

## Vascular Calcification in Patients With Renal Failure: Culprit or Innocent Bystander?

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There is an emerging epidemic of chronic kidney disease (CKD) in developed countries, driven primarily by the aging of the global population and the escalating numbers of patients who have type 2 diabetes mellitus [1]. Recent reports suggest that as many as 6% to 11% of the adult population could have some degree of CKD, and this estimate is supported by the dramatic rise in the number of people with end-stage renal disease (ESRD) [2]. What is not readily appreciated is that the preponderance of patients who have CKD are more likely to die from cardiovascular disease than to go on to ESRD requiring renal replacement therapy [3]. This likelihood is reflected in the increased referrals to cardiologists of patients who have cardiovascular disease and coexisting CKD.

CKD has clearly emerged as 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 patients (approximately 1 million individuals) [7]. The concomitance of a higher incidence of traditional cardiovascular risk factors, such as older age, hypertension, dyslipidemia, and diabetes, and risk

factors specific to CKD (ie, albuminuria, anemia, abnormal calcium and phosphate metabolism, extracellular fluid volume overload, electrolyte imbalance) may partly explain the high prevalence of cardiovascular disease in these patients [8]. A number of other pathophysiologic variables that are driven by the uremic milieu, such as oxidative stress, inflammation, and endothelial dysfunction, may promote the atherosclerotic process.

The interaction among this multiplicity of factors has been hypothesized to promote the myocardial and vascular complications commonly encountered in CKD patients. In particular, atherosclerosis is common in patients who have CKD; the lesions typically are associated with marked vascular calcification (VC) [9,10].

The traditional variables of risk are poorly predictive of cardiovascular events in this population. With the availability of feasible and reproducible imaging modalities, however, there has been a great interest in surrogate markers of cardiovascular risk in patients who have renal failure. Specifically, in view of the higher predilection for VC in patients who have CKD, it has been hypothesized that determining vessel calcium scores by CT may be a helpful marker of the extension of atherosclerosis and in predicting events in this population.

This article briefly summarizes the current knowledge regarding (1) the mechanisms responsible for VC and its relationship to the atherosclerotic process (with a focus on uremic patients) and (2) the detection of VC and its prevalence in patients who have CKD and ESRD.

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### **Mechanisms of vascular calcification in renal failure**

In patients who have renal failure, VC frequently may be observed in two distinct pathologic sites: in the intima, where it is invariably associated with atherosclerosis, and in the tunica media, where it is relevant to the loss of vascular elasticity and compliance. Medial calcification (Mönckeberg's sclerosis) is particularly common in patients who have ESRD and may occur independently of atherosclerosis, thus suggesting etiologic mechanisms different from those involved with intimal calcification [11]. The hemodynamic consequences of medial wall calcification are quite different from those caused by atherosclerotic calcification, and they are less widely understood [12]. Medial wall calcification increases vascular stiffness and reduces vascular compliance. As a result, systolic blood pressure rises, pulse pressure widens, and pulse wave velocity increases. The amount of coronary calcium correlates with arterial stiffness and the extent of calcification in abdominal aorta in dialysis patients [13].

In atherosclerosis, VC probably occurs throughout the course of plaque development, but it is most pronounced in larger, presumably more mature lesions [14]. Heavily calcified plaques are traditionally considered to be associated with a stable phenotype. Whether the presence of small areas of VC contributes to plaque rupture and subsequent arterial thrombosis is still unclear [15,16].

Based on biomechanical considerations, the lipid-rich areas, rather than areas with VC, have heightened stress [16]. Another possibility is that the risk of plaque rupture caused by calcification is biphasic and dose dependent. Model calculations support an increased mural tension in the transition area between the calcified plaque and the circumferential nonatherosclerotic wall [17]. As the degree of calcification increases, the initial transition area between rigid and distensible plaque increases until the calcified plaques coalesce (Fig. 1). In theory, calcification beyond this point may reduce transition zones, resulting in lower mural tension, and may be associated with a lowered risk of plaque rupture. Thus, the most relevant prognostic parameter may not be the extent of VC but rather the extent of the total transition area [18]. Although this concept is appealing, arriving at such a metric in the clinical realm remains unrealistic.

### *General mechanisms of vascular calcification*

Numerous mechanisms have been proposed to explain VC. Traditionally, VC was considered a passive process associated with atherosclerosis or normal aging, but recent evidence indicates that intimal and medial VC may be determined by an active process [19–21].

### *Bone and mineral metabolism*

Experimental works indicate that the plethora of genes and proteins that normally function as key modulators of bone and mineral metabolism are also involved, either directly or indirectly, in the process of VC [19,22]. 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 in sites of medial arterial calcification [21–25].

The recent discovery of osteoprotegerin, a member of the tumor necrosis factor- $\alpha$  receptor family with inhibitory effects on osteoclastogenesis, introduces another link between bone and vascular metabolism [26]. Osteoprotegerin is a soluble molecule that binds and inhibits the ligand for receptor activator of NF- $\kappa$ B, a member of the tumor necrosis factor- $\alpha$  superfamily member demonstrated in the vasculature and essential for the maturation of osteoclast progenitors [27]. In keeping with the possible role of osteoprotegerin in promoting VC, serum levels of osteoprotegerin are elevated in patients who have ESRD (Fig. 2) [28].

The expression of various mineral-regulating proteins in vascular tissue may reflect predominantly phenotypic alterations in vascular smooth muscle cell (VSMC) and possibly vascular endothelial cells [29]. VSMCs can be induced to transform into an osteoblast-like phenotype in vitro. 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 the switch that converts this precursor to the osteoblast phenotype [30].

Conventionally, phosphate levels were thought to influence mineralization only through physicochemical means. New evidence, however, 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  $\beta$ -glycerophosphate, which serves as an inorganic phosphate donor in the

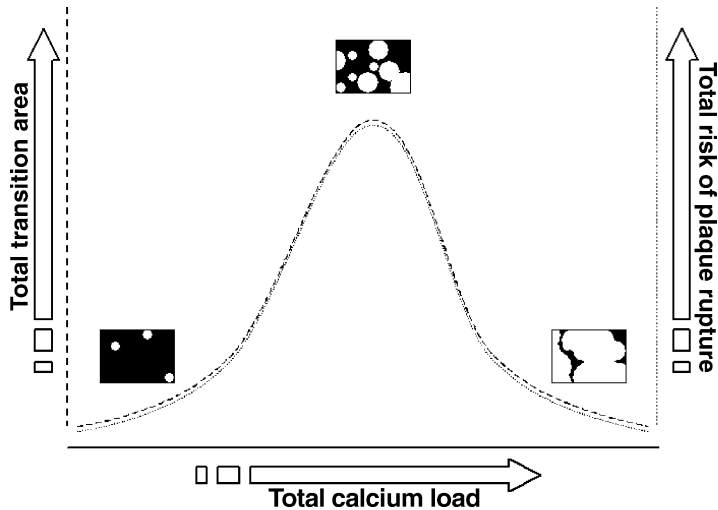


Fig. 1. Hypothetical relationships of total calcium load with transition area (between rigid and nonrigid vessel wall) and risk of plaque rupture. As the degree of vascular calcification increases, the total area of transition initially increases and then decreases (*dashed line*), with the coalescence of the foci of calcification (*insets*). The risk of plaque rupture in relation to the amount of calcium in the vessel wall should follow the same trend (*dotted line*). (Modified from Abedin M, Tintut Y, Demer LL. Vascular calcification: mechanisms and clinical ramifications. *Arterioscler Thromb Vasc Biol* 2004;24(7):1165; with permission.)

presence of alkaline phosphatase [29]. Moreover, high intracellular phosphate levels reduce the expression of typical VSMC genes and induce various osteoblastic-like phenotypic changes in VSMCs (see Fig. 2). In particular, phosphate stimulates the expression of alkaline phosphatase on the surface of VSMCs and the production of Cbfa-1 and of calcium-binding proteins, such as osteocalcin and osteopontin (OPN) [31,32]. Recent studies demonstrate that Cbfa-1, alkaline phosphatase, and OPN are present in calcified arteries but are absent from the vessel wall of noncalcified arteries [20,21].

#### *Molecular inhibitors of calcification*

Elevated serum phosphorus levels and high values for the calcium–phosphorus ion product in serum have often been associated with VC, supporting their obligatory involvement in the calcification process [21]. Plasma calcium and phosphate levels, however, are already at or above their theoretic solubility limits in healthy persons, who normally do not develop VC. Why then do normal persons not develop VC?

Plasma components (such as citrate and magnesium) play a key physiologic role by maintaining mineral in solution. Furthermore, specific proteins at sites other than bone 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 (see Fig. 2). Serum levels of fetuin-A are significantly reduced in patients who have renal failure [33,34]. Furthermore, circulating levels of fetuin-A decline with increasing inflammation in patients receiving dialysis [33]. MGP is a small protein found in normal arterial wall, and its expression seems to be increased in atherosclerotic plaques [22]. The MGP knockout mouse has extensive aortic calcification, and recent evidence indicates that MGP inhibits mesenchymal cell differentiation to the osteogenic lineage [35,36]. OPN is another important negative regulator of calcification. It operates mostly by inducing mineral resorption [37,38]. Giachelli and colleagues [39] showed that OPN colocalizes with calcified atherosclerotic plaques; within the plaque, OPN is expressed by macrophages, smooth muscle cells, and endothelial cells. Mice deficient in both OPN and MGP have accelerated aortic calcification compared with mice deficient only in MGP, a finding consistent with the concept that OPN inhibits mineralization [40].

#### *Mechanisms of vascular calcification in renal failure*

The high prevalence of traditional risk factors for atherosclerosis combined with specific factors



Table 1  
Risk factors for intimal and medial vascular calcification

Risk factor	Intimal vascular calcification	Medial vascular calcification
Advanced age	+	+
Male sex	+	-
Diabetes mellitus	+	+
Dyslipidemia	+	-
Hypertension	+	-
Smoking	+	-
Renal failure		
Reduced glomerular filtration rate	-	+
Hypercalcemia	-	+
Hyperphosphatemia	+	+
Parathyroid hormone abnormalities	-	-
Vitamin D administration	-	+
Inflammation	+	+

*Abbreviations:* +, association; -, no association.

*Adapted from* Goodman WG, London G, Amann K, et al. Vascular calcification in chronic kidney disease. *Am J Kidney Dis* 2004;43(3):575.

digital subtraction angiography) have been applied to detect and measure VC. At present, electron-beam computed tomography (EBCT) and multidetector computed tomography (MDCT) are the most accurate techniques available for calcium quantification (Table 2). Calcium scoring with EBCT and MDCT does not require the use of contrast media, a potential serious contraindication in persons with renal failure.

EBCT has been used with good results for more than a decade to detect and quantify cardiovascular calcification and is currently considered the reference standard [47]. Most medical centers, however, do not have access to EBCT scanners because of their relatively high cost and limited applications other than the calcium scoring. MDCT scanners, which are more widely available and can be used for a number of cardiac and noncardiac applications, are therefore more practical for assessment of VC (Fig. 3) [48].

A variety of studies have compared EBCT and MDCT (4- and 16-slice) directly, demonstrating excellent correlation between these techniques for calcium quantification [49-51]. Three different methods of calcium quantification and scoring have been applied by various investigators: the Agatston method, the volumetric method, and the mass method [52-54]. The Agatston score has been the most commonly used index in clinical

Table 2  
Relative advantages for the use of electron-beam computed tomography or multidetector computed tomography in the assessment of coronary calcification

Advantages	EBCT	MDCT
High temporal resolution	+	-
High in-plane spatial resolution	-	+
Low occurrence of motion artifacts	+	-
Low image noise	-	+
Widespread availability	-	+
Used for other applications	-	+
Low radiation exposure	+	-
High interstudy reproducibility	+	+

*Abbreviations:* +, present; -, absent; EBCT, electron-beam computed tomography; MDCT, multidetector computed tomography.

investigations, and most epidemiologic data have been derived from it. Reproducibility, however, seems to be worst for the Agatston method, intermediate for the volumetric approach, and best for the mass method [55].

The coronary calcium score is a sensitive test for the presence of coronary artery disease, but it is not specific for prediction of significant coronary lesions [56,57]. The American Heart Association and American College of Cardiology recently published guidelines for the use of the coronary artery calcium score as a diagnostic tool for clinical decision making [47]. It is recommended that the coronary calcium score be used only to identify asymptomatic patients at low to intermediate risk who may benefit from more aggressive risk factor modification.

Coronary calcification closely correlates with the presence of calcium in the aorta (at thoracic and abdominal levels) and in the aortic valve, suggesting a common pathophysiologic mechanism for dystrophic calcification (Fig. 4) [58,59].

There is still controversy regarding the prognostic significance of coronary calcium. In recent years, several studies involving distinct target populations have investigated the prognostic value of calcium scoring [60]. As expected, coronary VC detected by EBCT was strongly associated with all-cause mortality [61,62]. On the other hand, evidence regarding the usefulness of coronary VC in

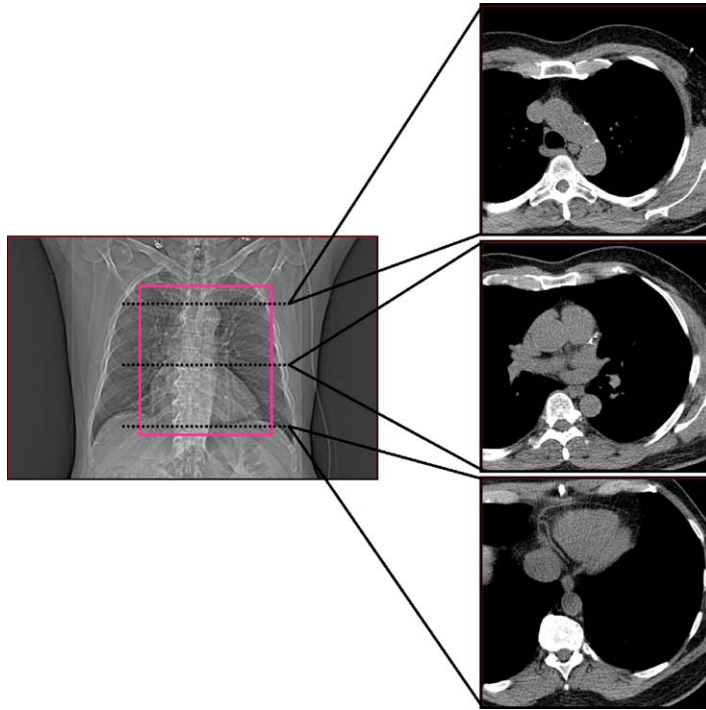


Fig. 3. MDCT (16-slice) for vascular calcium scoring. A continuous volume containing the heart and the thoracic aorta is scanned in one breathhold, ECG-gated acquisition. The postprocessing of the resulting axial images allows the quantification of calcium score at level of the coronaries, the thoracic aorta, and the cardiac valves.

predicting severe cardiovascular events (myocardial infarction and cardiac death) is conflicting [63–65]. Although a number of methodologic limitations (ie, large loss of patients to follow-up and lack of a standardized method for calcium scoring) may account for some of this discrepancy, part of the explanation may relate to coronary VC's representing an “innocent bystander,” at least in advanced lesions, rather than a direct determinant of cardiovascular risk [66,67].

#### *Vascular calcification in patients who have end-stage renal disease*

For many years, VC has been recognized as a common complication in patients who have ESRD [68,69]. Table 3 lists the available studies evaluating the presence of coronary VC in patients who have renal failure.

Braun and colleagues [70] first reported the use of EBCT in 49 hemodialysis patients, showing coronary calcium scores 2.5 to fivefold higher than in nonhemodialysis patients. Subsequent studies have revealed pronounced VC even in young adults with ESRD, who are otherwise not at risk for VC

[44,45]. In another report, Raggi and colleagues [71] studied a population of 205 patients receiving maintenance hemodialysis therapy; they observed high calcium scores at level of the coronary arteries, thoracic aorta, and cardiac valves. Furthermore, the coronary calcium score was significantly related to a previous history of myocardial infarction ( $P < .0001$ ) and angina ( $P < .0001$ ).

#### *Vascular calcification in predialysis patients who have chronic kidney disease*

Patients with predialysis CKD constitute a large population with a documented high risk for cardiovascular events [7]. Recent data reveal that advanced atherosclerosis (as demonstrated by the thickening of arterial wall) is already present in patients who have CKD before they require hemodialysis [72].

VC has been studied much less intensively in patients who have predialysis CKD than in patients receiving hemodialysis. Mehrotra and colleagues [73] recently used EBCT to study a group of 60 patients who had diabetic nephropathy. They found a higher prevalence and severity

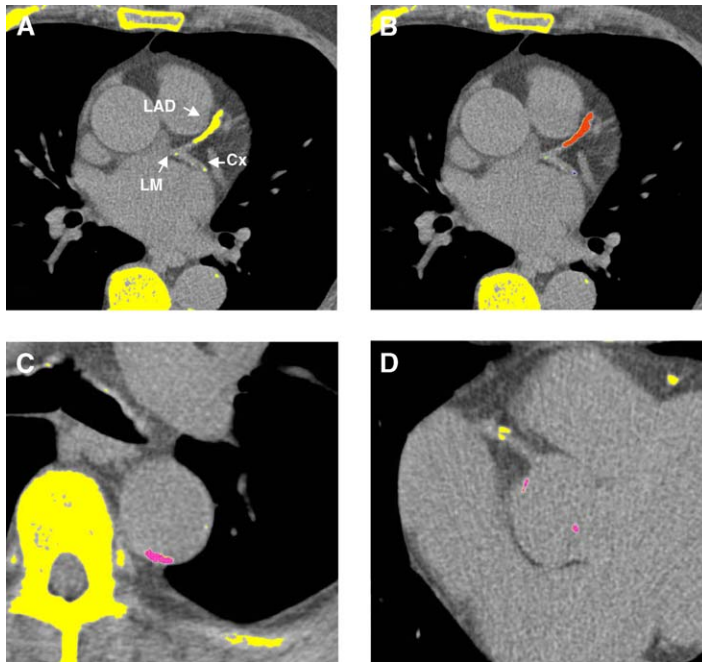


Fig. 4. Postprocessing analysis of MDCT images for quantification of calcium score at level of (A, B) coronary arteries, (C) thoracic aorta, and (D) aortic valve. Coronary calcifications are automatically detected by the software (yellow areas in A) and then are confirmed by the operator with the attribution to specific territories (B). Cx, left circumflex coronary artery; LAD, left anterior descending coronary artery; LM, left main coronary artery.

of coronary VC in these patients than in diabetic controls who had normal renal function. In the patients who had diabetic neuropathy, the high degree of VC was not related to measures of disordered mineral metabolism (see Table 3) [74].

No studies are available that used modern, fully quantifiable, CT-based technology to assess VC in unselected populations of patients who have CKD. As part of the Renal Research Institute (RRI)-CKD Study, the authors are evaluating the severity of VC at level of the coronary artery, thoracic aorta, and cardiac valves in a subgroup of approximately 100 patients studied by 16-slice MDCT [75]. This study is the first specifically designed to assess the prevalence and correlates of VC in an unselected population of patients who have CKD but do not require dialysis. The preliminary results seem to show a high prevalence of VC in this population, but no clear correlation with an index of abnormal mineral metabolism has been noted.

#### *Progression in vascular calcification*

VC progresses more rapidly in patients treated with dialysis than in the general population

(Table 4) [44,76]. In asymptomatic persons who have normal renal function, the Agatston score progresses at an average rate of 33% per year [77]. Bursztyn and colleagues [78] reported a twofold greater progression in coronary calcium score (measured by MDCT) in hypertensive patients who have CKD than in hypertensive patients with normal renal function. It is possible (although still a hypothesis) that medial wall calcification plays a dominant role in the progression of VC in patients who have ESRD, whereas VC progression in patients who have normal renal function mainly reflects the evolution of atherosclerotic calcification [79].

Do alterations in calcium and phosphate metabolism affect progression in dialysis patients? In a group of patients receiving peritoneal dialysis studied by MDCT at baseline and after 1 year of follow-up, Stompor and colleagues [80] reported a significant correlation between the change in coronary calcium score and 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 patients who have ESRD treated with large oral

Table 3

Studies using electron-beam computed tomography or multi-detector computed tomography to assess coronary calcium score in patients who have renal failure

Study	Study population	Imaging modality	Correlates for coronary calcium score				
			Mineral metabolism				
			Ca	P	Ca-P product	PTH	Others
Braun et al, 1996 [70]	49 HD	EBCT	-	-	NA	-	Age, hypertension
Goodmann et al, 2000 [44]	39 HD	EBCT	-	-	+	-	Age, body mass index, cholesterolemia, dialysis vintage
Oh et al, 2002 [45]	39 ESRD (13 HD + 26 RT)	EBCT	-	-	+	+	C-reactive protein, homocysteine
Raggi et al, 2002 [71]	205 HD	EBCT	+	+	-	-	Age, diabetes mellitus
Moe et al, 2003 [46]	55 ESRD (33 HD + 38 RT)	MDCT	-	-	-	-	Age, longer dialysis
Haydar et al, 2004 [74]	46 HD	EBCT	NA	NA	NA	NA	Angiographic coronary artery disease
Mehrotra et al, 2004 [73]	60 CKD + DM	EBCT	-	-	-	-	Age, creatinine, GFR
Nitta et al, 2004 [13]	53 HD	MDCT	-	-	-	-	Age, C-reactive protein

*Abbreviations:* CKD, chronic renal disease; EBCT, electron-beam computed tomography; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HD, hemodialysis; MDCT, multidetector computed tomography; NA, not applicable; PTH, parathyroid hormone; RT, renal transplantation.

doses of calcium-containing compounds, in comparison with patients treated with the calcium-free, phosphate-binding agent sevelamer [81].

There are limited data regarding the progression of VC in patients who have predialysis CKD [78]. A subgroup of approximately 50 patients enrolled in the RRI-CKD Study has been studied with 16-slice MDCT at baseline and after about 1 year of follow-up. Preliminary data reveal a high rate of VC progression in this unselected population (authors' unpublished observations).

#### *Prognostic value of vascular calcification in patients who have renal failure*

The usefulness of VC measurements by EBCT or MDCT as a predictor of adverse cardiovascular outcomes is yet to be demonstrated in patients who have renal failure. A number of issues relevant to the renal patients need to be studied carefully. These issues include the evolution of VC and its relationship to decline in renal function.

Although it is likely that medial and intimal VC may have different impacts on prognosis in CKD and for dialysis patients, the image resolution of EBCT and MDCT is currently insufficient to distinguish between these two processes [82].

#### **Summary**

The mortality from cardiovascular events in CKD and dialysis patients is substantially higher than in the general population. VC is ubiquitous and progresses rapidly in this patient population.

Although there has been progress in the understanding of the pathogenesis and correlates of VC, much work needs to be done in this area. The role of calcium and, probably, phosphate (obligatory participants) is unquestionable, but the understanding of the paracrine and molecular determinants of VC in renal failure is continuously evolving. VC is probably a dynamic process resulting from the imbalance between molecules that promote and those that inhibit VC. The understanding of latter area has recently evolved with identification of new signaling pathways with molecules such as osteoprotegerin, fetuin-A, and MPG.

From a clinical perspective, new modalities such as EBCT and MDCT allow noninvasive detection and quantification of VC. VC may represent a potential useful index for prognostic stratification and treatment planning in patients who have renal failure. At present, however, the data on the prognostic value of VC are available only in populations of patients who have normal renal function.

Table 4

Studies using electron-beam computed tomography or multidetector computed tomography to assess the progression in coronary calcium score in patients who have renal failure

Study	Study population	Duration of follow-up	Imaging modality	Findings
Tamashiro et al, 2001 [76]	24 HD	17 months	EBCT	Progression correlates with higher triglycerides and lower HDL cholesterol
Chertow et al, 2002 [81]	132 HD	11 months	EBCT	Progression reduced by sevelamer
Bursztyl et al, 2003 [78]	53 CKD + HTN	3 years	MDCT	Progression faster in CKD compared with non-CKD
Stompór et al, 2004 [80]	47 PD	1 year	MDCT	Progression correlates with higher C-reactive protein, serum phosphate, and calcium-phosphate product

*Abbreviations:* CKD, chronic renal disease; EBCT, electron-beam computed tomography; MDCT, multidetector computed tomography; HD, hemodialysis; HDL, high-density lipoprotein; HTN, hypertension; PD, peritoneal dialysis.

Large-scale, prospective, observational studies should be designed to identify the determinants of VC and to define the prognostic role of calcium scoring in cohorts of patients who have predialysis CKD and with ESRD.

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