Clinical Kidney Journal, 2023, vol. 16, no. 9, 1403–1419

https://doi.org/10.1093/ckj/sfad059
Advance Access Publication Date: 23 March 2023
CKJ Review

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7083012 by Koç University Suna Kraç Library user on 30 January 2024

CKJ REVIEW

A new immune disease: systemic hypertension

Sidar Copur[1], Ibrahim B. Peltek[1], Ali Mutlu[1], Cem Tanriover[1] and Mehmet Kanbay[2]

[1]Department of Medicine, Koc University School of Medicine, Istanbul, Turkey and [2]Department of Medicine, Section of Nephrology, Koc University School of Medicine, Istanbul, Turkey

Correspondence to: Mehmet Kanbay; E-mail: mkanbay@ku.edu.tr

ABSTRACT

Systemic hypertension is the most common medical comorbidity affecting the adult population globally, with multiple associated outcomes including cerebrovascular diseases, cardiovascular diseases, vascular calcification, chronic kidney disease, metabolic syndrome and mortality. Despite advancements in the therapeutic field approximately one in every five adult patients with hypertension is classified as having treatment-resistant hypertension, indicating the need for studies to provide better understanding of the underlying pathophysiology and the need for more therapeutic targets. Recent pre-clinical studies have demonstrated the role of the innate and adaptive immune system including various cell types and cytokines in the pathophysiology of hypertension. Moreover, pre-clinical studies have indicated the potential beneficial effects of immunosuppressant medications in the control of hypertension. Nevertheless, it is unclear whether such pathophysiological mechanisms and therapeutic alternatives are applicable to human subjects, while this area of research is undoubtedly a rapidly growing field.

LAY SUMMARY

Systemic hypertension is the most common medical comorbidity affecting the adult population globally, with multiple associated outcomes including cerebrovascular diseases, cardiovascular diseases, vascular calcification, chronic kidney disease, metabolic syndrome and mortality. Despite advancements in the therapeutic field approximately one in every five adult patients with hypertension is classified as having treatment-resistant hypertension, indicating the need for studies for better understanding of the underlying pathophysiology and need for more therapeutic targets. Recent pre-clinical studies have demonstrated the role of the innate and adaptive immune system including various cell types and cytokines in the pathophysiology of hypertension. Moreover, pre-clinical studies have indicated the potential beneficial effects of immunosuppressant medications in the control of hypertension. Nevertheless, it is unclear whether such pathophysiological mechanisms and therapeutic alternatives are applicable to human subjects, while this area of research is undoubtedly a rapidly growing field.

Keywords: autoimmune disease, hypertension, immune system, immunosuppression, therapeutics

INTRODUCTION

Hypertension affects more than one-quarterof the global adult population while approximately 3.5 billion adults have non-optimal systolic blood pressure measurements [1, 2]. Almost 54% of strokes and 47% of ischemic heart diseases are direct consequences of hypertension according to the estimates of the World Health Organization. In addition, hypertension has been linked

Received: 5.3.2023; Editorial decision: 21.3.2023

© The Author(s) 2023. Published by Oxford University Press on behalf of the ERA. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

to 9.4 million annual deaths and 212 million loss of health life-years annually, accounting for the 8.5% of the total loss [3, 4]. Despite its considerable disease burden the diagnosis of hypertension is not straightforward, especially with masked hypertension and white-coat hypertension. Ambulatory blood pressure monitoring or home blood pressure monitoring gain crucial importance following the demonstration of statistically significant association between the lack of nighttime blood pressure dipping and/or nighttime hypertension and cardiovascular disease risk by the Japan Ambulatory Blood Pressure Monitoring Prospective clinical trial conducted in 6359 asymptomatic participants with at least one cardiovascular disease risk factor over a follow-up period of 4.5 years [5].

Primary (essential) hypertension, responsible for nearly 95% of the hypertension burden in adults, has a complicated underlying pathophysiology, with many mechanisms still not fully known [6]. Its pathogenesis is complex and related to aberrancies in metabolic parameters, genes and possibly immunity [6, 7]. The two major over-activated and extensively studied physiological systems in the pathophysiology of hypertension are the sympathetic nervous system and the renin–angiotensin–aldosterone system (RAAS), both of which are therapeutic targets via beta-adrenergic blockers, alpha-adrenergic blockers, renin inhibitors, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), aldosterone synthase inhibitors and mineralocorticoid receptor antagonists [8]. In addition to these established pathophysiological mechanisms, recent studies have shown a potential relationship between immune system dysfunction and high blood pressure, therefore suggesting an important role of aberrant immune function and autoimmunity in the etiopathogenesis of hypertension [9]. In this review, our aim is to describe the potential pathophysiological and therapeutic role of immune mechanisms, a novel aspect of hypertension research in arterial hypertension.

GENERAL BACKGROUND

The innate immune system includes various cell types including monocytes/macrophages, neutrophils, dendritic cells, natural killer (NK) cells, basophils and eosinophils, anatomical barriers such as skin, gastrointestinal or genitourinary mucosa, and certain chemicals such as cytokines, complement proteins and chemokines [10]. On the other hand, the adaptive immune system includes T-lymphocytes, B-lymphocytes, plasma cells and various subtypes of cytokines and complement proteins. Antigen-presenting cells including monocytes, macrophages and dendritic cells play crucial role in the link between innate and adaptive immune responses via the recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by their pathogen recognition receptors (PRRs) such as Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) and retinoic acid–inducible gene I–like helicases [11]. NK cells are crucial component of the innate immune response via the recognition and differentiation of self-antigen versus non-self-antigen, which is important in the anti-tumor or anti-viral response which is mediated via NK cell–mediated cytotoxicity [12]. Use of anti-NK antibodies inhibiting the functions of NK cells has shown to be protective against vascular dysfunction on pre-clinical studies [13].

Although the primary mechanism leading to the activation of innate and/or adaptive immune response in hypertension remains unclear, multiple hypothetical insults including reactive oxygen species (ROS), increased sympathetic output, over-activity of spleen and ROS, and changes in the gut microbiota have been proposed [14–16]. Dendritic cells have been proposed as the source of DAMPs in hypertension following the studies demonstrating the formation of ROS such as highly reactive gamma-ketoaldehydes via NADPH oxidase [17]. The recognition of DAMPs or PAMPs via various TLRs lead to the activation of different downstream signaling pathways while major downstream pathways include interferon regulatory factor (IRF)-3, nuclear factor kappa light chain enhancer of activated B cells (NF-κB) or mitogen-activated protein kinase (MAPK) [18].

A study in which peripheral monocytes have been obtained from 43 non-diabetic hypertensive patients and 16 non-diabetic normotensive patients has demonstrated that monocytes from hypertensive patients have higher levels of *TLR-4* mRNA while intensive anti-hypertensive treatment results in statistically significant decline in the levels of *TLR-4* and *TLR-2* messenger RNA (mRNA) [19]. Moreover, mouse models genetically modified to lack the *TLR-4* gene have been shown to demonstrate attenuated blood pressure elevation in response to either angiotensin II or NG-nitro-l-arginine methyl ester (L-NAME; an inhibitor of nitric oxide), infusions [20, 21]. Additionally, antibody-mediated blockage of TLR-4 leads to attenuated blood pressure elevation in DOCA-salt salt (deoxycorticosterone acetate + 0.9% NaCl) rats and spontaneously hypertensive rats but not in angiotensin II–infused rats unless TLR-4 is antagonized at periventricular nuclei [22–24]. Furthermore, recent studies have demonstrated that inhibition of TLR-9 has been linked to decline in angiotensin II–induced hypertension [25, 26]. Other types of TLRs, besides TLR-2/4/9, have rarely been investigated in models of hypertension except for pre-eclampsia and eclampsia [27]. The most commonly investigated NLR in the context of hypertension is NLRP3, whose polymorphism has been linked to both systolic and diastolic hypertension [28]. NLRP3 knockout mouse models have not developed hypertension in response to two kidneys–one clip (2K1C) or DOCA-salt treatment environments [29]. Despite rarely being studied, other subtypes of NLRs have been associated with blood pressure alterations such as NOD1-associated hypotension, and decline in vasoconstriction in response to contractile stimuli and NOD2-associated hypertension [30, 31]. The major importance of such studies is the identification of multiple TLRs and NLRs as potential therapeutic targets for clinical arterial hypertension. Furthermore, the gut microbiota is known to regulate the host's immunity, cell proliferation and metabolism, and to play a role in different cardiovascular and kidney diseases [15, 16, 32, 33]. The gut microbiota was shown to modulate blood pressure via short-chain fatty acids [34]. A study conducted in total of 196 participants, including 41 healthy controls, 56 individuals with pre-hypertension and 99 individuals with primary hypertension, showed that fecal transplantation from hypertensive patients to germ-free mice increased blood pressure [35]. Thus, gut microbiota dysbiosis can increase blood pressure, and future studies are needed to better understand this association.

INNATE IMMUNE SYSTEM IN HYPERTENSION

The innate immune system is a diverse network of mucosal barriers, various cell types, and chemicals including chemokines, cytokines and complement proteins. The role of the innate immune system in the pathophysiology of hypertension is a relatively new area of research, with the identification of promising therapeutic targets. Neutrophils are the most abundant white blood cell type in the circulation while macrophages are the most common type of immune cell in various tissue. A study

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

conducted in a mouse model demonstrated that monocytes and neutrophils are involved in the pathogenesis of angiotensin II–induced hypertension and endothelial dysfunction [36]. Selective ablation of lysozyme M–positive myelomonocytic cells via low-dose diphtheria toxin resulting in low circulating levels and low tissue infiltration attenuated angiotensin II–induced blood pressure elevation, formation of ROS and vascular smooth muscle cell dysfunction [36]. Another mouse model with functionally deficient osteopetrotic mice illustrates lower blood pressure measurements in response to angiotensin II infusion [37]. Moreover, hyperosmotic environment in response to either high salt intake or hyperglycemia leads to increased infiltration of renal interstitium via macrophages, conversion to pro-inflammatory phenotype and tissue damage due to the secretion of pro-inflammatory cytokines [38, 39]. Elevated levels of circulating monocytes have been demonstrated on multiple pre-clinical studies on angiotensin II or aldosterone-induced hypertension models [40–44]. A similar pattern has been observed in spontaneously hypertensive rats or models of salt-sensitive or deoxycorticosterone acetate–induced hypertension [45–50].

Only a few studies have been conducted in human subjects. According to a study in which peripheral monocytes were isolated from 22 hypertensive and 24 normotensive participants, monocytes from hypertensive individuals were shown to secrete higher levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) in response to either stimulation by angiotensin II which may be attenuated via incubation with losartan and lipopolysaccharides [51]. Another study conducted in 76 hypertensive and 146 normotensive male participants illustrated similar outcomes, while additionally monocytes derived from hypertensive individuals were found to be less susceptible to glucocorticoids [52]. A prospective clinical trial conducted in 42 patients with treatment-resistant hypertension demonstrated that renal denervation therapy leads to statistically significant decline in blood pressure during a 6-month follow-up period, along with a decline in monocyte activation and levels of pro-inflammatory cytokines such as TNF-α, IL-12, IL-1β and plasma monocyte chemoattractant protein-1 (MCP-1) levels [53].

An observational study conducted in over 9383 initially normotensive participants with normal white blood cell count over a 40-year follow-up period demonstrated that elevated neutrophil count is associated with hypertension risk after adjustment for multiple confounding factors [54]. Even though the elevated number of neutrophils and functional indicators such as myeloperoxidase activity have been recorded in animal models of hypertension, the causal link is missing since adoptive transfer of neutrophils fails to improve blood pressure measurements [36, 55, 56]. Moreover, depletion of CD11c-positive dendritic cells via diphtheria toxin results in the prevention of hypertension in response to either high-salt diet or angiotensin II infusion [57]. Another key aspect of dendritic cells in the pathogenesis of hypertension is the salt-sensing serum/glucocorticoid kinase1 (SGK1), while mouse models lacking SGK1 illustrate lower levels of dendritic cell activation or blood pressure elevation in response to a high-salt diet [55, 58]. The role of NK cells in hypertension is not well understood, with only a few pre-clinical studies investigating the association [59, 60].

Nevertheless, the data regarding the role of eosinophils and basophils in the pathogenesis of hypertension is limited. Even though observational studies have indicated a potential link between elevated peripheral eosinophil count and coronary artery disease or pulmonary artery hypertension, the exact relationship is yet to be demonstrated [61, 62]. Mouse models lacking eosinophils demonstrate higher mean arterial blood pressure and glucose intolerance, while such modifications are reversible with the reconstitution of eosinophils indicating the crucial role of eosinophils in the regulation of normal blood pressure [63, 64]. To the best of our knowledge, no pre-clinical or clinical study has yet evaluated the role of basophils in the pathogenesis of hypertension.

ADAPTIVE IMMUNE SYSTEM IN HYPERTENSION

The adaptive immune system is a complex network of multiple cell types and chemicals including cytokines and complement proteins with varying degree of relationship with the innate immune system. The pathophysiological role of the adaptive immune system in hypertension is a developing area of research. The role of T-lymphocytes in the pathogenesis of hypertension has been illustrated by mouse models of double-hit *rag1* mutation leading to lack of both T- and B-lymphocytes in which infiltration of perivascular tissue by T-cells, expression of intercellular adhesion molecule (ICAM)-1, secretion of pro-inflammatory cytokines such as TNF-α and endothelial cell–dependent vasodilation are all suppressed in response to angiotensin II [65]. Moreover, adoptive transfer of T-cells leads to restoration of all of the mentioned functions while adoptive transfer of B-cells does not lead to any improvement [65]. Moreover, mutation of the exon 1 of *rag1* gene in Dahl salt-sensitive rats led to decline in blood pressure elevations in response to a high-salt diet while pathological specimens demonstrate decline in renal infiltration by T-lymphocytes [66]. Another mouse model with *scid* mutation illustrates blunted hypertensive response to angiotensin II stimuli along with reduced cardiac and/or renal remodeling in response to such stimuli [67]. Nevertheless, multiple types of T-lymphocytes with distinct physiological functions are present in both animals and humans.

Even though one might expect the $CD4^+$ T-helper cell type to play a central role in the pathophysiology of T-cell-mediated hypertension, data from animal models suggest otherwise. Adoptive transfer of $CD4^+$ T-cells to the rag1 double-hit mouse model did not result in the restoration of angiotensin II–induced hypertension, while adoptive transfer of $CD8^+$ T-cells resulted in full restoration [65]. A similar finding has also been established in another mouse model study [68]. Another crucial T-cell type in the pathogenesis of arterial hypertension is the T-regulatory cells. Adoptive transfer of T-cells from the *Scurfy* mouse model lacking T-regulatory cells due to mutation at the *Foxp3* gene to the double-hit *rag1* mouse model results in exaggerated hypertensive response to stimuli of angiotensin II, implicating the potential protective role of T-regulatory cells against hypertension [69]. Administration of T-regulatory cells as a single dose or once weekly dose leads to improvement in cardiac hypertrophy, endothelial vasodilatation, formation of ROS and pro-inflammatory signals without any improvement in blood pressure measurements while administration of T-regulatory cells at sustained high doses leads to improvements at blood pressure [70–72]. Furthermore, oxidative stress can modify self-antigens and cause them to behave as novel antigens referred to as neo-antigens. Neo-antigens activate T-cells and sensitize them against specific antigens which results in infiltration and inflammation in the vasculature and kidney. Furthermore, elevated blood pressure can possibly generate neo-antigens by barotrauma [73]. The role of B-lymphocytes has largely been uninvestigated in hypertension research while early studies

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

indicated a potential role in the pathogenesis and identified them as a potential therapeutic target via administration of anti-CD20 antibodies [74]. However, there is clear need for future studies investigating the role of B-lymphocytes in the pathogenesis of hypertension.

CYTOKINES IN HYPERTENSION

A number of different cytokines are reported to be a factor in the pathophysiology of hypertension.

Interleukin-1

IL-1β levels have been suggested to be elevated in patients with essential hypertension [75, 76]. IL-1 has been shown to contribute to the inflammatory and remodeling processes in the vasculature as well as to affect the functionality and phenotype of the vascular smooth muscle cell in hypertension [77]. The two IL-1 isoforms were reported to be highly expressed in the renal tissues in cases of hypertension caused by the increased activity of RAAS in murine models [43, 78]. IL-1 has also been reported to promote diuresis and natriuresis through prostaglandin generation in the kidney tissues [79–84]. The prevention of the maturation of myeloid cells in the kidney to $Ly6C^{+}$ $Ly6G^{-}$ macrophages responsible for producing nitric oxide, a suppressor of Na-K-Cl cotransporter 2 (NKCC2), occurred following the activation of IL-1 receptor [78]. A deficient or blocked IL-1 receptor was shown to restrict the rise in blood pressure by lessening the amount of reabsorbed sodium through the NKCC2 co-transporter in mice [78]. Additional studies in mouse models reported that inhibiting IL-1 lowered angiotensin II–related hypertension as well as kidney damage, showing a potential role of this blockade in the treatment of hypertension [85].

The role of IL-1 has also been investigated in humans. In a meta-analysis of cohort studies assessing the relationship between inflammatory markers and the development of hypertension, elevated C-reactive protein (CRP), interleukin-6 (IL-6) and high-sensitive CRP (hs-CRP) were significantly related with a risk of the development of hypertension [86]. However, IL-1β was not associated with a significant risk [86]. Furthermore, two clinical trials have evaluated the effects of IL-1 blockade on blood pressure. In a secondary analysis of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), IL-1β, inhibited by canakinumab, decreased cardiac and vascular events; however, this was not linked to alterations in incident hypertension and blood pressure [87, 88]. In a separate trial, anakinra, an IL-1 receptor antagonist, resulted in the fall of blood pressure and peripheral vascular resistance in subjects with obesity and led to a rise in angiotensin-(1–7) levels, a molecule responsible for vasodilation [89].

Interleukin-6

IL-6 has also been thought to contribute to the pathophysiology of hypertension, with a number of studies reporting a correlation with IL-6 levels in the plasma and elevated blood pressure [90–93]. One study assessed the role of IL-6 when exposed prenatally on the development of hypertension; the authors suggested that IL-6 introduction before birth could result in hypertension via alterations in RAAS as well as fluid and electrolyte balance, particularly in female rats [94]. Furthermore, the vasculature is responsible for the release of IL-6 following angiotensin II exposure [95–99]. The prevention and attenuation of angiotensin II hypertension, to which IL-6 is thought be a contributor, has been shown to be possible by blocking IL-6 in wild-type mice or by IL-6 knockout mouse models [90, 95, 100, 101]. Similarly, IL-6 when inhibited by IL-6 neutralizing antibody was reported to mitigate hypertension and related injury to the kidneys in Dahl salt-sensitive rats [46].

The involvement of IL-6 in high blood pressure has also been studied in humans. One study suggested that IL-6 and TNF-α were potentially risk factors for an elevated blood pressure in healthy individuals [102]. Furthermore, a hypomethylated *IL-6* gene was associated with an elevated risk of hypertension and the variations in methylated promoter regions were related to alcohol consumption, gender and being a smoker [103]. As previously mentioned, a meta-analysis showed a significant relationship between high IL-6 levels and hypertension development [86]. The use of anti-hypertensive drugs has also affected IL-6 levels. One study reported a fall in IL-6 and TNF-α levels after anti-hypertensive medications in elderly females [104]. In a separate study, spironolactone led to a decrease in IL-6 and interferon-γ (IFN-γ) levels in subjects with diabetes and treatment-resistant hypertension [105]. These findings suggest a link between IL-6 and hypertension; future studies are needed to better understand this association.

Interleukin-8

A few studies have explored the role of interleukin-8 (IL-8) in hypertension. One study showed a higher calcium-dependent potassium efflux in hypertensive individuals, and IL-8 as well as ICAM-1 heightened this efflux in erythrocytes of individuals with hypertension in a significant manner [106]. In a different study, elevated degrees of IL-8 and MCP-1 were shown in the vitreous of subjects with retinopathy due to diabetes and hypertension [107]. Further studies are required to investigate the association between elevated blood pressure findings and IL-8.

Transforming growth factor-β

Transforming growth factor-β (TGF-β) plays an important role in the homeostasis of the body, cellular growth, tolerance against self-tissues and differentiation [108–110]. An overexpression of the mRNA and protein of TGF-β1, the principle TGF-β isoform responsible for immune function and having mainly inhibitory roles, is observed in individuals with primary hypertension [110–115]. TGF-β1 generation may be explained by elevated blood pressure values in itself but also by a higher shear stress of fluids as well as by increased angiotensin II levels [115]. Polymorphisms on Arg^{25} in the gene of this cytokine have shown an association with hypertension [115].

TGF-β has also been suggested to contribute to the development of fibrotic interstitium and tubules as well as glomerulosclerosis in the kidneys with angiotensin II inducing TGF-β production in renal tissues [116]. This interaction has been found to be important in several conditions such as cyclosporin nephrotoxicity, diabetic kidney disease, obstruction of a single ureter and different hypertension models, contributing to these diseases becoming progressive [116]. Furthermore, a higher level of TGF-β1 is seen in the bloodstream of individuals who have concurrently a hypertrophied left ventricle, hypertension and microalbuminuria [115]. A decrease in TGF-β1 levels was observed in these subjects after they received ARB and ACEi [115]. In a separate study, TGF-β1 was increased in the serum and was related to albumin in the urine in patients with primary hypertension [117]. The administration of valsartan and/or benazepril resulted in a mitigation of TGF-β1 in the bloodstream and

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

microalbuminuria, with the best effect achieved after the combination of both drugs [117]. Moreover, a different study showed that in diabetic and hypertensive individuals with an increased albumin excretion, losartan decreased TGF-β release in the urine [118]. In a double-blind, randomized clinical trial, losartan was shown to lower blood pressure and proteinuria together with a fall in TGF-β release in the urine among non-diabetic kidney disease patients exhibiting proteinuria [119].

These studies show that TGF-β is an important cytokine in hypertensive patients and could possibly function as a surrogate of kidney injury in hypertensive patients. Moreover, ACEi and ARB can benefit in decreasing TGF-β levels in the serum and urine. Further studies are needed to understand the role and utility of targeting TGF-β in hypertensive patients as well as investigate the association between the duration of TGF-β elevation and the development of hypertension.

Tumor necrosis factor-α

A variety of different cells are responsible for the generation of TNF-α such as dendritic cells, macrophages, lymphocytes and neutrophils [79]. TNF-α has been suggested as a mediator of end-organ damage according to hypertensive disease models [79]. Interestingly, TNF-α can lead to both rises and falls in blood pressure, with considerably TNF-α resulting in a reduction while modestly elevated levels increase blood pressure and NaCl preservation in the body [120]. The injuring results of TNF-α could potentially be caused by lymphocyte-based effects during angiotensin II–induced hypertension, meanwhile a lack of renal damage, even with increased levels of TNF-α, can potentially be explained by a rise in sodium release in the setting of RAAS activity [79].

Antagonizing TNF-α was associated with a mitigation of hypertension in the majority of disease models; however, conflicting results have also been reported. In one study, etanercept, an inhibitory agent of TNF-α, was shown to mitigate hypertension as well as the generation of the epithelial sodium channel a–subunit in a chronic kidney disease model in mice lacking angiotensin II type 1 receptor–associated protein (ATRAP), a molecule involved in internalizing the angiotensin II receptor type 1 and controlling the signaling surrounding this receptor [121]. Another study reported that the prevention of angiotensin II–related hypertension was possible following the application of etanercept [65]. Meanwhile, a separate study reported no effect of etanercept on hypertension but a decrease in kidney injury in DOCA-salt hypertensive rats [122].

The role of TNF-α on blood pressure has also been studied in humans. An elevated blood pressure was suggested to increase oxidative stress as well as to lead to a significant rise in TNF-α and malondialdehyde in a study on 60 individuals [123]. Similarly, TNF levels in the bloodstream and urine were reported to be significantly elevated in patients with hypertension compared with healthy controls in a different study [124]. In addition, TNF-α and IL-6 were considered to be potential risk factors for an elevated blood pressure in individuals who were apparently healthy, and increased levels of these two cytokines were suggested to be predictors of a dysfunctional endothelium in the coronary arteries in subjects with hypertension [102, 125]. Conflicting results regarding the impact of the inhibition of TNF-α on blood pressure was also seen in research conducted in human subjects. One study assessing the effect of infliximab, a drug inhibiting TNF-α, on blood pressure in 16 rheumatoid arthritis patients showed that infliximab decreased the 24-h systolic blood pressure, morning blood pressure and daytime blood pressure in a significant manner [126]. However, in a meta-analysis evaluating the impact of administering TNF-α inhibitors on hypertension in patients with rheumatoid arthritis consisting of 6321 rheumatoid arthritis patients derived from 11 trials, the results were significant regarding the effect of TNF-α inhibitors elevating the risk of hypertension development [127]. As seen from these studies, future research is warranted to better understand the role of TNF-α and its inhibition on blood pressure values. More detailed reviews regarding the role of TNF-α have recently been conducted by Crorkin *et al*. and Lamb *et al*. [79, 128].

THE EFFECT OF SODIUM ON THE IMMUNE SYSTEM

A high dietary sodium intake has been linked to hypertension in numerous studies [129]. Although several mechanisms have been proposed, the pathophysiology of sodium-induced hypertension is not fully understood. Growing evidence suggests that high sodium not only causes hemodynamic alterations but also modulates the immune system [130]. The salt-driven proinflammatory response causes immune cell activation, vascular endothelial dysfunction and cytokine secretion, typical of hypertension [131].

Several animal studies have demonstrated overexpression of leukocyte adhesion molecules, including ICAM-1, MCP-1, vascular cell adhesion protein 1 (VCAM-1) and macrophage adhesion ligand-1 [132, 133]. Overexpression of these leukocyte adhesion molecules is associated with local inflammation, which drives endothelial dysfunction [134]. Moreover, leukocyte adhesion molecule expression increased before hypertension developed [132]. Increased leukocyte infiltration may not be solely due to increased expression of these leukocyte adhesion markers. High perfusion pressure itself also promotes T-cell infiltration in the kidney [135].

A high-salt diet increases IL-6, one of the most prominent cytokines related to elevated blood pressure. A high-salt diet increased IL-6 in the kidney of Dahl salt-sensitive rats [136]. In angiotensin II–induced hypertension and deoxycorticosterone acetate-salt hypertension models, high sodium intake increases IL-17 expression via an SGK1-dependent pathway [137]. Increased IL-17 expression enhances sodium reabsorption by renal sodium transporters [138]. Increased sodium concentration elevates IL-2 expression, thus enhancing T-cell proliferation [139].

High sodium concentration also has direct effects on immune cells, promoting inflammation [130]. Increased sodium concentration impairs T-regulatory cell function with increased IFN-γ secretion [140]. Sodium also modulates macrophages. High sodium levels were found to stimulate proinflammatory M1 macrophages while suppressing anti-inflammatory M2 macrophages in a study with lipopolysaccharide-induced lung injury [141]. Increased intracellular sodium concentration in dendritic cells was found to secrete more IL-1β and stimulate T-cells to secrete IFN-γ and IL-17A [142]. Thus, these suggest a role of sodium on the immune system, and further studies are needed to understand how dietary salt intake and immune response link to hypertension and cardiovascular illnesses.

RENAL INFLAMMATION IN HYPERTENSION

Pressure natriuresis, a concept referring to increased renal salt excretion in response to elevation in blood pressure leading to the homeostasis of blood pressure, is commonly impaired in hypertensive subjects [143]. Moreover, kidney tissue is

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

involved in the regulation of blood pressure homeostasis via multiple mechanisms including the secretion of renin and control of RAAS, alterations at renal ultrafiltration, and secretion of pro-inflammatory and anti-inflammatory cytokines. In spontaneously hypertensive rats models, renal infiltration via immune system cells occurs prior to the development of clinical hypertension while impairment of such homeostasis mechanisms plays crucial role [144]. Moreover, the degree of infiltration by immune cells is highly correlated with the degree of systolic blood pressure measurements, indicating the clinical importance of such infiltration and potentially highlighting the importance of reversal of such infiltration in the treatment of hypertension [145]. Furthermore, the central role of IL-17 secreted from T-helper cells has been proposed following the preclinical study in double-hit IL-17 mouse models lacking vascular dysfunction or hypertension following angiotensin II infusion [138]. IL-17 leads to upregulation of glucocorticoid regulated kinase-1 at renal proximal tubules which causes upregulation of renal sodium–hydrogen exchanger-3 [138].

Additionally, renal inflammatory response has led to disruption of pressure natriuresis in response to deterioration of dopamine D1 receptor functions, loss of peritubular capillaries and increased concentration of intrarenal angiotensin II [146–149]. Furthermore, impaired production of renal angiotensin-converting enzyme leading to variable intrarenal angiotensin II concentration which is required for the control of glomerular filtration rate, and tubular sodium transport is another mechanism linking renal inflammation to hypertension via the impairment of the pressure-natriuresis model [150, 151]. Studies on animal models clearly demonstrate the central role of renal inflammation in the pathogenesis of hypertension while it is unclear whether renal inflammation is the triggering event leading to clinical hypertension or just a contributing factor to the development of hypertension.

VASCULAR INFLAMMATION IN HYPERTENSION

Multiple mediators including angiotensin II, aldosterone, shear stress and various cytokines contribute to the development of vascular inflammation via secretion of VCAM-1, ICAM-1 and MCP-1, while the end result includes over-production of ROS via myeloperoxidase enzyme of infiltrating neutrophils and/or NADH/NADPH oxidase enzyme of infiltrating monocytes/macrophages [152]. Such a response leads to upregulation of matrix metalloproteinases, secretion of pro-inflammatory and pro-fibrotic cytokines such as TGF-β, and further infiltration of vascular wall via immune system cells, thereby creating a vicious cycle [152]. The importance of monocyte/macrophages is demonstrated via a preclinical study conducted in a transgenic mouse model with monocyte/macrophage depletion which showed a decline in the formation of superoxide radical, attenuation of angiotensin II–induced hypertension and vascular dysfunction [36]. Such a condition is reversible via adoptive transfer of monocyte/macrophages, while it is not by the adoptive transfer of NADPH oxidase mutant monocytes [36]. Another major pathophysiological role of macrophages in vascular inflammation includes secretion of pro-fibrotic cytokines such as TGF-β and extracellular matrix remodeling via matrix metalloproteinases leading to vascular stiffness [74]. On the other hand, T-regulatory cells appear to have a protective role against vascular inflammation, as evident from double-hit IL-10 mouse models demonstrating higher mean arterial blood pressure measurement that is reversible via adoptive transfer of T-regulatory cells [153]. T-regulatory cells appear to inhibit monocyte/macrophage infiltration of vascular wall, as well as the inhibition of reactive oxygen species formation in response to angiotensin II or aldosterone stimuli [153]. The role of the immune system in the pathogenesis of hypertension is shown in Fig. 1.

THE PREVALENCE AND RISK FACTORS OF HYPERTENSION IN AUTOIMMUNE DISEASES

Cardiovascular diseases have a high prevalence and are the main causes of death in individuals with autoimmune diseases, while hypertension is an important risk factor for the development of cardiac and vascular diseases and is also highly common in this patient population [154–157]. One study consisting of 28 208 rheumatoid arthritis patients reported hypertension to have an elevated prevalence of 31% in the patient group in comparison with the public at 23% [157, 158]. In a separate observational cross-sectional study with 622 patients among which 39.2% had rheumatoid arthritis, 14.5% had osteoarthritis, 10.8% had seronegative spondyloarthropathies, 10.5% had systemic lupus erythematosus and 8.1% had psoriatic arthritis, 54.5% and 72.4% of the study group had hypertension according to the 2018 ESC/ESH and 2017 ACC/AHA guidelines, respectively [159]. Hypertension prevalence was 84.8% and 69.6% in patients with osteoarthritis, 80% and 57.8% in the psoriatic arthritis group, 75.2% and 60.9% in individuals with rheumatoid arthritis, and 63.5% and 35.7% in subjects with lupus according to the ACC/AHA and ESC/ESH guidelines, respectively [159]. Furthermore, other studies have reported a high prevalence of hypertension in individuals with scleroderma particularly those having kidney disease, and in subjects with lupus [157, 160–163].

A recent systematic review evaluated the risk factors of hypertension in individuals with rheumatoid arthritis from 14 studies and showed that regular exercise and methotrexate were protective against, whereas leflunomide, cyclooxygenase-2 inhibitors, prednisone were associated with heightened risk of, high blood pressure [164]. Disease-modifying anti-rheumatic drug use showed conflicting results [164]. In case of systemic lupus erythematosus, body mass index and smoking have been related to an elevated risk of hypertension development and worse outcomes; in addition genetic, environmental, metabolic and sex-specific factors have all contributed to a risk of high blood pressure in patients with lupus [156, 157, 165–167].

These findings suggest a high prevalence of hypertension in autoimmune conditions as well as different factors elevating the risk of having a high blood pressure. Clinicians should be aware of these conditions and manage patients accordingly.

ROLE OF IMMUNOSUPPRESSIVE AGENTS AS ANTI-HYPERTENSIVE MEDICATION

The role of various immunosuppressive agents in the treatment of hypertension has been investigated across multiple animal models (Table 1). According to a study conducted in spontaneously hypertensive rats chronic immunosuppression with cyclophosphamide results in statistically significant decline in systolic blood pressure to a mean of 158 mmHg compared with a mean of 174 mmHg in the control group, with effects recognizable after 2 weeks of therapy [168]. Another study investigating the effects of cyclophosphamide therapy on blood pressure conducted in genetically hypertensive rats of Lyon strain illustrated a statistically significant decline in blood

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

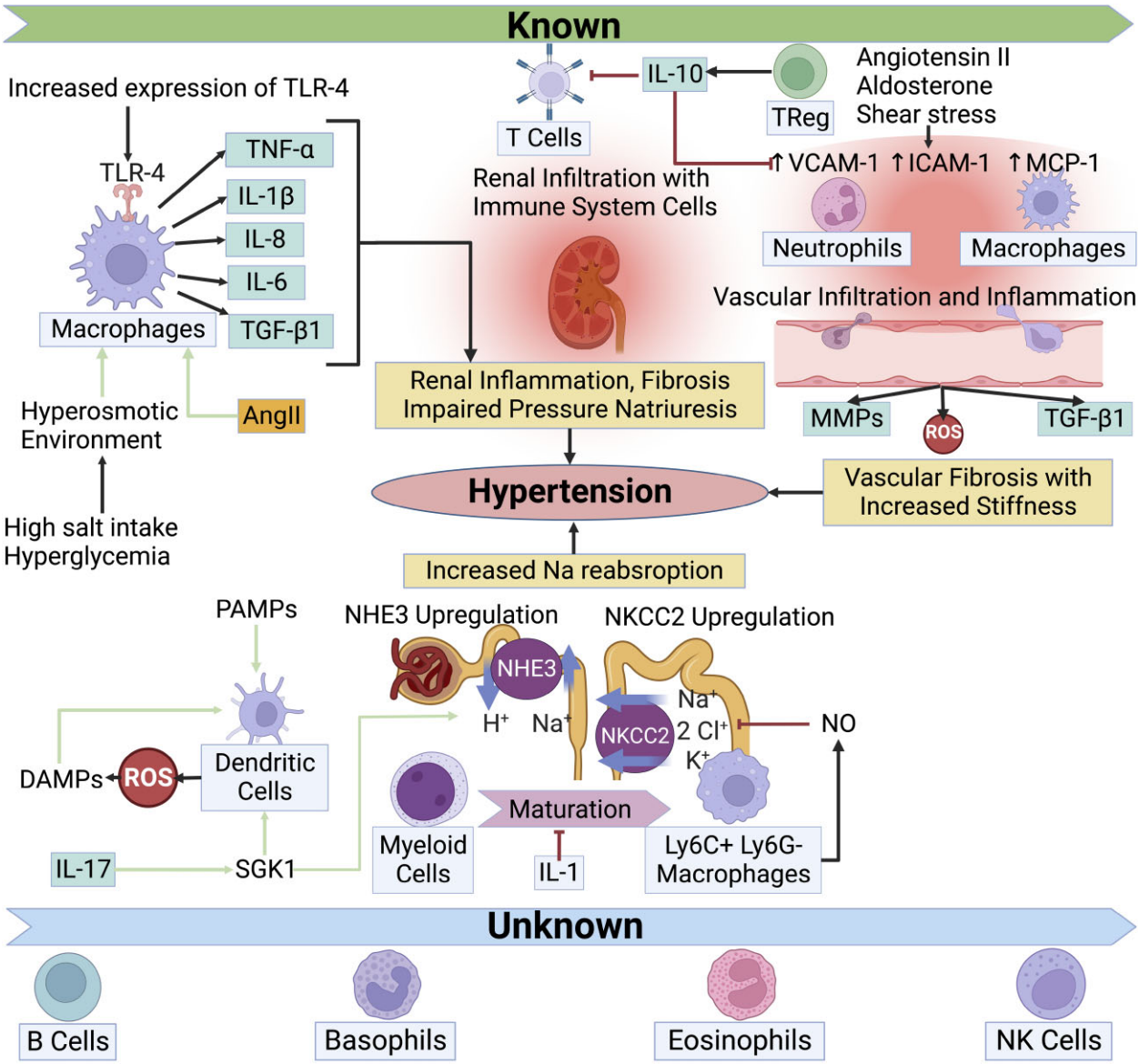


Figure 1: The role of the immune system in the pathogenesis of hypertension. AngII: Angiotensin 2; MMPs: matrix metalloproteinases; NHE3: sodium/hydrogen exchanger isoform 3; NO: nitric oxide; TReg: T regulatory cells.

pressure to a mean of 135 mmHg compared with a mean of 175 mmHg in the control group, while no significant difference was recorded in genetically normotensive subjects [169]. In a separate study on spontaneously hypertensive rats, treatment with mycophenolate mofetil resulted in a decline in blood pressure measurements correlated with the decline in renal infiltration by macrophages and lymphocytes, and renal and urinary markers of oxidative stress such as malondialdehyde in a statistically significant manner [145]. Comparable effects of mycophenolate mofetil treatment on blood pressure have been recorded in a study conducted in Dahl salt-sensitive rats [170]. Similarly, decline in renal tissue pro-inflammatory cells and markers of oxidative stress have been recorded via administration of pyrrolidine dithiocarbamate, which is an inhibitor of the pro-inflammatory NF-κB signaling pathway, leading to a decline in systolic blood pressure to a mean of 127 mmHg compared with a mean of 198 mmHg [171]. Additionally, a study conducted in fawn-hooded hypertensive rats illustrates that treatment with pyrrolidine dithiocarbamate leads to a statistically significant decline in systolic blood pressure to a mean of 128 mmHg compared with a mean of 159 mmHg in the control group [172]. Administration of tacrolimus, a calcineurin inhibitor, to Dahl salt-sensitive rats resulted in a decline in systolic blood pressure to a mean of 150 mmHg compared with a mean of 170 mmHg along with a decline in urinary albumin and thiobarbituric acid–reactive substances excretion and renal infiltration via pro-inflammatory cells and NADPH oxidase [173]. Another calcineurin inhibitor referred to as cyclosporine A results in comparable outcomes in terms of blood pressure control [174]. Moreover, anti-oxidant-enriched diet and melatonin therapy

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

Table 1: The role of various immunosuppressive agents in the treatment of hypertension has been investigated across multiple animal models.

Treatment	Experimental model	Effect on blood pressure
Cyclophosphamide	Spontaneously hypertensive rats [168]	Statistically significant decline in SBP to a mean of 158 mmHg compared with a mean of 174 mmHg in the control group, while effects are recognizable after two weeks of therapy.
Cyclophosphamide	Genetically hypertensive rats of Lyon strain [169]	Statistically significant decline in blood pressure to a mean of 135 mmHg compared with a mean of 175 mmHg in the control group, while no significant difference has been recorded in genetically normotensive subjects.
Cyclosporine A	dTGR harboring human renin and angiotensinogen genes [174]	Statistically significant decline in 24-h urinary albumin excretion, perivascular monocyte/macrophage infiltration in the kidney and decline in SBP to a mean of 150 mmHg compared with a mean of 190 mmHg observed in cyclosporine A–treated dTGR rats.
Etanercept	C57BL/6 mice and RAG-1-deficient mice [65]	Statistically significant decline in SBP to a mean of 130 mmHg compared with a mean of 150 mmHg with decrease in aortic superoxide formation observed in etanercept treated C57BL/6 mice. Etanercept also decreased aortic superoxide formation in RAG-1-deficient mice after adoptive transfer of T-cells.
Mycophenolate mofetil	Spontaneously hypertensive rats [145]	Statistically significant decline in blood pressures correlated with the decline in renal infiltration by macrophages and lymphocytes, renal and urinary markers of oxidative stress such as malondialdehyde.
Mycophenolate mofetil	Dahl salt-sensitive rats [170]	Statistically significant decline in mean arterial pressure (158 mmHg compared with 174 mmHg in the control group), protein and albumin excretion rate in mycophenolate administered rats, while creatinine levels and body weight were not different between the groups.
Pyrrolidine dithiocarbamate	Spontaneously hypertensive rats [171]	Statistically significant decline in urinary protein excretion, renal tissue pro-inflammatory cells and markers of oxidative stress, decline in SBP to a mean of 127 mmHg compared with a mean of 198 mmHg was recorded in pyrrolidine dithiocarbamate–treated rats.
Pyrrolidine dithiocarbamate	Fawn-hooded hypertensive rats [172]	Statistically significant decline in urinary protein excretion, glomerulosclerosis and SBP by an average of 25 mmHg observed in pyrrolidine dithiocarbamate–treated fawn-hooded hypertensive rats.
Tacrolimus	Dahl salt-sensitive rats [173]	Statistically significant decline in SBP to a mean of 150 mmHg compared with a mean of 170 mmHg, along with a decline in urinary albumin and thiobarbituric acid–reactive substances excretion and renal infiltration via pro-inflammatory cells, and NADPH oxidase was recorded.

dTGR: double transgenic rats; SBP: systolic blood pressure.

result in a decline in blood pressure measurements in spontaneously hypertensive rat subjects via suppression of oxidative stress and renal tissue infiltration by pro-inflammatory cells [175, 176].

Furthermore, animal models have demonstrated the beneficial effects of anti-TNF-α therapy, namely etanercept, anti-IL-6 therapy, anti-CD20 antibody and anti-TGF-β antibody, on blood pressure control [136, 177–181]. Neonatal thymectomy has also shown to be beneficial in the later development of hypertension with lower maximum systolic blood pressure measurement according to a study conducted in genetically hypertensive rats of Lyon strain [169]. Other hypothetical models for blood pressure control include the deletion of CD247 or mutation at *RAG1* or *SH2B3* genes [182, 66]. Despite growing literature on immunosuppressive agents in the treatment of hypertension on animal models, there is lack of clinical trials conducted in human subjects. Therefore, it is unclear whether such consistent findings of improved blood pressure with various immunosuppressive medications is applicable to humans. There is a clear need for clinical trials investigating the efficiency of such therapeutic approaches on patients with treatment-resistant hypertension.

ANTI-HYPERTENSIVE MEDICATIONS AS IMMUNOMODULATORS

There are multiple classes of anti-hypertensive medications that are currently being utilized in the management of hypertension while the latest studies indicate that their anti-hypertensive properties may include varying degrees of immunomodulatory effects.

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

Table 2: The knowns and unknowns of the role of the immune system in hypertension.

Knowns	Unknowns
TLR-4 gene–deficient mouse models have exhibited less blood pressure rise in reaction to angiotensin II or L-NAME infusions. Blocking TLR-9 is associated with a decrease in angiotensin II–induced hypertension.	Although early studies suggest a possible role in the pathophysiology and identification as a potential therapeutic target by injection of anti-CD20 antibodies, the significance of B-lymphocytes has largely been uninvestigated in research on hypertension. Further research on the function of B-lymphocytes in the pathophysiology of hypertension is highly necessary.
Numerous pre-clinical investigations using angiotensin II- or aldosterone-induced hypertension models have shown increased circulating monocytes. Rats that develop hypertension spontaneously or in salt-sensitive or deoxycorticosterone acetate–induced hypertension models have shown a similar trend.	There is little information on how eosinophils and basophils contribute to the etiology of hypertension. Observational studies have suggested a possible connection between coronary artery disease or pulmonary artery hypertension and a higher peripheral eosinophil count, although the precise relationship has not yet been proven.
Hs-CRP, IL-6 and elevated CRP were all substantially associated with an increased risk of developing hypertension. IL-1β, however, was not linked to a serious risk.	Although studies using on animal models clearly show the major involvement of renal inflammation in the pathogenesis of hypertension, it is not apparent whether renal inflammation is the triggering event that results in clinical hypertension or only a contributing factor to the onset of hypertension.
In people with primary hypertension, mRNA and protein of TGF-β1 are found to be overexpressed.	Further research is necessary to fully understand the impact of TNF- and its inhibition on blood pressure readings because there are conflicting results in the literature.
High blood pressure was hypothesized to enhance TNF and oxidative stress significantly. According to a different study, patients with hypertension had considerably higher TNF levels in their blood and urine than healthy controls.	Further studies are needed to understand how dietary salt intake and immune response are linked to hypertension and cardiovascular illnesses.
Immune system cells infiltrate the kidneys of spontaneously hypertensive rats before clinical hypertension manifests itself. Furthermore, there is a strong correlation between the level of SBP measurements and immune cell infiltration.	
A preclinical investigation using a transgenic mouse model with monocyte/macrophage depletion revealed a decrease in superoxide radical generation, a reduction in angiotensin II–induced hypertension and a reduction in vascular dysfunction.	
The release of pro-fibrotic cytokines like TGF and the remodeling of the extracellular matrix by matrix metalloproteinases, which cause vascular stiffness, are two crucial pathophysiological roles of macrophages in vascular inflammation.	
T-regulatory cells could prevent vascular inflammation. These cells seem to prevent angiotensin II- or aldosterone-induced ROS production and monocyte/macrophage infiltration of the vascular wall.	
T-regulatory cell administration as a single dose or once weekly dose improves cardiac hypertrophy, endothelial vasodilatation, the production of ROS and pro-inflammatory signals, but has no effect on blood pressure readings. In contrast, administering T-regulatory cells at sustained high doses improves blood pressure.	
High dietary sodium intake not only causes hemodynamic alterations but also modulates the immune system by immune cell activation, vascular endothelial dysfunction and cytokine secretion, eventually leading inflammation and hypertension.	

SBP: systolic blood pressure.

RAAS blockers

ACEi/ARBs are among the most commonly utilized anti-hypertensive medications globally, along with their use in congestive heart failure, ischemic cardiovascular diseases and diabetic nephropathy. The immune-modulating effects of ACEi have been highly investigated in multiple models. In mouse models of lupus nephritis–associated hypertension, early initiation of ACEi therapy may delay or reverse the degree of kidney involvement and proteinuria which may be attributable to the decline in T-helper cell polarization towards T-helper-2 type, decline in cytokine production such as IL-4 and decline in the production of TGF-β [183]. Also, ACEi therapy may lead to impairment ofm antigen presentation via major histocompatibility complex I/II [184]. On the other hand, high-dose telmisartan therapy, an ARB agent, leads to inhibition of NLRP3 inflammasome in dose-dependent manner and may result in

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

improvement in vascular function [185]. Other potential beneficial effects of ARB therapy may include suppression of T-cell activity and suppression of serum IL-6 levels [186, 187]. The immunomodulatory effects of mineralocorticoid receptor antagonists such as spironolactone are quite different from other RAAS blockers such as ACEi or ARB and include upregulation of T-regulatory cells, decline in T-helper-17 response, decline in IL-17 production and inhibition of leucocyte migration towards endothelium [188, 189].

Diuretics

Thiazide and loop diuretics are the most commonly prescribed diuretic-type anti-hypertensive medications while their effects on the immune system are unclear, with conflicting results from different studies. A prospective trial conducted in 110 elderly female subjects with multiple medical comorbidities demonstrated that diuretic therapy leads to a statistically significant decline in serum IL-6 and TNF-α levels without any considerable change in IFN-γ levels, whereas a study conducted in Dahl salt-sensitive rats demonstrated no change in oxidative stress or inflammation with thiazide therapy despite effective blood pressure control [104, 190]. Another clinical trial conducted in 88 hypertensive patients receiving either perindopril, hydrochlorothiazide or indapamide demonstrated that despite decline in blood pressure measurements and improvements in flow-mediated dilatation, thiazide therapy leads to elevation of immunoglobulin M–type anti-ApoB-D peptide antibodies without any change in immunoglobulin G–type antibodies [191]. Therefore, there is a clear need for future studies investigating the immune properties of diuretic therapy in order to enlighten such uncertainty.

Calcium channel blockers

Calcium channel blockers are commonly utilized in order to obtain target blood pressure, however their immunomodulatory properties are currently under-studied. Amlodipine therapy has been shown to lead to the downregulation of NADPH oxidase and VCAM-1 in the aortic wall and inhibition of the NF-κB pathway, thereby indicating that the potential anti-hypertensive potential of amlodipine therapy may not be limited to its vasodilatory properties [192].

CONCLUSION

Despite being responsible for almost 95% of hypertensive cases, the pathophysiology of primary hypertension is still unknown. Recent studies have suggested a potential role of the immune system in the etiopathogenesis of hypertension [9]. In this review, we provided the potential pathophysiological and therapeutic roles of the immune mechanisms in hypertension. Future studies are needed to better understand the current knowns, and shine a light on the unknowns, of the role of immunity in hypertension (Table 2).

FUNDING

This study was not funded by any grant.

AUTHORS' CONTRIBUTIONS

Conception or design of the work: M.K., C.T. and S.C. Literature search and screening: C.T., I.B.P., A.M. and S.C. Drafted the manuscript: C.T. and S.C. Generation of figures and tables: A.M. and I.B.P. Reviewed the manuscript for intellectual content: M.K. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

M.K. is member of the *CKJ* editorial board. All other authors declare that they have no conflict of interest.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors. The figure was crafted using biorender.com.

REFERENCES

1. Forouzanfar MH, Liu P, Roth GA *et al*. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990-2015. *JAMA* 2017;**317**:165–82. https://doi.org/10.1001/jama.2016.19043.
2. Oparil S, Acelajado MC, Bakris GL *et al*. Hypertension. *Nat Rev Dis Primers* 2018;**4**:18014. https://doi.org/10.1038/nrdp.2018.14.
3. Lawes CM, Vander Hoorn S, Rodgers A. Global burden of blood-pressure-related disease, 2001. *Lancet North Am Ed* 2008;**371**:1513–8. https://doi.org/10.1016/S0140-6736(08)60655-8.
4. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet North Am Ed* 2016;**388**:1659–724. https://doi.org/10.1016/S0140-6736(16)31679-8.
5. Kario K, Hoshide S, Mizuno H *et al*. Nighttime blood pressure phenotype and cardiovascular prognosis: practitioner-based nationwide JAMP study. *Circulation* 2020;**142**:1810–20. https://doi.org/10.1161/CIRCULATIONAHA.120.049730.
6. Kanbay M, Demiray A, Afsar B *et al*. Role of Klotho in the development of essential hypertension. *Hypertension* 2021;**77**:740–50. https://doi.org/10.1161/HYPERTENSIONAHA.120.16635.
7. Eren OC, Ortiz A, Afsar B *et al*. Multilayered interplay between fructose and salt in development of hypertension. *Hypertension* 2019;**73**:265–72. https://doi.org/10.1161/HYPERTENSIONAHA.118.12150.
8. Miller ED. The role of the renin-angiotensin-aldosterone system in circulatory control and hypertension. *Br J Anaesth* 1981;**53**:711–8. https://doi.org/10.1093/bja/53.7.711.
9. Solak Y, Afsar B, Vaziri ND *et al*. Hypertension as an autoimmune and inflammatory disease. *Hypertens Res* 2016;**39**:567–73. https://doi.org/10.1038/hr.2016.35.
10. Yatim KM, Lakkis FG. A brief journey through the immune system. *Clin J Am Soc Nephrol* 2015;**10**:1274–81. https://doi.org/10.2215/CJN.10031014.

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

11. Mikolajczyk TP, Guzik TJ. Adaptive immunity in hypertension. *Curr Hypertens Rep* 2019;**21**:68. https://doi.org/10.1007/s11906-019-0971-6.
12. Paul S, Lal G. The molecular mechanism of natural killer cells function and its importance in cancer immunotherapy. *Front Immunol* 2017;**8**:1124. https://doi.org/10.3389/fimmu.2017.01124.
13. Kossmann S, Schwenk M, Hausding M *et al*. Angiotensin II-induced vascular dysfunction depends on interferon-γ-driven immune cell recruitment and mutual activation of monocytes and NK-cells. *Arterioscler Thromb Vasc Biol* 2013;**33**:1313–9. https://doi.org/10.1161/ATVBAHA.113.301437.
14. Navaneethabalakrishnan S, Smith HL, Arenaz CM *et al*. Update on immune mechanisms in hypertension. *Am J Hypertens* 2022;**35**:842–51. https://doi.org/10.1093/ajh/hpac077.
15. Kanbay M, Onal EM, Afsar B *et al*. The crosstalk of gut microbiota and chronic kidney disease: role of inflammation, proteinuria, hypertension, and diabetes mellitus. *Int Urol Nephrol* 2018;**50**:1453–66. https://doi.org/10.1007/s11255-018-1873-2.
16. Onal EM, Afsar B, Covic A *et al*. Gut microbiota and inflammation in chronic kidney disease and their roles in the development of cardiovascular disease. *Hypertens Res* 2019;**42**:123–40. https://doi.org/10.1038/s41440-018-0144-z.
17. Kirabo A, Fontana V, de Faria AP *et al*. DC isoketal-modified proteins activate T cells and promote hypertension. *J Clin Invest* 2014;**124**:4642–56. https://doi.org/10.1172/JCI74084.
18. Kawasaki T, Kawai T. Toll-like receptor signaling pathways. *Front Immunol* 2014;**5**:461. https://doi.org/10.3389/fimmu.2014.00461.
19. Marketou ME, Kontaraki JE, Zacharis EA *et al*. TLR2 and TLR4 gene expression in peripheral monocytes in nondiabetic hypertensive patients: the effect of intensive blood pressure-lowering. *J Clin Hypertens (Greenwich)* 2012;**14**:330–5. https://doi.org/10.1111/j.1751-7176.2012.00620.x.
20. Dange RB, Peng H, Feng Y *et al*. *Mice lacking the gene for Toll like receptor-4 (TLR4) had an attenuated blood pressure response to Angiotensin II infusion*. Wiley Online Library, 2013. https://faseb.onlinelibrary.wiley.com/doi/abs/10.1096/fasebj.27.1_supplement.696.4.
21. Sollinger D, Eißler R, Lorenz S *et al*. Damage-associated molecular pattern activated Toll-like receptor 4 signalling modulates blood pressure in L-NAME-induced hypertension. *Cardiovasc Res* 2014;**101**:464–72. https://doi.org/10.1093/cvr/cvt265.
22. Dange RB, Agarwal D, Masson GS *et al*. Central blockade of TLR4 improves cardiac function and attenuates myocardial inflammation in angiotensin II-induced hypertension. *Cardiovasc Res* 2014;**103**:17–27. https://doi.org/10.1093/cvr/cvu067.
23. Bomfim GF, Dos Santos RA, Oliveira MA *et al*. Toll-like receptor 4 contributes to blood pressure regulation and vascular contraction in spontaneously hypertensive rats. *Clin Sci (Lond)* 2012;**122**:535–43. https://doi.org/10.1042/CS20110523.
24. Nunes KP, Bomfim GF, Toque HA *et al*. Toll-like receptor 4 (TLR4) impairs nitric oxide contributing to Angiotensin II-induced cavernosal dysfunction. *Life Sci* 2017;**191**:219–26. https://doi.org/10.1016/j.lfs.2017.10.014.
25. Ishikawa T, Abe K, Takana-Ishikawa M *et al*. Chronic inhibition of toll-like receptor 9 ameliorates pulmonary hypertension in rats. *JAHA* 2021;**10**:e019247. https://doi.org/10.1161/JAHA.120.019247.
26. Pushpakumar S, Ren L, Kundu S *et al*. Toll-like receptor 4 deficiency reduces oxidative stress and macrophage mediated inflammation in hypertensive kidney. *Sci Rep* 2017;**7**:6349. https://doi.org/10.1038/s41598-017-06484-6.
27. Bomfim GF, Cau SBA, Bruno AS *et al*. Hypertension: a new treatment for an old disease? Targeting the immune system. *Br J Pharmacol* 2019;**176**:2028–48. https://doi.org/10.1111/bph.14436.
28. Kunnas T, Määttä K, Nikkari ST. NLR family pyrin domain containing 3 (NLRP3) inflammasome gene polymorphism rs7512998 (C>T) predicts aging-related increase of blood pressure, the TAMRISK study. *Immun Ageing* 2015;**12**:19.
29. Wang Q, So A, Nussberger J *et al*. Impact of NLRP3 inflammasome on the development of hypertension and renal and cardiac hypertrophy in 2K1C and DOCA/salt mice. *Kidney Res Clin Pract* 2012;**31**:A83.
30. Cartwright N, Murch O, McMaster SK *et al*. Selective NOD1 agonists cause shock and organ injury/dysfunction in vivo. *Am J Respir Crit Care Med* 2007;**175**:595–603. https://doi.org/10.1164/rccm.200608-1103OC.
31. Gu CC, Hunt SC, Kardia S *et al*. An investigation of genome-wide associations of hypertension with microsatellite markers in the family blood pressure program (FBPP). *Hum Genet* 2007;**121**:577–90. https://doi.org/10.1007/s00439-007-0349-8.
32. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol* 2016;**16**:341–52. https://doi.org/10.1038/nri.2016.42.
33. Tanriover C, Ucku D, Basile C *et al*. On the importance of the interplay of residual renal function with clinical outcomes in end-stage kidney disease. *J Nephrol* 2022;**35**:2191–204. https://doi.org/10.1007/s40620-022-01388-9.
34. Jose PA, Raj D. Gut microbiota in hypertension. *Curr Opin Nephrol Hypertens* 2015;**24**:403–9. https://doi.org/10.1097/MNH.0000000000000149.
35. Li J, Zhao F, Wang Y *et al*. Gut microbiota dysbiosis contributes to the development of hypertension. *Microbiome* 2017;**5**:14. https://doi.org/10.1186/s40168-016-0222-x.
36. Wenzel P, Knorr M, Kossmann S *et al*. Lysozyme M-positive monocytes mediate angiotensin II-induced arterial hypertension and vascular dysfunction. *Circulation* 2011;**124**:1370–81. https://doi.org/10.1161/CIRCULATIONAHA.111.034470.
37. De Ciuceis C, Amiri F, Brassard P *et al*. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. *Arterioscler Thromb Vasc Biol* 2005;**25**:2106–13. https://doi.org/10.1161/01.ATV.0000181743.28028.57.
38. Fehrenbach DJ, Mattson DL. Inflammatory macrophages in the kidney contribute to salt-sensitive hypertension. *Am J Physiol Renal Physiol* 2020;**318**:F544–8. https://doi.org/10.1152/ajprenal.00454.2019.
39. Kanbay M, Aslan G, Afsar B *et al*. Acute effects of salt on blood pressure are mediated by serum osmolality. *J Clin Hypertens* 2018;**20**:1447–54. https://doi.org/10.1111/jch.13374.
40. Martín-Fernández B, Rubio-Navarro A, Cortegano I *et al*. Aldosterone induces renal fibrosis and inflammatory M1-macrophage subtype via mineralocorticoid receptor in rats. *PLoS One* 2016;**11**:e0145946. https://doi.org/10.1371/journal.pone.0145946.
41. Mervaala EM, Müller DN, Park JK *et al*. Monocyte infiltration and adhesion molecules in a rat model of high human

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

renin hypertension. *Hypertension* 1999;**33**:389–95. https://doi.org/10.1161/01.HYP.33.1.389.
42. Ishibashi M, Hiasa K, Zhao Q *et al*. Critical role of monocyte chemoattractant protein-1 receptor CCR2 on monocytes in hypertension-induced vascular inflammation and remodeling. *Circ Res* 2004;**94**:1203–10. https://doi.org/10.1161/01.RES.0000126924.23467.A3.
43. Crowley SD, Song YS, Sprung G *et al*. A role for angiotensin II type 1 receptors on bone marrow-derived cells in the pathogenesis of angiotensin II-dependent hypertension. *Hypertension* 2010;**55**:99–108. https://doi.org/10.1161/HYPERTENSIONAHA.109.144964.
44. Huang L, Wang A, Hao Y *et al*. Macrophage depletion lowered blood pressure and attenuated hypertensive renal injury and fibrosis. *Front Physiol* 2018;**9**:473. https://doi.org/10.3389/fphys.2018.00473.
45. Hartner A, Porst M, Gauer S *et al*. Glomerular osteopontin expression and macrophage infiltration in glomerulosclerosis of DOCA-salt rats. *Am J Kidney Dis* 2001;**38**:153–64. https://doi.org/10.1053/ajkd.2001.25209.
46. Harwani SC, Ratcliff J, Sutterwala FS *et al*. Nicotine mediates CD161a+ renal macrophage infiltration and premature hypertension in the spontaneously hypertensive rat. *Circ Res* 2016;**119**:1101–15. https://doi.org/10.1161/CIRCRESAHA.116.309402.
47. Wenstedt EF, Verberk SG, Kroon J *et al*. Salt increases monocyte CCR2 expression and inflammatory responses in humans. *JCI Insight* 2019;**4**:**e130508**. https://doi.org/10.1172/jci.insight.130508.
48. Asagami T, Reaven GM, Tsao PS. Enhanced monocyte adherence to thoracic aortae from rats with two forms of experimental hypertension. *Am J Hypertens* 1999;**12**:890–3. https://doi.org/10.1016/S0895-7061(99)00072-2.
49. Clozel M, Kuhn H, Hefti F *et al*. Endothelial dysfunction and subendothelial monocyte macrophages in hypertension. Effect of angiotensin converting enzyme inhibition. *Hypertension* 1991;**18**:132–41. https://doi.org/10.1161/01.HYP.18.2.132.
50. Schmid-Schönbein GW, Seiffge D, DeLano FA *et al*. Leukocyte counts and activation in spontaneously hypertensive and normotensive rats. *Hypertension* 1991;**17**:323–30. https://doi.org/10.1161/01.HYP.17.3.323.
51. Dörffel Y, Lätsch C, Stuhlmüller B *et al*. Preactivated peripheral blood monocytes in patients with essential hypertension. *Hypertension* 1999;**34**:113–7. https://doi.org/10.1161/01.HYP.34.1.113.
52. Wirtz PH, von Känel R, Frey K *et al*. Glucocorticoid sensitivity of circulating monocytes in essential hypertension. *Am J Hypertens* 2004;**17**:489–94. https://doi.org/10.1016/j.amjhyper.2004.01.010.
53. Zaldivia MT, Rivera J, Hering D *et al*. Renal denervation reduces monocyte activation and monocyte-platelet aggregate formation: an anti-inflammatory effect relevant for cardiovascular risk. *Hypertension* 2017;**69**:323–31. https://doi.org/10.1161/HYPERTENSIONAHA.116.08373.
54. Tatsukawa Y, Hsu WL, Yamada M *et al*. White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. *Hypertens Res* 2008;**31**:1391–7. https://doi.org/10.1291/hypres.31.1391.
55. Lu X, Rudemiller NP, Privratsky JR *et al*. Classical dendritic cells mediate hypertension by promoting renal oxidative stress and fluid retention. *Hypertension* 2020;**75**:131–8. https://doi.org/10.1161/HYPERTENSIONAHA.119.13667.
56. Zhang R, Inagawa H, Kazumura K *et al*. Evaluation of a hypertensive rat model using peripheral blood neutrophil activity, phagocytic activity and oxidized LDL evaluation. *Anticancer Res* 2018;**38**:4289–94. https://doi.org/10.21873/anticanres.12726.
57. Hevia D, Araos P, Prado C *et al*. Myeloid CD11c(+) antigen-presenting cells ablation prevents hypertension in response to Angiotensin II plus high-salt diet. *Hypertension* 2018;**71**:709–18. https://doi.org/10.1161/HYPERTENSIONAHA.117.10145.
58. Van Beusecum JP, Barbaro NR, McDowell Z *et al*. High salt activates CD11c(+) antigen-presenting cells via SGK (serum glucocorticoid kinase) 1 to promote renal inflammation and salt-sensitive hypertension. *Hypertension* 2019;**74**:555–63. https://doi.org/10.1161/HYPERTENSIONAHA.119.12761.
59. Kossmann S, Schwenk M, Hausding M *et al*. Angiotensin II–induced vascular dysfunction depends on interferon-γ–driven immune cell recruitment and mutual activation of monocytes and NK-cells. *Arterioscler Thromb Vasc Biol* 2013;**33**:1313–9. https://doi.org/10.1161/ATVBAHA.113.301437.
60. Taherzadeh Z, VanBavel E, de Vos J *et al*. Strain-dependent susceptibility for hypertension in mice resides in the natural killer gene complex. *Am J Physiol Heart Circ Physiol* 2010;**298**:H1273–82. https://doi.org/10.1152/ajpheart.00508.2009.
61. Weng M, Baron DM, Bloch KD *et al*. Eosinophils are necessary for pulmonary arterial remodeling in a mouse model of eosinophilic inflammation-induced pulmonary hypertension. *Am J Physiol Lung Cell Mol Physiol* 2011;**301**:L927–36. https://doi.org/10.1152/ajplung.00049.2011.
62. Tanaka M, Fukui M, Tomiyasu K *et al*. Eosinophil count is positively correlated with coronary artery calcification. *Hypertens Res* 2012;**35**:325–8. https://doi.org/10.1038/hr.2011.191.
63. Withers SB, Forman R, Meza-Perez S *et al*. Eosinophils are key regulators of perivascular adipose tissue and vascular functionality. *Sci Rep* 2017;**7**:44571. https://doi.org/10.1038/srep44571.
64. Wu D, Molofsky AB, Liang HE *et al*. Eosinophils sustain adipose alternatively activated macrophages associated with glucose homeostasis. *Science* 2011;**332**:243–7. https://doi.org/10.1126/science.1201475.
65. Guzik TJ, Hoch NE, Brown KA *et al*. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med* 2007;**204**:2449–60. https://doi.org/10.1084/jem.20070657.
66. Mattson DL, Lund H, Guo C *et al*. Genetic mutation of recombination activating gene 1 in Dahl salt-sensitive rats attenuates hypertension and renal damage. *Am J Physiol Regul Integr Comp Physiol* 2013;**304**:R407–14. https://doi.org/10.1152/ajpregu.00304.2012.
67. Crowley SD, Song YS, Lin EE *et al*. Lymphocyte responses exacerbate angiotensin II-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:R1089–97. https://doi.org/10.1152/ajpregu.00373.2009.
68. Trott DW, Thabet SR, Kirabo A *et al*. Oligoclonal CD8+ T cells play a critical role in the development of hypertension. *Hypertension* 2014;**64**:1108–15. https://doi.org/10.1161/HYPERTENSIONAHA.114.04147.
69. Mian MO, Barhoumi T, Briet M *et al*. Deficiency of T-regulatory cells exaggerates angiotensin II-induced mi-

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

crovascular injury by enhancing immune responses. *J Hypertens* 2016;**34**:97–108. https://doi.org/10.1097/HJH.0000000000000761.
70. Matrougui K, Abd Elmageed Z, Kassan M *et al*. Natural regulatory T cells control coronary arteriolar endothelial dysfunction in hypertensive mice. *Am J Pathol* 2011;**178**:434–41. https://doi.org/10.1016/j.ajpath.2010.11.034.
71. Kvakan H, Kleinewietfeld M, Qadri F *et al*. Regulatory T cells ameliorate angiotensin II-induced cardiac damage. *Circulation* 2009;**119**:2904–12. https://doi.org/10.1161/CIRCULATIONAHA.108.832782.
72. Kasal DA, Barhoumi T, Li MW *et al*. T regulatory lymphocytes prevent aldosterone-induced vascular injury. *Hypertension* 2012;**59**:324–30. https://doi.org/10.1161/HYPERTENSIONAHA.111.181123.
73. Trott DW, Harrison DG. The immune system in hypertension. *Adv Physiol Educ* 2014;**38**:20–4. https://doi.org/10.1152/advan.00063.2013.
74. Chan CT, Sobey CG, Lieu M *et al*. Obligatory role for B cells in the development of Angiotensin II-dependent hypertension. *Hypertension* 2015;**66**:1023–33. https://doi.org/10.1161/HYPERTENSIONAHA.115.05779.
75. Dalekos GN, Elisaf MS, Papagalanis N *et al*. Elevated interleukin-1 beta in the circulation of patients with essential hypertension before any drug therapy: a pilot study. *Eur J Clin Invest* 1996;**26**:936–9. https://doi.org/10.1111/j.1365-2362.1996.tb02141.x.
76. Dalekos GN, Elisaf M, Bairaktari E *et al*. Increased serum levels of interleukin-1beta in the systemic circulation of patients with essential hypertension: additional risk factor for atherogenesis in hypertensive patients? *J Lab Clin Med* 1997;**129**:300–8. https://doi.org/10.1016/S0022-2143(97)90178-5.
77. Melton E, Qiu H. Interleukin-1β in multifactorial hypertension: inflammation, vascular smooth muscle cell and extracellular matrix remodeling, and non-coding RNA regulation. *Int J Mol Sci* 2021;**22**:8639. https://doi.org/10.3390/ijms22168639.
78. Zhang J, Rudemiller NP, Patel MB *et al*. Interleukin-1 receptor activation potentiates salt reabsorption in Angiotensin II-induced hypertension via the NKCC2 co-transporter in the nephron. *Cell Metab* 2016;**23**:360–8. https://doi.org/10.1016/j.cmet.2015.11.013.
79. Crorkin P, Hao S, Ferreri NR. Responses to Ang II (Angiotensin II), salt intake, and lipopolysaccharide reveal the diverse actions of TNF-alpha (tumor necrosis factor-alpha) on blood pressure and renal function. *Hypertension* 2022;**79**:2656–70. https://doi.org/10.1161/HYPERTENSIONAHA.122.19464.
80. Beasley D, Dinarello CA, Cannon JG. Interleukin-1 induces natriuresis in conscious rats: role of renal prostaglandins. *Kidney Int* 1988;**33**:1059–65. https://doi.org/10.1038/ki.1988.111.
81. Kohan DE, Schreiner GF. Interleukin 1 modulation of renal epithelial glucose and amino acid transport. *Am J Physiol* 1988;**254**:F879–86.
82. Boesen EI. Chronic elevation of IL-1beta induces diuresis via a cyclooxygenase 2-mediated mechanism. *Am J Physiol Renal Physiol* 2013;**305**:F189–98. https://doi.org/10.1152/ajprenal.00075.2013.
83. Kohan DE, Merli CA, Simon EE. Micropuncture localization of the natriuretic effect of interleukin 1. *Am J Physiol* 1989;**256**:F810–13.
84. Kohan DE. Interleukin-1 regulation of prostaglandin E2 synthesis by the papillary collecting duct. *J Lab Clin Med* 1989;**114**:717–23.
85. Akita K, Isoda K, Ohtomo F *et al*. Blocking of interleukin-1 suppresses angiotensin II-induced renal injury. *Clin Sci (Lond)* 2021;**135**:2035–48. https://doi.org/10.1042/CS20201406.
86. Jayedi A, Rahimi K, Bautista LE *et al*. Inflammation markers and risk of developing hypertension: a meta-analysis of cohort studies. *Heart* 2019;**105**:686–92. https://doi.org/10.1136/heartjnl-2018-314216.
87. Rothman AM, MacFadyen J, Thuren T *et al*. Effects of interleukin-1beta inhibition on blood pressure, incident hypertension, and residual inflammatory risk: a secondary analysis of CANTOS. *Hypertension* 2020;**75**:477–82. https://doi.org/10.1161/HYPERTENSIONAHA.119.13642.
88. Ridker PM, Everett BM, Thuren T *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–31. https://doi.org/10.1056/NEJMoa1707914.
89. Urwyler SA, Ebrahimi F, Burkard T *et al*. IL (interleukin)-1 receptor antagonist increases Ang (Angiotensin [1-7]) and decreases blood pressure in obese individuals. *Hypertension* 2020;**75**:1455–63. https://doi.org/10.1161/HYPERTENSIONAHA.119.13982.
90. Lee DL, Sturgis LC, Labazi H *et al*. Angiotensin II hypertension is attenuated in interleukin-6 knockout mice. *Am J Physiol Heart Circ Physiol* 2006;**290**:H935–40. https://doi.org/10.1152/ajpheart.00708.2005.
91. Chae CU, Lee RT, Rifai N *et al*. Blood pressure and inflammation in apparently healthy men. *Hypertension* 2001;**38**:399–403. https://doi.org/10.1161/01.HYP.38.3.399.
92. Ridker PM, Rifai N, Stampfer MJ *et al*. Plasma concentration of interleukin-6 and the risk of future myocardial infarction among apparently healthy men. *Circulation* 2000;**101**:1767–72. https://doi.org/10.1161/01.CIR.101.15.1767.
93. Chamarthi B, Williams GH, Ricchiuti V *et al*. Inflammation and hypertension: the interplay of interleukin-6, dietary sodium, and the renin-angiotensin system in humans. *Am J Hypertens* 2011;**24**:1143–8. https://doi.org/10.1038/ajh.2011.113.
94. Samuelsson AM, Alexanderson C, Molne J *et al*. Prenatal exposure to interleukin-6 results in hypertension and alterations in the renin-angiotensin system of the rat. *J Physiol* 2006;**575**:855–67. https://doi.org/10.1113/jphysiol.2006.111260.
95. Brands MW, Banes-Berceli AK, Inscho EW *et al*. Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/signal transducer and activator of transcription 3 activation. *Hypertension* 2010;**56**:879–84. https://doi.org/10.1161/HYPERTENSIONAHA.110.158071.
96. Kranzhofer R, Schmidt J, Pfeiffer CA *et al*. Angiotensin induces inflammatory activation of human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol* 1999;**19**:1623–9. https://doi.org/10.1161/01.ATV.19.7.1623.
97. Funakoshi Y, Ichiki T, Ito K *et al*. Induction of interleukin-6 expression by angiotensin II in rat vascular smooth muscle cells. *Hypertension* 1999;**34**:118–25. https://doi.org/10.1161/01.HYP.34.1.118.
98. Han Y, Runge MS, Brasier AR. Angiotensin II induces interleukin-6 transcription in vascular smooth muscle

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

cells through pleiotropic activation of nuclear factor-kappa B transcription factors. *Circ Res* 1999;**84**:695–703. https://doi.org/10.1161/01.RES.84.6.695.
99. Moriyama T, Fujibayashi M, Fujiwara Y *et al*. Angiotensin II stimulates interleukin-6 release from cultured mouse mesangial cells. *J Am Soc Nephrol* 1995;**6**:95–101. https://doi.org/10.1681/ASN.V6195.
100. Lee DL, Leite R, Fleming C *et al*. Hypertensive response to acute stress is attenuated in interleukin-6 knockout mice. *Hypertension* 2004;**44**:259–63. https://doi.org/10.1161/01.HYP.0000139913.56461.fb.
101. Coles B, Fielding CA, Rose-John S *et al*. Classic interleukin-6 receptor signaling and interleukin-6 trans-signaling differentially control angiotensin II-dependent hypertension, cardiac signal transducer and activator of transcription-3 activation, and vascular hypertrophy in vivo. *Am J Pathol* 2007;**171**:315–25. https://doi.org/10.2353/ajpath.2007.061078.
102. Bautista LE, Vera LM, Arenas IA *et al*. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. *J Hum Hypertens* 2005;**19**:149–54. https://doi.org/10.1038/sj.jhh.1001785.
103. Mao SQ, Sun JH, Gu TL *et al*. Hypomethylation of interleukin-6 (IL-6) gene increases the risk of essential hypertension: a matched case-control study. *J Hum Hypertens* 2017;**31**:530–6. https://doi.org/10.1038/jhh.2017.7.
104. Toledo JO, Moraes CF, Souza VC *et al*. Tailored antihypertensive drug therapy prescribed to older women attenuates circulating levels of interleukin-6 and tumor necrosis factor-α. *Clin Interv Aging* 2015;**10**:209–15.
105. Thangaraj SS, Oxlund CS, Fonseca MPD *et al*. The mineralocorticoid receptor blocker spironolactone lowers plasma interferon-gamma and interleukin-6 in patients with type 2 diabetes and treatment-resistant hypertension. *J Hypertens* 2022;**40**:153–62. https://doi.org/10.1097/HJH.0000000000002990.
106. Buemi M, Marino D, Floccari F *et al*. Effect of interleukin 8 and ICAM-1 on calcium-dependent outflow of K+ in erythrocytes from subjects with essential hypertension. *Curr Med Res Opin* 2004;**20**:19–24. https://doi.org/10.1185/030079903125002720.
107. Wakabayashi Y, Usui Y, Okunuki Y *et al*. Increases of vitreous monocyte chemotactic protein 1 and interleukin 8 levels in patients with concurrent hypertension and diabetic retinopathy. *Retina* 2011;**31**:1951–7. https://doi.org/10.1097/IAE.0b013e31820d3cee.
108. Letterio JJ, Roberts AB. Regulation of immune responses by TGF-beta. *Annu Rev Immunol* 1998;**16**:137–61. https://doi.org/10.1146/annurev.immunol.16.1.137.
109. Li MO, Flavell RA. TGF-beta: a master of all T cell trades. *Cell* 2008;**134**:392–404. https://doi.org/10.1016/j.cell.2008.07.025.
110. Kim HS, Kim HY. Hypertensive effects of transforming growth factor-beta1 in vascular smooth muscles cells from spontaneously hypertensive rats are mediated by sulfatase 2. *Cytokine* 2022;**150**:155754. https://doi.org/10.1016/j.cyto.2021.155754.
111. Zhang Q, Liu H, Yang J. Regulation of TGF-beta1 on PI3KC3 and its role in hypertension-induced vascular injuries. *Exp Ther Med* 2019;**17**:1717–27.
112. Fu S, Li YL, Wu YT *et al*. Icariside II attenuates myocardial fibrosis by inhibiting nuclear factor-kappaB and the TGF-beta1/Smad2 signalling pathway in spontaneously hypertensive rats. *Biomed Pharmacother* 2018;**100**:64–71. https://doi.org/10.1016/j.biopha.2018.01.138.
113. Laviades C, Varo N, Diez J. Transforming growth factor beta in hypertensives with cardiorenal damage. *Hypertension* 2000;**36**:517–22. https://doi.org/10.1161/01.HYP.36.4.517.
114. Li B, Khanna A, Sharma V *et al*. TGF-beta1 DNA polymorphisms, protein levels, and blood pressure. *Hypertension* 1999;**33**:271–5. https://doi.org/10.1161/01.HYP.33.1.271.
115. Lijnen PJ, Petrov VV, Fagard RH. Association between transforming growth factor-beta and hypertension. *Am J Hypertens* 2003;**16**:604–11. https://doi.org/10.1016/S0895-7061(03)00847-1.
116. Wolf G. Link between angiotensin II and TGF-beta in the kidney. *Miner Electrolyte Metab* 1998;**24**:174–80. https://doi.org/10.1159/000057367.
117. Zhu S, Liu Y, Wang L *et al*. Transforming growth factor-beta1 is associated with kidney damage in patients with essential hypertension: renoprotective effect of ACE inhibitor and/or angiotensin II receptor blocker. *Nephrol Dial Transplant* 2008;**23**:2841–6. https://doi.org/10.1093/ndt/gfn159.
118. Houlihan CA, Akdeniz A, Tsalamandris C *et al*. Urinary transforming growth factor-beta excretion in patients with hypertension, type 2 diabetes, and elevated albumin excretion rate: effects of angiotensin receptor blockade and sodium restriction. *Diabetes Care* 2002;**25**:1072–7. https://doi.org/10.2337/diacare.25.6.1072.
119. Praga M, Andrade CF, Luno J *et al*. Antiproteinuric efficacy of losartan in comparison with amlodipine in non-diabetic proteinuric renal diseases: a double-blind, randomized clinical trial. *Nephrol Dial Transplant* 2003;**18**:1806–13. https://doi.org/10.1093/ndt/gfg284.
120. Ramseyer VD, Garvin JL. Tumor necrosis factor-alpha: regulation of renal function and blood pressure. *Am J Physiol Renal Physiol* 2013;**304**:F1231–42. https://doi.org/10.1152/ajprenal.00557.2012.
121. Kobayashi R, Wakui H, Azushima K *et al*. An angiotensin II type 1 receptor binding molecule has a critical role in hypertension in a chronic kidney disease model. *Kidney Int* 2017;**91**:1115–25. https://doi.org/10.1016/j.kint.2016.10.035.
122. Elmarakby AA, Quigley JE, Imig JD *et al*. TNF-alpha inhibition reduces renal injury in DOCA-salt hypertensive rats. *Am J Physiol Regul Integr Comp Physiol* 2008;**294**:R76–83. https://doi.org/10.1152/ajpregu.00466.2007.
123. Verma MK, Jaiswal A, Sharma P *et al*. Oxidative stress and biomarker of TNF-alpha, MDA and FRAP in hypertension. *JMedLife* 2019;**12**:253–9. https://doi.org/10.25122/jml-2019-0031.
124. Puszkarska A, Niklas A, Gluszek J *et al*. The concentration of tumor necrosis factor in the blood serum and in the urine and selected early organ damages in patients with primary systemic arterial hypertension. *Medicine (Baltimore)* 2019;**98**:e15773. https://doi.org/10.1097/MD.0000000000015773.
125. Naya M, Tsukamoto T, Morita K *et al*. Plasma interleukin-6 and tumor necrosis factor-alpha can predict coronary endothelial dysfunction in hypertensive patients. *Hypertens Res* 2007;**30**:541–8. https://doi.org/10.1291/hypres.30.541.
126. Yoshida S, Takeuchi T, Kotani T *et al*. Infliximab, a TNF-alpha inhibitor, reduces 24-h ambulatory blood pressure in rheumatoid arthritis patients. *J Hum Hypertens* 2014;**28**:165–9. https://doi.org/10.1038/jhh.2013.80.
127. Zhao Q, Hong D, Zhang Y *et al*. Association between anti-TNF therapy for rheumatoid arthritis and hyperten-

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

sion: a meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2015;**94**:e731. https://doi.org/10.1097/MD.0000000000000731.
128. Lamb FS, Choi H, Miller MR *et al.* TNFalpha and reactive oxygen signaling in vascular smooth muscle cells in hypertension and atherosclerosis. *Am J Hypertens* 2020;**33**:902–13. https://doi.org/10.1093/ajh/hpaa089.
129. Ma Y, He FJ, MacGregor GA. High salt intake: independent risk factor for obesity? *Hypertension* 2015;**66**:843–9. https://doi.org/10.1161/HYPERTENSIONAHA.115.05948.
130. Afsar B, Kuwabara M, Ortiz A *et al.* Salt intake and immunity. *Hypertension* 2018;**72**:19–23. https://doi.org/10.1161/HYPERTENSIONAHA.118.11128.
131. Rucker AJ, Rudemiller NP, Crowley SD. Salt, hypertension, and immunity. *Annu Rev Physiol* 2018;**80**:283–307. https://doi.org/10.1146/annurev-physiol-021317-121134.
132. Takahashi H, Nakagawa S, Wu Y *et al.* A high-salt diet enhances leukocyte adhesion in association with kidney injury in young Dahl salt-sensitive rats. *Hypertens Res* 2017;**40**:912–20. https://doi.org/10.1038/hr.2017.31.
133. Dmitrieva NI, Burg MB. Secretion of von Willebrand factor by endothelial cells links sodium to hypercoagulability and thrombosis. *Proc Natl Acad Sci USA* 2014;**111**:6485–90. https://doi.org/10.1073/pnas.1404809111.
134. Krieglstein CF, Granger DN. Adhesion molecules and their role in vascular disease. *Am J Hypertens* 2001;**14**:S44–54. https://doi.org/10.1016/S0895-7061(01)02069-6.
135. Evans LC, Petrova G, Kurth T *et al.* Increased perfusion pressure drives renal T-cell infiltration in the Dahl salt-sensitive rat. *Hypertension* 2017;**70**:543–51. https://doi.org/10.1161/HYPERTENSIONAHA.117.09208.
136. Hashmat S, Rudemiller N, Lund H *et al.* Interleukin-6 inhibition attenuates hypertension and associated renal damage in Dahl salt-sensitive rats. *Am J Physiol Renal Physiol* 2016;**311**:F555–61. https://doi.org/10.1152/ajprenal.00594.2015.
137. Norlander AE, Saleh MA, Pandey AK *et al.* A salt-sensing kinase in T lymphocytes, SGK1, drives hypertension and hypertensive end-organ damage. *JCI Insight* 2017;**2**:**e92801**. https://doi.org/10.1172/jci.insight.92801.
138. Norlander AE, Saleh MA, Kamat NV *et al.* Interleukin-17A regulates renal sodium transporters and renal injury in angiotensin II-induced hypertension. *Hypertension* 2016;**68**:167–74. https://doi.org/10.1161/HYPERTENSIONAHA.116.07493.
139. Junger WG, Hoyt DB, Hamreus M *et al.* Hypertonic saline activates protein tyrosine kinases and mitogen-activated protein kinase p38 in T-cells. *J Trauma* 1997;**42**:437–45; discussion 443–5. https://doi.org/10.1097/00005373-199703000-00011.
140. Hernandez AL, Kitz A, Wu C *et al.* Sodium chloride inhibits the suppressive function of FOXP3+ regulatory T cells. *J Clin Invest* 2015;**125**:4212–22. https://doi.org/10.1172/JCI81151.
141. Zhang WC, Zheng XJ, Du LJ *et al.* High salt primes a specific activation state of macrophages, M(Na). *Cell Res* 2015;**25**:893–910. https://doi.org/10.1038/cr.2015.87.
142. Barbaro NR, Foss JD, Kryshtal DO *et al.* Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. *Cell Rep* 2017;**21**:1009–20. https://doi.org/10.1016/j.celrep.2017.10.002.
143. Guyton AC, Coleman TG, Cowley AV *et al.* Arterial pressure regulation. Overriding dominance of the kidneys in long-term regulation and in hypertension. *Am J Med* 1972;**52**:584–94. https://doi.org/10.1016/0002-9343(72)90050-2.
144. Rodríguez-Iturbe B, Quiroz Y, Ferrebuz A *et al.* Evolution of renal interstitial inflammation and NF-kappaB activation in spontaneously hypertensive rats. *Am J Nephrol* 2004;**24**:587–94. https://doi.org/10.1159/000082313.
145. Rodríguez-Iturbe B, Quiroz Y, Nava M *et al.* Reduction of renal immune cell infiltration results in blood pressure control in genetically hypertensive rats. *Am J Physiol Renal Physiol* 2002;**282**:F191–201. https://doi.org/10.1152/ajprenal.0197.2001.
146. Franco M, Martínez F, Quiroz Y *et al.* Renal angiotensin II concentration and interstitial infiltration of immune cells are correlated with blood pressure levels in salt-sensitive hypertension. *Am J Physiol Regul Integr Comp Physiol* 2007;**293**:R251–6. https://doi.org/10.1152/ajpregu.00645.2006.
147. Franco M, Tapia E, Bautista R *et al.* Impaired pressure natriuresis resulting in salt-sensitive hypertension is caused by tubulointerstitial immune cell infiltration in the kidney. *Am J Physiol Renal Physiol* 2013;**304**:F982–90. https://doi.org/10.1152/ajprenal.00463.2012.
148. Johnson RJ, Schreiner GF. Hypothesis: the role of acquired tubulointerstitial disease in the pathogenesis of salt-dependent hypertension. *Kidney Int* 1997;**52**:1169–79. https://doi.org/10.1038/ki.1997.442.
149. Asghar M, Chugh G, Lokhandwala MF. Inflammation compromises renal dopamine D1 receptor function in rats. *Am J Physiol Renal Physiol* 2009;**297**:F1543–9. https://doi.org/10.1152/ajprenal.00366.2009.
150. Gonzalez-Villalobos RA, Janjoulia T, Fletcher NK *et al.* The absence of intrarenal ACE protects against hypertension. *J Clin Invest* 2013;**123**:2011–23. https://doi.org/10.1172/JCI65460.
151. Giani JF, Bernstein KE, Janjulia T *et al.* Salt sensitivity in response to renal injury requires renal angiotensin-converting enzyme. *Hypertension* 2015;**66**:534–42. https://doi.org/10.1161/HYPERTENSIONAHA.115.05320.
152. Zhang RM, McNerney KP, Riek AE *et al.* Immunity and hypertension. *Acta Physiol* 2021;**231**:e13487. https://doi.org/10.1111/apha.13487.
153. Lima VV, Zemse SM, Chiao CW *et al.* Interleukin-10 limits increased blood pressure and vascular RhoA/Rho-kinase signaling in angiotensin II-infused mice. *Life Sci* 2016;**145**:137–43. https://doi.org/10.1016/j.lfs.2015.12.009.
154. Giannelou M, Mavragani CP. Cardiovascular disease in systemic lupus erythematosus: a comprehensive update. *J Autoimmun* 2017;**82**:1–12. https://doi.org/10.1016/j.jaut.2017.05.008.
155. Panoulas VF, Douglas KM, Milionis HJ *et al.* Prevalence and associations of hypertension and its control in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2007;**46**:1477–82. https://doi.org/10.1093/rheumatology/kem169.
156. Neimann AL, Shin DB, Wang X *et al.* Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006;**55**:829–35. https://doi.org/10.1016/j.jaad.2006.08.040.
157. Wolf VL, Ryan MJ. Autoimmune disease-associated hypertension. *Curr Hypertens Rep* 2019;**21**:10. https://doi.org/10.1007/s11906-019-0914-2.
158. Han C, Robinson DW, Hackett MV *et al.* Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2006;**33**:2167–72.
159. Anyfanti P, Gkaliagkousi E, Triantafyllou A *et al.* Hypertension in rheumatic diseases: prevalence, awareness, treat-

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

ment, and control rates according to current hypertension guidelines. *J Hum Hypertens* 2021;**35**:419–27. https://doi.org/10.1038/s41371-020-0348-y.
160. Al-Herz A, Ensworth S, Shojania K *et al*. Cardiovascular risk factor screening in systemic lupus erythematosus. *J Rheumatol* 2003;**30**:493–6.
161. Sabio JM, Vargas-Hitos JA, Navarrete-Navarrete N *et al*. Prevalence of and factors associated with hypertension in young and old women with systemic lupus erythematosus. *J Rheumatol* 2011;**38**:1026–32. https://doi.org/10.3899/jrheum.101132.
162. Shaharir SS, Mustafar R, Mohd R *et al*. Persistent hypertension in lupus nephritis and the associated risk factors. *Clin Rheumatol* 2015;**34**:93–7. https://doi.org/10.1007/s10067-014-2802-0.
163. Shanmugam VK, Steen VD. Renal manifestations in scleroderma: evidence for subclinical renal disease as a marker of vasculopathy. *Int J Rheumatol* 2010;**2010**:1–8. https://doi.org/10.1155/2010/538589.
164. Hadwen B, Stranges S, Barra L. Risk factors for hypertension in rheumatoid arthritis patients-a systematic review. *Autoimmun Rev* 2021;**20**:102786. https://doi.org/10.1016/j.autrev.2021.102786.
165. Barbhaiya M, Costenbader KH. Environmental exposures and the development of systemic lupus erythematosus. *Curr Opin Rheumatol* 2016;**28**:497–505. https://doi.org/10.1097/BOR.0000000000000318.
166. Teh P, Zakhary B, Sandhu VK. The impact of obesity on SLE disease activity: findings from the Southern California Lupus Registry (SCOLR). *Clin Rheumatol* 2019;**38**:597–600. https://doi.org/10.1007/s10067-018-4336-3.
167. Speyer CB, Costenbader KH. Cigarette smoking and the pathogenesis of systemic lupus erythematosus. *Expert Rev Clin Immunol* 2018;**14**:481–7. https://doi.org/10.1080/1744666X.2018.1473035.
168. Khraibi AA, Norman RA, Dzielak DJ. Chronic immunosuppression attenuates hypertension in Okamoto spontaneously hypertensive rats. *Am J Physiol* 1984;**247**:H722–6.
169. Bataillard A, Vincent M, Sassard J *et al*. Antihypertensive effect of an immunosuppressive agent, cyclophosphamide, in genetically hypertensive rats of the Lyon strain. *Int J Immunopharmacol* 1989;**11**:377–84. https://doi.org/10.1016/0192-0561(89)90084-2.
170. Mattson DL, James L, Berdan EA *et al*. Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. *Hypertension* 2006;**48**:149–56. https://doi.org/10.1161/01.HYP.0000228320.23697.29.
171. Rodríguez-Iturbe B, Ferrebuz A, Vanegas V *et al*. Early and sustained inhibition of nuclear factor-kappaB prevents hypertension in spontaneously hypertensive rats. *J Pharmacol Exp Ther* 2005;**315**:51–7. https://doi.org/10.1124/jpet.105.088062.
172. Koeners MP, Wesseling S, Sánchez M *et al*. Perinatal inhibition of NF-kappaB has long-term antihypertensive and renoprotective effects in fawn-hooded hypertensive rats. *Am J Hypertens* 2016;**29**:123–31. https://doi.org/10.1093/ajh/hpv065.
173. De Miguel C, Guo C, Lund H *et al*. Infiltrating T lymphocytes in the kidney increase oxidative stress and participate in the development of hypertension and renal disease. *Am J Physiol Renal Physiol* 2011;**300**:F734–42. https://doi.org/10.1152/ajprenal.00454.2010.
174. Mervaala E, Müller DN, Park JK *et al*. Cyclosporin A protects against angiotensin II-induced end-organ damage in double transgenic rats harboring human renin and angiotensinogen genes. *Hypertension* 2000;**35**:360–6. https://doi.org/10.1161/01.HYP.35.1.360.
175. Nava M, Quiroz Y, Vaziri N *et al*. Melatonin reduces renal interstitial inflammation and improves hypertension in spontaneously hypertensive rats. *Am J Physiol Renal Physiol* 2003;**284**:F447–54. https://doi.org/10.1152/ajprenal.00264.2002.
176. Rodriguez-Iturbe B, Zhan CD, Quiroz Y *et al*. Antioxidant-rich diet relieves hypertension and reduces renal immune infiltration in spontaneously hypertensive rats. *Hypertension* 2003;**41**:341–6. https://doi.org/10.1161/01.HYP.0000052833.20759.64.
177. Huang B, Cheng Y, Usa K *et al*. Renal tumor necrosis factor α contributes to hypertension in Dahl salt-sensitive rats. *Sci Rep* 2016;**6**:21960. https://doi.org/10.1038/srep21960.
178. Venegas-Pont M, Manigrasso MB, Grifoni SC *et al*. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. *Hypertension* 2010;**56**:643–9. https://doi.org/10.1161/HYPERTENSIONAHA.110.157685.
179. Mathis KW, Wallace K, Flynn ER *et al*. Preventing autoimmunity protects against the development of hypertension and renal injury. *Hypertension* 2014;**64**:792–800. https://doi.org/10.1161/HYPERTENSIONAHA.114.04006.
180. Murphy SR, Dahly-Vernon AJ, Dunn KM *et al*. Renoprotective effects of anti-TGF-β antibody and antihypertensive therapies in Dahl S rats. *Am J Physiol Regul Integr Comp Physiol* 2012;**303**:R57–69. https://doi.org/10.1152/ajpregu.00263.2011.
181. Dahly AJ, Hoagland KM, Flasch AK *et al*. Antihypertensive effects of chronic anti-TGF-beta antibody therapy in Dahl S rats. *Am J Physiol Regul Integr Comp Physiol* 2002;**283**:R757–67. https://doi.org/10.1152/ajpregu.00098.2002.
182. Rudemiller NP, Lund H, Priestley JR *et al*. Mutation of SH2B3 (LNK), a genome-wide association study candidate for hypertension, attenuates Dahl salt-sensitive hypertension via inflammatory modulation. *Hypertension* 2015;**65**:1111–7. https://doi.org/10.1161/HYPERTENSIONAHA.114.04736.
183. De Albuquerque DA, Saxena V, Adams DE *et al*. An ACE inhibitor reduces Th2 cytokines and TGF-beta1 and TGF-beta2 isoforms in murine lupus nephritis. *Kidney Int* 2004;**65**:846–59. https://doi.org/10.1111/j.1523-1755.2004.00462.x.
184. Bernstein KE, Khan Z, Giani JF *et al*. Angiotensin-converting enzyme in innate and adaptive immunity. *Nat Rev Nephrol* 2018;**14**:325–36. https://doi.org/10.1038/nrneph.2018.15.
185. Liu W, Yamashita T, Kurata T *et al*. Protective effect of telmisartan on neurovascular unit and inflammasome in stroke-resistant spontaneously hypertensive rats. *Neurol Res* 2015;**37**:491–501. https://doi.org/10.1179/1743132815Y.0000000002.
186. Sepehri Z, Masoumi M, Ebrahimi N *et al*. Losartan and captopril lead to upregulation of TGF-β, and downregulation of IL-6 in coronary artery disease and hypertension. *PLoS One* 2016;**11**:e0168312. https://doi.org/10.1371/journal.pone.0168312.
187. Sonmez A, Kisa U, Uckaya G *et al*. Effects of losartan treatment on T-cell activities and plasma leptin concentrations in primary hypertension. *J Renin Angiotensin Aldosterone Syst* 2001;**2**:112–6. https://doi.org/10.3317/jraas.2001.011.
188. Hofbauer R, Frass M, Pasching E *et al*. Furosemide and spironolactone reduce transmigration of leukocytes

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024

through endothelial cell monolayers. *J Toxicol Environ Health A* 2002;**65**:685–93. https://doi.org/10.1080/15287390252900386.

189. Amador CA, Barrientos V, Peña J *et al*. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the downregulation of regulatory T lymphocytes. *Hypertension* 2014;**63**:797–803. https://doi.org/10.1161/HYPERTENSIONAHA.113.02883.
190. Zhou MS, Schulman IH, Jaimes EA *et al*. Thiazide diuretics, endothelial function, and vascular oxidative stress. *J Hypertens* 2008;**26**:494–500. https://doi.org/10.1097/HJH.0b013e3282f3e39d.
191. Fonseca HA, Fonseca FA, Lins LC *et al*. Antihypertensive therapy increases natural immunity response in hypertensive patients. *Life Sci* 2015;**143**:124–30. https://doi.org/10.1016/j.lfs.2015.10.030.
192. Toba H, Nakagawa Y, Miki S *et al*. Calcium channel blockades exhibit anti-inflammatory and antioxidative effects by augmentation of endothelial nitric oxide synthase and the inhibition of angiotensin converting enzyme in the N(G)-nitro-L-arginine methyl ester-induced hypertensive rat aorta: vasoprotective effects beyond the blood pressure-lowering effects of amlodipine and manidipine. *Hypertens Res* 2005;**28**:689–700.

Downloaded from https://academic.oup.com/ckj/article/16/9/1403/7085012 by Koç University Suna Kraç Library user on 30 January 2024