Molecular Pathways in Hypertensive Renal Damage

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26.1 Introduction

Hypertension is a chronic disease that afflicts close to one-third of the adult population worldwide [1–3]. This disease increases the risk for strokes, heart attacks, atherosclerosis, and chronic kidney disease. There are numerous drugs that are used to decrease blood pressure and control hypertension. These antihypertensive drugs fall into four major classes:β-blockers, vasodilators, renin-angiotensin system inhibitors, and diuretics. Antihypertensive drugs have been fairly effective in lowering blood pressure but have varying effects on progression of diseases associated with hypertension [3–6]. Patients with hypertension also become less responsive to drugs and can be treated with up to three antihypertensive drugs to control blood pressure [7, 8]. Moreover, there are a number of patients that eventually become resistant to antihypertensive drugs [3, 9, 10]. This suboptimal control of blood pressure results in a higher incidence of strokes, heart attacks, atherosclerosis, and chronic kidney disease [1–3]. This chapter will focus on the molecular pathways responsible for hypertensive renal damage that results in the progression of chronic kidney disease to end-stage renal disease (ESRD).

Chronic kidney disease and ESRD prevalence have been steadily increasing with the incidence of ESRD rising at a rate of 5–8% per year in the USA and worldwide [2]. Elevated blood pressure is clearly associated with chronic kidney disease, and decreasing blood pressure clearly slows but does not stop the progression of

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chronic kidney disease [3, 7, 11]. To this end, the increase in ESRD is beginning to plateau and could be the result of improved rates of blood pressure control [3, 5]. In addition to elevated blood pressure, there are a number of molecular pathways that contribute to hypertensive renal damage. These factors include hormonal and paracrine factors, genetic and environmental factors, nephron number, renal hemodynamic changes, tubulointerstitial changes, and inflammatory factors (Fig. 26.1). Pathological changes in these factors during hypertension ultimately cause glomerulosclerosis and tubulointerstitial fibrosis in the kidney resulting in progression to chronic kidney disease.

Renal damage and chronic kidney disease in hypertension have become even more complex by the coexistence of these diseases and also the presence of other disease such as diabetes [12–16]. Patients in the category of uncomplicated hypertension will develop minimal renal damage in the absence of a severe elevation in blood pressure [12, 13, 16]. Kidney injury in uncomplicated hypertension has been separated into distinct clinical and histopathological categories of benign or malignant nephrosclerosis [12, 15, 16]. On the other hand, patients with diabetes and nondiabetic chronic kidney disease have increased susceptibility to even moderate

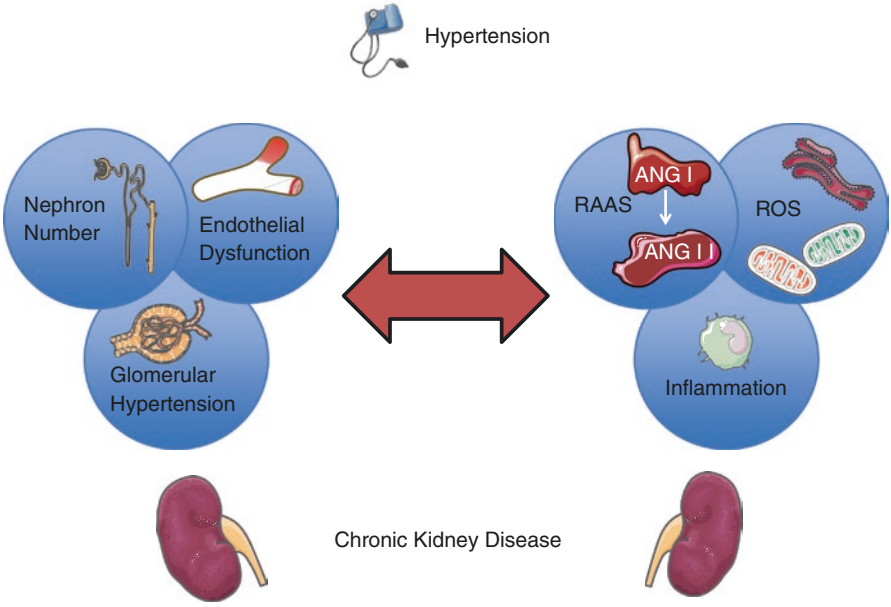

Fig. 26.1 Schematic representation of mechanisms contributing to the development of hypertension-induced chronic kidney disease. Renal and vascular function and structural aspects contribute to progression of kidney disease. These include low nephron number, endothelial dysfunction, and glomerular hypertension. Hormonal and paracrine factors, for example, an elevated renin-angiotensin-aldosterone system (RAAS), oxidative stress (ROS), and inflammation, also contribute to chronic kidney disease in hypertension. Interactions between renal vascular functional and structural factors and hormonal and paracrine factors ultimately lead to glomerulosclerosis and tubulointerstitial fibrosis resulting in progressive chronic kidney disease

elevations in blood pressure [17–19]. The development of chronic kidney disease increases the risk for adverse cardiovascular events and death in patients with hypertension [2]. Kidney histopathology demonstrating vascular lesions of hyaline arteriosclerosis is a hallmark of hypertensive injury [14, 16]. This vascular pathology is not always prominent in chronic kidney disease; however, there can be accelerated segmental or global glomerulosclerosis evident in hypertension [14, 16]. Experimental investigations are beginning to understand the pathology observed under these different clinical pathologies of renal disease in hypertension. Relevant major underlying pathological and molecular mechanisms underlying hypertensive renal damage will be addressed.

26.2 Blood Pressure, Glomerular Hypertension, and Nephron Number

Elevated blood pressure and nephron number are major contributing factors to hypertensive renal damage and progression to chronic kidney disease (Fig. 26.2) [14–16]. A systemic elevation in blood pressure has consequences on the renal vascular bed and can eventually result in increased glomerular capillary pressure [15, 16]. The renal vasculature has autoregulatory mechanisms to maintain constant

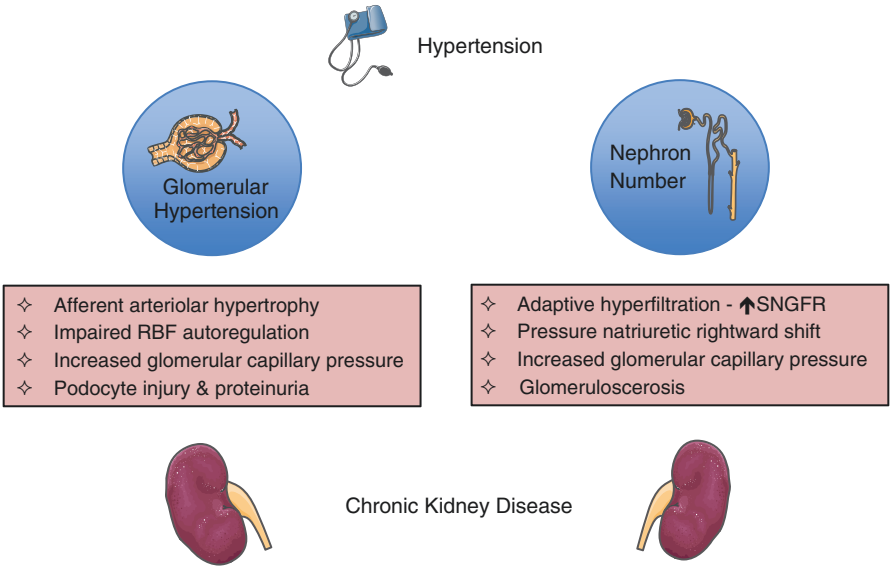

Fig. 26.2 Elevated glomerular pressure and nephron deficiency contribute to hypertension-induced chronic kidney disease. Elevated vascular and glomerular pressure causes afferent arteriolar hypertrophy, impaired renal blood flow (RBF) autoregulation, and podocyte injury and proteinuria. Low nephron number results in an increase in single nephron glomerular filtration rate (SNGFR), rightward shift of the pressure-natriuretic relationship, and glomerular hypertension to result in glomerulosclerosis

renal blood flow and glomerular hydrostatic pressure [15]. Afferent arterioles respond to an increase in systemic blood pressure by contracting through the vascular smooth muscle cell myogenic response and the macula densa-mediated tubuloglomerular feedback response [15, 20]. A sustained elevation in blood pressure does not lead to glomerular lesions or damage as long as this afferent arteriolar autoregulatory response is properly maintained [15]. Glomerular nephron number, endothelial dysfunction, elevated renin-angiotensin system, oxidative stress, and inflammation contribute to changes in afferent autoregulation in hypertension [15, 20]. Renal blood flow autoregulation will ultimately be impaired and result in an elevated glomerular capillary pressure [20]. The increase in glomerular capillary pressure results in an increased filtration fraction and loss of glomerular filtration barrier. Glomerular barrier breakdown and an increased glomerular capillary hydrostatic pressure will lead to clinical proteinuria and glomerular destruction [14–16].

Glomerular hypertension is a critical component in progression of kidney damage in hypertension [13, 15, 21]. Afferent arterioles and glomerular capillaries will have structural adaptations to the elevated systemic blood pressure [15, 22]. Adaptive structural changes of the afferent arterioles include narrowing of the lumen diameter to combat the increase in wall stress [22–24]. Decreases in afferent arteriolar diameter will result in amplifying the already elevated blood pressure [15, 23]. Over time the afferent arteriole will develop hypertrophy in response to chronic blood pressure elevations [15, 23]. Afferent arteriolar hypertrophy leads to an ischemic injury in the glomeruli and tubulointerstitial structures [15, 22, 23]. At the level of the glomerulus, increased capillary pressure results in capillary stretching, endothelial damage, and breakdown of the capillary barrier [15, 23]. This leads to increased glomerular protein filtration that causes segmental necrosis and glomerulosclerosis [15, 22, 23]. Glomerular sclerosis and preglomerular vascular structural alterations can cause a further reduction in renal blood flow and enhancing the progression of chronic kidney disease [21–24].

Nephron number is another key component to the development of hypertension and the likelihood for the development of hypertension-induced chronic kidney disease [25–27]. The human kidney can have anywhere from 200,000 to 2.5million nephrons [25, 28, 29]. Brenner and colleagues proposed and provided convincing data that low nephron number increased the potential for a person to develop hypertension in adulthood [27, 28]. Approximately 50% of the children born with one kidney will have a reduced glomerular filtration rate and develop hypertension by the age of 18 [29, 30]. Hypertension occurs because a low nephron number leads to a maladaptive glomerular hyperfiltration [25, 26]. Congenital or acquired nephron deficiency reduces filtration surface area, thus reducing filtered load and renal excretory capacity [27, 31]. Ultimately, this shifts the pressure-natriuretic curve to the right and requires a higher arterial pressure to maintain proper sodium balance over time [25, 26].

There is a strong association between low nephron number and hypertension in humans [25–27]. Patients with primary hypertension have been demonstrated to have significantly fewer nephrons when compared to match control subjects [28, 32]. Australian Aboriginal population has a low nephron number and has been

extensively studied [33, 34]. This unique human population has a high prevalence of hypertension and chronic kidney disease [34]. There is still debate as to whether hypertension is the cause or the consequence of nephron deficiency. The contribution for nephron deficiency to a progressive decline in glomerular filtration rate and onset of hypertension is not clear. In line with decreased nephron number contributing to the hypertension, there are data from adult kidney donors. Normotensive adult kidney donors had a 5 mmHg greater increase in arterial pressure 5–10 years following donation compared to age-matched individuals with two intact kidneys [35, 36]. Although a small increase, this significantly increases the risk for cardiovascular diseases. Renal compensatory growth in congenital or acquired low nephron number could be a factor that leads to hypertension-induced kidney damage [25, 26]. The kidney compensates for low nephron number by increasing the glomerular filtration carried out by each glomerulus or the single nephron glomerular filtration rate [25, 27, 31]. This compensation results in the rightward shift in the pressure-natriuretic relationship and eventually leads to extracellular fluid volume expansion. To overcome this increase in extracellular volume, there is an increase in arterial pressure. Increases in arterial pressure in a setting of low nephron number have a feed forward effect of increasing glomerular capillary pressure and promoting hyperfiltration to the point where single nephron glomerular filtration rate can no longer be increased [25, 27]. The increase in glomerular capillary pressure results in glomerulosclerosis and further nephron loss and progression to chronic kidney disease [25, 27]. Human studies support this scenario because there is an inverse association between nephron number and glomerulosclerosis and intimal thickening of interlobular arteries [29, 37]. Therefore, renal adaptation in response to nephron deficiency increases the risk for developing hypertension and chronic kidney disease.

The podocyte and filtration barrier appears to be a critical component with glomerular hypertension and low nephron number in hypertension-induced chronic kidney disease [22, 38]. Podocyte density or insufficiency has been demonstrated to be a contributor to the rapid progression of diabetic nephropathy in Pima Indians [39]. Glomerular hyperfiltration associated with hypertension and low nephron number damages the glomerular filtration barrier [22]. Damage to the glomerular filtration barrier causes proteinuria and podocyte effacement [22, 38]. Podocytes respond to injurious stimuli in different ways including gradual simplification of the interdigitating process pattern until the cell flattens and lengthens [22, 38]. Podocyte injury progresses and the podocytes will detach from the basal membrane or undergo apoptosis [38]. Other factors such as an increased renin-angiotensin system and oxidative stress associated with hypertension can accelerate podocyte hypertrophy and apoptosis [22, 38]. This podocyte injury leads to passage of tubular-derived products into the interstitium and peritubular capillary spaces to accelerate tubulointerstitial injury and renal fibrosis [22, 38].

Progression of renal injury in hypertension can vary widely across animal models and human populations [14, 25]. The increase in blood pressure can cause renal structural adaptations that contribute to chronic kidney disease [14, 22]. These include vascular structural adaptations and responses to increases in glomerular

capillary pressure [22–24]. Another factor is nephron number and if nephron deficiency is congenital or acquired [25–27]. Other mechanisms responsible for susceptibility to hypertension-induced renal injury include the complex interaction between an elevated blood pressure, altered hormonal and paracrine factors, inflammation, and underlying endothelial function and renal diseases [14–16]. The contributions for endothelial function, renin-angiotensin system, oxidative stress, and inflammation to hypertension-induced progression of chronic kidney disease will be discussed in subsequent sections.

26.3 Endothelial Dysfunction

Endothelial cells are at an interface between circulating factors and organs including the kidney. The endothelial layer contributes importantly to vascular function and is critically involved in the control of vasomotor tone and permeability [40, 41]. It has become readily apparent that changes in the endothelial cells during diseases can be predictive of long-term health [14–16]. During the course of hypertension, there are changes in endothelial cells to a point where dysfunction occurs [14, 15]. Endothelial dysfunction is a precursor and predictor for chronic kidney disease as well as cardiovascular morbidity and mortality [15, 40].

Endothelial cells produce important autocrine and paracrine factors and respond to changes in circulating hormonal factors and cellular components such as inflammatory cells [40]. Major factors that vasodilate blood vessels and promote endothelial cell health include nitric oxide, prostacyclin, and epoxyeicosatrienoic acids (EETs) [40]. Generation of these endothelial factors tends to be decreased in disease states that result in endothelial dysfunction [15, 40]. On the other hand, endothelial cells generate or regulate vasoconstrictor factors such as thromboxane, angiotensin II, and endothelin-1. Endothelial dysfunction in hypertension is associated with elevated levels of these vasoconstrictor endothelial factors [15, 40]. Lastly, reactive oxygen species and oxidative stress contribute significantly to endothelial dysfunction in hypertension [42]. Endothelial cell nitric oxide synthase (eNOS) uncoupling and NADPH oxidase activity result in increased reactive oxygen species generation and oxidative stress [42]. Hypertension causes endothelial dysfunction by tilting the balance of the various endothelial cell factors (Fig. 26.3) [14, 40, 42].

Endothelial dysfunction in hypertension leads to renal vasoconstriction and vascular damage [14, 16, 43]. The capillary system in the renal medulla becomes damaged in hypertension [43]. Renal medulla hypoxia occurs with hypertension and endothelial damage resulting in vascular rarefaction of the capillaries [15, 43, 44]. Reduced nitric oxide synthesis by endothelial cells is a key event underlying damage to kidney arteries, arterioles, and capillaries [45, 46]. This reduced nitric oxide bioavailability can enhance the progression of chronic kidney disease in hypertension [43, 46].

Nitric oxide signaling is impaired in spontaneously hypertensive rats (SHR) and deoxycorticosterone (DOCA)-salt hypertensive rodents and is linked to renal injury [47, 48]. Factors that contribute to impaired nitric oxide signaling include decreased

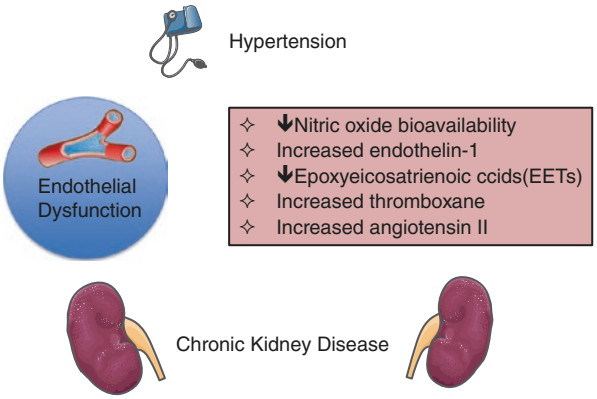

Fig. 26.3 Endothelial dysfunction is an early event that precedes cardiovascular events and end-organ damage in hypertension. Generation of endothelial nitric oxide and epoxyeicosatrienoic acids (EETs) are decreased in hypertension. Endothelin-1, angiotensin II, and thromboxane generation are increased and contribute to endothelial dysfunction. Chronic kidney disease progression is accelerated in the presence of endothelial dysfunction

L-arginine bioavailability, decrease in cofactors required for nitric oxide synthesis, and increased production of superoxide [42, 43]. Nitric oxide production could be decreased due to inappropriate phosphorylation of eNOS to decrease enzymatic activity [49]. Endothelial cell oxidative stress during hypertension has been connected with renal damage [43, 47]. An increase in reactive oxygen species production and decreased antioxidant defense capacity predispose tissues to damage [43, 47]. Overall, there is strong evidence for decreased nitric oxide and increased oxidative stress that contributes to endothelial dysfunction and the progression of chronic kidney disease.

Decreased cyclooxygenase (COX) generation of prostacyclin (PGI_2) and epoxygenase generation of EETs by endothelial cells also contribute to renal vasoconstriction and endothelial dysfunction in hypertension [50, 51]. Decreased EET levels are a key factor early in the progression of endothelial dysfunction in hypertension [50, 52]. Angiotensin II hypertension is associated with an increased renal vascular expression of soluble epoxide hydrolase (sEH) enzyme that degrades EETs and results in decreased EET levels [52]. Likewise, sEH inhibition has been demonstrated to increase renal vascular EET levels, decrease blood pressure, and prevent hypertensive kidney injury [52–54]. Inflammatory responses are another factor critically involved in endothelial dysfunction [55, 56]. Endothelial cell upregulation of adhesion molecules, chemokine generation, and production of plasminogen activator inhibitor-1 occur in hypertension [57]. Elevated circulating IL-6 and TNF-α levels are key inflammatory factors leading to endothelial dysfunction and chronic kidney disease progression in hypertension [58–60]. Recent efforts have focused on increasing EETs and decreasing inflammation as a means to improve endothelial function in hypertension and prevent renal injury [61].

Vasoconstrictor factors also influence endothelial function in hypertension and the progression of kidney disease. Endothelin-1 (ET-1) is generated by endothelial

cells and is a potent renal vasoconstrictor [55, 62, 63]. Renal ET-1 levels are increased in hypertension and can contribute to arteriolar remodeling [62, 63]. Increased oxidative stress results from increased ET-1 levels [64–66]. ET-1 can also increase TGF-β that contributes to renal vascular inflammation and fibrosis in hypertension [62, 67]. Elevated angiotensin II levels contribute to endothelial dysfunction and renal damage in hypertension [14, 63, 68]. Angiotensin II causes renal vasoconstriction, increases oxidative stress and inflammation in endothelial cells, and results in vascular remodeling [42, 69]. An endothelial and vascular factor linked to angiotensin II is 20-hydroxyeicosatetraenoic acid (20-HETE). 20-HETE is a renal vasoconstrictor with pro-inflammatory actions. Endothelial cell angiotensin converting enzyme activity is increased by 20-HETE and contributes to angiotensin-dependent hypertension [70]. 20-HETE has also been associated with chronic kidney disease [50, 71, 72]. Taken together, there is strong evidence that increased endothelial cell 20-HETE, angiotensin II, and ET-1 in hypertension participate in endothelial dysfunction and chronic kidney disease.

26.4 Renin-Angiotensin-Aldosterone System

An inappropriate activation of the renin-angiotensin-aldosterone system (RAAS) contributes not only to hypertension but also to the progression of chronic kidney disease to ESRD (Fig. 26.4) [73, 74]. Angiotensin II has numerous hormonal actions that alter cardiovascular and renal function. Synthesis of angiotensin II depends on the release of renin by the juxtaglomerular cells in the kidney [73]. The hydrostatic pressure at the level of the afferent arterioles, angiotensin II levels, and salt delivery to the macula densa cells regulates renin release [20]. Angiotensinogen is converted to angiotensin I by renin. ACE then converts angiotensin I to angiotensin II at the level of endothelial cells and cell membranes in the heart, brain, and kidney [20, 73]. Angiotensin II has biological actions on the renal arterioles and epithelial cells that are mediated via the angiotensin type 1 (AT1) or angiotensin type 2 (AT2) receptors [20, 72]. AT1 receptors are responsible for the majority of the actions attributed to angiotensin II. Angiotensin II AT1 receptor activation mediates renal hemodynamic actions, endocrine actions, and mitogenic effects in the kidney [73]. AT2 receptors in the kidney can oppose the AT1 receptor activities [73]. Hypertension is accompanied by an inappropriate AT1 receptor activation that results in deleterious events and renal damage [72, 73].

Renal hemodynamic actions of angiotensin II are due to actions on the afferent and efferent arterioles [20]. Angiotensin II causes vasoconstriction of afferent and efferent arterioles leading to a reduction in renal blood flow and an elevated glomerular capillary in hypertension [20]. Increased intrarenal angiotensin II levels in hypertension enhance preglomerular arteriolar and tubuloglomerular feedback sensitivity [74, 75]. These angiotensin actions in hypertension increase renal vascular resistance, increase glomerular capillary pressure, and shift the pressure-natriuretic curve to the right [15, 76]. Angiotensin II also stimulates aldosterone secretion that causes a further shift in the pressure-natriuretic curve [15, 74, 76]. The renal

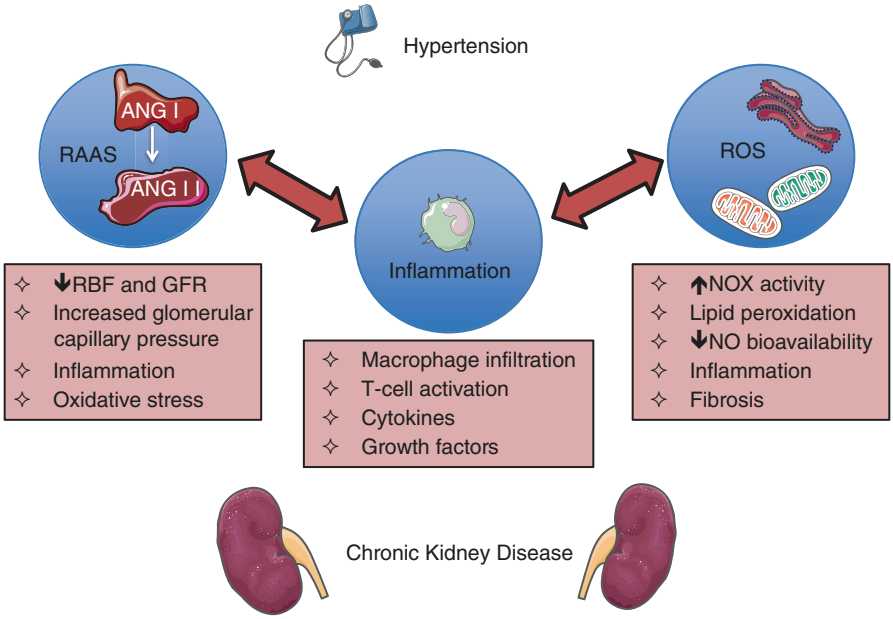

Fig. 26.4 Hormonal and paracrine factors contribute to hypertension-induced chronic kidney disease. Elevated renin-angiotensin-aldosterone system (RAAS) leads to decreased renal blood flow (RBF) and glomerular filtration rate (GFR), inflammation, and oxidative stress. Inflammation involves macrophage infiltration and T-cell activation with generation of cytokines and growth factors. Reactive oxygen species (ROS) increases NADPH oxidase (NOX) activity, decreases nitric oxide (NO) bioavailability, and causes lipid peroxidation and inflammation. There are extensive interactions between RAAS, inflammation, and ROS that contribute to hypertension-induced chronic kidney disease

hemodynamic actions of angiotensin II are not the only actions contributing to hypertension-induced chronic kidney damage.

Angiotensin II has potent inflammatory actions that contribute to the pathogenesis of chronic kidney disease [72, 73]. Immune and inflammatory responses in renal endothelial and epithelial cells are intensified by angiotensin II [58, 59, 77, 78]. Chemotaxis, proliferation, and differentiation of monocytes into macrophages are stimulated by angiotensin II [59, 78]. Angiotensin II stimulation of pro-fibrotic cytokines and growth factors have detrimental effects on the kidney [59, 74]. Activation of TGF-β causes hypertrophy and proliferation of mesangial cells [59, 79]. TGF-β upregulates type 1 procollagen, plasminogen activator inhibitor-1, and fibronectin [59, 79]. Increases in growth factors such as TGF-β, VEGF, and IGF cause proliferation of fibroblasts and increase extracellular matrix protein synthesis as well as by decreasing apoptosis of resident interstitial cells leading to glomerulosclerosis and renal interstitial fibrosis [14, 59, 79]. Likewise, aldosterone potentiates TGF-β mitogenic activity and exerts pro-inflammatory and pro-fibrotic actions [55, 59]. Consequently, an elevated RAAS in hypertension makes a critical contribution to renal fibrosis and glomerulosclerosis.

In addition to and linked to the inflammatory actions, angiotensin II stimulates ET-1 generation and increases oxidative stress [67, 80]. Angiotensin II via AT1 receptors is a potent stimulator of NADPH oxidase and increases ET-1 generation in renal arterioles [67, 68, 80]. ET-1 is a factor that in the kidney recruits T cells and macrophages and increases NF-kB in activated B cells [59, 67, 77, 78]. Increases in reactive oxygen species lead to additional renal injury that enhances inflammation and fibrosis [43, 47]. Angiotensin II actions in hypertension include inflammation, accumulation of cells and matrix, and exacerbation by increased cell adhesion to result in renal injury [73, 74]. Glomerulosclerosis and tubulointerstitial fibrosis in response to an elevated RAAS create a progressive course of chronic kidney disease, proteinuria, decline in glomerular filtration rate, and a vicious cycle of continuous RAAS activation [73, 74].

RAAS inhibition is a common and effective treatment for hypertension. Evidence in humans suggests that blockade of the RAAS provides renal protection beyond blood pressure lowering in hypertension [6, 81, 82]. RAAS blockade reduces urinary protein and overall renal risk to a greater degree than other blood pressure-lowering therapies [81, 82]. This additional renal protection could be in part due to the anti-inflammatory actions demonstrated for RAAS inhibitors [73, 82, 83]. RAAS inhibition reduces renal cell proliferation, circulating T cells, and cytokine production [56, 84, 85]. The renin inhibitor, aliskiren, markedly reduces TGF-β, albuminuria, and renal fibrosis in hypertensive mice independently of a change in blood pressure [14, 16]. On the other hand, AT2 receptor activation could combat hypertension-induced chronic kidney disease [73]. AT2 receptor activation reduces renal inflammation in a mouse model of renal fibrosis [72, 73]. Taken together, RAAS inhibition appears to be a therapeutic approach that can combat progressive kidney disease in hypertension by mechanisms independent of blood pressure lowering.

26.5 Reactive Oxygen Species

Oxidative stress and the generation of reactive oxygen species are due to an imbalance between oxidants and antioxidants that can result in kidney damage (Fig. 26.4) [42, 86, 87]. Patients with mild to moderate renal insufficiency or ESRD have oxidative stress [14, 16, 88]. Elevated reactive oxygen species production has been shown in humans with renovascular, essential, and malignant hypertension [14, 16]. Increased plasma malondialdehyde levels, a marker of oxidative stress, are increased in patients with chronic renal failure when compared to those with essential hypertension despite similar blood pressures suggesting that inflammation and an altered redox state could be the reason for the increase in oxidative stress [16, 88].

Hypertension and chronic kidney disease have increased levels of oxidant molecules including hydrogen peroxide or hydroxyl radicals and decreased antioxidants like catalase, glutathione dismutase, or superoxide dismutase [42, 43, 87]. Asymmetric dimethylarginine, a nitric oxide synthase inhibitor, is increased in chronic kidney

disease [86, 87]. These changes result in reactive oxygen species generation by the arterioles, macula densa, podocytes, and epithelial cells [86, 87]. NADPH oxidase (NOX) has surfaced as the main source for reactive oxygen species in renal arterioles [87]. Vasoactive agents such as angiotensin II, shear stress, and inflammation can induce NOX or mitochondrial reactive oxygen species generation [87]. Reactive oxygen species have renal vascular actions to cause afferent arteriolar constriction, reduce nitric oxide levels, and contribute to hypertension and kidney injury [87, 89].

Indeed, elevated reactive oxygen species production by NOX and hypertension is closely associated with kidney damage as shown in different models of hypertension Dahl salt-sensitive rats, deoxycorticosterone acetate (DOCA) salt rats, and angiotensin II hypertensive rats [90, 91]. In regard to a prominent role of oxidative stress in hypertensive kidney injury, it is important to note that NOX-mediated reactive oxygen species production in hypertension is linked to endoplasmic reticulum (ER) stress. Accumulating evidence shows that during ER stress, reactive oxygen species production by NOX is increased [92, 93]. It is also demonstrated that in a setting of ER stress, reactive oxygen species are produced by NOX2 and NOX4 and play a critical role in hypertension [94]. Indeed, hypertension has been recently linked to ER stress, and there is accumulating evidence that ER stress is an important factor in hypertensive kidney injury [95–97]. The role of NOX-mediating ER stress in the above models of hypertensive renal injury remains to be explored, but a role of NOX2 has been shown to be associated with ERstress-induced renal cell death [98]. These findings provide a link between oxidative stress and ER stress in hypertensive renal injury.

Interactions between oxidative stress, renal vascular function, and inflammation are contributing factors to kidney disease progression in hypertension. Excess reactive oxygen species leads to oxidative stress and predisposes the kidney to tissue damage [14, 42, 43]. Reactive oxygen species enzyme activation in renal arterioles results in redox signaling to generate inflammation transcription factors [86, 87]. A subsequent decrease in nitric oxide bioavailability leads to lipid peroxidation and production of growth factors to induce renal fibrosis [42, 87]. Reactive oxygen species also promote accumulation of myofibroblasts via epithelial-mesenchymal transition of proximal tubular and mesangial cells [99]. This results in remodeling of the extracellular matrix of the tubulointerstitium leading to renal fibrosis, a common feature of hypertensive renal injury [99]. In addition to direct actions to constrict the afferent arteriole, reactive oxygen species can enhance tubuloglomerular feedback responses to further increase renal vascular resistance [87]. Endothelial cell generation of COX-derived thromboxane increases in response to elevations in oxidative stress [87]. Thromboxane causes afferent arteriolar vasoconstriction and increases platelet activity [86, 87]. At the level of kidney epithelial transport, reactive oxygen species diminishes oxygen utilization for sodium transport [87]. Overall, increases in reactive oxygen species cause endothelial dysfunction, afferent arteriolar constriction, and renal inflammation resulting in progression of chronic kidney disease to ESRD in hypertension.

26.6 Inflammation

Inflammation is an important contributing aspect to endothelial dysfunction and renal injury in hypertension. In addition, there have been a number of rodent studies that have demonstrated that the adaptive immune response and renal inflammation participate in the development of hypertension [56, 59]. Multiple studies with immunosuppressive agents such as mycophenolate mofetil (MMF) and the TNF-α receptor blocker etanercept lower blood pressure and decrease renal damage [59, 100–102]. A role for T cells and B cells in hypertension and progression of kidney disease has also been examined [56, 103, 104]. Mice deficient in T and B cells demonstrate attenuated angiotensin-dependent hypertension [59, 104, 105]. Interestingly, adoptive transfer of T cells but not B cells restored the hypertensive response to angiotensin II [59, 78]. Mice lacking T and B cells also attenuated renal injury associated with angiotensin hypertension [59, 78]. MMF inhibition of T and B cell proliferation was demonstrated to lower blood pressure in Dahl salt-sensitive hypertension [106]. Other studies have determined a potential contribution for CCR5-positive cells and RANTES [59, 60, 106]. As a whole, experimental studies have supported the concept that activated T cells in the kidney and cytokine release contribute to the development of hypertension.

Cytokine activation has deleterious actions on renal vascular and tubular epithelial cells that contribute to hypertension and progression of chronic kidney disease (Fig. 26.4). Elevations in Th1 cytokines such as TNF-α and IL-6 associate with increased blood pressure [58, 59, 107]. Likewise, hypertensive patients have an upregulation of the T-cell renin-angiotensin system [77]. Glomerular epithelial and endothelial cell has an increased production of TNF-α in angiotensin hypertension [108]. TNF-α receptor antagonism decreases blood pressure and reduces renal injury in DOCA-salt, angiotensin, and autoimmune-associated hypertension [102, 107, 108]. Renal injury prevention by etanercept can be independent of blood pressure lowering. IL-6 is another cytokine that can contribute to renal inflammation, hypertension, and progressive renal damage [56, 58]. Angiotensin-dependent hypertension is attenuated in IL-6-deficient mice [58]. These findings have demonstrated that T-cell infiltration into the kidney and generation of TNF-α and IL-6 contribute to hypertension and kidney damage.

MCP-1 and activation of CCR2 receptor can contribute to hypertension and chronic kidney disease. The MCP-1 inhibitor bindarit decreases renal inflammation and fibrosis and improves renal endothelial function independent of blood pressure lowering [109]. CCR2 inhibition also decreases renal inflammation and delays the progression of angiotensin hypertension [107]. The inflammatory cytokine IL-17 produced by Th17m CD8+ cells, neutrophils, and T cells also contributes to hypertension [110]. Angiotensin-dependent hypertension and renal inflammation are decreased in IL-17-deficient mice (110). Finally, Tregs are another cell type that influences blood pressure control and progressive renal injury in hypertension [59, 60]. Tregs reduce T-cell activation and are protective in hypertension. Dahl salt-sensitive hypertensive rats that harbor Brown Norway chromosome 2 have increased Treg cells and increased generation of the cytokine IL-10 to reduce blood pressure

and decrease renal injury [60]. Taken together, T-cell activation of pro-inflammatory cytokines contributes to hypertension and kidney disease progression that can be opposed by Tregs that limit T-cell activation.

The actions of renal inflammatory cytokines on the renal vascular and epithelial cells contribute significantly to kidney disease associated with hypertension. Renal hemodynamic consequences for elevated kidney cytokines are a reduced renal blood flow and rightward shift of the pressure-natriuretic relationship [56, 111]. Although the contribution for specific cytokines has been difficult to determine, renal inflammation decreases renal blood flow and glomerular filtration rate and leads to a progressive decline that results in ESRD [56]. One cytokine that could contribute to impaired renal hemodynamics is MCP-1 and CCR2 receptors. CCR2 receptor inhibition improves renal hemodynamics in hypertension [107]. TNF-α that is administered acutely can lower renal blood flow and glomerular filtration rate [112]. TGF-β is a growth factor that impairs afferent arteriolar autoregulatory responses [113]. The impaired afferent arteriolar autoregulatory responses have been attributed to TGF-β stimulation of reactive oxygen species [113]. IL cytokines also have renal vascular actions. IL-2 has been demonstrated to decrease glomerular filtration rate when given to patient [114]. Overall, these findings demonstrate that cytokines and inflammation can have detrimental actions on renal hemodynamics that contribute to the progression of chronic kidney disease in hypertension.

Glomerular and interstitial macrophage infiltrations are characteristic to progressive chronic kidney disease in hypertension [14–16]. Glomerular hypertension and increased angiotensin II can stimulate renal inflammation [14–16]. Cytokines and chemokines including MCP-1 and VEGF have direct actions on renal tubular and glomerular cells [56]. Macrophage infiltration increases production of IL-1, TNF-α, and MCP-1 contributing to the progressive renal injury [115, 116]. All glomerular cell types such as podocytes, mesangial cells, and endothelial cells contribute to the progression of glomerular injury in hypertension [56]. VEGF has been demonstrated to be increased in podocytes and contributes to the development of glomerular sclerosis [56, 117]. IL-1, RANTES, MCP-1, and TGF-β are activated at the level of mesangial cells to result in mesangial cell proliferation [117, 118]. Mesangial cells fibroblast phenotype then secretes extracellular matrix and further contributes to glomerular sclerosis in hypertension [117, 119, 120]. Endothelin-1, TGF-β, and PDGF increase in glomerular endothelial cells in response to increased shear stress in hypertension [117, 121]. Glomerular endothelial cell activation can also increase TNF-α and MCP-1 to increase inflammatory cell infiltration [122, 123]. Endothelial cell inflammation can result in microthrombi, hyaline deposition, and destruction of the glomerular basement membrane in hypertension [117, 124]. Renal inflammation also is involved in tubulointerstitial damage in hypertension. Interstitial infiltration of inflammatory cells occurs in the early phases of kidney disease associated with hypertension [117, 124, 125]. Macrophages and T and B cells and their migration to the interstitium in hypertension are driven by tubular expression of chemokines and adhesion molecules [124, 125]. Thus, inflammation and cytokines contribute significantly to progressive glomerular and tubulointerstitial injury in hypertension.

Conclusion

Renal damage and progression to ESRD in hypertension is due to the interaction of complex mechanisms. Factors such as blood pressure, elevated glomerular pressure, and low nephron number can accelerate renal damage in hypertension. Although blood pressure is a contributing factor to hypertensive renal damage, other mechanisms act independent of blood pressure.Endothelial dysfunction and altered regulation of endothelial-derived factors contribute to chronic kidney disease progression. A central role for the RAAS in hypertensive renal damage has been demonstrated, and pharmacological RAAS blockade is an extremely valuable approach to decrease progressive kidney disease in hypertension. There is also a complex interaction between the RAAS, reactive oxygen species, and inflammation that accelerate renal damage in hypertension. A deeper understanding of the molecular mechanisms that contribute to chronic kidney disease in hypertension will identify novel therapeutic targets to prevent renal damage in hypertension.

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References

1. Schoenborn C (2009) Health characteristics of adults aged 55 years and over: United States, 2004–2007. Natl Health Stat Report 16:1–31
2. U.S. Renal Data System (2009) USRDS 2009 annual data report: Atlas of chronic kidney disease and end-stage renal disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda
3. Appel LJ (2010) Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med 363:918–929
4. Agodoa LY, Appel L, Bakris GL et al (2001) Effect of ramipril vs amlodipine on renal outcomes in hypertensive nephrosclerosis: a randomized controlled trial. JAMA 6:2719–2728
5. Tocci G, Volpe M (2011) End-organ protection in patients with hypertension: focus on the role of angiotensin receptor blockers on renal function. Drugs 71:1003–1017
6. Arici M (2009) Dual blockade of the renin-angiotensin system for cardio-renal protection: an update. Am J Kidney Dis 53:332–345
7. Klag MJ, Whelton PK, Randall BL et al (1996) Blood pressure and end-stage renal disease in men. N Engl J Med 334:13–18
8. Bakris GL (1996) Calcium channel blockers versus other antihypertensive therapies on progression of NIDDM associated nephropathy. Kidney Int 50:1641–1650
9. Chobanian AV (2003) Joint committee on prevention, definition, evaluation and treatment of high blood pressure. Hypertension 42:1206–1256
10. Kaplan NM (2005) Treatment of hypertension: drug therapy. In: Kaplan NM, Flynn JT (eds) Clinical hypertension, 9th edn. Lippincott Williams & Wilkins, Philadelphia, pp 217–230
11. Acosta JH (1982) Hypertension in chronic renal disease. Kidney Int 22:702–712

12. Segura J, Campo C, Gil P et al (2004) Development of chronic kidney disease and cardiovascular prognosis in essential hypertensive patients. J Am Soc Nephrol 15:1616–1622
13. Olson JL (2007) Renal disease caused by hypertension. In: Jennette JC, Olson JL, Schwartz MM, Silva FG (eds) Heptinstall's pathology of the kidney, 6th edn. Lippincott Williams & Wilkins, Philadelphia, pp 937–988
14. Morgado E, Neves PL (2012) Hypertension and chronic kidney disease: cause and consequence—therapeutic considerations. In: Babaei H, editor. antihypertensive drugs. InTech. doi: 10.5772/36916.
15. Bidani AK, Griffin KA (2004) Pathophysiology of hypertensive renal damage: implications for therapy. Hypertension 44:595–601
16. Udani S, Lazich I, Bakris GL (2011) Epidemiology of hypertensive kidney disease. Nat Rev Nephrol 7:11–21
17. Romagnani P, Remuzzi G (2013) Renal progenitors in non-diabetic and diabetic nephropathies. Trends Endocrinol Metab 24:13–20
18. Cushman WC, Evans GW, Byington RP et al (2010) Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 362:1575–1585
19. Atkins RC, Briganti EM, Lewis JB et al (2005) Proteinuria reduction and progression to renal failure in patients with type 2 diabetes mellitus and overt nephropathy. Am J Kidney Dis 45:281–287
20. Navar LG, Inscho EW, Majid DSA et al (1996) Paracrine regulation of the renal microcirculation. Physiol Rev 76:425–536
21. Hemmelgarn BR, Manns BJ, Lloyd A et al (2010) Relation between kidney function, proteinuria, and adverse outcomes. JAMA 303:423–429
22. Shankland SJ (2006) The podocyte's response to injury: role in proteinuria and glomerulosclerosis. Kidney Int 69:2131–2147
23. Folkow B, Gothberg G, Lundin S, Ricksten SE (1977) Structural "resetting" of the renal vascular bed in spontaneously hypertensive rats (SHR). Acta Physiol Scand 100:270–272
24. Campese VM (1991) Abnormal renal hemodynamics in black salt-sensitive patients with hypertension. Hypertension 18:805–812
25. Fong D, Denton KM, Moritz KM et al (2014) Compensatory responses to nephron deficiency: adaptive or aladaptive? Nephrology (Carlton) 19:119–128
26. Bertram JF, Douglas-Denton RN, Diouf B et al (2011) Human nephron number: implications for health and disease. Pediatr Nephrol 26:1529–1533
27. Luyckx VA, Brenner BM (2010) The clinical importance of nephron mass. J Am Soc Nephrol 21:898–910
28. Brenner BM, Garcia DL, Anderson S (1988) Glomeruli and blood pressure. Less of one, more the other? Am J Hypertens 1:335–347
29. Puelles VG, Hoy WE, Hughson MD et al (2011) Glomerular number and size variability and risk for kidney disease. Curr Opin Nephrol Hypertens 20:7–15
30. Schreuder MF, Langemeijer ME, Bokenkamp A et al (2008) Hypertension and microalbuminuria in children with congenital solitary kidneys. J Paediatr Child Health 44:363–368
31. Brenner BM, Lawler EV, Mackenzie HS (1996) The hyperfiltration theory: a paradigm shift in nephrology. Kidney Int 49:1774–1777
32. Keller G, Zimmer G, Mall G et al (2003) Nephron number in patients with primary hypertension. N Engl J Med 348:101–108
33. Hoy WE, Wang Z, VanBuynder P et al (2001) The natural history of renal disease in Australian aborigines: part 1. Changes in albuminuria and glomerular filtration rate over time. Kidney Int 60:243–248
34. Hoy WE, Wang Z, VanBuynder P et al (2001) The natural history of renal disease in Australian aborigines: part 2. Albuminuria predicts natural death and renal failure. Kidney Int 60:249–256
35. Abdi R, Slakey D, Kittur D et al (1998) Baseline glomerular size as a predictor of function in human renal transplantation. Transplantation 66:329–333
36. Sommerer C, Morath C, Andrassy J, Zeier M (2004) The long-term consequences of living-related or unrelated kidney donation. Nephrol Dial Transplant 19(Suppl 4):iv45–iv47

37. Manalich R, Reyes L, Herrera M et al (2000) Relationship between weight at birth and the number and size of renal glomeruli in humans: a histomorphometric study. Kidney Int 58:770–773
38. Pavenstädt H, Kriz W, Kretzler M (2003) Cell biology of the glomerular podocyte. Physiol Rev 83:253–307
39. Lemley KV (2003) A basis for accelerated progression of diabetic nephropathy in pima Indians. Kidney Int Suppl 63:S38–S42
40. Luscher TF, Barton M (1997) Biology of the endothelium. Clin Cardiol 20(11 Suppl 2):II3–II10
41. Ignarro LJ (1999) Nitric oxide: a unique endogenous signaling molecule in vascular biology. Biosci Rep 19:51–71
42. Griendling KK, Sorescu D, Ushio-Fukai M (2000) NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res 86:494–501
43. Agarwal R (2004) Chronic kidney disease is associated with oxidative stress independent of hypertension. Clin Nephrol 61:377–383
44. Johnson RJ, Lanaspa MA, Gabriela Sánchez-Lozada L, Rodriguez-Iturbe B (2015) The discovery of hypertension: evolving views on the role of the kidneys, and current hot topics. Am J Physiol Renal Physiol 308:F167–F178
45. Vaziri ND (1997) Altered nitric oxide metabolism and increased oxygen free radical activity in lead-induced hypertension: effect of lazaroid therapy. Kidney Int 52:1042–1046
46. Vaziri ND (2002) Enhanced nitric oxide inactivation and protein nitration by reactive oxygen species in renal insufficiency. Hypertension 39:135–141
47. Tian N (2008) NADPH oxidase contributes to renal damage and dysfunction in Dahl salt-sensitive hypertension. Am J Physiol Regul Integr Comp Physiol 295:R1858–R1865
48. Hirata Y, Hayakawa H, Kakoki M et al (1996) Nitric oxide release from kidneys of hypertensive rats treated with imidapril. Hypertension 27:672–678
49. Fulton D, Gratton JP, Sessa WC (2001) Post-translational control of endothelial nitric oxide synthase: why isn't calcium/calmodulin enough? J Pharmacol Exp Ther 299:818–824
50. Roman RJ (2002) P-450 metabolites of arachidonic acid in the control of cardiovascular function. Physiol Rev 82:131–185
51. Imig JD, Falck JR, Wei S, Capdevila JH (2001) Epoxygenase metabolites contribute to nitric oxide-independent afferent arteriolar vasodilation in response to bradykinin. J Vasc Res 38: 247–255
52. Zhao X, Pollock DM, Inscho EW et al (2003) Decreased renal cytochrome P450 2C enzymes and impaired vasodilation are associated with angiotensin salt-sensitive hypertension. Hypertension 41:709–714
53. Imig JD, Zhao X, Zaharis CZ et al (2005) An orally active epoxide hydrolase inhibitor lowers blood pressure and provides renal protection in salt-sensitive hypertension. Hypertension 46:975–981
54. Imig JD, Zhao X, Capdevila JH et al (2002) Soluble epoxide hydrolase inhibition lowers arterial blood pressure in angiotensin II hypertension. Hypertension 39:690–694
55. Luft FC (2002) Proinflammatory effects of angiotensin II and endothelin: targets for progression of cardiovascular and renal diseases. Curr Opin Nephrol Hypertens 11:59–66
56. Imig JD, Ryan MJ (2013) Immune and inflammatory role in renal disease. Compr Physiol 3: 957–976
57. Imig JD, Inscho EW (2002) Adaptations of the renal microcirculation to hypertension. Microcirculation 9:315–328
58. Brands MW, Banes-Berceli AK, Inscho EW et al (2010) Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/signal transducer and activator of transcription 3 activation. Hypertension 56:879–884
59. Harrison DG, Guzik TJ, Lob HE et al (2011) Inflammation, immunity, and hypertension. Hypertension 57:132–140
60. Viel EC, Lemarie CA, Benkirane K et al (2010) Immune regulation and vascular inflammation in genetic hypertension. Am J Physiol Heart Circ Physiol 298:H938–H944

61. Imig JD (2012) Epoxides and soluble epoxide hydrolase in cardiovascular physiology. Physiol Rev 92:101–130
62. Ammarguellat F, Larouche I, Schiffrin EL (2001) Myocardial fibrosis in DOCA-salt hypertensive rats: effect of endothelin ET(a) receptor antagonism. Circulation 103:319–324
63. Ergul S, Parish DC, Puett D, Ergul A (1996) Racial differences in plasma endothelin-1 concentrations in individuals with essential hypertension. Hypertension 28:652–655
64. Wedgwood S, Dettman RW, Black SM (2001) ET-1 stimulates pulmonary arterial smooth muscle cell proliferation via induction of reactive oxygen species. Am J Physiol Lung Cell Mol Physiol 281:L1058–L1067
65. Elmarakby AA, Loomis ED, Pollock JS, Pollock DM (2005) NADPH oxidase inhibition attenuates oxidative stress but not hypertension produced by chronic ET-1. Hypertension 45:283–287
66. Elmarakby AA, Loomis DE, Pollock JS, Pollock DM (2004) ETA receptor blockade attenuates hypertension and decreases reactive oxygen species in ETB receptor-deficient rats. J Cardiovasc Pharmacol 44:S7–S10
67. Pollock DM (2000) Renal endothelin in hypertension. Curr Opin Nephrol Hypertens 9:157–164
68. Rajagopalan S, Kurz S, Munzel T et al (1996) Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest 97:1916–1923
69. Kawada N, Imai E, Karber A et al (2002) A mouse model of angiotensin II slow pressor response: role of oxidative stress. J Am Soc Nephrol 13:2860–2868
70. Alonso-Galicia M, Maier KG, Greene AS et al (2002) Role of 20-hydroxyeicosatetraenoic acid in the renal and vasoconstrictor actions of angiotensin II. Am J Physiol Regul Integr Comp Physiol 283:R60–R68
71. Stec DE, Mattson DL, Roman RJ (1997) Inhibition of renal outer medullary 20-HETE production produces hypertension in Lewis rats. Hypertension 29:315–319
72. Pueyo ME, Gonzalez W, Nicoletti A et al (2000) Angiotensin II stimulates endothelial vascular cell adhesion molecule-1 via nuclear factor kappaB activation induced by intracellular oxidative stress. Arterioscler Thromb Vasc Biol 20:645–651
73. Ruster C, Wolf G (2006) Renin-angiotensin-aldosterone system and progression of renal disease. J Am Soc Nephrol 17:2985–2991
74. Imig JD (2000) Afferent arteriolar reactivity to angiotensin II is enhanced during the early phase of angiotensin II hypertension. Am J Hypertens 13:810–818
75. de Paula RB, da Silva AA, Hall JE (2004) Aldosterone antagonism attenuates obesity-induced hypertension and glomerular hyperfiltration. Hypertension 43:41–47
76. Raij L (2005) The pathophysiologic basis for blocking the renin-angiotensin system in hypertensive patients with renal disease. Am J Hypertens 18:95S–99S
77. Coppo M, Bandinelli M, Berni A et al (2011) Ang II upregulation of the T-lymphocyte renin-angiotensin system is amplified by low-grade inflammation in human hypertension. Am J Hypertens 24:716–723
78. Guzik TJ, Hoch NE, Brown KA et al (2007) Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. J Exp Med 204:2449–2460
79. Ruiz-Ortega M, Egido J (1997) Angiotensin II modulates cell growth-related events and synthesis of matrix proteins in renal interstitial fibroblasts. Kidney Int 52:1497–1510
80. Sasser JM, Pollock JS, Pollock DM (2002) Renal endothelin in chronic angiotensin II hypertension. Am J Physiol Regul Integr Comp Physiol 283:R243–R248
81. Mann JF, Schmieder RE, McQueen M et al (2008) Renal outcomes with telmisartan, ramipril, or both, in people at high vascular risk (the ONTARGET study): a multicentre, randomised, double-blind, controlled trial. Lancet 372:547–553
82. Pohl MA, Blumenthal S, Cordonnier DJ et al (2005) Independent and additive impact of blood pressure control and angiotensin II receptor blockade on renal outcomes in the irbesartan diabetic nephropathy trial: clinical implications and limitations. J Am Soc Nephrol 16: 3027–3037

83. Campbell R (2003) Effects of combined ACE inhibitor and angiotensin II antagonist treatment in human chronic nephropathies. Kidney Int 63:1094–1103
84. Norris K, Vaughn C (2003) The role of renin-angiotensin-aldosterone system inhibition in chronic kidney disease. Expert Rev Cardiovasc Ther 1:51–63
85. Hilgers KF, Mann JF (2002) ACE inhibitors versus AT(1) receptor antagonists in patients with chronic renal disease. J Am Soc Nephrol 13:1100–1108
86. Baylis C (2012) Nitric oxide synthase derangements and hypertension in kidney disease. Curr Opin Nephrol Hypertens 21:1–6
87. Wilcox CS (2005) Oxidative stress and nitric oxide deficiency in the kidney: a critical link to hypertension? Am J Physiol Regul Integr Comp Physiol 289:R913–R935
88. Bakris GL (2003) Hypertension and nephropathy. Am J Med 115(Suppl 8A):49S–54S
89. Montezano AC, Touyz RM (2012) Molecular mechanisms of hypertension-reactive oxygen species and antioxidants: a basic science update for the clinician. Can J Cardiol 28:288–295
90. Chabrashvili T, Tojo A, Onozato ML et al (2002) Expression and cellular localization of classic NADPH oxidase subunits in the spontaneously hypertensive rat kidney. Hypertension 39:269–274
91. Montezano AC, Touyz RM (2012) Oxidative stress, Noxs, and hypertension: experimental evidence and clinical controversies. Ann Med 44:S2–S16
92. Chen K, Kirber MT, Xiao H et al (2008) Regulation of ROS signal transduction by NADPH oxidase 4 localization. J Cell Biol 181:1129–1139
93. Cullinan SB, Diehl JA (2004) PERK-dependent activation of Nrf2 contributes to redox homeostasis and cell survival following endoplasmic reticulum stress. J Biol Chem 279:20108–20117
94. Pedruzzi E, Guichard C, Ollivier V et al (2004) NAD(P)H oxidase Nox-4 mediates 7-ketocholesterol-induced endoplasmic reticulum stress and apoptosis in human aortic smooth muscle cells. Mol Cell Biol 24:10703–10717
95. Hasty AH, Harrison DG (2012) Endoplasmic reticulum stress and hypertension—a new paradigm? J Clin Invest 122:3859–3861
96. Kassan M, Galan M, Partyka M et al (2012) Endoplasmic reticulum stress is involved in cardiac damage and vascular endothelial dysfunction in hypertensive mice. Arterioscler Thromb Vasc Biol 32:1652–1661
97. Hye Khan MA, Neckár J, Manthati V et al (2013) Orally active epoxyeicosatrienoic acid analog attenuates kidney injury in hypertensive Dahl salt-sensitive rat. Hypertension 62:905–913
98. Li G, Scull C, Ozcan L, Tabas I (2010) NADPH oxidase links endoplasmic reticulum stress, oxidative stress, and PKR activation to induce apoptosis. J Cell Biol 191:1113–1125
99. Eddy AA (2000) Molecular basis of renal fibrosis. Pediatr Nephrol 15:290–301
100. Boesen EI, Williams DL, Pollock JS, Pollock DM (2010) Immunosuppression with mycophenolate mofetil attenuates the development of hypertension and albuminuria in deoxycorticosterone acetate-salt hypertensive rats. Clin Exp Pharmacol Physiol 37:1016–1022
101. Dzielak DJ (1991) Immune mechanisms in experimental and essential hypertension. Am J Phys 260:R459–R467
102. Elmarakby AA, Quigley JE, Imig JD et al (2008) TNF-alpha inhibition reduces renal injury in DOCA-salt hypertensive rats. Am J Physiol Regul Integr Comp Physiol 294:R76–R83
103. Duffield JS (2010) Macrophages and immunologic inflammation of the kidney. Semin Nephrol 30:234–254
104. De Miguel C, Das S, Lund H, Mattson DL (2010) T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol 298:R1136–R1142
105. Barhoumi T, Kasal DA, Li MW, Shbat L, Laurant P, Neves MF, Paradis P, Schiffrin EL (2011) T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. Hypertension 57:469–476
106. Mattson DL, James L, Berdan EA, Meister CJ (2006) Immune suppression attenuates hypertension and renal disease in the Dahl salt-sensitive rat. Hypertension 48:149–156

107. Elmarakby AA, Quigley JE, Olearczyk JJ et al (2007) Chemokine receptor 2b inhibition provides renal protection in angiotensin II—salt hypertension. Hypertension 50:1069–1076
108. Elmarakby AA, Quigley JE, Pollock DM, Imig JD (2006) Tumor necrosis factor alpha blockade increases renal Cyp2c23 expression and slows the progression of renal damage in salt-sensitive hypertension. Hypertension 47:557–562
109. Muller DN, Shagdarsuren E, Park JK et al (2002) Immunosuppressive treatment protects against angiotensin II-induced renal damage. Am J Pathol 161:1679–1693
110. Madhur MS, Lob HE, McCann LA et al (2010) Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. Hypertension 55:500–507
111. Knight SF, Imig JD (2007) Obesity, insulin resistance, and renal function. Microcirculation 14:349–362
112. Shahid M, Francis J, Majid DS (2008) Tumor necrosis factor-alpha induces renal vasoconstriction as well as natriuresis in mice. Am J Physiol Renal Physiol 295:F1836–F1844
113. Sharma K, Cook A, Smith M et al (2005) TGF-beta impairs renal autoregulation via generation of ROS. Am J Physiol Renal Physiol 288:F1069–F1077
114. Shalmi CL, Dutcher JP, Feinfeld DA et al (1990) Acute renal dysfunction during interleukin-2 treatment: suggestion of an intrinsic renal lesion. J Clin Oncol 8:1839–1846
115. Holdsworth SR, Summers SA (2008) Role of mast cells in progressive renal diseases. J Am Soc Nephrol 19:2254–2261
116. Wilson HM, Walbaum D, Rees AJ (2004) Macrophages and the kidney. Curr Opin Nephrol Hypertens 13:285–290
117. Harris RC, Neilson EG (2006) Toward a unified theory of renal progression. Annu Rev Med 57:365–380
118. Taal MW, Omer SA, Nadim MK, Mackenzie HS (2000) Cellular and molecular mediators in common pathway mechanisms of chronic renal disease progression. Curr Opin Nephrol Hypertens 9:323–331
119. Floege J, Burns MW, Alpers CE et al (1992) Glomerular cell proliferation and PDGF expression precede glomerulosclerosis in the remnant kidney model. Kidney Int 41:297–309
120. Johnson RJ, Raines EW, Floege J et al (1992) Inhibition of mesangial cell proliferation and matrix expansion in glomerulonephritis in the rat by antibody to platelet-derived growth factor. J Exp Med 175:1413–1416
121. Malek AM, Greene AL, Izumo S (1993) Regulation of endothelin 1 gene by fluid shear stress is transcriptionally mediated and independent of protein kinase C and cAMP. Proc Natl Acad Sci U S A 90:5999–6003
122. Hirschberg R, Wang S (2005) Proteinuria and growth factors in the development of tubulointerstitial injury and scarring in kidney disease. Curr Opin Nephrol Hypertens 14:43–52
123. Lee LK, Meyer TW, Pollock AS, Lovett DH (1995) Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney. J Clin Invest 96:953–964
124. Noronha IL, Fujihara CK, Zatz R (2002) The inflammatory component in progressive renal disease—are interventions possible? Nephrol Dial Transplant 17:363–368
125. Sanchez-Lozada LG, Tapia E, Johnson RJ et al (2003) Glomerular hemodynamic changes associated with arteriolar lesions and tubulointerstitial inflammation. Kidney Int Suppl (86):S9–S14