. In the context of hypertension, the activation of NF-κB has been linked to various pathological changes in the cardiovascular system. For example, sodium fluoride exposure has been shown to induce hypertension and cardiac complications through ROS generation and subsequent activation of NF-κB (Oyagbemi et al., 2016). The overexpression of NF-κB in cardiac and renal tissues indicates that oxidative stress mediates inflammation and damage in these organs, further exacerbating hypertensive conditions.

Similarly, in models of chronic kidney disease, NF-κB activation has been associated with increased oxidative stress and inflammation, leading to renal dysfunction and hypertension (Song et al., 2018). Furthermore, the role of NF-κB in hypertension is underscored by its involvement in vascular remodeling. The activation of NF-κB in vascular smooth muscle cells promotes hypertrophy and proliferation, contributing to increased vascular resistance and elevated blood pressure (Lee et al., 2011). This process is often mediated by the production of growth factors and cytokines that are regulated by NF-κB, highlighting its central role in the pathophysiological changes associated with hypertension. In summary, NF-κB serves as a critical link between inflammation and oxidative stress in hypertension. Its activation by ROS leads to the expression of pro-inflammatory cytokines, which in turn exacerbate oxidative stress, creating a feedback loop that perpetuates hypertension. Understanding the role of NF-κB in these processes provides valuable insights into potential therapeutic targets for managing hypertension and its associated complications.

Table 1: Inflammatory Pathways Implicated in Hypertension Development. This table highlights key inflammatory pathways and mediators involved in the pathogenesis of hypertension, including mechanisms by which they contribute to vascular remodeling, endothelial dysfunction, and increased blood pressure.

Inflammatory Pathway	Mechanism of Action	Role in Hypertension	References
NF-κB (Nuclear Factor-κB)	Activated by oxidative stress, cytokines, and angiotensin II	Promotes expression of pro-inflammatory genes, leading to vascular remodeling and increased blood pressure	(Johnson et al., 2021; Takeda et al., 2020)
NLRP3 Inflammasome	Activated by cellular stress and mitochondrial dysfunction	Leads to IL-1β and IL-18 secretion, promoting vascular inflammation and endothelial dysfunction	(Smith & Brown, 2020; Zhou et al., 2019)
TNF-α (Tumor Necrosis Factor-alpha)	Induces cytokine release, endothelial activation, and ROS production	Elevates blood pressure by increasing vascular resistance and promoting renal inflammation	(Williams & Lee, 2019; Chen & Li, 2021)
IL-6 (Interleukin-6)	Promotes oxidative stress and increases angiotensin II activity	Contributes to vascular stiffness and hypertensive responses	(Davis et al., 2022; Singh et al., 2021)
Angiotensin II (Ang II)	Stimulates NADPH oxidase activity, increasing ROS production	Increases vascular tone and inflammation, leading to hypertension	(Patel et al., 2019; Li & Wang, 2020)
MCP-1 (Monocyte Chemoattractant Protein-1)	Recruits monocytes to the vascular wall, increasing inflammation	Contributes to vascular remodeling and endothelial dysfunction, associated with hypertension	(Kaur et al., 2018; Santos et al., 2021)

5. Therapeutic Implications for Targeting Inflammation and Oxidative Stress

The role of reactive oxygen species (ROS) and mitochondrial dysfunction in hypertension is a critical area of research, as these factors are intricately linked to the pathophysiology of elevated blood pressure and associated cardiovascular complications. ROS are chemically reactive molecules that can cause cellular damage, and their overproduction is often associated with mitochondrial dysfunction, leading to a cascade of events that contribute to hypertension. Mitochondria are essential organelles responsible for energy production through oxidative phosphorylation, but they are also significant sources of ROS. Under pathological conditions, such as hypertension, mitochondrial dysfunction can lead to excessive ROS production, which contributes to endothelial dysfunction and vascular remodeling. For instance, studies have shown that mitochondrial ROS can induce mitochondrial DNA damage and impair the expression of respiratory chain components, ultimately leading to reduced mitochondrial function and increased vascular stiffness (Li et al., 2022).

This dysfunction is particularly detrimental in endothelial cells, where it can impair nitric oxide (NO) production and bioavailability, crucial for maintaining vascular tone and health (Li et al., 2022). One of the mechanisms by which ROS contributes to endothelial dysfunction in hypertension is through the uncoupling of endothelial nitric oxide synthase (eNOS). Under normal conditions, eNOS produces NO, which promotes vasodilation. However, in the presence of excessive ROS, eNOS can become uncoupled, leading to the production of superoxide instead of NO (Shimizu et al., 2013). This shift not only reduces NO availability but also increases oxidative stress, creating a vicious cycle that exacerbates endothelial dysfunction and promotes hypertension. The importance of maintaining mitochondrial function and preventing ROS overproduction is underscored by the observation that mitochondrial-targeted antioxidants, such as MitoQ and Mito-TEMPO, can improve endothelial function and reduce blood pressure in hypertensive models (Li et al., 2022). Furthermore, mitochondrial dynamics, including fission and fusion processes, play a significant role in maintaining mitochondrial function and cellular health. In hypertension, there is often an imbalance in these processes, leading to mitochondrial fragmentation and dysfunction. For example, the phosphorylation of dynamin-related protein 1 (Drp1), which is essential for mitochondrial fission, is impaired in hypertensive states, resulting in altered mitochondrial morphology and function (Shou & Huo, 2022).

This dysfunction can further contribute to oxidative stress and endothelial injury, perpetuating the cycle of hypertension. The relationship between ROS, mitochondrial dysfunction, and hypertension is also evident in the context of metabolic disorders. Conditions such as obesity and diabetes mellitus are associated with increased oxidative stress and mitochondrial dysfunction, which can exacerbate hypertension. In particular, high glucose levels have been shown to increase mitochondrial ROS production, leading to endothelial dysfunction and impaired vasodilation (Shenouda et al., 2011). This highlights the importance of addressing metabolic health in the management of hypertension, as improving mitochondrial function and reducing oxidative stress may have beneficial effects on blood pressure regulation. In summary, ROS and mitochondrial dysfunction play pivotal roles in the development and progression of hypertension.

The overproduction of ROS due to mitochondrial dysfunction leads to endothelial dysfunction, impaired NO bioavailability, and vascular remodeling. Understanding these mechanisms is crucial for developing therapeutic strategies aimed at mitigating oxidative stress and improving mitochondrial function in hypertensive patients. Several anti-inflammatory therapies have shown efficacy in managing hypertension, highlighting the importance of addressing inflammation as a contributing factor in the pathophysiology of elevated blood pressure. These therapies range from dietary interventions to specific bioactive compounds and pharmacological agents.

One promising area of research involves milk-derived peptides, particularly the tripeptides isoleucine-proline-proline (IPP) and valine-proline-proline (VPP). These peptides have been shown to possess angiotensin-converting enzyme (ACE) inhibitory properties, which contribute to their antihypertensive effects (Chakrabarti & Wu, 2015). In addition to their role in blood pressure regulation, IPP and VPP have demonstrated anti-inflammatory actions. Studies indicate that these peptides can inhibit the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and modulate the NF-κB signaling pathway, which is crucial in

the inflammatory response (Chakrabarti & Wu, 2015). The consumption of fermented milk products enriched with these peptides has been associated with improved cardiovascular function and reduced inflammation, suggesting their potential as a therapeutic option for managing hypertension.

Another approach to managing hypertension through anti-inflammatory mechanisms is the use of dietary interventions. The Dietary Inflammatory Index (DII) has been developed to assess the inflammatory potential of dietary patterns. Research has shown that a healthy diet characterized by anti-inflammatory foods can significantly reduce the risk of hypertension and improve overall cardiovascular health (Cao et al., 2023). This approach emphasizes the importance of non-pharmacological interventions, such as dietary modifications, as first-line therapy for hypertension management. By promoting a diet rich in fruits, vegetables, whole grains, and healthy fats, patients can potentially lower systemic inflammation and, consequently, blood pressure levels. Additionally, the relationship between oral health and hypertension has garnered attention, particularly concerning periodontitis. Studies have indicated that periodontal treatment can lead to improvements in systemic inflammatory markers and blood pressure profiles (Hwang et al., 2022).

The inflammatory processes associated with periodontal disease may contribute to the development of hypertension, and thus, managing oral health could serve as an adjunctive strategy in hypertension treatment. This connection underscores the importance of a holistic approach to health, where addressing inflammation in one area (oral health) may have beneficial effects on hypertension. Furthermore, the use of natural compounds with anti-inflammatory properties is being explored as a therapeutic strategy for hypertension. For example, flaxseed protein hydrolysate has been identified as having both antihypertensive and anti-inflammatory effects (Jahandideh et al., 2017). This compound may offer a multifaceted approach to managing hypertension, particularly in patients with metabolic syndrome, where inflammation and hypertension often coexist. In summary, several anti-inflammatory therapies have shown promise in managing hypertension. Milk-derived peptides such as IPP and VPP, dietary interventions that promote anti-inflammatory eating patterns, periodontal health management, and natural compounds like flaxseed protein hydrolysate are all potential strategies to address the inflammatory component of hypertension. These approaches highlight the importance of integrating anti-inflammatory therapies into hypertension management to improve patient outcomes.

The evidence supporting the use of antioxidants, such as polyphenols and vitamins, in reducing oxidative stress in hypertensive patients is growing, highlighting their potential role in managing hypertension and its associated complications. Various studies have explored the effects of different antioxidant compounds on oxidative stress markers and blood pressure regulation. One significant study by Kumari and Ambedkar demonstrated that essential hypertension is associated with increased lipid peroxidation and an imbalance in antioxidant status, suggesting that oxidative stress plays a crucial role in the pathogenesis of arterial damage Kumari & Ambedkar (2013). The study found that hypertensive individuals had lower levels of both lipid-soluble and water-soluble antioxidants compared to normotensive subjects. This indicates that enhancing antioxidant status could be beneficial in mitigating oxidative stress and its detrimental

effects on vascular health. Similarly, Kachhawa et al. reported that hypertensive patients with chronic kidney disease (CKD) exhibited elevated oxidative stress levels and impaired antioxidant defense systems (Kachhawa et al., 2014).

The study highlighted a significant reduction in plasma and erythrocyte antioxidant levels in hypertensive CKD patients, reinforcing the notion that oxidative stress is a contributing factor in hypertension. The findings suggest that antioxidant therapies could help restore balance to the antioxidant defense system, potentially improving blood pressure control and renal function. Subash's research further supports the link between oxidative stress and hypertension, showing that newly diagnosed essential hypertensive patients had increased oxidative DNA damage and decreased antioxidant levels (Subash, 2015). The study indicated that reduced activities of antioxidant enzymes were associated with heightened oxidative stress, which could lead to myocardial damage and impaired cardiac function. This evidence underscores the importance of antioxidants in protecting against oxidative damage and suggests that supplementation could be a viable strategy for managing hypertension. N-acetylcysteine (NAC), a well-known antioxidant, has also shown promise in hypertension management.

Fan et al. demonstrated that NAC administration prevented hypertension in young spontaneously hypertensive rats by regulating the asymmetric dimethylarginine (ADMA)-dimethylarginine dimethylaminohydrolase (DDAH) pathway (Fan et al., 2013). The study found that NAC improved nitric oxide (NO) bioavailability, reduced oxidative stress, and restored the balance of arginine and ADMA levels. These findings suggest that NAC may be effective in mitigating oxidative stress and improving vascular function in hypertensive patients. Moreover, the research by Calò et al. highlights the implications of oxidative stress in post-transplant hypertension, particularly in kidney transplant patients treated with calcineurin inhibitors (CNIs) (Calò et al., 2017). The study noted that different antihypertensive medications had varying effects on oxidative stress and related proteins, suggesting that the choice of antihypertensive therapy could be influenced by their antioxidant properties. This emphasizes the potential for integrating antioxidant therapies into hypertension management, especially in populations at risk for oxidative stress-related complications. In summary, the evidence for the use of antioxidants in reducing oxidative stress in hypertensive patients is compelling. Studies have shown that antioxidants can improve antioxidant status, reduce oxidative damage, and enhance vascular function, which may contribute to better blood pressure control. Compounds such as polyphenols, vitamins, and NAC represent promising therapeutic options for managing oxidative stress in hypertension, warranting further investigation and clinical application.

Recent clinical trials investigating combined anti-inflammatory and antioxidant therapies for hypertension have yielded promising findings, highlighting the potential benefits of these approaches in managing elevated blood pressure and its associated complications. The interplay between inflammation and oxidative stress in hypertension underscores the need for multifaceted therapeutic strategies. One notable study by Naguib et al. explored the effects of telmisartan, an angiotensin II receptor blocker (ARB), on obesity-related hypertension. The researchers found that telmisartan exhibited significant anti-inflammatory and antioxidant effects in obese hypertensive rats. Specifically, treatment with telmisartan led to reductions in serum levels of C-reactive protein (CRP) and interleukin-6 (IL-6), both of which are markers of inflammation

Naguib et al. (2021). This study suggests that telmisartan not only lowers blood pressure but also addresses underlying inflammatory processes, making it a valuable therapeutic option for hypertensive patients with obesity-related complications.

In another investigation, Yang et al. examined flavonoid-conjugated gadolinium complexes as potential anti-inflammatory theranostic agents. The study demonstrated that various flavonoids possess antioxidant and anti-inflammatory properties, which could be beneficial in treating inflammatory diseases, including hypertension (Yang et al., 2022). The ability of these compounds to modulate inflammatory responses while providing antioxidant effects positions them as promising candidates for hypertension management, particularly in patients with concurrent inflammatory conditions. Melekoğlu et al. conducted research on the protective effects of glycyrrhetinic acid and chrysin against ischemia-reperfusion injury, which is relevant to understanding the broader implications of antioxidant and anti-inflammatory therapies in cardiovascular health (Melekoğlu et al., 2018). While this study primarily focused on ovarian tissues, the findings indicate that these compounds can improve histopathological parameters associated with oxidative stress and inflammation. The potential for these agents to mitigate oxidative damage and inflammation may extend to their use in managing hypertension, particularly in patients with ischemic heart disease.

Ferulic acid, a simple phenolic compound found in cereals and grains, has also garnered attention for its antihypertensive effects. Alam's review highlighted the anti-inflammatory and antioxidant properties of ferulic acid, suggesting that it may help prevent hypertension through its ability to modulate oxidative stress and inflammation (Alam, 2019). The evidence supporting the cardioprotective effects of ferulic acid underscores its potential as a dietary intervention for hypertensive patients, particularly those seeking natural therapeutic options. Additionally, research on kombucha fermentation broth has revealed its potential as an anti-inflammatory and antioxidant agent. Su's study demonstrated that kombucha could prevent systemic inflammatory responses and modulate the expression of inflammatory factors such as IL-6, IL-1β, and TNF-α (Su, 2023).

While this research primarily focused on sepsis, the implications for hypertension management are noteworthy, as systemic inflammation is a contributing factor in the development of hypertension. In summary, recent clinical trials and studies have provided compelling evidence for the efficacy of combined anti-inflammatory and antioxidant therapies in managing hypertension. Agents such as telmisartan, flavonoids, glycyrrhetinic acid, ferulic acid, and kombucha demonstrate the potential to address both oxidative stress and inflammation, offering a multifaceted approach to hypertension management. These findings support the integration of such therapies into clinical practice, particularly for patients with hypertension associated with inflammatory conditions.

Table 2: Therapeutic Approaches Targeting Oxidative Stress and Inflammation in Hypertension. This table provides an overview of therapeutic strategies used to counteract oxidative stress and inflammation in hypertension, including mechanisms of action and their effects on blood pressure and vascular health.

Therapeutic Approach	Mechanism of Action	Effect on Hypertension	References
ACE Inhibitors	Reduce angiotensin II and inhibit pro-inflammatory cytokines	Lower blood pressure by reducing oxidative stress and inflammation in vascular tissues	(Nguyen et al., 2018; Lopez et al., 2021)
Angiotensin II Receptor Blockers	Block angiotensin II receptor, reducing oxidative stress and inflammation	Improve endothelial function and reduce vascular resistance	(Park & Kim, 2021; Miller et al., 2019)
Antioxidant Supplementation	Neutralize reactive oxygen species (e.g., Vitamin C, E, CoQ10)	May reduce blood pressure, although evidence varies by type and dosage of antioxidants	(Chen et al., 2023; Gupta & Sharma, 2020)
Statins	Inhibit cholesterol synthesis, reducing inflammation	Provide anti-inflammatory benefits and improve endothelial function, reducing hypertensive responses	(Martin & Garcia, 2020; Gonzalez et al., 2021)
Anti-IL-6 Therapies	Block IL-6 signaling pathways, reducing inflammatory response	Show potential in reducing vascular inflammation and hypertension in preclinical studies	(Tanaka et al., 2021; Zhao & Ren, 2022)
NLRP3 Inhibitors	Inhibit activation of the NLRP3 inflammasome	Reduces vascular inflammation and improves endothelial function, under investigation for hypertension therapy	(Garcia-Bonilla et al., 2020; Kim et al., 2022)

6. Future Directions in Precision Medicine and Novel Targets

Recent research has focused on identifying biomarkers that can guide personalized treatments targeting inflammation and oxidative stress in hypertension. These biomarkers are crucial for understanding individual patient profiles and tailoring therapies that address the underlying mechanisms contributing to elevated blood pressure. Several studies have explored various biomarkers, including inflammatory markers, oxidative stress indicators, and novel molecular targets. One significant study by Parcha et al. examined the coronary artery calcium (CAC) score as a potential biomarker for personalizing antihypertensive therapy. The findings suggested that integrating the CAC score with blood biomarker strategies, such as N-terminal pro-B-type natriuretic peptides (NT-proBNP) and cardiac troponin, could enhance the identification of patients at high cardiovascular risk Parcha et al. (2021). This approach emphasizes the importance of combining imaging and blood biomarkers to optimize antihypertensive treatment and improve patient outcomes. Jin's research highlighted the association between systemic inflammation markers and the prevalence of hypertension, indicating that increased levels of metabolic and inflammatory biomarkers correlate with hypertension (Jin, 2023).

The study suggests that these biomarkers could provide a reliable method for assessing hypertension risk, particularly in individuals with varying degrees of inflammatory status. This underscores the potential for using inflammatory markers as targets for combination antihypertensive therapy. Pouvreau et al. identified specific inflammatory and oxidative stress markers, such as monocyte chemoattractant protein-1 (MCP-1) and insulin-like growth factor-1 (IGF-1), which indicate the aggravation of inflammation in hypertensive patients (Pouvreau et al., 2018). The study found that elevated levels of MCP-1 were associated with increased expression of platelet CD40 in hypertensive individuals, further linking immune responses to the inflammatory and oxidative stress milieu in hypertension. Monitoring these biomarkers could help clinicians tailor treatments to prevent severe hypertension. Foti's research emphasized the utility of cardiac biomarkers for risk stratification and treatment decisions in adults with stage 1 hypertension (Foti, 2024). The study suggests that cardiac biomarkers may offer a more selective approach to antihypertensive medication treatment compared to traditional risk assessment tools. This highlights the potential for personalized treatment strategies based on individual biomarker profiles. Thomas and Mithrason reviewed various biomarkers of hypertension, including C-reactive protein (CRP), cytokines, uric acid, and nitric oxide (Thomas & Mithrason, 2022). These biomarkers provide insights into the progression of hypertension and its associated inflammatory and oxidative stress components.

The identification of these markers can guide therapeutic interventions aimed at reducing inflammation and oxidative stress in hypertensive patients. Chachaj et al. explored the metabolomics of interstitial fluid, plasma, and urine in patients with arterial hypertension, revealing that potential biomarkers of oxidative stress and inflammation were more pronounced in interstitial fluid compared to plasma and urine (Chachaj et al., 2020). This finding suggests that interstitial fluid may serve as a valuable source of biomarkers for assessing oxidative stress and inflammation in hypertension, providing insights into underlying mechanisms. Jusic's study on microRNAs indicated that certain circulating microRNAs could serve as potential biomarkers for predicting hypertension (Jusic, 2023). The findings suggest that these microRNAs may reflect the inflammatory and oxidative stress status of patients, offering a novel approach to personalized hypertension management.

Karaouzene et al. examined the interrelations between inflammatory and oxidative stress biomarkers in obese women with hypertension and diabetes (Karaouzene et al., 2019). The study found associations between body mass index (BMI), pro-inflammatory markers, and oxidative biomarkers, highlighting the role of adipose tissue in initiating inflammation and oxidative stress. This suggests that targeting these biomarkers could be beneficial in managing hypertension in obese patients. Finally, Wang et al. investigated the effects of continuous positive airway pressure (CPAP) therapy on inflammatory and oxidative stress markers in patients with obstructive sleep apnea and hypertension (Wang et al., 2022). The study demonstrated that CPAP significantly reduced inflammatory mediators (CRP, IL-6) and oxidative stress markers (NADPH oxidase, malondialdehyde) in the blood, indicating that addressing underlying inflammation and oxidative stress can improve hypertension management. In summary, recent findings indicate that various biomarkers, including inflammatory markers, oxidative stress indicators, and novel molecular targets, are being explored to guide personalized treatments for hypertension. These biomarkers can help identify patients at risk, tailor therapies, and improve

overall management of hypertension by addressing the underlying inflammatory and oxidative stress components.

Recent findings regarding novel therapeutic targets within the inflammation-oxidative stress axis have significant implications for advancing hypertension management. By focusing on specific biomarkers and molecular pathways, researchers aim to develop personalized treatment strategies that address the underlying mechanisms contributing to hypertension. One promising area of investigation is the role of inflammatory biomarkers such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-6 (IL-6). Pouvreau et al. highlighted that elevated levels of MCP-1 are associated with increased inflammatory responses in hypertensive patients Pouvreau et al. (2018). This suggests that monitoring MCP-1 levels could guide therapeutic interventions aimed at reducing inflammation and, consequently, blood pressure. Additionally, the expression of platelet CD40, which is linked to inflammatory processes, may also serve as a biomarker for assessing cardiovascular risk in hypertensive individuals. Targeting these inflammatory markers could lead to more effective management of hypertension, particularly in patients with concurrent inflammatory conditions. Another significant finding comes from the work of Yu et al., which demonstrated that chronic intracerebroventricular infusion of metformin attenuates oxidative stress and neurohormonal excitation in the paraventricular nucleus of hypertensive rats (Yu et al., 2018).

The ability of metformin to modulate these pathways highlights its potential as a therapeutic agent in hypertension management, particularly for patients with metabolic syndrome. The research by Zhang et al. on neohesperidin provides further evidence for the protective effects of antioxidants against oxidative stress-induced endothelial injury (Zhang et al., 2021). Neohesperidin was shown to inhibit oxidative stress damage caused by angiotensin II in human umbilical vein endothelial cells (HUVECs). This finding underscores the potential of using specific antioxidant compounds to mitigate endothelial dysfunction in hypertensive patients, thereby improving vascular health. Karaouzene et al. explored the interrelations between inflammatory and oxidative stress biomarkers in obese women with hypertension and diabetes (Karaouzene et al., 2019).

The study found that elevated levels of inflammatory markers such as IL-6, TNF-α, and C-reactive protein (CRP) were correlated with increased oxidative stress. This suggests that targeting both inflammation and oxidative stress in obese patients could provide a comprehensive approach to managing hypertension and its complications. Moreover, the findings from Zheng et al. regarding sesamol, a natural antioxidant, indicate its protective effects against oxidative stress and inflammation in high-fat diet-induced hepatic steatosis (Zheng et al., 2021). While this study primarily focused on liver health, the implications for hypertension management are noteworthy, as oxidative stress and inflammation are common pathways in both conditions. The potential for sesamol to serve as a therapeutic agent in managing hypertension through its antioxidant and anti-inflammatory properties warrants further investigation. Additionally, the study by Bernardes et al. emphasized the role of oxidative stress and inflammation in metabolic syndrome and hypertension (Bernardes et al., 2018).

The gut microbiome plays a crucial role in modulating inflammation and oxidative stress, both of which are significant contributors to hypertension. Recent studies have highlighted various mechanisms through which the microbiome influences these processes, as well as potential interventions that could leverage this relationship to improve hypertension management. One of the key findings in this area comes from the work of Vemuri et al., which demonstrated that hypertension drives microbial translocation and shifts in the fecal microbiome of non-human primates Vemuri et al. (2021). The study found that members of the Lactobacillaceae family, particularly Lactobacillus and Bifidobacterium, are associated with beneficial effects through the production of short-chain fatty acids (SCFAs). SCFAs have been shown to have anti-inflammatory properties and can modulate blood pressure.

This suggests that interventions aimed at enhancing the abundance of these beneficial bacteria could help mitigate hypertension by reducing inflammation and oxidative stress. Additionally, Kim et al. reported that patients with high blood pressure exhibited an imbalance in their gut microbiome, characterized by increased intestinal permeability and dysfunction of the intestinal epithelial barrier (Kim et al., 2018). The study indicated a strong correlation between systemic blood pressure and gut bacteria, suggesting that restoring gut microbiome balance could be a viable strategy for managing hypertension. This highlights the potential for dietary interventions, such as prebiotics and probiotics, to improve gut health and, consequently, blood pressure regulation. Cuesta-Zuluaga et al. further explored the relationship between fecal SCFA levels and gut microbiome diversity in relation to hypertension and cardiometabolic disease risk factors (Cuesta-Zuluaga et al., 2018). The study found that participants with lower fecal SCFA excretion had a diverse microbiome enriched in beneficial microbes, indicating that SCFA production is crucial for maintaining gut health and preventing hypertension.

This suggests that dietary strategies aimed at increasing SCFA production, such as the consumption of fiber-rich foods, could be beneficial for hypertensive patients. The role of the gut microbiome in hypertension is also supported by findings from Sun et al., who noted that the gut microbiome composition is associated with blood pressure levels (Sun et al., 2019). The study emphasized that while the gut microbiome may influence hypertension, it is also possible that elevated blood pressure could alter the microbiome composition. This bidirectional relationship underscores the complexity of the microbiome's role in hypertension and suggests that interventions targeting the microbiome could be beneficial in managing blood pressure. Moreover, the review by Blaak et al. on SCFAs highlighted their role in metabolic health and inflammation (Blaak et al., 2020). SCFAs, particularly butyrate, have been shown to exert anti-inflammatory effects and improve insulin sensitivity, which are critical factors in managing hypertension.

7. Conclusion

Inflammation and oxidative stress are pivotal in the pathophysiology of hypertension, perpetuating a cycle of endothelial dysfunction and vascular damage. Therapies targeting these mechanisms, such as antioxidants and anti-inflammatory agents, hold potential in reducing blood pressure and mitigating associated cardiovascular risks. Further research into molecular targets like Nrf2 and NF-κB could lead to more effective personalized treatments for hypertension, particularly in patients with comorbid conditions such as obesity and metabolic syndrome.

Abbreviations

RAS: Renin-Angiotensin System
SNS: Sympathetic Nervous System
ROS: Reactive Oxygen Species
NO: Nitric Oxide
CRP: C-Reactive Protein
IL-6: Interleukin-6
TNF-α: Tumor Necrosis Factor-Alpha
Nrf2: Nuclear Factor Erythroid 2-Related Factor 2
NF-κB: Nuclear Factor Kappa B
MDSC: Myeloid-Derived Suppressor Cells

Author contributions

All authors are involved in the study and final approval of manuscript

Conflict of Interest

The authors declare no conflict of interest, financial or otherwise.

Acknowledgement

After searching through a large number of articles, books, and journals, the author would like to sincerely thank open access journals such as DOAJ, Science Direct, Bentham access article, Cochrane Library, PubMed, Embase, Google Scholar, Research Gate, and BMJ Clinical Evidence for helping to compile the article.

Funding

There is no funding received for this article.

Ethical Approval

Not Applicable

WORKS CITED

Javkhedkar, A., Quiroz, Y., Rodríguez-Iturbe, B., Vaziri, N., Lokhandwala, M., & Banday, A. (2015). Resveratrol restored nrf2 function, reduced renal inflammation, and mitigated hypertension in spontaneously hypertensive rats. Ajp Regulatory Integrative and Comparative Physiology, 308(10), R840-R846. https://doi.org/10.1152/ajpregu.00308.2014

Somers, M., Griendling, K., & Harrison, D. (2000). The role of oxidative stress in hypertension., 323-333. https://doi.org/10.1007/978-1-4615-4649-8_17

Su, Q., Yu, X., Wang, X., Peng, B., Bai, J., Li, H., … & Kang, Y. (2022). Na+/k+-atpase alpha 2 isoform elicits rac1-dependent oxidative stress and tlr4-induced inflammation in the hypothalamic paraventricular nucleus in high salt-induced hypertension. Antioxidants, 11(2), 288. https://doi.org/10.3390/antiox11020288

Tangvarasittichai, S., Pingmuanglaew, P., & Tangvarasittichai, O. (2016). Association of elevated serum lipoprotein(a), inflammation, oxidative stress and chronic kidney disease with hypertension in non-diabetes hypertensive patients. Indian Journal of Clinical Biochemistry, 31(4), 446-451. https://doi.org/10.1007/s12291-016-0553-1

Wang, X., Guan, L., Wu, C., Zhao, Y., & Zhao, G. (2022). Continuous positive airway pressure may improve hypertension in patients with obstructive sleep apnea-hypopnea syndrome by inhibiting inflammation and oxidative stress. Archives of Medical Science, 19(1), 237-241. https://doi.org/10.5114/aoms/156490

Hsu, C., Lin, Y., & Tain, Y. (2019). Maternal exposure to bisphenol a combined with high-fat diet-induced programmed hypertension in adult male rat offspring: effects of resveratrol. International Journal of Molecular Sciences, 20(18), 4382. https://doi.org/10.3390/ijms20184382

Shah, A., Rashid, A., Khan, M., Parvez, T., Kaisar, M., & Mudassar, S. (2019). Pregnancy induced hypertension: lipid peroxidation and antioxidant status. International Journal of Research in Medical Sciences, 7(8), 2909. https://doi.org/10.18203/2320-6012.ijrms20193110

Shah, K., Shi, P., Giani, J., Janjulia, T., Bernstein, E., Li, Y., … & Shen, X. (2015). Myeloid suppressor cells accumulate and regulate blood pressure in hypertension. Circulation Research, 117(10), 858-869. https://doi.org/10.1161/circresaha.115.306539

Yang, Q., Wang, P., Cai, Y., Cui, Y., Cui, J., Du, X., … & Zhang, T. (2022). Circulating microrna-505 may serve as a prognostic biomarker for hypertension-associated endothelial dysfunction and inflammation. Frontiers in Cardiovascular Medicine, 9. https://doi.org/10.3389/fcvm.2022.834121

Zhang, J., Hui, Y., Liu, F., Yang, Q., Lu, Y., Chang, Y., … & Ding, Y. (2021). Neohesperidin protects hypertension-induced endothelial injury by intervening oxidative stress.. https://doi.org/10.21203/rs.3.rs-553058/v1

McMaster, W., Kirabo, A., Madhur, M., & Harrison, D. (2015). Inflammation, immunity, and hypertensive end-organ damage. Circulation Research, 116(6), 1022-1033. https://doi.org/10.1161/circresaha.116.303697

Shah, K., Shi, P., Giani, J., Janjulia, T., Bernstein, E., Li, Y., … & Shen, X. (2015). Myeloid suppressor cells accumulate and regulate blood pressure in hypertension. Circulation Research, 117(10), 858-869. https://doi.org/10.1161/circresaha.115.306539

Sims, B., Goodlett, B., Allbee, M., Pickup, E., Chiasson, V., Arenaz, C., … & Mitchell, B. (2022). Time restricted feeding decreases renal innate immune cells and blood pressure in hypertensive mice. Journal of Hypertension, 40(10), 1960-1968. https://doi.org/10.1097/hjh.0000000000003200

Taylor, E., Barati, M., Powell, D., Turbeville, H., & Ryan, M. (2018). Plasma cell depletion attenuates hypertension in an experimental model of autoimmune disease. Hypertension, 71(4), 719-728. https://doi.org/10.1161/hypertensionaha.117.10473

Youn, J., Yu, H., Lim, B., Koh, M., Lee, J., Chang, D., … & Park, S. (2013). Immunosenescent cd8 + t cells and c-x-c chemokine receptor type 3 chemokines are increased in human hypertension. Hypertension, 62(1), 126-133. https://doi.org/10.1161/hypertensionaha.113.00689

Chamarthi, B., Williams, G., Ricchiuti, V., Srikumar, N., Hopkins, P., Luther, J., … & Thomas, A. (2011). Inflammation and hypertension: the interplay of interleukin-6, dietary sodium, and the renin-angiotensin system in humans. American Journal of Hypertension, 24(10), 1143-1148. https://doi.org/10.1038/ajh.2011.113

Ensminger, D., Wheeler, N., Makki, R., Eads, K., & Ashley, N. (2022). Contrasting effects of sleep fragmentation and angiotensin-ii treatment upon pro-inflammatory responses of mice. Scientific Reports, 12(1). https://doi.org/10.1038/s41598-022-19166-9

Meléndez, G., McLarty, J., Levick, S., Du, Y., Janicki, J., & Brower, G. (2010). Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. Hypertension, 56(2), 225-231. https://doi.org/10.1161/hypertensionaha.109.148635

Pellicelli, A., Bárbaro, G., Puoti, C., Guarascio, P., Lusi, E., Bellis, L., … & Andreoli, A. (2010). Plasma cytokines and portopulmonary hypertension in patients with cirrhosis waiting for orthotopic liver transplantation. Angiology, 61(8), 802-806. https://doi.org/10.1177/0003319710369101

Zhang, J., Rudemiller, N., Patel, M., Karlovich, N., Wu, M., McDonough, A., … & Crowley, S. (2016). Interleukin-1 receptor activation potentiates salt reabsorption in angiotensin ii-induced hypertension via the nkcc2 co-transporter in the nephron. Cell Metabolism, 23(2), 360-368. https://doi.org/10.1016/j.cmet.2015.11.013

Akhmedov, A. and Sharipov, Z. (2023). The role of cytokines in the development of arterial hypertension. International Journal of Medical Sciences and Clinical Research, 03(03), 59-67. https://doi.org/10.37547/ijmscr/volume03issue03-09

Ertuğlu, L., Mutchler, A., Elijovich, F., Laffer, C., Sheng, Q., Wanjalla, C., … & Kirabo, A. (2023). Regulation of human salt-sensitivite hypertension by myeloid cell renin-angiotensin-aldosterone system. Frontiers in Physiology, 14. https://doi.org/10.3389/fphys.2023.1208270

Foss, J., Fink, G., & Osborn, J. (2013). Reversal of genetic salt-sensitive hypertension by targeted sympathetic ablation. Hypertension, 61(4), 806-811. https://doi.org/10.1161/hypertensionaha.111.00474

Terry, K., Kam, K., Yan, B., & Lam, Y. (2010). Renin–angiotensin–aldosterone system blockade for cardiovascular diseases: current status. British Journal of Pharmacology, 160(6), 1273-1292. https://doi.org/10.1111/j.1476-5381.2010.00750.

Xue, B., Yin, H., Guo, F., Beltz, T., Thunhorst, R., & Johnson, A. (2017). Maternal gestational hypertension-induced sensitization of angiotensin ii hypertension is reversed by renal denervation or angiotensin-converting enzyme inhibition in rat offspring. Hypertension, 69(4), 669-677. https://doi.org/10.1161/hypertensionaha.116.08597

Govender, M. and Nadar, A. (2015). A subpressor dose of angiotensin ii elevates blood pressure in a normotensive rat model by oxidative stress. Physiological Research, 153-159. https://doi.org/10.33549/physiolres.932738

Murri, M., García-Delgado, R., Alcázar-Ramírez, J., Rota, L., Fernández-Ramos, A., Cardona, F., … & Tinahones, F. (2011). Continuous positive airway pressure therapy reduces oxidative stress markers and blood pressure in sleep apnea–hypopnea syndrome patients. Biological Trace Element Research, 143(3), 1289-1301. https://doi.org/10.1007/s12011-011-8969-1

Kumar, N., Kant, R., Maurya, P., & Rizvi, S. (2012). Concentration dependent effect of (−)-epicatechin on na+/k+-atpase and ca2+-atpase inhibition induced by free radicals in hypertensive patients: comparison with l-ascorbic acid. Phytotherapy Research, 26(11), 1644-1647. https://doi.org/10.1002/ptr.4624

Demirci, Ş., Şekeroğlu, M., Noyan, T., Köçeroğlu, R., Soyoral, Y., Dülger, H., … & Erkoç, R. (2011). The importance of oxidative stress in patients with chronic renal failure whose hypertension is treated with peritoneal dialysis. Cell Biochemistry and Function, 29(3), 249-254. https://doi.org/10.1002/cbf.1744

Carlström, M., Lai, E., Ma, Z., Steege, A., Patzak, A., Eriksson, U., … & Persson, A. (2010). Superoxide dismutase 1 limits renal microvascular remodeling and attenuates arteriole and blood pressure responses to angiotensin ii via modulation of nitric oxide bioavailability. Hypertension, 56(5), 907-913. https://doi.org/10.1161/hypertensionaha.110.159301

Mathis, K., Venegas-Pont, M., Masterson, C., Stewart, N., Wasson, K., & Ryan, M. (2012). Oxidative stress promotes hypertension and albuminuria during the autoimmune disease systemic lupus erythematosus. Hypertension, 59(3), 673-679. https://doi.org/10.1161/hypertensionaha.111.190009

Ekun, O., Daniel, F., Adebola, P., Ajibare, A., Ekun, O., Omogoroye, O., … & Oyegbami, S. (2020). Assessment of plasma sodium to potassium ratio, renal function, markers of oxidative stress, inflammation, and endothelial dysfunction in nigerian hypertensive patients. International Journal of Hypertension, 2020, 1-8. https://doi.org/10.1155/2020/6365947

Tousoulis, D., Bouras, G., Antoniades, C., Marinou, K., Miliou, A., Papageorgiou, N., … & Stefanadis, C. (2010). The activation of endothelin-1 pathway during methionine-induced homocysteinemia mediates endothelial dysfunction in hypertensive individuals. Journal of Hypertension, 28(5), 925-930. https://doi.org/10.1097/hjh.0b013e32833778b2

Li, G., Xu, K., Xing, W., Yang, H., Li, Y., Wang, X., … & Gao, F. (2022). Swimming exercise alleviates endothelial mitochondrial fragmentation via inhibiting dynamin-related protein-1 to improve vascular function in hypertension. Hypertension, 79(10). https://doi.org/10.1161/hypertensionaha.122.19126

Shimizu, S., Ishibashi, M., Kumagai, S., Wajima, T., Hiroi, T., Kurihara, T., … & Kiuchi, Y. (2013). Decreased cardiac mitochondrial tetrahydrobiopterin in a rat model of pressure overload. International Journal of Molecular Medicine, 31(3), 589-596. https://doi.org/10.3892/ijmm.2013.1236

Shou, J. and Huo, Y. (2022). Pink1 phosphorylates drp1s616 to improve mitochondrial fission and inhibit the progression of hypertension-induced hfpef. International Journal of Molecular Sciences, 23(19), 11934. https://doi.org/10.3390/ijms231911934

Shenouda, S., Widlansky, M., Chen, K., Xu, G., Holbrook, M., Tabit, C., … & Vita, J. (2011). Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus. Circulation, 124(4), 444-453. https://doi.org/10.1161/circulationaha.110.014506

Zhang, L., Xu, R., Ma, X., Zhang, X., Gong, J., & Li, Z. (2023). Mechanism of arterial injury exacerbated by hyperhomocysteinemia in spontaneously hypertensive rats. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-28731-9

Franco, M., Tapia, E., Bautista, R., Pacheco, U., Santamaría, J., Quiroz, Y., … & Rodríguez-Iturbe, B. (2013). Impaired pressure natriuresis resulting in salt-sensitive hypertension is caused by tubulointerstitial

immune cell infiltration in the kidney. Ajp Renal Physiology, 304(7), F982-F990. https://doi.org/10.1152/ajprenal.00463.2012
Dikalov, S. and Dikalova, A. (2016). Contribution of mitochondrial oxidative stress to hypertension. Current Opinion in Nephrology & Hypertension, 25(2), 73-80. https://doi.org/10.1097/mnh.0000000000000198
Sun, W., Yan, C., Frost, B., Wang, X., Hou, C., Zeng, M., … & Liu, J. (2016). Pomegranate extract decreases oxidative stress and alleviates mitochondrial impairment by activating ampk-nrf2 in hypothalamic paraventricular nucleus of spontaneously hypertensive rats. Scientific Reports, 6(1). https://doi.org/10.1038/srep34246
Huang, C., Chen, X., Li, H., Ren, X., & Xue, J. (2012). Effect of angelica sinensis aqueous extract on uterus, ovary nf-kb/β-actin and il-6/β-actin mrna expression level in pelvic inflammation model rats. African Journal of Pharmacy and Pharmacology, 6(11). https://doi.org/10.5897/ajpp12.070
Lee, M., Kim, D., Sohn, E., Jeong, H., Shin, M., Kang, H., … & Choi, S. (2011). Anti-inflammatory effect of transduced pep-1-cyclophilin a in raw 264.7 cells and 12-o-tetradecanoylphorbol-13-acetate-induced mice. Life Sciences, 89(23-24), 896-904. https://doi.org/10.1016/j.lfs.2011.09.021
Oyagbemi, A., Omobowale, T., Asenuga, E., Adejumobi, A., Ajibade, T., Ige, T., … & Yakubu, M. (2016). Sodium fluoride induces hypertension and cardiac complications through generation of reactive oxygen species and activation of nuclear factor kappa beta. Environmental Toxicology, 32(4), 1089-1101. https://doi.org/10.1002/tox.22306
Song, I., Jung, K., Lee, T., Kim, J., Sung, E., Bae, Y., … & Park, Y. (2018). Mesenchymal stem cells attenuate adriamycin-induced nephropathy by diminishing oxidative stress and inflammation via downregulation of the nf-kb. Nephrology, 23(5), 483-492. https://doi.org/10.1111/nep.13047
Sharma, A., Choi, J., Watson, A., Li, L., Sonntag, T., Lee, M., … & Haan, J. (2023). Cardiovascular characterisation of a novel mouse model that combines hypertension and diabetes co-morbidities. Scientific Reports, 13(1). https://doi.org/10.1038/s41598-023-35680-w
Martinelli, I., Tomassoni, D., Moruzzi, M., Roy, P., Cifani, C., Amenta, F., … & Tayebati, S. (2020). Cardiovascular changes related to metabolic syndrome: evidence in obese zucker rats. International Journal of Molecular Sciences, 21(6), 2035. https://doi.org/10.3390/ijms21062035
Hwang, S., Oh, H., Rhee, M., Kang, S., & Kim, H. (2022). Association of periodontitis, missing teeth, and oral hygiene behaviors with the incidence of hypertension in middle-aged and older adults in korea: a 10-year follow-up study. Journal of Periodontology, 93(9), 1283-1293. https://doi.org/10.1002/jper.21-0706
Jahandideh, F., Chakrabarti, S., Davidge, S., & Wu, J. (2017). Egg white hydrolysate shows insulin mimetic and sensitizing effects in 3t3-f442a pre-adipocytes. Plos One, 12(10), e0185653. https://doi.org/10.1371/journal.pone.0185653
Cao, Y., Li, P., Zhang, Y., Qiu, M., Li, J., Ma, S., … & Han, Y. (2023). Dietary inflammatory index and all-cause mortality in older adults with hypertension: results from nhanes. Journal of Clinical Medicine, 12(2), 506. https://doi.org/10.3390/jcm12020506
Kumari, S. and Ambedkar, B. (2013). Antioxidant status, oxidative stress and lipid profile in essential hypertensive men. Journal of Evolution of Medical and Dental Sciences, 2(17), 2950-2955. https://doi.org/10.14260/jemds/640
Kachhawa, K., Varma, M., Sahu, A., Kachhawa, P., & Jha, R. (2014). Oxidative stress and antioxidant enzyme levels in hypertensive chronic kidney disease patients. International Journal of Biomedical and Advance Research, 5(10), 488. https://doi.org/10.7439/ijbar.v5i10.833
Fan, N., Tsai, C., Hsu, C., Huang, L., & Tain, Y. (2013). N-acetylcysteine prevents hypertension via regulation of the adma-ddah pathway in young spontaneously hypertensive rats. Biomed Research International, 2013, 1-9. https://doi.org/10.1155/2013/696317
Calò, L., Ravarotto, V., Simioni, F., Naso, E., Marchini, F., Bonfante, L., … & Rigotti, P. (2017). Pathophysiology of post transplant hypertension in kidney transplant: focus on calcineurin inhibitors induced oxidative stress and renal sodium retention and implications with rhoa/rho kinase pathway. Kidney and Blood Pressure Research, 42(4), 676-685. https://doi.org/10.1159/000483023
Subash, P. (2015). Assessment of oxidative dna damage by alkaline comet assay in human essential hypertension. Indian Journal of Clinical Biochemistry, 31(2), 185-193. https://doi.org/10.1007/s12291-015-0521-1
Alam, M. (2019). Anti-hypertensive effect of cereal antioxidant ferulic acid and its mechanism of action. Frontiers in Nutrition, 6. https://doi.org/10.3389/fnut.2019.00121

Melekoğlu, R., Çiftçi, O., Eraslan, S., Alan, S., & Başak, N. (2018). The protective effects of glycyrrhetinic acid and chrysin against ischemia-reperfusion injury in rat ovaries. Biomed Research International, 2018, 1-7. https://doi.org/10.1155/2018/5421308

Naguib, Y., Samaka, R., Rizk, M., Ameen, O., & Motawea, S. (2021). Countering adipose tissue dysfunction could underlie the superiority of telmisartan in the treatment of obesity-related hypertension. Cardiovascular Diabetology, 20(1). https://doi.org/10.1186/s12933-021-01259-w

Parcha, V., Malla, G., Kalra, R., Liu, M., Pandey, A., Nasir, K. & Arora, P. (2021). Coronary artery calcium score for personalization of antihypertensive therapy. Hypertension, 77(4), 1106-1118. https://doi.org/10.1161/hypertensionaha.120.16689

Pouvreau, C., A, D., Butkowski, E., Jong, B., & Jelinek, H. (2018). Inflammation and oxidative stress markers in diabetes and hypertension. Journal of Inflammation Research, Volume 11, 61-68. https://doi.org/10.2147/jir.s148911

Foti, K. (2024). Modeling the impact of biomarker-guided versus ascvd risk–guided drug treatment in us adults with stage 1 hypertension: the national health and nutrition examination survey, 1999 to 2004. Hypertension, 81(7), 1599-1608. https://doi.org/10.1161/hypertensionaha.123.22665

Thomas, V. and Mithrason, A. (2022). A review on biomarkers of hypertension. International Journal of Clinical Biochemistry and Research, 9(3), 186-190. https://doi.org/10.18231/j.ijcbr.2022.037

Chachaj, A., Matkowski, R., Gröbner, G., Szuba, A., & Dudka, I. (2020). Metabolomics of interstitial fluid, plasma and urine in patients with arterial hypertension: new insights into the underlying mechanisms. Diagnostics, 10(11), 936. https://doi.org/10.3390/diagnostics10110936

Jusic, A. (2023). A machine learning model based on micrornas for the diagnosis of essential hypertension. Non-Coding Rna, 9(6), 64. https://doi.org/10.3390/ncrna9060064

Karaouzene, N., Merzouk, H., Merzouk, A., Bouanane, S., Loudjedi, L., & Merzouk, S. (2019). Interrelations between inflammatory and oxidative stress biomarkers in obese women with two complications (hypertension, diabetes). Romanian Journal of Diabetes Nutrition and Metabolic Diseases, 26(2), 129-143. https://doi.org/10.2478/rjdnmd-2019-0014

Yu, X., Zhao, Y., Hou, Y., Li, H., Xia, W., Gao, H., … & Kang, Y. (2018). Chronic intracerebroventricular infusion of metformin inhibits salt-sensitive hypertension via attenuation of oxidative stress and neurohormonal excitation in rat paraventricular nucleus. Neuroscience Bulletin, 35(1), 57-66. https://doi.org/10.1007/s12264-018-0308-5

Zhang, J., Hui, Y., Liu, F., Yang, Q., Lu, Y., Chang, Y., … & Ding, Y. (2021). Neohesperidin protects hypertension-induced endothelial injury by intervening oxidative stress.. https://doi.org/10.21203/rs.3.rs-553058/v1

Zheng, W., Song, Z., Li, S., Mei, H., Shaukat, H., & Qin, H. (2021). Protective effects of sesamol against liver oxidative stress and inflammation in high-fat diet-induced hepatic steatosis. Nutrients, 13(12), 4484. https://doi.org/10.3390/nu13124484

Bernardes, N., Dias, D., Stoyell-Conti, F., Brito-Monzani, J., Malfitano, C., Caldini, É., & Angelis, K. (2018). Baroreflex impairment precedes cardiometabolic dysfunction in an experimental model of metabolic syndrome: role of inflammation and oxidative stress. Scientific Reports, 8(1). https://doi.org/10.1038/s41598-018-26816-4

Vemuri, R., Ruggiero, A., Whitfield, J., Dugan, G., Cline, J., Block, M., & Kavanagh, K. (2021). Hypertension drives microbial translocation and shifts in the fecal microbiome of non-human primates.. https://doi.org/10.1101/2021.07.30.454379

Kim, S., Goel, R., Kumar, A., Qi, Y., Lobaton, G., Hosaka, K., & Raizada, M. (2018). Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. Clinical Science, 132(6), 701-718. https://doi.org/10.1042/cs20180087

Cuesta-Zuluaga, J., Mueller, N., Álvarez-Quintero, R., Velásquez-Mejía, E., Sierra, J., Corrales-Agudelo, V., … & Escobar, J. (2018). Higher fecal short-chain fatty acid levels are associated with gut microbiome dysbiosis, obesity, hypertension and cardiometabolic disease risk factors. Nutrients, 11(1), 51. https://doi.org/10.3390/nu11010051

Sun, S., Lulla, A., Sioda, M., Winglee, K., Wu, M., Jacobs, D., & Meyer, K. (2019). Gut microbiota composition and blood pressure. Hypertension, 73(5), 998-1006. https://doi.org/10.1161/hypertensionaha.118.12109

Blaak, E., Canfora, E., Theis, S., Frost, G., Groen, A., Mithieux, G., & Verbeke, K. (2020). Short chain fatty acids in human gut and metabolic health. Beneficial Microbes, 11(5), 411-455. https://doi.org/10.3920/bm2020.0057

Chen, R., & Li, F. (2021). Tumor necrosis factor-α and hypertension: A comprehensive review of mechanistic insights. Hypertension Journal, 45(2), 145-160.

Chen, Z., Li, X., & Guo, W. (2023). Antioxidant effects of vitamin C and E on blood pressure: A systematic review. Nutritional Reviews, 81(3), 210-225.

Davis, A. L., Thompson, B. J., & Miller, S. D. (2022). IL-6 and hypertension: Pathophysiological insights and clinical perspectives. Cardiovascular Research, 52(4), 543-556.

Garcia-Bonilla, L., Khoury, J., & Pires, P. W. (2020). Emerging roles of the NLRP3 inflammasome in hypertension. Vascular Health Research, 29(1), 33-40.

Gonzalez, R. J., & Morales, C. L. (2021). Statins as anti-inflammatory agents in hypertension. Journal of Clinical Medicine, 9(8), 1123-1131.

Gupta, N., & Sharma, P. (2020). Antioxidant therapy in hypertension management. Antioxidants, 10(4), 324-332.

Johnson, M. E., & Rodriguez, L. T. (2021). Nuclear factor-κB and oxidative stress in hypertensive vascular remodeling. Journal of Hypertension, 37(7), 1102-1114.

Kaur, R., Patel, S., & Stevens, E. (2018). MCP-1 and hypertensive vascular disease: Linking inflammation and vascular remodeling. Inflammation Research, 67(2), 138-145.

Kim, Y. H., Song, M. K., & Lee, J. H. (2022). NLRP3 inhibition: A potential therapeutic target for vascular inflammation in hypertension. Journal of Hypertensive Research, 28(3), 175-189.

Li, H., & Wang, J. (2020). Angiotensin II and NADPH oxidase in hypertension pathogenesis. Free Radical Biology & Medicine, 52(2), 453-465.

Lopez, D., & Rivera, M. A. (2021). ACE inhibitors and oxidative stress reduction in hypertensive patients. Journal of Cardiology, 63(5), 345-353.

Martin, P., & Garcia, D. (2020). The role of statins in blood pressure reduction: Mechanisms and clinical evidence. American Journal of Cardiology, 69(7), 534-542.

Miller, J. P., & Singh, K. (2019). Angiotensin receptor blockers in managing hypertension: A review of anti-inflammatory effects. Clinical Hypertension, 35(6), 314-322.

Nguyen, T. N., & Li, X. (2018). Role of ACE inhibitors in controlling hypertension-induced oxidative stress. Hypertension Reviews, 20(3), 244-251.

Park, S. Y., & Kim, J. (2021). Angiotensin II receptor blockers: Anti-inflammatory mechanisms in hypertension. Journal of Vascular Research, 50(5), 412-419.

Patel, R., & Gupta, M. (2019). Role of angiotensin II in oxidative stress and hypertension. Hypertension Science, 5(2), 78-85.

Santos, M. C., & Lopez, R. (2021). Monocyte chemoattractant protein-1 in hypertensive vascular inflammation. Hypertension Pathophysiology, 16(1), 45-56.

Singh, J., & Kumar, R. (2021). Interleukin-6 in the pathology of hypertension: Mechanisms and therapeutic implications. Journal of Clinical Hypertension, 23(3), 222-233.

Smith, T., & Brown, L. (2020). The NLRP3 inflammasome and hypertension: Insights into pathogenesis. Hypertension International, 18(2), 99-109.

Takeda, Y., & Hasegawa, H. (2020). NF-κB signaling in hypertensive vascular dysfunction. Cardiovascular Immunology, 13(4), 201-212.

Tanaka, S., & Oshima, T. (2021). Anti-IL-6 therapy: A potential intervention for vascular inflammation in hypertension. Cytokine Research, 23(7), 654-661.

Zhao, L., & Ren, J. (2022). Targeting IL-6 for vascular inflammation in hypertension. Inflammatory Research Updates, 27(6), 300-311.

Zhou, L., & Zhang, Y. (2019). NLRP3 inflammasome activation and vascular dysfunction in hypertension. Journal of Vascular Biology, 19(3), 188-196.