Journal of Human Hypertension (2013), 1–6

www.nature.com/jhh

REVIEW

Hypertension and kidneys: unraveling complex molecular mechanisms underlying hypertensive renal damage

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Kidney damage represents a frequent event in the course of hypertension, ranging from a benign to a malignant form of nephropathy depending on several factors, that is, individual susceptibility, degree of hypertension, type of etiology and underlying kidney disease. Multiple mechanisms are involved in determination of kidney glomerular, tubular and interstitial injuries in hypertension. The present review article discusses relevant contributory molecular mechanisms underpinning the promotion of hypertensive renal damage, such as the renin–angiotensin–aldosterone system (RAAS), oxidative stress, endothelial dysfunction, and genetic and epigenetic determinants. We highlighted major pathways involved in the progression of inflammation and fibrosis leading to glomerular sclerosis, tubular atrophy and interstitial fibrosis, thus providing a state of the art review of the pathogenetic background useful for a better understanding of current and future therapeutic strategies toward hypertensive nephropathy. An adequate control of high blood pressure, obtained through an appropriate therapeutic intervention, still represents the key strategy to achieve a satisfactory control of renal damage in hypertension. In this regard, we reviewed the impact of currently available antihypertensive pharmacological treatment on kidney damage, with particular regard to RAAS inhibitors. Notably, recent findings underscored the ability of the kidneys to regenerate and to repair tissue injuries through the differentiation of resident embryonic stem cells. Pharmacological modulation of the renal endogenous reparative process (that is, with angiotensin-converting enzyme inhibitors and AT1 angiotensin II receptor blockers), as well as future therapeutic strategies targeted to the renopoietic system, offers interesting perspectives for the management of hypertensive nephropathy.

Journal of Human Hypertension advance online publication, 27 June 2013; doi:10.1038/jhh.2013.55

Keywords: hypertension; kidney damage; oxidative stress; renin–angiotensin system; inflammation; genetics

INTRODUCTION

The association between hypertension and renal disease is a well-known condition. Although the relative risk of serious renal damage in patients with uncomplicated essential hypertension is low, as compared with other cardiovascular complications, hypertension still remains owing to its huge prevalence in the general population, the second leading cause of end-stage renal disease (ESRD) after diabetes.[1] Patients with pre-existing renal disease and/or diabetes exhibit a greatly enhanced susceptibility to accelerated renal damage even with mild-to-moderate hypertension.[2] Moreover, subtle target organ damage, such as microalbuminuria, left ventricular hypertrophy and cognitive dysfunction, takes place early in the course of hypertension and can be left unrecognized until major complications occur.

Historically, renal damage induced by hypertension has been separated into two distinct clinical and histological patterns of 'benign' and 'malignant' nephrosclerosis.

In the context of hypertension, the development of chronic kidney disease (CKD) has to be considered as a cause of worsening prognosis due to cardiovascular adverse events and death.[2] However, CKD may not progress to its end-stage in all hypertensive patients, as many of them would eventually die for other hypertension-dependent cardiovascular diseases.

In the present work, we aimed at providing a state of the art review of relevant molecular mechanisms involved in the pathogenesis of hypertensive nephropathy as a useful tool for both basic and clinical readership, and for a better understanding of current and future therapeutic strategies.

The impact of current therapeutic interventions for the control of hypertensive nephropathy, such as the renin–angiotensin–aldosterone system (RAAS) inhibitors, is also discussed with regard to novel implications on the endogenous renopoietic reparative system.

MATERIALS AND METHODS

Literature search methodology

Potentially eligible articles, available until December 2012 on electronic database (PubMed), and related references were used for our literature search. Search strategies were designed to identify articles that reported renal damage in hypertensive disease. In particular, we searched MEDLINE using multiple terms and combinations starting with 'Hypertension and kidney'. Subsequently, we used the following as keywords: renal damage, hypertension, CKD, glomerulosclerosis, RAAS, oxidative stress, inflammation, fibrosis, endothelial dysfunction, genetics and epigenetic determinants, and renopoietic system. The search identified 470 articles from 1977 to 2013, 200 of them provided relevant data on hypertensive renal damage and its mechanisms. When multiple articles were published on the same topic, the articles with the most complete set of data were considered. Some articles were excluded because there were no original available data, no mechanisms of renal damage and low quality analysis or evidence.

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Received 5 February 2013; revised 12 April 2013; accepted 28 May 2013

Non-English articles were also excluded. A final number of 35 references (to fulfill the journal's requirements) was selected. Two investigators independently reviewed papers for eligibility. Disagreements about articles eligibility after full-text review were resolved by consensus of all investigators.

Parenchimal and vascular alterations in hypertensive nephropathy

Classically, the kidney is thought to be protected from acute systemic increase in blood pressure (BP) by auto-regulatory mechanisms, namely by glomerular afferent arteriole contraction due to myogenic response and by a tubuloglomerular feedback.[3] In fact, the extent of kidney damage due to hypertension is proportional to the degree of arterial pressure exposure of renal microvasculature. As long as afferent arteriolar structure remains intact, the transmission of either episodic or sustained arterial pressure elevation to the renal microvasculature is largely prevented, thus successfully avoiding acute lesions to glomeruli. However, if the arterial pressure increase becomes more severe and exceeds the range of auto-regulatory protection, it results in the transmission of even modest and transient arterial pressure increases to the glomerular capillaries, which can cause acute disruptive vascular and glomerular injuries with fibrinoid necrosis in afferent arterioles (malignant nephrosclerosis). Accordingly, differences in susceptibility to hypertensive injury, either as a result of alterations in auto-regulatory capacity (genetic or acquired) or of an intrinsic local tissue susceptibility (genetic or acquired), are reflected in differences in BP threshold or in the slope of the relationship between the latter and glomerulosclerosis.

The alteration of vascular structure, in turn, has an important role in the maintenance of hypertension.[4] In fact, in response to hypertension, adaptive structural changes (an increase in medial wall thickness, as well as a narrowing of the lumen diameter, which represent the earliest changes), will ensure that blood vessels withstand the increase in wall stress. Then, small changes in the lumen diameter would translate into greater changes in arterial pressure, further amplifying the already elevated BP values. Hypertrophy of afferent vessels represents the physiological vascular wall adaptation aimed at reducing the degree of vascular wall stress in response to chronic elevations in renal perfusion pressure. Nevertheless, as the diffusion distance of oxygen across the smooth muscle wall increases, hypertrophy causes ischemic injury of both the glomeruli and tubulo-interstitial structures. Tubular degeneration is due to misdirected filtration from an area with glomerular segmental sclerosis and reduced blood flow to the postglomerular peritubular capillaries.

Glomerular hypertension results in glomerular capillary stretching, endothelial damage and elevated glomerular protein filtration causing glomerular collapse, segmental necrosis and glomerulosclerosis. Decreased perfusion mainly leads to glomeruli collapse, whereas increased pressure causes either glomerular sclerosis or necrosis. Sclerosis of preglomerular vessels causes further reduction in renal blood flow (RBF).

Whereas RBF is reduced, glomerular filtration rate (GFR) is maintained and filtration fraction is increased, thus enhancing glomerular permeability to macromolecules. Plasma proteins hyperfiltration causes both tubular reabsorption of proteins and mesangial proliferation, thus leading to tubulo-interstitial inflammation and glomerulosclerosis. Glomerular hypertension also exerts a direct action on glomerular structures, causing signaling regulatory responses aimed to compensate. Adaptive mechanisms include contraction, transcriptional activity, proliferation, remodeling and fibrosis, involving glomerular, endothelial cells, mesangial cells, podocytes, basement membranes and extracellular matrix. Owing to the stretch, endothelial cells proliferate, remodel their shape and change their signaling pathways, both synthesizing extracellular matrix and reorienting their cytoskeleton. Mesangial cells proliferate and activate the RAAS, producing at the same time vascular permeability factors, tumor growth factor (TGF)-β and fibronectin. Podocytes modify their shape and their signaling pathway.[5] These adaptive mechanisms become maladaptive in the long term, finally leading to glomerulosclerosis.

The glomerular filtration barrier damage causes proteinuria and podocytes effacement. Podocytes may respond to injurious stimuli in different ways. The primary pathway leading to podocyte dysfunction is effacement, consisting in a gradual simplification of the interdigitating foot process pattern until the cell looks flat and lengthened.[6] As injury persists, podocytes either detach from basal membrane or undergo apoptosis causing denuded areas of glomerular basal membrane responsible for a marked proteinuria. Proteinuria, with or without loss of renal function, is partially due to podocyte injury. Moreover, both angiotensin II (ang II) and reactive oxygen species (ROS) can directly cause apoptosis and hypertrophy of podocytes. The damage of tubular basement membrane facilitates the passage of tubular-derived products into the interstitium and peritubular capillaries spaces, thereby accelerating fibrosis and inflammation, whereas several protein casts may obstruct the urinary flow, aggravating tubulo-interstitial injury.[7]

Hypertension is also a major independent risk factor for progression to ESRD in all forms of glomerulonephrites.[8]

Notably, even in the presence of high BP levels, a certain amount of glomeruli may not show significant changes.[3]

Susceptibility to hypertensive renal injury varies greatly across human populations, as well as in experimental and genetic models of hypertension. The mechanisms responsible for the different susceptibility to hypertension-induced renal injury are uncertain, but they are likely attributable to complex interactions among elevated BP, altered paracrine and endocrine factors, genetic factors and/or the presence of underlying renal disease (Figure 1). Notably, based on recent knowledge on mechanisms of renal regeneration, a balance between injury and regeneration has been proposed to explain the severity of glomerulosclerosis.[9]

Role of RAAS

Ang II has direct effects on renal vascular smooth muscle cells causing vasoconstriction of both afferent and efferent arterioles, resulting in the development of both glomerular capillary hypertension and reduced RBF. The effect is particularly evident at the medullary level, where enhanced reabsorption of salt and water is stimulated in multiple nephron segments. Moreover, increased intrarenal Ang II levels are responsible for the amplified sensitivity of the tubuloglomerular feedback. Overall, the renal hemodynamic actions of Ang II lead to the reduction of RBF and GFR. Furthermore, Ang II stimulates secretion of aldosterone from the adrenal cortex, which causes augmented reabsorption of sodium and water into the distal tubule, and the expression of renal endothelin-1 (ET-1), a potent vasoconstrictor peptide with pro-inflammatory and pro-fibrotic actions.

Ang II also has several non-hemodynamic effects involved in the pathogenesis of hypertensive CKD.[10] In particular, Ang II is a potent pro-inflammatory agent that is able to modulate immune and inflammatory responses in endothelial, renal tubular and smooth muscle cells, such as chemotaxis, proliferation and differentiation of monocytes into macrophages.[11] Ang II stimulates ROS production by inducing vascular NADPH oxidase and ET-1 expression in the kidneys. Ang II has been shown to cause both hypertrophy and proliferation of mesangial cells, and it stimulates, either directly or through the expression of TGF-β, the processes of proliferation, apoptosis and collagen synthesis.[12] Finally, Ang II causes tissue remodeling by increasing proliferation of interstitial fibroblasts, as well as by decreasing apoptosis of resident interstitial cells.

The classical view of Ang II-mediated actions is based on the binding to its own receptor at the plasma membrane, with consequent receptor phosphorylation and activation of downstream signaling, leading to intracellular responses. However, increasing evidence suggests that binding of Ang II to AT1receptor activates endocytotic processes that promote trafficking of both the effector and the receptor into intracellular compartments. Upon internalization, Ang II stimulates cytoplasmic and nuclear AT1-receptors to increase intracellular calcium, and it activates nuclear transcription factor nuclear factor-κB, leading to increased expression of the $Na+/H+$ exchanger NHE-3, pro-inflammatory cytokines and growth factors.[13]

Apart from Ang II, other RAAS components are involved in the inflammatory and fibrotic renal damage. In particular, aldosterone exerts a pro-oxidant action mediated through different pathways, including NADPH oxidase-dependent mechanisms. The pro-inflammatory and pro-fibrotic effects of aldosterone were proposed to be mediated by nuclear factor-κB activation, a factor involved in inflammation, immunity, cell proliferation and apoptosis.[14] Furthermore, aldosterone potentiates the mitogenic activity of TGF-β, thus leading to renal fibrosis and glomerulosclerosis.

ET-1, once stimulated by Ang II, also exerts autocrine/paracrine pro-inflammatory, mitogen and pro-fibrotic actions. ET-1 produces relevant biological effects such as constriction of cortical and medullary vessels, mesangial contraction, as well as extracellular matrix overproduction. In addition, ET-1 is able to activate and maintain inflammation and fibrosis by interacting with the renal tissue growth factor-β and by activating nuclear

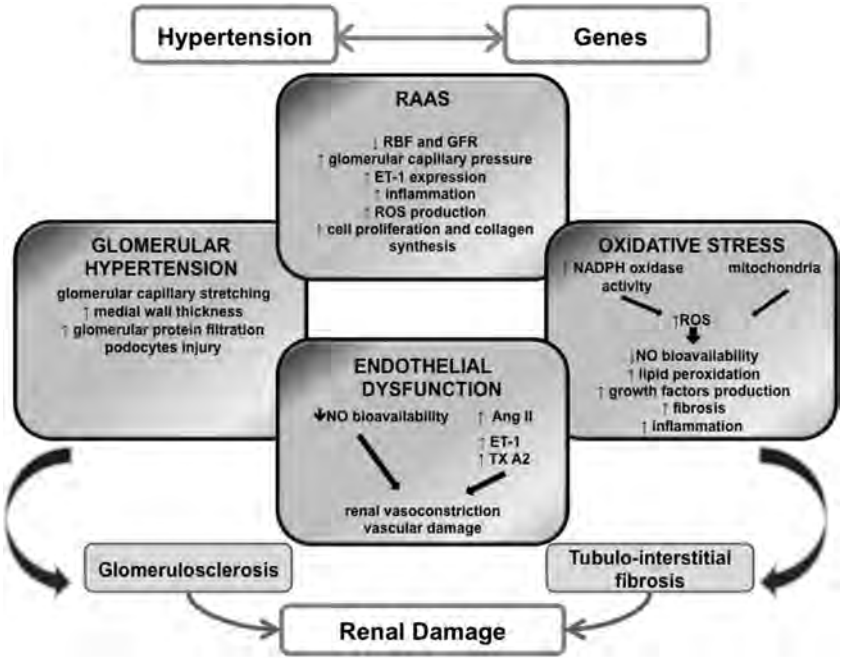

Figure 1. Schematic representation of mechanisms involved in development of hypertensive nephropathy. High BP levels favor the interaction between RAAS, oxidative stress and endothelial dysfunction in the presence of genetic predisposition. ET-1, endothelin-1; GFR, glomerular filtration rate; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; RBF, renal blood flow; ROS, reactive oxygen species; TX A2, Thromboxane A2.

factor-κB. Therefore, ET-1 appears to have an important role in causing acute kidney injury, in mediating ischemic damage, as well as RBF and GFR reductions.[15]

The great relevance of RAAS components in determination of hypertensive nephropathy has important therapeutic implications, as discussed below.

Role of oxidative stress

The reactive oxygen product hydrogen peroxide is known to be a mediator of cellular injury. Within the kidneys, ROS are produced in arterioles, glomerular and tubular cells, macula densa and podocytes. Vasoactive agents, mechanical factors such as shear stress and metabolic factors stimulate cellular inflammation and ROS production, inducing either NADPH oxidase or mitocondria.

Activation of ROS-generating enzyme in endothelial and vascular smooth muscle cells results in redox signaling that activates inflammation transcription factors. ROS are potent modulators of vascular contraction/dilation and decrease nitric oxide (NO) bioavailability, lead to lipid peroxidation, activate pro-inflammatory transcription factors, increase production of growth factors and induce fibrosis. ROS can enhance afferent arteriolar tone and reactivity both indirectly, via potentiation of tubuloglomerular feedback, and directly by microvascular mechanisms that diminish endothelium-derived relaxing factor/NO responses. They generate a cyclo-oxygenase-2-dependent endothelial-derived contracting factor that activates thromboxane–prostanoid receptors and enhance vascular smooth muscle cells reactivity. ROS can diminish the efficiency with which the kidney uses O_2 for Na^+ transport and thereby diminish the pO_2 within the kidney cortex. This may reduce ROS generation, although it could further enhance vascular damage and hypertension. There is a tight relationship between renal oxidative stress and both development and maintenance of hypertension.[16]

Of interest, recent work from our group has demonstrated that differential modulation of UCP2 (a mitocondrial carrier of ROS able to reduce their intracellular accumulation) occurs in an animal model of hypertension and increased susceptibility to renal vascular damage in the presence of Japanese-style high-salt diet.[17] In fact, in this experimental context, oxidative stress was highly increased in the damaged renal tissue.

Notably, there is evidence that uric acid can stimulate oxidative stress, endothelial dysfunction, inflammation and vasoconstriction, therefore, having a role in the pathogenesis of hypertensive nephropathy. Raising uric acid levels in rats can induce glomerular hypertension and renal disease as noted by the development of arteriolosclerosis, glomerular injury and tubulo-interstitial fibrosis.[18]

Role of endothelial dysfunction

Endothelial cells are metabolically very active and the integrity of the endothelial layer has a pivotal role in many aspects of vascular function, that is, control of vasomotor tone and permeability. Activation of endothelium by elevated BP is followed by endothelial dysfunction, which finally results in endothelial disintegration if the offending stimulus lasts longer. At the end, disappearance of whole vessels (vascular rarefaction) may result in reduction of tissue perfusion and consequent hypoxia. In patients with CKD, the endothelium has a pivotal role not only with respect to their cardiovascular morbidity and mortality but also with regard to disease progression. It has become clear from experimental studies that vascular rarefaction in the capillary system of the renal medulla, as a result of endothelial damage, is a central step toward tissue hypoxia and kidney damage. Here, reduced availability of NO as a result of reduced synthesis by endothelial cells is thought to be a key event underlying vascular damage. An increase in blood levels of endogenous inhibitors of NO synthase, such as asymmetric dimethylarginine, has been reported to be an important mechanism related to reduced NO availability and accelerated renal damage progression in CKD hypertensive patients.[19]

Ca_2 release from the endoplasmic reticulum increases endothelial NO synthase activity and NO production in renal vascular endothelial cells. NO diffuses into renal vascular smooth muscle cells causing relaxation by inhibiting Ca^{++} influx and by stimulating Ca^{++} extrusion mechanisms. Activation of cyclo-oxygenase increases PGI_2 production, which amplifies vascular smooth muscle cells relaxation. Renal endothelial release of endothelium-derived hyperpolarizing factor, such as epoxeicosatrienoic acids, activates K^+ channels and causes hyperpolarization of vascular smooth muscle cells and inhibition of Ca_2 influx through Ca_2 channels. The endothelium also releases ET-1, Ang II and thromboxane A2, all responsible for renal vasoconstriction. A decrease in endothelium-derived vasodilators and an increase in endothelium-derived vasoconstrictors are associated with renal vasoconstriction and hypertension. When the release of

vasodilators is compromised, Ang II acts unopposed to induce renal vasoconstriction, leading to decreased RBF, thus promoting renin release and further activating RAAS.[20]

Role of genetic factors

Clinical experience shows that not all hypertensive patients develop kidney damage. Moreover, when hypertensive renal damage occurs, the degree of renal injury varies among different individuals. Finally, when hypertensive nephropathy advances to the ESRD, a heritability component is suggested by the observation that other family members often have similar conditions.[21]

The independence of risk for renal damage in hypertension and its genetic origin is supported in at least one animal model of polygenic hypertension, the spontaneously hypertensive rat, in which similar susceptibility to hypertension is accompanied in distinct lines by difference in susceptibility to renal disease.[22] In fact, in the search for genetic factors involved into predisposition to renal damage, several hypertensive rat models were used in the past. In particular, by performing linkage studies in segregating populations, it was discovered that kidney damage developed in part independently from high BP levels and that it was genetically determined. Development of kidney injury was associated to gene mapping within selected quantitative trait loci located on different chromosomes, depending on the strain of interest. Subsequently, transfer of either the whole quantitative trait locus or of its fragments from the donor to the recipient background, or vice versa, was able to confirm the genetic determination of the hypertensive renal phenotype. Several putative candidate genes were identified within the quantitative trait loci identified in the various rat models, but no single-gene variant has been yet definitively confirmed.[22]

With regard to humans, estimates of heritability were provided in hypertensive sibships of different racial groups.[23] Several linkage studies in different populations examining kidney function traits have been reported. However, they generally failed to find loci with statistically significant trait effects on creatinine clearance or urinary albumin excretion. One locus with statistical significance for creatinine clearance was identified on chromosome 3 (Chr 3p).[24] A chromosome 7 locus was mapped, affecting serum creatinine levels in African–Americans.[23]

Subsequently, the introduction of genome-wide association study has made important contributions for the discovery of genes contributing to hypertensive nephropathy, although genome-wide association study have been unable to discover genetic factors containing variants with moderate-to-large effects. They also have been unable to clarify whether genes predisposing to hypertension and those predisposing to renal injury overlap. In this regard, the two most notable genetic findings relate to UMOD[25] and ATXN2 loci.[26] A highly significant association with variants within *UMOD*—the gene encoding uromodulin, which is also termed Tamm–Horsfall protein—was identified and subsequently replicated in an independent population.[27] *UMOD* is a good candidate gene given its renal-specific expression in cells lining the thick ascending limb of the loop of Henle, and its known association with autosomal-dominant medullary cystic kidney disease type 2. Although its function remains somewhat unclear, uromodulin is abundantly produced within the kidney and it may have an important role in immune modulation within the urinary tract, renal iron transportation and water impermeability of the thick ascending limb of the loop of Henle.[25]

Genome-wide admixture mapping has been used successfully to identify a major genetic locus affecting risk of reduced renal function in African–Americans.[28] The risk appears to be dissociated from diabetic renal injury, but not from renal injury attributable to hypertension or HIV infection, and appears to produce a histological phenotype resembling focal segmental glomerulosclerosis. The locus mapping on chromosome 22 contains two possibly important genes, *MYH9* and *APOL1*. MYH9 encodes the non-muscle myosin heavy chain type II isoform A. It is highly expressed in the glomeruli, specifically in the foot processes, beneath the podocyte plasma membrane, as well as in the tubules. Moreover, the non-muscle myosin heavy chain isoform IIA co-localizes with actin, suggesting an important role in the contractile structure of cells and, specifically, in the podocyte foot processes.[29] APOL1 is an apolipoprotein that appears to provide resistance to trypanosome infection.[30] This raises the possibility that renal risk-enhancing alleles of MYH9 (in linkage disequilibrium with APOL1) may have increased in frequency in African–American population secondary to selection acting on the adaptive APOL1 variation. However, the mechanism of the nephropathy associated with variation in *MYH9* gene still remains to be elucidated.

As all the loci strongly associated with hypertensive CKD are located within intronic or intergenic regions and, therefore, they are unable to change the protein coding sequence, the biology underlying these statistical associations remains unclear. Larger sample sizes are required for replication of these associations. Moreover, the identified loci are unable to explain the overall genetic variance in renal function, suggesting that additional loci remain to be identified.

Epigenetic phenomena are also being recognized as potential contributors to hypertensive nephropathy. Although clear findings are not available with regard to miRNAs involvement in hypertensive renal damage, the role of few of them is emerging in selected animal models.[31] For instance, lack of miR24a and miR34 downregulation under high-salt diet in the kidneys of stroke-prone spontaneously hypertensive rat paralleled the marked renal reduction of UCP2 (gene target of both miRs) seen in association to the increased susceptibility to renal damage of this strain.[17] Furthermore, upregulation of miR324-3p has been related to renal fibrosis in a rat model of spontaneous progressive nephropathy. Interestingly, angiotensin-converting enzyme (ACEI) are able to turn down miR324-3p overexpression.[32]

Current therapeutic implications

As anticipated in the above section, RAAS inhibitors are currently considered as first line therapy for hypertensive patients with kidney disease, as they effectively reduce proteinuria and CKD progression, despite being almost equally effective compared with other antihypertensive drugs at reducing BP. The UKPDS trial demonstrated for the first time the beneficial effect of lowering BP levels in terms of reduction of CKD progression (Table 1). Several other clinical trials supported this evidence in hypertension, even when associated with diabetes (Table 1). In fact, AT1 receptor blocker (ARB)-based therapy significantly reduced the development of microalbuminuria, as compared with beta-blocker, in the LIFE substudy (Table 1). In hypertensive patients with type 2 diabetes mellitus and overt nephropathy losartan significantly reduced the risk of doubling baseline serum creatinine, development of ESRD and urinary albumin excretion rate in the RENAAL study (Table 1). Similar results were obtained with irbesartan in hypertensive patients with type 2 diabetes and evidence of microalbuminuria in the IDNT study (Table 1). A preventive role toward renal damage occurrence of RAAS inhibitors has been shown in the BENEDICT trial (Table 1).

However, excessive BP reduction, particularly in older patients with likely ischemic hypertensive nephropathy, and/or unacceptable increase in serum potassium concentration lead to withdrawal of RAAS inhibitors in the setting of acute worsening of renal failure.[33] Moreover, given the increasing evidence of exacerbation of renal failure with RAAS inhibitors in hospitalized patients during acute illness or in the peri-operative period, it is recommended that these drugs would be preferably withheld in these conditions for protection of renal function.

Notably, although monotherapy with RAAS blockers results beneficial, dual RAAS inhibition did not demonstrate to provide additional benefits in terms of renal protection, but rather led to a frequent worsening of renal function as observed in the ONtarget study (Table 1). Recently, the addition of a direct renin inhibitor to either ACEI or ARB therapy confirmed the lack of clinical benefits with regard to renal function in the ALTITUDE study.[34]

As a consequence of these evidences, dual RAAS inhibition is currently not recommended in hypertensive patients at high or very high risk, as well as in diabetic patients with renal damage.

Perspectives

A new scenario has been recently brought to the attention of the medical community, that is, that regenerative mechanisms exist within the adult kidney.[9] Regenerative phenomena appear to be promoted within the adult kidney (as in other adult organs) by a stem/progenitor cell system defined as the 'renopoietic system'. Renal progenitors act as precursors of renal epithelial cells of cortical nephrons. They are able to differentiate into glomerular or tubular epithelial cells through podocyte-committed progenitors.[9] Treatment with ACEI and ARBs has the potential to increase the number of glomerular and parietal podocytes, a phenomena contributing to glomerulosclerosis regression under ACEI therapy.[35] In particular, remodeling of the Bowman's capsule epithelial cells appears as a key feature of ACEI renoprotection.

Table 1. Most relevant clinical trials which evaluated the impact of renin–angiotensin–aldosterone system inhibitors on CKD in hypertension (for references quoted in this Table please see Supplementary information)

Clinical trial	*Year*	*Patients*	*Renal endpoints*	*Comparison*	*rr for primary endpoint*
AIPRI (SI: ref. 1)	1996	$N=583$; chronic nephropathies, mostly non-diabetic patients	Creatinine clearance $\leqslant 45\,ml\,min^{-1}$ or need for dialysis	Benazepril vs placebo	0.46 (0.12–0.67)
REIN stratum 2 (SI: ref. 2)	1997	$N=117$; chronic nephropathies, non-diabetic patients proteinuria $>3\,g$ per day	Rate of decline in GFR Reducing proteinuria Preventing ESRD	Ramipril vs placebo	NA
UKPDS 39 (SI: ref. 3)	1998	$N=758$; type 2 diabetes and hypertension	Endpoints related to diabetes	Atenolol vs Captopril	1.10 (0.86–1.41)
REIN stratum 1 (SI: ref. 4)	1999	$N=186$; chronic nephropathies, non-diabetic patients proteinuria $>1\,g$ per day but $<3\,g$ per day	Rate of decline in GFR decline time to ESRD or overt proteinuria (3 g per 24 h)	Ramipril vs placebo	2.72 (1.22–6.08)
AASK interim analysis: ramipril and amlodipine arms (SI: ref. 5)	2001	$N=653$; African–American subjects with hypertension and probable hypertensive nephrosclerosis	Rate of decline in GFR Composite endpoint: rate of change in GFR, ESRD and death	Ramipril vs amlodipine	0.41 (0.05–0.63)
RENAAL (SI: ref. 6)	2001	$N=1513$; type 2 diabetes and nephropathy	Composite endpoint: doubling baseline serum creatinine, ESRD or death. Composite endpoint: morbidity and mortality from cardiovascular causes proteinuria. Rate of progression of renal disease	Losartan vs placebo	0.16 (0.02–0.28)
IDNT (SI: ref. 7)	2001	$N=1715$; type 2 diabetes and hypertension	Composite endpoint: doubling baseline serum creatinine, development of ESRD or death from any cause	Irbesartan vs placebo	0.80 (0.66–0.97)
				Irbesartan vs amlodipine	0.77 (0.63–0.93)
LIFE substudy (SI: ref 8)	2003	$N=8206$; hypertension and left ventricular hypertrophy	Urine albumin/creatinineratio	Losartan vs atenolol	33 vs 25% in albuminuria reduction[a]
BENEDICT (SI: ref. 9)	2004	$N=1204$; hypertension, type 2 diabetes mellitus with normal urinary albumin excretion	Development of persistent microalbuminuria	Trandolapril/verapamil vs placebo	0.39 (0.19–0.80)
				Trandolapril vs verapamil	0.47 (0.26–0.83)
				Verapamil vs placebo	0.85 (0.45–1.51)
Hou *et al.* (SI: ref. 10)	2006	$N=224$; serum creatinine level between 3.1 and $5.0\,mg\,dl^{-1}$	Composite endpoint: doubling serum creatinine, ESRD, or death. Changes in the level of proteinuria. Rate of progression of renal disease	Benazepril vs placebo	NA
ONTARGET (SI: ref. 11)	2008	$N=25\,620$; established atherosclerotic vascular disease or diabetes with end-organ damage	Composite endpoint: dialysis, doubling serum creatinine, and death	Telmisartan vs ramipril	1.00 (0.92–1.09)
				Telmisartan/ramipril vs ramipril	1.09 (1.01–1.18)
STAR (SI: ref. 12)	2009	$N=140$; atherosclerotic renal artery stenosis ($\leqslant 50\%$)	Changes of creatinine clearance	PTA plus medical therapy[b] vs medical therapy only	0.73 (0.33–1.61)
ACCOMPLISH (SI: ref. 13)	2010	$N=11\,506$; hypertension and high risk for cardiovascular events	Doubling of serum creatinine concentration or ESRD	Benazepril/Amlodipine vs Benazepril/HCT	0.52 (0.41–0.65)

Abbreviations: CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HCT, hydrochlorothiazide; NA, not available; PTA, percutaneous transluminal angioplasty; RR, risk reduction. [a]RR of losartan vs atenolol for renal endpoint was not estimated in the LIFE substudy. [b]Medical therapy included diuretics, calcium-antagonists, β-blockers, α-blockers, followed by ACE inhibitors and ARBs.

Thus, although the exact role of hypertension in modulating (that is, reducing) the regenerative potential of the kidney still needs to be ascertain, pharmacological modulation of the regenerative capacity of the kidneys, by both traditional and future therapeutic strategies, opens new perspective for the management of hypertensive nephropathy.

CONCLUSIONS

Complex mechanisms, often interacting with each other, stimulated by both high BP and genetic predisposition, have great relevance in the pathogenesis of hypertensive nephropathy. A deeper understanding of the molecular mechanisms will allow the identification of suitable targets of pharmacological treatments that are able to achieve an appropriate control of renal damage in hypertension. Owing to the relevant contribution of RAAS into the pathogenesis of hypertensive CKD, RAAS blockers, given as monotherapy, still represent the most valuable pharmacological tool toward hypertensive nephropathy.

Novel therapeutic strategies are expected to overcome current conventional therapies by their ability to interact with the endogenous renopoietic reparative system.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

The present work was supported by a grant (Ricerca Corrente) from the Italian Ministry of Health to MV and SR; by the 5‰ grant to MV and SR; by PRIN 2009 to SR; and by InGenious Hypercare European project to MV.

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