Hypertension in Chronic Kidney Disease – Role of Arterial Calcification and Impact on Treatment

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Abstract

Hypertension contributes to the progression of kidney diseases as well as to the occurrence of cardiovascular events such as myocardial infarction, heart failure and stroke. The prevalence of hypertension is elevated in patients with kidney disease, and increases progressively as glomerular filtration rate falls. A better understanding of the mechanisms leading to hypertension in renal diseases has been gained in recent years; in this article we will review the pathogenesis of hypertension in chronic kidney disease (CKD) with a special focus on vascular calcification because calcification is associated with an increased incidence of cardiovascular morbidity in CKD patients. Although calcification of large arteries and blood pressure increase with age, few studies have specifically investigated a possible connection between these two factors as determinants of the severity of hypertension in CKD. Finally, we will review the trends in hypertension treatment in CKD patients. Expanded understanding of the role of CKD as both a cause and a target of hypertension highlights key points of pathophysiology of hypertension and may contribute to the identification of new strategies for its prevention and treatment.

Keywords

Hypertension, chronic kidney disease, vascular calcification, proteinuria, treatment

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Chronic kidney disease (CKD) is characterised by progressive nephron loss leading to increased intraglomerular pressure, glomerular permeability, proteinuria and systemic hypertension. The prevalence of CKD defined as estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m² ranges from 2 to 12 % in Europe and in the US.^{1,2} CKD is an independent risk factor for the development of cardiovascular diseases (CVDs), showing a graded risk of cardiovascular events as eGFR declines, with a sharp rise in events as eGFR falls <45 mL/min per 1.73 m².³ Hypertension prevalence increases as renal function declines and may be present in more than 80 % of patients with stage 4 to 5 CKD.⁴ Hypertension contributes to progression of kidney disease as well as to cardiovascular (CV) events such as myocardial infarction, congestive heart failure and stroke. In Western countries, approximately 20–30 % of incident end-stage renal disease (ESRD) cases are attributed to hypertension.^{1,2}

One characteristic of hypertension is the remodelling of the arterial wall in response to the increase in blood pressure (BP). Moreover, with time, significant modifications in extracellular matrix composition and in vascular cell phenotype occur in the vasculature.⁵ Vascular tissue remodelling associated with hypertension, might actually create an environment for calcium deposition within the arteries.⁶ This phenomenon is particularly important in CKD patients. Indeed, in CKD, vascular calcifications are clearly associated with a higher CV morbidity and mortality.³ Although calcification of large arteries and BP increase with ageing, only a few studies specifically investigated the interaction between these two factors as aggravating mechanisms of hypertension and CV events, and as promoters of a

more rapid decline of renal function in CKD. In this review, we will focus on accelerated vascular calcification and its association with CKD and hypertension.

Accelerated Vascular Calcification in Chronic Kidney Disease and Hypertension – Implications for New Concepts

The risk of CV diseases in patients with chronic renal disease appears to be far greater than in the general population.³ Among patients treated by dialysis, the prevalence of coronary artery disease is approximately 40 % and the prevalence of left ventricular hypertrophy is approximately 75 %. CV mortality of dialysis patients has been estimated to be approximately 9 % per year.³ Even after stratification by age, gender, race and the presence or absence of diabetes, CV mortality in dialysis patients is 10–20 times higher than in the general population.³ These findings have prompted most hypertension guidelines to include the presence of CKD as a CV risk factor.⁷

Premature arterial calcification in CKD patients is one factor possibly increasing the CV risk. The natural history of coronary artery calcification has been studied in 22 young adults with ESRD by electron-beam computed tomography (EBCT).⁸ After a baseline assessment, computed tomography (CT) scanning was repeated at a mean of 22 ± 7 months later. Among 12 patients who had no evidence of coronary artery calcification on the initial scan, two had evidence of calcification on follow-up scanning. Among 10 of these 22 patients who had evidence of coronary artery calcification on the initial scan, nine had a higher calcification score on follow-up

scanning; the values nearly doubled (from 125 ± 104 to 249 ± 216) over a mean period of 20 ± 3 months ($p=0.02$).

The mechanisms responsible for vascular calcifications in CKD patients remain uncertain, and the relation between arterial wall calcification and the atherosclerotic process is not fully understood. The factors involved in these complications are complex. Numerous metabolic and endocrine abnormalities involving calcium and phosphorus metabolism are found in CKD. Furthermore, CKD is believed to be a state of inflammation and oxidative stress. Most of these abnormalities occur early in the course of CKD and may contribute to the development and progression of vascular calcification and atherosclerosis. The mechanisms regulating the process of vascular calcification and the factors involved are subject to continued investigation. Both calcium and phosphorus directly stimulate vascular smooth muscle cell transformation into osteoblast-like cells and abnormal mineralization *in vitro*. The mechanisms whereby smooth muscle cells calcify appears to result from a complex interplay between factors that activate and inhibit tissue calcification.⁹ Matrix vesicles initiate mineral nucleation during skeletogenesis; similar vesicular structures are deposited at sites of pathologic vascular calcification. *In vitro* studies have shown that elevated levels of extracellular calcium and phosphorus can induce mineralization of vascular smooth muscle cells.¹⁰ In addition, numerous other factors have been shown, both *in vitro* and *in vivo*, to promote this process, in part through the production and activity of proteins like osteopontin, osteoprotegerin, osteocalcin, bone morphogenetic proteins and matrix Gla protein.⁸

Calcium deposits are found, however, in a large proportion of atherosclerotic lesions, providing the basis for the use of EBCT to screen for coronary artery disease.¹¹ Arterial layers are more frequently and more intensively calcified in uraemic patients than in non-uraemic patients, and participated to the progression of CKD.¹² Both the intima and media arterial layers are more frequently and more intensively calcified in uraemic patients than in non-uraemic individuals, and vascular and valvular calcification are both predictors of increased CV mortality and morbidity.¹³ In the atheromatous plaque, the most marked difference between uraemic and non-uraemic patients is not in its size but its composition, with a marked increase in calcium content in CKD patients.¹⁴

Vascular Calcification – Role of Vitamin D and Vitamin D Analogues

Calcitriol and various analogues are commonly used to suppress secondary hyperparathyroidism in CKD but may also exacerbate vascular calcification in experimental models; the mechanisms by which high doses of vitamin D or its derivatives induce vascular calcification include an increase in serum calcium and phosphate, the formation of fetuin-A mineral complexes in association with a decrease in free serum levels of fetuin-A.¹⁵ Some active vitamin D derivatives, when given in high amounts to animals with CKD, are not endowed with the same calcification-inducing capacity. For example, paricalcitol has been shown to be less pro-calcifying in uraemic rats than calcitriol or doxercalciferol. However, there are no prospective randomised controlled trials in CKD patients comparing the effect of native vitamin D or active vitamin D derivatives with placebo on vascular calcification. So far, the results of the PRIMO study (Paricalcitol capsules benefits in Renal failure Induced cardiac MORbidity in subjects with chronic kidney disease Stage 3/4) that failed to show a beneficial effect of long-term paricalcitol administration over placebo on cardiac structure and function in CKD patients confirms the need for further intervention studies with firm outcomes.¹⁶

Pulse Wave Velocity, Systolic Hypertension and Vascular Calcification in Chronic Kidney Disease Patients

Pulse wave velocity (PWV) is the gold standard method for evaluating arterial stiffness non-invasively. It depends on the arterial wall structure and function but is mainly influenced by age-associated alterations and BP.¹⁷ Temmar et al. studied the temporal link between PWV and aortic and coronary calcifications in a cohort of 150 patients with different stages of CKD.¹⁸ They found that both vascular stiffness and vascular calcification appeared early in CKD patients. Age, mean arterial BP, diabetes and aortic calcification score were all independent determinants of increased PWV. The relationship between measures of arterial stiffness PWV and the extent of calcification in the coronary arteries was also examined by Haydar et al. in a small population of 66 haemodialysis patients.¹⁹ The mean age of the 55 patients was 56.4 years and the mean duration of dialysis was 65.4 months; they demonstrated that PWV is strongly related to the degree of EBCT-derived coronary artery calcium score in CKD patients. The next step in validating PWV as a useful tool for the risk assessment of CKD patients was to study the effect of pharmacological intervention. Clinical studies involving essential hypertension and CKD patients have shown that angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists decreased aortic PWV to a large extent in response to BP lowering.²⁰ The results indicate that independent of BP changes, survival was substantially better for those subjects whose aortic PWV decreased in response to decreased BP. Guerin et al. hypothesised that the PWV is partly dependent on BP.²¹ They evaluated if the changes in PWV in response to decreases in BP can predict mortality in dialysis patients. They showed that the loss of aortic PWV sensitivity to BP was predictive of adverse outcome, indicating that arterial stiffness is not only a risk factor contributing to the development of CV disease but also a marker of more advanced, less reversible arterial damage. Taken together, these results support the hypothesis that measurement of arterial parameters exploring both structural and functional properties, such as quantification of arterial calcium deposit and determination of PWV, could help in stratifying the risk but also in evaluating the risk reduction strategies by monitoring these arterial parameters under different drug regimens. Significant alterations of the aortic PWV appear at an early stage of the disease; mild-to-moderate renal insufficiency, an elevated stiffness of the central arteries seems to be significantly associated with a reduced creatinine clearance, independent of BP and other standard CV risk factors.²² These results suggest that alterations of the viscoelastic properties of the arterial wall are significantly connected to renal alterations, and that this association is present long before the appearance of ESRD and macrovascular complications.²³

High BP and proteinuria are major factors in the progression of CKD.²⁴ Weir et al. have evaluated whether PWV was associated with increased risk of proteinuria in CKD patients.²⁴ Systolic BP was important as an explanatory factor for variations in proteinuria, whereas PWV incrementally accounted for a significant portion of variation in proteinuria beyond that explained by brachial artery systolic BP in diabetics but not in non-diabetic patients.

Importance of Blood Pressure Control and Antihypertensive Therapy

The main goal of BP reduction in CKD patients is to reduce the risk of CV events and to slow the decline of GFR. Most of the evidence for reducing BP comes from large randomised controlled trials in the general population. These trials showed that treatment of BP

reduces CV outcomes. In CKD patients with proteinuria, it has been shown that BP reduction is associated with a slower decline of renal function.^{25,26} The Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for the management of BP in CKD acknowledges that no single BP target is optimal for all CKD patients and encourages individualisation of treatment depending on age, the severity of albuminuria and co-morbidities. In general, the available evidence indicates that in CKD patients without albuminuria the target BP should be ≤ 140 mmHg systolic and ≤ 90 mmHg diastolic. However, in most patients with an albumin excretion rate of ≥ 30 mg/24 hour (i.e. those with both micro- and macroalbuminuria), a lower target of ≤ 130 mmHg systolic and ≤ 80 mmHg diastolic is suggested.^{26,27} In achieving BP control, the value of lifestyle changes and the need for multiple pharmacological agents is acknowledged in all guidelines.

Blocking the renin-angiotensin-aldosterone system (RAAS), using ACE inhibitors or angiotensin receptor blockers (ARBs), is the current gold standard pharmacological treatment approach for hypertension and proteinuria in CKD. Numerous randomised controlled trials in diabetic and non-diabetic CKD patients have shown that these agents slow the decline of CKD compared with placebo or with other antihypertensive agent.^{28–33} The beneficial effect was confirmed in a meta-analysis.³⁴ These agents act not only to lower BP but also through a BP-independent effect on proteinuria. The most recent analysis of the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) have documented that the initial treatment-induced reduction in albuminuria is highly predictive of reduction of fatal and non-fatal renal and CV events.³⁵ This predictive effect of the decrease in proteinuria prompted trials, which studied the effect of intensive blockade of the renin-angiotensin system (RAS). Unfortunately, the results from ONTARGET showing a lack of an additional benefit of double blockade (ramipril–telmisartan) over monotherapy (ramipril or telmisartan alone), with an increased risk of hyperkalaemia, renal failure, discourage the use of ACE inhibitors/ARBs combination in patients at high-risk of CV events. Aliskiren, the first direct renin inhibitor to receive approval for hypertension treatment, was thought to provide additional renoprotective effects over standard treatment.^{36,37} The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE), which included 8,606 patients with type 2 diabetes, compared the effects of aliskiren or placebo added to standard treatment of RAS blockade. This study was terminated prematurely due to higher adverse events occurring in patients receiving aliskiren in addition to the standard care, such as an increased incidence of a non-fatal stroke, renal failure, hyperkalaemia and hypotension. The use of a single drug to block the RAAS is therefore recommended or suggested in all patients with an albumin excretion rate of ≥ 30 mg/24 hour.

In order to achieve BP targets, more than one drug is often necessary, particularly in CKD.³⁸ Therefore, the question arising is which is the best antihypertensive drug to combine with a RAS blocker? In the Avoiding Cardiovascular Events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, a randomised controlled trial comparing fixed-dose combination of the ACE inhibitor benazepril and the dihydropyridine calcium channel blocker amlodipine with the combination of benazepril and hydrochlorothiazide in reducing CV morbidity and mortality, the progression of CKD was a prespecified endpoint. This study, which included 11,506 high-risk hypertensive patients, showed that events of CKD defined as double serum creatinine or ESRD were lower in the benazepril–amlodipine group

compared with the benazepril–hydrochlorothiazide group (hazard ratio [HR] 0.52, 0.42–0.65). A possible explanation may come from the differential effect of calcium channel blockers compared with thiazides on vascular calcification.

In fact, no study has really investigated the effect of treatment on vascular calcifications and BP and the progression of renal diseases. A substudy of the International Nifedipine GITS Study of Intervention as a Goal in Hypertension Therapy (INSIGHT) trial,³⁹ which compared the effect of nifedipine once-daily versus co-amilofide (hydrochlorothiazide 25 mg, amiloride 2.5 mg) on mortality and morbidity in high-risk hypertensive patients, was interested in progression of coronary calcification in a subgroup of patients (n=201). While the main study failed to show any difference in mortality and morbidity between the two arms, the substudy showed a slower progression of coronary calcification in the nifedipine versus the co-amilofide group.⁴⁰ This finding may be of relevance since even CKD patients with mild renal dysfunction have accelerated coronary calcifications independently of other risk factors.⁴¹ However, it is worth mentioning that the use of calcium channel blockers is associated with more peripheral oedema that might limit its use in CKD.^{39,42}

As salt and fluid retention are largely responsible for the high BP in CKD patients, it is not surprising that diuretics still play an important role in the control of hypertension in these patients. Most guidelines recommend using loop diuretics over thiazides for the treatment of hypertension once CKD reaches stage 4 (eGFR < 30 ml/min/1.73 m²). However, recent evidence from small trials suggest that thiazides may still be useful in advanced CKD.⁴³ The combined use of blockers of the RAS, diuretics and a low sodium diet appears to be particularly useful in reducing BP and proteinuria.⁴⁴

The use of beta-blockers may be particularly useful in patients with CKD and systolic heart failure. Indeed, a meta-analysis reported that compared with placebo the risk ratio of all-cause mortality (relative risk [RR] 0.72, 95 % confidence interval [CI] 0.64–0.80) and CV mortality (RR 0.66, 95 % CI 0.49–0.89) was reduced.⁴⁵ Beta-blockers, however, are not the preferred first-line drugs because it has been shown that if peripheral (brachial) BP is lowered similarly by atenolol and amlodipine, central BP is decreased more intensively by amlodipine.⁴⁶ This may be of importance because in the same cohort, central BP was significantly associated with a composite outcome of total CV events/procedures and the development of renal impairment.

Finally, as renal function declines, the pharmacokinetics of drugs due to impaired renal clearance may be affected. It is important to adapt the dose of antihypertensive drugs to the eGFR in order to avoid accumulation, which may result in serious side effects.

Lifestyle interventions are recommended in most hypertension or renal disease guidelines. If restriction of sodium intake makes sense from a pathophysiological point of view (reduced capacity to excrete sodium in CKD, effect on proteinuria, effect on nocturnal BP, increased effectiveness of RAS blockade), the level of sodium intake that should be targeted in CKD remains a matter of debate since recent *post hoc* analysis have shown that a J-curve may exist.⁴⁷ This indicates that a restriction in sodium intake that is too strict may actually be deleterious. Well-designed prospective trials targeting sodium intake are needed to confirm this phenomenon. In addition to sodium intake, moderate alcohol intake, regular exercise,⁴⁸ weight

loss in those with a body mass index >25 kg/m² and reduced amount of saturated fat help to reduce BP.⁴⁹

Is Accelerated Renal Calcification a Reason for the Failure of Renal Denervation to Lower Blood Pressure in Chronic Kidney Disease?

There is a current surge in research investigating renal denervation as a potential treatment for resistant hypertension, as an overactive renal sympathetic system is known to exert an influence on the underlying pathophysiology of both hypertension and CKD. In a uraemic rat model, Campese et al. have shown in subtotaly nephrectomised rats that BP rapidly increases after surgery, which was abolished by afferent denervation.⁵⁰ Interestingly, renal afferent denervation has also prevented the progression of renal disease in this model.⁵¹ They have also showed that a small lesion in one kidney by an intrarenal phenol injection, not affecting kidney function, increases sympathetic activity and leads to a long-term increase in noradrenaline secretion and to hypertension. These effects are also abolished by afferent denervation. In humans, it has been shown that the activity of the sympathetic nervous, assessed by microneurography, increases as renal function declines.⁵² Taken together, these results indicate that the sympathetic nervous system is a logical target for intervention. Catheter-based radiofrequency ablation technology to disrupt both efferent and afferent renal nerves has recently been introduced to clinical medicine after the demonstration of significant systolic and diastolic BP reductions. Prior unblinded studies have suggested that catheter-based renal artery denervation reduces office BP in patients with resistant hypertension;⁴¹ the results of the SYMPPLICITY HTN-3 study, a single-blind, randomised, sham-controlled trial, failed to show a significant reduction of systolic BP six months after renal artery denervation as compared with a sham control.⁵³ Interestingly, subgroup analysis suggested that patients with eGFR

<60 ml/min/1.73 m² were less responsive (between-group difference in change in office BP 0.54 [-8.29–9.37, 95 % CI]) than patients with eGFR ≥ 60 ml/min/1.73 m² (between-group difference in change in office BP -5.22 [-10.51–0.06, 95 % CI]).⁵⁴ The effect of renal function in response to renal denervation is consistent with an earlier report showing that higher baseline creatinine was associated with lower probability of 24 hour BP improvement (odds ratio for each 20 μ mol/L increase, 0.60; $p=0.05$). The degree of renal artery calcification may limit the efficacy of renal denervation; however, this remains to be proven. Recently, a study was conducted to investigate the proportion of patients eligible for renal denervation and the reasons for non-eligibility at 11 expert centres participating in the European Network COordinating Research on renal Denervation in treatment-resistant hypertension (ENCOREd).⁵⁵ The most frequent cause of ineligibility (approximately half of cases) was BP normalisation after treatment adjustment by a hypertension specialist. These results highlight that hypertension centres with a record in clinical experience and research should remain the gatekeepers before renal denervation is considered.⁵⁶ Further evaluation in rigorously designed clinical trials will be necessary to bring evidence that renal denervation may be a therapeutic option for CKD patients.

In conclusion, the burden of hypertension in CKD patients is high. These patients are at increased risk of target organ damages and CV events. Vascular lesions due to hypertension-induced remodelling and vascular calcifications play an important role in the development of CV and renal complications. In the absence of specific treatment of arterial stiffness and calcifications, reduction of BP using non-pharmacological or/and pharmacological interventions is crucial to reduce these risks. Most of the time, several drugs are necessary to reach the targeted BP. Today, the combination of drugs including a blocker of the RAS and a calcium channel blocker appear to be one of the most effective associations in high-risk patients. ■

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