Editorial review

Hypertension and Chronic Kidney Disease: Pathophysicsology and Management Strategies

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Abstract

Hypertension is extremely prevalent in CKD patients and hypertensive nephrosclerosis is very common in end-stage renal disease (ESRD). Salt intake may be considered a factor for hypertension and risk of progression of kidney disease in CKD patients. Proteinuria is a sensitive and independent predictor for the progression of nephropathy and is frequently used as a surrogate end point in clinical research. The renin-angiotensin-aldosterone system (RAAS) is a well-coordinated hormonal system to be considered in the selection of the antihypertensive medication. Aggressive management of hypertension with the combination of drugs slows the decline in kidney function. New classes of antihypertensive agents are promising for the treatment of hypertension. Adherence to prescribed therapies is of great importance to control blood pressure in patients with kidney impairment.

Key words: anti-hypertensive drugs, chronic kidney disease, hypertension, proteinuria, patient adherence renal angiotensin aldosterone system, salt intake

Introduction

Chronic kidney disease (CKD) is a major, worldwide public-health problem [1]. Eight million people in United States (US) had an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m² [2]. The estimated prevalence is about 14.8 percent of the general population [3]. Patients with CKD have significant morbidity, increased risk of cardiovascular disease [4] and progression to end-stage renal disease (ESRD) [5]. Furthermore, patients with CKD are five to 10 times more likely to die than to advance to ESRD [3,6].

The increase in CKD prevalence is relevant to hypertension because hypertension is extremely common in CKD patients. Of note, as GFR decreases the prevalence of hypertension rises significantly [7]. Current knowledge from the NHANES data put the prevalence of hypertension in 2004 at 72 million [8-10]. In clinical trials, it is strongly supported that hypertension increases the risk of cardiovascular mortality and accelerates the progression of kidney dysfunction [6]. In the contrary, aggressive management of hypertension improves morbidity and mortality from cerebrovascular and cardiovascular disease and is critical to slow the decline in kidney function [11]. Despite adequate control, however patients continue to progress to end-stage renal disease.

In 2006 the estimated cost of treating hypertension and its co-morbid conditions in the US exceeded an annual amount of 55 billion dollars [12]. Similarly, the estimated cost for Medicare patients with CKD exceeded to $49 billion—nearly five times greater than costs in 1993. Overall, Medicare expenditures, in contrast, have grown only 91 percent over the same period [13].

Hypertensive nephrosclerosis

The relationship between elevated blood pressure and kidney came to attention first by Bright [14]. However, only in recent decades the importance of the kidney in the pathogenesis of hypertension was recognized. The most controversial relationship is that of the “victim and the perpetrator”. The classical question is whether hypertension is the cause or the consequence of kidney disease. The kidney is unique among the target organs of elevated blood pressure. It both suffers damage and still contributes to the pathophysiologic sustenance of hypertension through many avenues [15].

Hypertensive nephrosclerosis is the second most common cause of ESRD. Despite this, it is interesting that only a small percentage of patients with hypertensive nephrosclerosis will go on to develop ESRD. Recent data suggest that there are two different processes leading to glomerulosclerosis. The net result of the mixture of the two types blurs and weakens any potential correlation with hypertension [16]. It is therefore clear that individual factors are involved. Racial differences in the distribution of the lesion may play a significant role. For example, black patients have an approximate eight-fold elevation in risk of hypertension induced ESRD [17]. Many of these differences may be attributed to low birth weight due to maternal malnutrition [18]. It has recently been suggested that the issue is more complex and additional promoters of hypertension beyond low nephron numbers need to be sought in US blacks [19].
Arterial stiffening in kidney parenchyma and progressive intimal thickening as a part of the normal aging process are pathogenetic mechanisms, and provided a solid background explanation for the hypertrophic glomerular sclerosis. This mechanism has a strong correlation with hypertension especially in blacks [20]. Furthermore, it is accompanied by afferent arteriosclerosis or afferent arteriolar hyalinosis which was common finding in aging kidneys [21]. Loss of autoregulation may be responsible for the progression in hypertensive nephrosclerosis, a finding in diabetic patients with proteinuria [22], more common in blacks than whites [23] and in patients with severe but not moderate hypertension [24].

Ischemic glomerulosclerosis is the second principal model of hypertensive sclerosis and may be the most important lesion. Evidence suggests that there is tubular atrophy and interstitial fibrosis associated with loss of capillaries [25], while chronic hypoxia is the final common pathway for the progression in this process [26]. In addition, interstitial inflammation, monocyte chemoattractant protein (MCP-1) [27], osteopontin [28] and transforming growth factor β1(TGF-β1) [29] may also play a role in renal pathology in hypertensive nephrosclerosis.

Overall current evidence suggest that ACE inhibitors and ARBs are the drugs of choice in patients with CKD and proteinuria [7]. The issue of kidney protection in black patients with nephrosclerosis was in part addressed in the African-American Study of Kidney Disease and Hypertension (AASK) study [30,31]. The rate of loss of GFR after first 3 months was significantly less in patients with proteinuria receiving ramipril compared with those receiving amlopidine [31]. However, accumulating data from ten-year follow up of shows that neither ACE inhibitor nor aggressive BP lowering affected the long-term rate of CKD progression among these patients [32]. Most patients had a year decline in GFR greater than 1ml/min per 1.73m².

**RAAS system and the kidney**

The renin-angiotensin-aldosterone system (RAAS) is a well-coordinated hormonal scheme that regulates adrenal, renal and cardiovascular function by controlling fluid and electrolyte balance. A number of mechanisms have been proposed to be responsible for modifying blood pressure via homeostasis of renal salt and water, alteration in sympathetic nerve activity and changes in vascular tone [33]. Reacting to changes in renal perfusion pressure, cells of the juxtaglomerular apparatus, release renin which catalyze the conversion of angiotensinogen to angiotensin I (Ang I), a peptide with no pharmacologic activity. The angiotensin-converting enzyme (ACE) further removes two C-terminal amino acids thereby generating Angiotensin II (Ang II) the principal effector peptide of the system. Ang II has two receptors, AT1 and AT2 expressed in many cardiovascular and other tissues, and binding to AT1 receptor confers most classical actions such as systemic vasoconstriction, aldosterone release, salt retention in the renal proximal tubules and stimulation of the sympathetic nervous system via receptors in the brain [34,35]. In addition to the classical RAAS components, several new participants have been discovered in recent years such as an homolog of ACE, ACE2 which degraded Ang II yielding Ang-(1-7) [36]. The RAAS system was thought to be a hormone system by which the kidney influences systemic cardiovascular regulation. The kidney is the source of initiating enzyme of the renin cascade. The local RAAS in the kidney may be of high relevance for BP regulation as an amplifier of circulating Ang II actions. In striking contrast however, the local kidney MAS may have a pivotal role for kidney damage caused by hypertension. Ang II enhances the vascular tone of both afferent and efferent arterioles and modulates intaglomerullary capillary pressure and GFR [37]. In addition, Ang II is very effective and under positive feedback, stimulates the proximal tubular reabsorption, of salt and water and lead to increased extracellular fluid volume and elevated arterial BP [38]. Apart from hemodynamic effects, other studies showed several non-hemodynamic effects and suggested that Ang II may alter permissive properties of the glomerular capillary barrier by mediating contraction of foot processes, ultimately changing slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space [39]. Furthermore, Ang II elicits an inflammatory and immunologic response, which leads to interstitial fibrosis, glomerulosclerosis, albuminuria and renal failure [40]. A large body of experimental and clinical research showed that pharmacologic blockade of the RAAS slows the progression of renal dysfunction more effectively than other antihypertensive strategies [41-44]. With RAAS blockade there is a decrease in glomerular hyperfiltration and an improvement in glomerular sieving properties.

**Salt intake and the kidney**

Kidneys are believed to be the primary link between salt intake and arterial pressure and the mechanisms are related to inability to excrete large amounts of salt [45]. This ability declines with age, as that smaller increases in salt intake lead to a rise in BP with aging. Short term effects of sodium retention on BP reduction have been demonstrated among hypertensive and prehypertensive patients [46]. Until recently its long-term effects on cardiovascular endpoints remain under debate [47]. Overall, current evidence suggests that as dietary salt intake increases so does BP. In a recent meta-analyses a median reduction of 1.8g/d (78mmol/d) lowered systolic/diastolic BP by 2.0/1.0 mmHg in non hypertensive and by 5.0/2.7 mmHg in hypertensive patients [48]. The change in BP in response to a change in salt intake has a continuous rather than binary distribution [49]. With regard to BP effects with sodium reduction these tend to be greater in blacks, middle and older-aged persons and patients with hypertension, diabetes and CKD. Of note, these individuals tend to have a less responsive RAS [50]. The response to sodium reduction is also influenced by other dietary factors. In the Dietary Approaches to Stop Hypertension (DASH) study [51] with high potassium intake, the rise in BP is blunted for a given increase in sodium intake. In addition, recent data showed that the interaction of sodium and potassium may be the dominant factor in the development
of hypertension and its sequelae [52]. Potassium deficits and sodium retention have effects on vascular smooth cells and vasodilatation. Diet low in potassium and high in sodium can lead to sodium retention and increases BP. Increased dietary potassium can reduce apparent sodium sensitivity [52]. A reduced sodium intake can produce a large fall in BP similar to that of single drug therapy [53], can prevent hypertension [54], facilitate hypertension control [55], which is associated with reduced risk of atherosclerotic cardiovascular events [56] and the risk of development congestive heart failure [57].

The relationship between salt intake and the risk of progression of renal disease in CKD patients may be concerning. Salt may be directly nephrotoxic by increasing oxidant stress [58] and indirectly harmful by increasing BP and attenuating the antihypertensive and antiproteinuric effects of RAAS blockers. A diet high in sodium chloride appears to mitigate against the antiproteinuric benefit of RAAS blockade [59]. In 12 patients with proteinuria and high BP, lisinopril 5–10 mg brought about a dose-dependent reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric benefit of RAAS blockade [59]. In 12 patients with proteinuria and high BP, lisinopril 5–10 mg brought about a dose-dependent reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric benefit of RAAS blockade [59]. In 12 patients with proteinuria and high BP, lisinopril 5–10 mg brought about a dose-dependent reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric benefit of RAAS blockade [59]. In 12 patients with proteinuria and high BP, lisinopril 5–10 mg brought about a dose-dependent reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric benefit of RAAS blockade [59]. In 12 patients with proteinuria and high BP, lisinopril 5–10 mg brought about a dose-dependent reduction in proteinuria. When the patients’ salt intake was increased from 50 to 200 mmol/day, the antiproteinuric benefit of RAAS blockade [59].

Greater salt intake can enhance oxidative stress in skeletal tissue beds, increase BP and stimulate renal interstitial fibrosis with a consequent decline in kidney function in various model of CKD while salt restriction showed a benefit in CKD progression [61,62]. High salt intake and Ang II both regulate the balance of nicotinamide phosphate dehydrogenase oxidase and superoxide dismutase and consequent production of reactive oxygen species (ROS). They synergize with increased BP and cause kidney injury [63,64]. Increased salt intake could lead to changes in BP, salt sensitivity, and increased risk of renal injury through direct and indirect effects on ROS production. The policy advice in US to reduce salt intake has been placed for about 30 years. The recent publications of the US Dietary Guidelines recommended upper limit of sodium of 100 mmol/d in the general population and 65mmol/d in individuals who are especially sensitive to the adverse effects of sodium including African Americans, middle- and older age individuals and patients with hypertension, diabetes and CKD [65]. Compelling and still increasing body evidence supports population-wide sodium reduction as an integral component of public health efforts to lower BP and prevent the overall complications.

Proteinuria and CKD

Proteinuria is a sensitive and independent predictor for the progression of nephropathy and is frequently used as a surrogate end point in clinical research. In primary care practice, proteinuria is a common finding in adult population. Of the types of protein, albumin is only detectable using conventional sticks and is measured routinely in the evaluation of abnormal protein excretion especially in diabetes and CKD. Microalbuminuria is defined as urine albumin excretion (UAE) between 30-300 mg/day if measured in a 24 hour urine collection, or 30-300 mg/g if measured with the use of urinary albumin-creatinine ratio in a spot urine collection. Macroalbuminuria or clinical proteinuria represents every albumin or protein excretion greater than those levels [7]. Use of these cut-offs defining, macroalbuminuria, and microalbuminuria facilitate determining the risk of progression of nephropathy.

Microalbuminuria is considered a marker of abnormal vascular function and risk factor for cardiovascular disease [66]. Macroalbuminuria is a manifestation of overt nephropathy and is associated with impairment of kidney function and an increased risk of cardiovascular disease [7,67]. In general population the prevalence of macroalbuminuria is low. It was estimated at around 1.3%, ranging from 1% in white individuals to 2.4 in black individuals [68]. It is now clear that proteinuria increases with age. For example, the prevalence of proteinuria is 3.9% in people >70 years [68] and is more common in individuals with hypertension and diabetes [69]. Without specific interventions 80% of patients with type 1 diabetes and 20% to 40% of those with type 2 diabetes and microalbuminuria will progress to macroalbuminuria during 10 to 15 years [70]. On the other hand, there is evidence showing that in patients with type 1 diabetestes, normoalbuminuria reverted to microalbuminuria within 5 years [71].

Drug classes for hypertension in patients with kidney impairment

It is noteworthy that there is an important interplay between levels of extracellular fluid (ECF) volume expansion and treatment of CKD-related hypertension. By far volume dependent hypertension occurs more commonly in CKD patients and diuretics often need to be included in the anti-hypertensive regimen in patients with kidney disease. Diuretics are very effective in reducing BP but are associated with metabolic complications that are particularly evident when used in high doses. When used in combination with RAAS blockade, metabolic complications such as hypokalemia are minimized [72]. Moreover, control of ECF volume expansion improves antiproteinuric effect of drugs that interfere with RAAS [73]. However, thiazide diuretics become less effective when GFR falls below 40 mL/min /1.73 m² [74] and adequate BP control in these patients need a loop diuretic. If furosemide is used it should be dosed 2 to 3 times daily because it has very short duration of action. Potassium-sparing diuretics should be avoided in patients with pre-existing hyperkalemia, that is, serum potassium more than 5.5mEq/L and when used serum potassium must be followed closely, and a dose adjustment of the concomitant conventional diuretic therapy should always be considered.

Addition of aldosterone receptor antagonists such as spironolactone and eplerenone in low doses in patients already in RAAS blocking agents may be indicated in patients with proteinic CKD, especially if heart failure is present [75]. The rationale for such as a combination is that plasma al-
dosterone levels increase in CKD patients and may contribute to renal injury [76]. In patients already receiving a RAAS blocking agent blockade further reduced proteinuria [77-79]. Calcium antagonist (CAs) is frequently used in patients with CKD and hypertension. CAs do not need to be dose-adjusted in CKD based on pharmacokinetic considerations [80]. These agents comprise 2 subclasses, diidropyridines and nondihydropyridines which appear to offer similar anti-hypertensive efficacy but were shown to have divergent effects on respect to high levels of proteinuria as well as to the progression of kidney function. In patients with overt nephropathy, non-dihydropyridine CAs (verapamil, diltiazem) has been shown to reduce proteinuria and the rate of clearance decline [81,82] while dihydropyridine CAs do not, unless used in the presence of a RAAS blocker [83,84]. An explanation for the proteinuria difference relates to the more pronounced impairment in renal autoregulation and glomerular transmission produced by dihydropyridine CAs [85] which increases intraglomerular pressure and thereafter permeability to albumin [86,87]. On the other hand, non dihydropyridine CAs do not interfere with glomerular autoregulation to the same degree and reduce glomerular permeability to a greater extent.

Additional evidence to support a lack of renoprotection comes from clinical trials. In the IDNT study, amloidipine was associated with 6% increase in proteinuria versus baseline and 23% greater incidence of primary composite outcome compared with irbesartan [88]. Similarly findings have been observed in nondiabetic population in the aforementioned AASK trial, the 58% increase in proteinuria at 6 months in those treated with amloidipine correlated with a greater incidence of the composite end point of 50% or greater decreased in GFR, ESRD and/or death compared with those treated with ramipril who had a 20% decrease in proteinuria [30]. These clear differences between these subclasses seem to manifest only in patients with advanced disease and proteinuria [87]. In the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT), progression to microalbuminuria was significantly lower in the subjects treated with trandolapril or the combination compared to the subjects receiving verapamil or placebo respectively [89].

Based on the above, although dihydropyridine CAs are effective in lowering BP in patients with CKD, these drugs should not be used as monotherapy in diabetic or nondiabetic kidney disease with proteinuria, but always in combination with an ACE inhibitor or an ARB, if BP is not adequately controlled [7,86]. Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study [90] showed that CAs agents appear to have particular efficacy for CV risk reduction when paired with an ACE inhibitor. In this trial patients that were at high risk for a CV event were treated with a background of maximal ACE inhibition had a 20% relative risk reduction in CV events when treated with amloidipine compared to those treated with hydrochlorothiazide. Similarly, verapamil when paired with an ACE inhibitor is effective in reducing CV outcomes in patients with hypertension and coronary artery disease [91].

Data directly comparing ARBs and ACE inhibitors on renal outcomes were limited. Hence, there is no difference between the two classes. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) evaluated the use of either an ACE inhibitor or ARB alone or together. This trial was powered for cardiovascular outcomes in high-risk patients but failed to show a benefit of the ACE inhibitor/ARB combination over either agent alone. Moreover, it showed a higher risk of hyperkalemia with the use of the combination. A post-hoc analysis of the trial also evaluated CKD progression assessed by change in creatinine over time [92]. This trial does not answer the question about progression of CKD in patients with advanced nephropathy, because few patients with advanced nephropathy were included [93]. Moreover, the interpretation that the group receiving a combination regimen had more renal events was troubling since, it was driven by the number of acute dialysis events for hyperkalemia. Thus, to date, there are no clear data to support use of combined RAAS blockade to slow nephropathy progression further.

Combining two or more antihypertensive agents is imperative to achieve the current BP goal in most patients with CKD. A diuretic should be the first agent added to the ACE inhibitor or the ARB regimen if necessary in all patients with diabetic kidney disease and in patients with nondiabetic kidney disease with spot urine total protein-to-creatinine ratio ≥200 mg/g [7]. In addition, in patients with nondiabetic kidney disease with spot urine total protein-to-creatinine ratio <200 mg/g a diuretic should be one of the initial choices to achieve blood pressure goal [7]. There is no direct evidence that conventional β-blockers provide additional renoprotective effects. It has been shown that, in diabetic patients with proteinuria, a non dihydropyridine CAs, verapamil showed a significant reduction in the rate of creatinine clearance and proteinuria compared with atenolol [81]. In the UKPDS 39 study the comparison of captopril and atenolol shows no significant differences in the levels of BP achieved, in the incidence of overt nephropathy and in the rate of plasma creatinine doubling, suggesting that any renoprotective effect was caused by blood pressure lowering [94].

The newer β-blocker carvedilol, with a better metabolic profile [95] in the presence of RAAS blockade, was associated with significant reductions in risk of microalbuminuria development in type 2 diabetic hypertensive patients compared with metoprolol [96,97] due to better glycemic control and reduction of oxidative stress [98]. However, BP targets were not uniformly reached, particularly in more advanced stages of diabetic nephropathy. For this reason β-blockers were suggested to be used in patients with proteinuria as third-line agents to achieve BP control [7]. Alpha-blockers were not shown to slow renal disease progression or decrease UAE in diabetic patients with proteinuria [99]. An interim analysis of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) trial found that the alpha-blocker doxazosin increases the risk of heart failure compared with that associated with chlorothalidone [100,101]. Alpha-1-blockers should be used as third line treatment, especially in older men who also have symptomatic benign prostatic hyperplasia in whom an alpha-1-blocker may lead to symptomatic improvement [102].
The new era of antihypertensive drugs, renin inhibitors & endothelin antagonists

Renin Inhibitors

Aliskiren is the first agent of a new class of orally effective direct renin inhibitors for treatment of hypertension. Unlike other drugs that modify RAAS such as ACE inhibitors who limit the conversion of Ang I to Ang II via ACE inhibition or the ARBs who blockade the preferred angiotensin AT1 receptor binding site for Ang II, direct renin inhibitors bind to the renin molecule and limit its catalytic activity. It is responsible for decreasing plasma renin activity, Ang I and Ang II levels. With the use of these agents there are different biochemical responses in terms of BP lowering effects and vascular bed protection from atherosclerotic disease progression [103].

The antihypertensive effects of aliskiren were well known and it was approved for the treatment of hypertension in 2007. It was efficacious in controlling BP in monotherapy as well in combination with other antihypertensive agents [104-106]. Aliskiren was responsible for decreasing albuminuria, lowering BP and normalizing serum creatinine in transgenic rats for human renin and angiotensinogen genes [107]. In another rat model aliskiren in comparison to perindopril reduced BP to the same extent as perindopril but attenuated tubulointerstitial fibrosis more than perindopril which is an important factor in diabetic nephropathy [108]. It also reduced albuminuria and glomerulosclerosis similar to the levels achieved by perindopril [108]. Feldman et al. [109] reported similar findings of lowering BP, decreased albuminuria and suppressed TGF-β levels in another rat model. Finally, aliskiren inhibited atherosclerosis development and improved plaque stability alone and in combination with atorvastatin [110].

A dual blockage of the RAAS system was studied in “Aliskiren in the Evaluation of proteinuria in Diabetes” (AVOID) trial [111]. It was a randomized double-blind study involving 599 patients. Subjects enrolled in this study entered into a 3-month open label period where any previously administered drug that interfered with RAAS, was discontinued except beta-blockers. Treatment was initiated with 100 mg of losartan. Patients were randomly assigned to either aliskiren (150 mg for 3 months and then 300 mg for next three months) or placebo for total of 6 months. Primary outcome was the reduction of urine albumin to creatinine ratio (UACR). A reduction of 20 % of UACR was noticed in aliskiren group when compared to placebo, with a reduction of 50 % or more in 24.7 % of patients who received aliskiren when compared with 12.5 % of those receiving placebo. Similar results were obtained in a smaller study of 15 diabetic patients who were initiated on 300 mg of aliskiren [112]. Reduction in the UACR by 17 % in 2-4 days and by 44 % in 28 days was achieved. Finally, a retrospective analysis of the Aliskiren Observation of Heart Failure Treatment (ALOFT) trial showed that aliskiren causes neurohumoral suppression in heart failure, even in patients treated with a recommended-dose of an ACE inhibitor [113]. Recently, ALiskiren Trial In Type 2 Diabetics Nephropathy (ALITUDE) study, was testing the effect of aliskiren in type 2 diabetics at high risk for cardiovascular and renal events. Patients in ALITUDE were randomized to receive aliskiren or placebo in addition to an ACE inhibitor or an ARB. The trial was terminated based on the recommendation of the independent Data Monitoring Committee because aliskiren was unlikely to show any benefit, and there was a higher incidence of adverse events compared to placebo in these high-risk patients.

Endothelin antagonist

A pivotal role for the endothelin-1 (ET-1) system has been documented in normal renal function as well as in kidney disease. In the kidney ET-1 acts in an autocrine and paracrine manner in renal vasculature and nephron segments modulating renal hemodynamics and tubular water and sodium reabsorption respectively. Alterations in ET-1 system have been documented in kidney disease with coexisted cardiovascular disorders, hypertension and endothelial dysfunction. ET-1 has implicated in the development of hypertension, cardiovascular hypertrophy, renal fibrosis and glomerulosclerosis [114].

Given the role of ET-1 in several processes that lead to the progression of CKD the possibility that ET-1 antagonism may be beneficial has been examined. In a study ET-1 antagonist was highly effective in lowering BP and reducing proteinuria in CKD patients [115]. In a subsequent study of healthy individuals ET-1 receptor blockade increased renal blood flow and natriuresis but only given with an ACE inhibitor [116].

In a recent randomized controlled trial a selective ET-1 antagonist danusertan have been shown to be effective and could potentially play a role in high risk patients with resistant hypertension [117]. This study enrolled 379 individuals with uncontrolled hypertension with the use of tree antihypertensive drugs, including a diuretic, and demonstrated a dose-dependent reduction of BP over a 14-week study period [117].

Endothelin levels have been shown to correlate with the level of albuminuria in patients with diabetic nephropathy [118]. However this theoretical benefit of the use of ET-1 receptor blockade on albuminuria reduction is not yet known given that a recent trial in phase III, with a selective ET-1 receptor antagonist, avosentan in patients with diabetic nephropathy, was halted due to fluid retention [119]. A recent randomized placebo-controlled trial of 286 patients with diabetic nephropathy and macroalbuminuria, demonstrated that UAER decreased in a dose-dependent fashion in patients receiving avosentan in a 12-week period compared with placebo and furthermore the reduction in proteinuria was independent of BP, suggesting that this effect is predominantly mediated by endothelin antagonism [120].

Blood pressure goals, patient’s education and adherence to prescribed therapies

In patients with CKD, most guidelines, including those of The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), National Kidney Foundation [7]
and the recent reappraisal of guidelines for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) [121], uniformly recommend for more aggressive treatment goals in proteinuric patients (protein excretion greater than 1g/day) with BP targets be maintained <130/80 mmHg which are associated with lower risk of CV disease and progression of renal disease [11].

On the other hand in non proteinuric CKD patients (proteinuria <1g/day) a goal BP less than 140/90 is recommended, because several important questions regarding the aggressive lowering BP levels that should be targeting by treatment are still unanswered since this paucity of data does not support aggressive BP targets. In conclusion, a BP goal <130/80 mmHg is not supported by appropriately powered randomized trials for the CKD group as whole while it will yield a greater benefit in slowing CKD in a subgroup of patients with advanced proteinuric nephropathy.

Considering the treatment strategies in clinical practice, a general approach, which could be set out in CKD patients is the use of a RAAS blocker (ACE inhibitor or ARB or aliskiren) in combination with a non-diuretic diuretic or a long acting thiazide diuretic. If blood pressure still is not at goal the next logical step is the addition of a long acting thiazide diuretic in the combination of the RAAS blocker with the non-diuretic diuretic or a non-diuretic diuretic CAs or a non-diuretic diuretic CAAs in the combination of RAAS blockers with the long acting diuretic thiazide diuretic. Consequently, if blood pressure is still not at goal a consideration to add an aldosterone receptor blocker, or another subgroup of CAs could be an alternative (i.e., amiodipine-like agent if verapamil or diltiazem is already used) and the converse, or the addition of a vasodilating β-blocker with alpha effects.

At the turn of the century as many as 30% of patients with hypertension in the US and United Kingdom were undiagnosed and of those known to health care providers 40% to 60% were untreated [9]. Of the hypertensive patients who received treatment only 50% in US managed care plans had adequately controlled BP [122]. In US the number of patients in managed care organizations with adequately controlled BP increased from 40% in 1999 to 70% in 2005 [123]. A lower rate of blood pressure control has been reported in patients with CKD [124]. One factor contributing to less than ideal BP control is patient non adherence to prescribed therapies. A recent meta-analysis revealed that the odds of BP control among patients adhered to antihypertensive medications, compared with those who were non adherent was 3.44 (95% confidence interval, 1.6-7.37) [125]. Multiple factors influence patient adherence to prescribed therapies, among them we can include quality of life, complexity and side effects of medications, health care system issues, demographic, behavioral, treatment and clinical variables and the lack of knowledge regarding hypertension [126]. Recently, it has been suggested that there have been improvements in knowledge of hypertension risks, percentage of patients receiving specific medications and number of patients controlled [127]. Lower adherence rate have been reported among younger individuals [128], men [129] and black persons [128]. Furthermore, a negatively impact of adherence to prescribed therapies include deprevension [130], lack of knowledge regarding hypertension and its treatment [131], complexity of medication regimen [132], side effects of medication, sexual dysfunction [133] and poor quality of life [134]. It is noteworthy that individuals with CKD had similarly poor medication-taking behaviors as those without CKD [135]. Active physician education, audit, and feedback proved effective when used in combination and sustained over time [136,137]. Patient education, self-management [138] and team approaches that involved nurses and pharmacist [139,140] play a great role especially to increase knowledge regarding hypertension treatment. Furthermore, an effective communication between the physician and the patient can improve adherence to appropriate medical therapy for hypertension and can result in controlled BP and reduction in adverse outcomes [141,142].

Conclusions

The evidence discussed in this article suggests that the prevalence of CKD relevant to hypertension increased and hypertensive nephrosclerosis are two different processes, hypertrophic and ischemic leading to glomerulosclerosis and ESRD. The reduction of proteinuria is of great importance to reduce kidney function deterioration and cardiovascular disease. The pharmacologic blockade of the RAAS slows the progression of renal dysfunction more effectively than other antihypertensive strategies. A diet high in sodium chloride appears to mitigate against the antiproteinuric benefit of RAAS blockade. Furthermore, salt restriction showed a benefit in CKD progression. The combination of two or more antihypertensive agents is imperative to achieve the current BP goal in most patients with CKD. Recently new classes of effective antihypertensive agents such as renin inhibitors are involved effectively in the treatment of hypertension. Non adherence to prescribed therapies is one important factor contributing to less than ideal BP control. Active physician and patient education, proved effective when used in combination and sustained over time.

In conclusion, there are a lot of challenges when treating hypertensive patients with CKD. The physician must take into account important factors such as salt intake, proteinuria levels, the necessity of RAAS blockade and most importantly the adherence to prescribed therapies.

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