Vascular Calcification in Patients with Chronic Kidney Disease

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Introduction

Chronic kidney disease (CKD) is globally emerging as an important risk factor for morbidity and mortality. The progressive aging of the global population and the escalating numbers of patients with type 2 diabetes mellitus are clearly major factors responsible for its growing significance [1]. As many as 6–11% of the adult population could have some degree of CKD, with a number of these patients progressing to end-stage renal disease (ESRD) [2]. The preponderance of subjects with CKD are more likely to die of cardiovascular disease than to go on to ESRD requiring renal replacement therapy [3]. Therefore, CKD is not surprisingly an independent risk factor for cardiovascular events, particularly in higher-risk populations [4–6]. Recently, an independent and graded association between reduced renal function and risk of cardiovascular events has been demonstrated in a single large cohort of subjects (approximately 1,000,000 individuals) [7]. A higher incidence of traditional cardiovascular risk factors, such as older age, hypertension, dyslipidemia and diabetes, in combination with risk factors specific to CKD (i.e. albuminuria, anemia, abnormal calcium/phosphate metabolism, extracellular fluid volume...
overload, electrolyte imbalance) may partly explain the very high prevalence of cardiovascular disease in these patients [8]. Additionally, it has been hypothesized that a number of pathophysiologic variables that are driven by the ‘uremic milieu’, such as oxidative stress, inflammation and endothelial dysfunction, may potentially promote atherosclerosis. A hallmark of the atherosclerotic process in CKD is vascular calcification (VC) [9, 10]. In view of the higher predilection of CKD patients for VC, measures of VC have been hypothesized to serve as non-invasive surrogates, especially in light of the fact that traditional risk factors are not good predictors in the CKD patient population.

This article briefly summarizes the state of the art of our knowledge regarding the mechanisms responsible for VC and its detection in patients with CKD and ESRD.

Mechanisms of VC in CKD

VC is observed either in the tunica intima (atherosclerosis) or in the tunica media. Medial calcification (Mönckeberg’s sclerosis) is particularly common in patients with ESRD and CKD and may occur independent of atherosclerosis, implying different etiological mechanisms from intimal calcification [11]. Medial wall calcification increases vascular stiffness and reduces vascular compliance. Reduction in compliance (reflected as an increase in pulse wave velocity) may contribute to an increase in systolic blood pressure, loss of diastolic augmentation (fall in diastolic blood pressure) and rise in pulse pressure. Not surprisingly, the amount of coronary calcium correlates with arterial stiffness and the extent of calcification in the abdominal aorta in dialysis patients [12]. In atherosclerosis, VC probably occurs predominantly in the intima and through most stages of atherosclerosis, although it is lacking in the very early ‘fatty streak’ stage [13].

The impact of VC on plaque vulnerability is controversial, with some studies demonstrating an increase in stability and some noting increased vulnerability. To some extent, this may relate to the stage of atherosclerosis and the extent of calcification, with the larger more heavily calcified lesions reflecting lesions at an advanced stage lacking the extent of inflammation and lipid core seen in earlier plaques [14, 15]. An interesting hypothesis that may potentially explain the somewhat paradoxical increased and decreased association of VC with vulnerability is the possibility that VC may confer a biphasic risk depending on the stage of atherosclerosis and the extent of VC. Model calculations support an increased wall stress in the transition areas between the calcified plaques and the adjacent non-involved areas [16]. As the degree of calcification increases, the extension of the transition area between rigid and distensible plaque would initially increase until the point at which the calcified plaques coalesce. Calcification beyond this point may theoretically reduce transition zones, result in lower wall stress and may be associated with a lower risk of plaque rupture. Thus, it could be hypothesized that the most relevant prognostic parameter may not be the extent of VC but rather the ‘total transition area’ [17]. The ability to arrive at such a metric in the clinical realm remains unrealistic at this point.

Molecular Potentiators of VC

VC has been traditionally considered a passive process, associated with atherosclerosis or aging. However, recent evidence refutes this notion and supports the concept that VC is a dynamically regulated process [18–20]. A plethora of genes and proteins that normally function as key modulators of bone and mineral metabolism are involved, either directly or indirectly in the process of VC [18, 21]. Bone-related proteins, such as osteonectin, parathyroid hormone, parathyroid hormone-related peptide and bone morphogenic protein 7, are expressed in the atherosclerotic plaques as well as at sites of medial arterial calcification [20–24]. Osteoprotegerin (OPG), a member of the tumor necrosis factor-α receptor family with inhibitory effects on osteoclastogenesis, introduces another link between bone and vascular metabolism [25]. OPG is a soluble molecule that binds and inhibits the ligand for receptor activator of nuclear factor-κB, a tumor necrosis factor-α superfamily member demonstrated in the vasculature and essential for the maturation of osteoclast progenitors [26]. In agreement with the permissive role of OPG in VC, serum levels of OPG are elevated in patients with ESRD [27]. Vascular smooth muscle cells (VSMCs) and possibly vascular endothelial cells can be induced to transform into an osteoblast-like phenotype in vitro [28]. VSMCs and osteoblasts derive from a common mesenchymal precursor cell, and core binding factor (Cbfa)-1 is a transcription factor thought to be responsible for this switch that turns this precursor to the osteoblast phenotype [29].

Phosphate levels were long thought to influence mineralization only through physicochemical means. However, new evidence indicates that phosphate regulates and coordinates cell signaling and gene expression by dynamic transport processes. Primary cultures of human VSMCs
express bone proteins and mineralize when treated with β-glycerophosphate, which serves as an inorganic phosphate donor in the presence of alkaline phosphatase [28]. High intracellular phosphate downregulates typical VSMC genes and induces osteoblastic-like phenotypic changes of VSMCs. In particular, phosphate stimulates the expression of alkaline phosphatase on their surface and the production of Cbfa-1 and calcium-binding proteins, such as osteocalcin and osteopontin (OPN) [30, 31]. Recent studies demonstrate that Cbfa-1, alkaline phosphatase and OPN are present in calcified arteries, but are absent from the vessel wall of non-calcified arteries [19, 20].

Molecular Inhibitors of Calcification

Plasma components (such as citrate and magnesium) play a key physiological role by maintaining mineral in solution. Specific proteins may serve an inhibitory function and prevent ectopic calcification. For instance, fetuin-A, matrix Gla protein (MGP) and OPN are important inhibitors of calcification in vivo. Serum levels of fetuin-A are significantly reduced in subjects with renal failure [32, 33]. Circulating levels of fetuin-A decline with increasing inflammation in patients on dialysis and may additionally provide a link between inflammation and propensity for VC [32]. MGP is a small-size protein and is found in normal arterial wall and appears to be upregulated in atherosclerotic plaques [21]. The MGP knockout mouse has extensive aortic calcification, and recent evidence indicates that MGP inhibits mesenchymal cell differentiation to osteogenic phenotype [34, 35]. OPN is another important negative regulator of calcification and is expressed by macrophages, smooth muscle cells and endothelial cells [36–38], and is found to colocalize with these cell types in calcified atherosclerotic plaques. Mice deficient in both OPN and MGP have accelerated aortic calcification compared with mice deficient in only MGP, consistent with the concept that OPN inhibits mineralization [39].

The high prevalence of traditional risk factors for atherosclerosis combined with uremia-specific factors may be responsible for the increased VC observed in these patients. Inflammation in CKD may play a central role in the predisposition of patients with renal failure to VC [22]. Inflammation is a fundamental component of the atherosclerotic process and high level of serum inflammatory markers (i.e. C-reactive protein) have been reported in patients with ESRD [40]. The role of inflammation in VC is further strengthened by recent observations linking levels of circulating inhibitors of VC, such as fetuin-A and OPN, with increase inflammatory markers [32].

Role of Calcium and Phosphate Flux in VC

Recent evidence suggests that abnormalities in calcium and phosphorus metabolism, including therapeutic interventions affecting total body calcium balance, may also influence the development and progression of VC. Thus, it has been postulated that accelerated VC at the medial level may be favored (especially in ESRD patients) by the putative systemic calcium load arising from the use of calcium-containing phosphate binders and the use of high concentrations of calcium salts in the dialysate [41]. This may be distinct from the concomitant intimal VC that may occur in the same patients through disparate mechanisms. In direct agreement with these hypotheses is the correlation between VC and the calcium-phosphate product observed in studies involving young patients with ESRD (who have predominantly medial VC) but not in studies including older ESRD subjects who may have concomitant intimal VC [12, 42–44].

Detection and Significance of VC in CKD and ESRD

Although various methods have been proposed, electron beam computed tomography (EBCT) and multi-detector computer tomography (MDCT) represent the most accurate techniques available for calcium quantification. EBCT has been applied for more than a decade in the detection and quantification of cardiac and VC with good results and is currently considered the gold standard [45]. However, most medical centers do not have access to EBCT scanners due to relatively high costs and limited applications other than the calcium scoring. MDCT scanners which are more widely available and can be employed for a number of cardiac and non-cardiac applications are therefore more practical for the assessment of VC [46]. A number of studies have directly compared EBCT and MDCT (4- and 16-slice), demonstrating excellent correlation between these techniques for calcium quantification [47–49]. There are three different methods of calcium quantification and scoring: the Agatston method, the volumetric method and the mass method [50–52]. The Agatston score, although the most commonly used index to date, has the worst reproducibility (inter-scan). Reproducibility appears to be intermediate for the volumetric approach and best for the mass method [53].

The presence of coronary calcium, although a sensitive test for the presence of coronary artery disease, is not specific for prediction of ‘significant’ coronary lesions [54, 55]. Coronary calcification closely correlates with the
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presence of calcium in the aorta (at thoracic and abdominal levels) and in the aortic valve, suggesting common pathophysiologic mechanisms for this process, be it in the valve or in conduit arteries [56, 57]. According to published guidelines, the coronary calcium score may help in identifying asymptomatic patients at low-to-intermediate risk, who may benefit from more aggressive risk factor modification [45]. In recent years, several studies have investigated the prognostic value of calcium scoring [58]. As expected, coronary VC detected by EBCT was strongly associated with all-cause mortality [59, 60]. VC also predicts cardiovascular death in different patient populations, although the predictive value ranges quite widely depending on the patient population and the underlying mix of risk factors [61–63].

VC has been recognized for many years as a common complication in patients with ESRD [64, 65]. Table 1 reports a list of the available studies that have evaluated the presence of coronary VC in patients with renal failure. Braun et al. [66] first reported the use of EBCT in 49 hemodialysis patients, showing coronary calcium score values 2.5- to 5-fold higher than non-hemodialysis patients. Other studies have revealed pronounced VC even in young adults with ESRD, who are otherwise not at risk for VC [42, 43]. In another report, Raggi et al. [67] studied a population of 205 patients on maintenance hemodialysis therapy observing high values of calcium score at the level of coronary arteries, thoracic aorta and cardiac valves. Furthermore, the coronary calcium score was significantly related to previous history of myocardial infarction (p < 0.0001) and angina (p < 0.0001).

Predialysis CKD patients constitute a very large population with a documented high risk for cardiovascular events [7]. VC in predialysis patients with CKD, in contrast to hemodialysis patients, is much less intensively studied. Recent data revealed that advanced atherosclerosis (as demonstrated by the thickening of the arterial wall) is already present in patients with CKD before starting hemodialysis treatment [68]. Mehrotra et al. [69] studied a group of 60 patients with diabetic nephropathy with EBCT, revealing a higher prevalence and severity of coronary VC compared with diabetic controls with normal renal function. Interestingly, in this population, the high degree of VC was not related to measures of disordered mineral metabolism (table 1).

The Renal Research Institute (RRI)-CKD study is currently evaluating the severity of VC at the level of the coronary artery, thoracic aorta and cardiac valves in a subgroup of approximately 100 patients studied by 16-slice MDCT [70]. This is the first prospective study that will be specifically addressed to study prevalence and correlates of VC in an unselected population of predialysis CKD patients. In this population, the preliminary results seem to show the presence of high prevalence of VC, whereas no clear correlation with an index of abnormal mineral metabolism has been noted. The National Institutes of Health-sponsored Chronic Renal Insufficiency Cohort study will also address some of the same issues.

Table 1. Studies using EBCT or MDCT to assess coronary calcium score in patients with renal failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Imaging modality</th>
<th>Correlates for coronary calcium score</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>mineral metabolism</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ca</td>
</tr>
<tr>
<td>Braun et al. [66], 1996</td>
<td>49 HD</td>
<td>EBCT</td>
<td>–</td>
</tr>
<tr>
<td>Goodmann et al. [42], 2000</td>
<td>39 HD</td>
<td>EBCT</td>
<td>–</td>
</tr>
<tr>
<td>Oh et al. [43], 2002</td>
<td>39 ESRD (13 HD + 26 RT)</td>
<td>EBCT</td>
<td>–</td>
</tr>
<tr>
<td>Raggi et al. [67], 2002</td>
<td>205 HD</td>
<td>EBCT</td>
<td>+</td>
</tr>
<tr>
<td>Moe et al. [44], 2003</td>
<td>55 ESRD (33 HD + 38 RT)</td>
<td>MDCT</td>
<td>–</td>
</tr>
<tr>
<td>Haydar et al. [78], 2004</td>
<td>46 HD</td>
<td>EBCT</td>
<td>NA</td>
</tr>
<tr>
<td>Mehrotra et al. [69], 2004</td>
<td>60 CKD + DM</td>
<td>EBCT</td>
<td>–</td>
</tr>
<tr>
<td>Nitta et al. [12], 2004</td>
<td>53 HD</td>
<td>MDCT</td>
<td>–</td>
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PTH = Parathyroid hormone; HD = hemodialysis; NA = not assessed; RT = renal transplantation; DM = diabetes mellitus; GFR = glomerular filtration rate.
Progression in VC in ESRD and CKD

VCs progress more rapidly in patients treated with dialysis than in the general population (table 2) [42, 71]. In asymptomatic subjects with normal renal function, the Agatston score progresses at an average rate of 33% per year [72]. Coronary calcium score progression (measured by MDCT) was 2-fold greater in hypertensive patients with CKD compared with hypertensives with normal renal function [73]. It is possible (although still a hypothesis) that medial wall calcification plays a dominant role in the progression of VC in patients with ESRD, while VC progression in patients with normal renal function mainly reflects the evolution of atherosclerotic calcification [74]. In a group of peritoneal dialysis patients, studied by MDCT at baseline and after 1 year of follow-up, Stompor et al. [75] reported a significant correlation between the change in coronary calcium score and the mean values of phosphate and calcium-phosphate product. Corroborating the association of VC progression with abnormal mineral metabolism, greater rates of VC progression have been demonstrated in ESRD patients treated with large oral doses of calcium-containing compounds, in comparison with patients treated with the calcium-free, phosphate-binding agent sevelamer [76].

There are limited data regarding the progression of VC in predialysis CKD patients [73]. A subgroup of approximately 50 patients enrolled in the RRI-CKD study have been studied with 16-slice MDCT at baseline and after about 1 year of follow-up. Our preliminary data reveal a high rate of VC progression in this unselected population of CKD patients (unpublished observations).

The utility of VC measurements (by EBCT or MDCT) as a predictor of adverse cardiovascular outcomes is yet to be demonstrated in patients with renal failure. A number of issues relevant to the renal patients need to be carefully studied. These include the evolution of VC and its relationship to decline in renal function. Although it is likely that medial versus intimal VC may have a differential impact on prognosis in CKD and for that matter dialysis patients, the image resolution of EBCT and MDCT is currently insufficient to distinguish between these two processes [77].

Conclusions

VC is ubiquitous and progresses rapidly in patients with advanced kidney disease. The paracrine and molecular determinants of VC in renal failure are continuously evolving. Modalities such as EBCT and MDCT allow non-invasive detection and quantification of VC and may provide useful prognostic information in this patient population. The ongoing Chronic Renal Insufficiency Cohort study and the RRI-CKD study should help provide information on the role for calcium scoring in cohorts of patients with predialysis CKD.

Table 2. Studies using EBCT or MDCT to assess the progression in coronary calcium score in patients with renal failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Duration of follow-up</th>
<th>Imaging modality</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamashiro et al. [71], 2001</td>
<td>24 HD</td>
<td>17 months</td>
<td>EBCT</td>
<td>progression correlates with higher triglycerides and lower high-density lipoprotein cholesterol</td>
</tr>
<tr>
<td>Chertow et al. [76], 2002</td>
<td>132 HD</td>
<td>11 months</td>
<td>EBCT</td>
<td>progression reduced by sevelamer</td>
</tr>
<tr>
<td>Bursztyn et al. [73], 2003</td>
<td>53 CKD + HTN</td>
<td>3 years</td>
<td>MDCT</td>
<td>progression faster in CKD compared with non-CKD</td>
</tr>
<tr>
<td>Stompor et al. [75], 2004</td>
<td>47 PD</td>
<td>1 year</td>
<td>MDCT</td>
<td>progression correlates with higher C-reactive protein, serum phosphate and calcium-phosphate product</td>
</tr>
</tbody>
</table>

HD = Hemodialysis; HTN = hypertension; PD = peritoneal dialysis.
References


