

Vascular Calcification in Chronic Kidney Disease

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VASCULAR calcification, specifically arterial calcification, has been recognized for many years as a common complication of chronic kidney disease (CKD).¹⁻³ The mechanisms responsible are not well understood, but abnormalities in mineral metabolism in general, and disturbances in phosphorus metabolism in particular, have traditionally been considered important determinants. In this context, vascular calcification is seen as one component of a more generalized process of dystrophic, extra-skeletal calcification that affects a variety of soft-tissues in patients with advanced renal failure, or stage 5 CKD.⁴⁻⁶

During the past few years, several observations have heightened interest in, and concerns about, the long-term consequences of vascular calcification in patients with CKD. Key among these was the finding that hyperphosphatemia per se represented an independent risk factor for death, predominantly from cardiovascular causes, among patients treated with hemodialysis in the United States.^{7,8} Although the pathways through which phosphorus retention might account for excess cardiovascular mortality remain to be defined, vascular calcification represents one potentially important mechanism.⁹ Arterial calcification has a number of adverse hemodynamic consequences that can cause cardiovascular disease or aggravate its severity in patients with advanced kidney failure and in those treated with dialysis.¹⁰ Accordingly, hyperphosphatemia must now be recognized as more than just a common, persistent, and recurrent biochemical abnormality to be detected, monitored, and managed in patients undergoing long-term dialysis. It repre-

sents a potentially preventable cause of serious adverse clinical outcomes.

Apart from alterations in phosphorus metabolism, several therapeutic interventions that are commonly utilized to manage mineral metabolism and renal bone disease in patients undergoing regular dialysis have also been implicated in the development of vascular calcification.¹¹ The use of very large oral doses of calcium as a phosphate-binding agent and the administration of large doses of vitamin D sterols to treat secondary hyperparathyroidism both contribute to episodes of hypercalcemia and/or hyperphosphatemia, changes that can aggravate soft-tissue and vascular calcification.¹¹⁻¹³ Indeed, total body calcium balance can be quite positive and contribute to extraskeletal calcification without overt increases in serum calcium concentration in patients undergoing dialysis. As such, the absence of hypercalcemia offers little assurance that excess amounts of calcium are not being retained continuously in patients with advanced CKD who are treated with calcium-containing phosphate-binding medications either alone or together with vitamin D sterols. Current therapeutic recommendations are thus being revised in an effort to maximize benefit while reducing risk.¹⁴

Recent experimental work indicates that various genes and proteins that function normally as key modulators of bone and mineral metabolism are involved, either directly or indirectly, in the process of mineral deposition within the arterial wall.^{15,16} Such findings suggest that disturbances in the regulation of one or more physiological modifiers of bone and mineral metabolism may be intimately involved in the development of vascular calcification in patients with CKD. A better understanding of these regulatory pathways may thus offer new insights into mechanisms that account for the development and progression of the disorder and to the identification of new therapeutic strategies to alter its course.

For many years, clinical research efforts to better understand the process of vascular calcifi-

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cation in CKD were hampered by the paucity of techniques capable of detecting reliably and measuring objectively the extent of arterial calcification. Conventional radiographic methods were utilized most often, but their sensitivity for detecting soft-tissue calcification was limited and quantification was problematic.¹⁷ New imaging methods such as electron-beam computed tomography (EBCT) and spiral, or helical, computed tomography thus represent significant technical developments that provide sensitive and reliable measurements.^{18,19} Vascular ultrasound provides semiquantitative information about the extent of arterial calcification and can be used to make hemodynamic assessments that are relevant to understanding the consequences of vascular calcification in patients with CKD.^{10,20} Such methods should prove to be valuable tools for clinical investigation.^{12,13,21}

Because knowledge about the relationship between mineral metabolism and vascular calcification is evolving rapidly, it is useful to review currently available information as part of broader efforts to provide a framework for future investigation and to refine existing therapeutic recommendations. Much has yet to be learned, but there are sufficient data to offer preliminary guidance that should be useful in the clinical management of patients with CKD. It is appropriate to do so considering the substantial, if not overwhelming, risk of cardiovascular disease in this patient population.

WHAT WE KNOW. . .

There are 2 distinct types of arterial calcification.^{2,3} One affects the intimal layer of arteries and occurs within atherosclerotic plaques. The other involves the medial wall, or tunica media, of arteries. The second type of vascular calcification is common in patients with CKD and those with diabetes mellitus. The consequences of each form of arterial calcification differ fundamentally.

The manifestations of atherosclerotic vascular disease are well established both in the general population and in those with CKD. Here, intimal lesions impinge upon the lumen of arteries and, in advanced stages of the disease, can compromise blood flow, leading to tissue ischemia and necrosis. Ischemic events can occur acutely, however, in previously unobstructed vessels when

atherosclerotic plaques rupture causing thrombus formation and arterial occlusion. Together with disturbances in lipid metabolism and inflammation, calcification is now generally recognized as an integral part of the atherosclerotic process, occurring in 80% to 90% of atheromatous lesions.²² This strong association serves as the basis for using sensitive noninvasive radiographic methods such as EBCT to detect calcium deposits in the coronary arteries as an indicator of atherosclerotic burden in the general population.²³⁻²⁵

Atherosclerotic calcification is patchy and discontinuous along the course of arteries. Calcification probably occurs throughout the course of plaque development, but it is most pronounced in larger, presumably more mature lesions. The calcium content of atherosclerotic lesions is greater in patients undergoing dialysis than in persons of the same age with normal renal function.²⁶ However, whether this difference simply reflects the more extensive soft-tissue calcification that is common in CKD or more subtle disturbances in the regulation of atherosclerotic calcification (*vide infra*) is uncertain. Whether the presence of rigid, friable calcium deposits contributes to plaque rupture and subsequent arterial thrombosis is also unclear.^{27,28} Although vascular disease is often quite extensive in patients with CKD, little evidence exists that kidney failure *per se* aggravates the atherosclerotic process.

The hemodynamic consequences of medial wall calcification, or Mönckeberg's sclerosis, are quite different from those due to atherosclerotic calcification, and they are appreciated less widely.²⁹ Mineral deposition occurs diffusely throughout the tunica media, which is rich in elastic collagen. Medial wall calcification increases vascular stiffness and reduces vascular compliance—changes that adversely affect the capacity of the arterial circulation to dampen increases in arterial pressure with each ventricular systole. As a result, systolic blood pressure rises, pulse pressure widens, and pulse wave velocity increases.^{10,29} These hemodynamic alterations lead to left ventricular hypertrophy and they can compromise coronary artery blood flow during diastole. They are also associated with high mortality rates among patients undergoing hemodialysis.³⁰ Although the process of medial

wall calcification is generalized, vessels in the lower extremities are affected most often.

Recent work has demonstrated that the extent of arterial calcification in patients with CKD who are treated with dialysis far exceeds that of persons in the general population.^{12,18,21} Such data using recently developed imaging methods thus confirm results from earlier radiographic and pathological studies.^{1,6} The presence of vascular calcification in patients with CKD offers little insight, however, into the underlying cause.^{3,31} The image resolution of techniques such as EBCT is insufficient to distinguish between atherosclerotic calcification that is located along the intimal layer of arteries and that located in the medial wall. Although coronary artery calcification scores as measured by EBCT are a useful index of atherosclerotic burden in the general population,²³⁻²⁵ similar relationships have yet to be established in patients with CKD. As such, the implications of arterial calcification in patients with CKD are not only different but also more complex than in the general population.³¹

In adults with CKD, the extent of arterial calcification represents the aggregate of both atherosclerotic and medial wall calcification. This combination of factors probably accounts for the very high coronary artery calcification scores that are common in patients undergoing dialysis,^{12,18,21} and also explains why calcification scores as measured by EBCT in patients with CKD cannot be used as an indicator of atherosclerotic burden alone. The combined impact of both processes may, however, contribute to the very high rates of cardiovascular disease in patients with CKD. In children and adolescents who are treated with dialysis, medial wall calcification likely accounts for most arterial calcification, but some younger persons with CKD also harbor risk factors for atherosclerosis.¹²

Evidence of arterial calcification in adults with CKD is associated with adverse clinical outcomes, including myocardial infarction, congestive heart failure, endocarditis, valvular heart disease, and death.^{21,32} Survival among patients undergoing regular hemodialysis is inversely related to the extent of vascular calcification as measured by B-mode ultrasound.³² When present, arterial calcification progresses more rapidly, as judged by interval changes in coronary artery calcification scores measured by EBCT, in pa-

tients treated with dialysis than in subjects from the general population.^{12,13} Such findings suggest but do not prove that medial wall calcification plays a dominant role in the progression of vascular calcification in patients with CKD. Progression rates are much lower, however, in persons who do not have CKD, where interval changes in calcification scores presumably reflect the evolution of atherosclerotic calcification only.³³

For patients with CKD who are treated with hemodialysis, the rate of progression of coronary artery and aortic calcification is greater in those who use large oral doses of calcium-containing compounds rather than the calcium-free, phosphate-binding agent sevelamer.¹³ Although changes in lipid metabolism in those given sevelamer may contribute to such differences,^{34,35} the results emphasize the potentially critical link between disturbances in mineral metabolism and the progression of arterial calcification in patients with CKD.

For many years, vascular and soft-tissue calcification in CKD was considered to occur predominantly by passive unregulated physicochemical mechanisms.^{1,5,6} Elevated serum phosphorus levels and high values for the calcium-phosphorus ion product in serum have often been associated with vascular calcification, findings that tended to support such a view. These biochemical changes increase the state of supersaturation that exists normally in plasma, favoring the deposition of mineral in soft tissues including the blood vessels.

Vascular calcification is now, however, considered to be a regulated process that is influenced by tissue-specific cellular mechanisms and by selected components present in plasma.^{15,36,37} Because of the normal supersaturated state of aqueous plasma with respect to calcium and phosphorus, certain plasma constituents such as citrate and magnesium play a key physiological role by maintaining mineral in solution. Proteins such as fetuin-A (α -2-HS glycoprotein) serve a similar function.³⁸⁻⁴⁰ Inhibitors of mineral deposition are thus required to prevent soft-tissue and vascular calcification even under basal conditions *in vivo*.³⁶

In addition, there is now abundant evidence that a variety of proteins normally involved in bone and mineral metabolism can be expressed

Table 1. Risk Factors for Vascular Calcification in CKD

Risk Factor	Intimal/Atherosclerotic Calcification	Medial/Mönkeberg's Calcification
Dyslipidemia	Yes	No
Advanced age	Yes	Yes
Elevated blood pressure	Yes	Reciprocal (medial lesions worsen blood pressure)
Male	Yes	No
Smoking	Yes	No
Inflammation	Yes (local)	Yes (systemic mediators)
Diabetes/glucose intolerance	Yes	Yes
Kidney disease		
Reduced GFR	No	Yes
Calcium		
Hypercalcemia	No	Yes
Positive balance	No	Yes
Hyperphosphatemia	Yes	Yes
PTH abnormalities	No	No
Vitamin D administration	No	Yes
Duration of treatment with dialysis	No	Yes

in arterial tissue.^{16,41-45} These may influence the process of arterial calcification. Such findings were first reported in studies of calcified atherosclerotic lesions, but similar changes have been found in vessels affected by medial wall calcification. A functional role for some of these proteins in arterial tissue remains to be determined, but the importance of others is established.

Matrix Gla-protein (MGP) plays a crucial role in preventing the calcification of arteries and epiphyseal growth plate cartilage during embryonic and postnatal development.⁴⁶ The use of warfarin, which interferes with the γ -carboxylation of MGP, has been identified as a risk factor for calciphylaxis, or calcific uremic arteriopathy, in patients undergoing dialysis. Moreover, sustained warfarin administration in rats causes osteoporosis and cardiac valve calcification.⁴⁷⁻⁵⁰ Such findings underscore the importance of MGP as a physiological inhibitor of soft-tissue calcification including arterial and cardiac valve calcification. They also highlight the relevance of basic research using mouse genetics to address selected issues in clinical medicine.

Other noncollagenous bone proteins such as osteopontin (OPN) represent additional regulators of vascular calcification whose functional roles are just now being clarified.⁵¹⁻⁵⁴ Selected disturbances in the tissue-specific expression of one or more of these genes may contribute to the reciprocal relationship that has been recognized

for many years between bone mass and the extent of arterial calcification.^{55,56}

The expression of various mineral-regulating proteins in vascular tissue may reflect changes in the phenotype of vascular smooth muscle cells and possibly, but less likely, vascular endothelial cells.^{2,57} Whether such changes arise before or after the process of arterial calcification has begun is less certain. Vascular smooth muscle cells can be induced, however, to express an osteoblast-like phenotype in vitro under certain cell culture conditions.^{2,57} Selected disturbances in mineral metabolism in CKD possibly have similar effects in vivo. These issues are currently the subject of intense investigation.

Certain risk factors, such as age, cigarette smoking, diabetes mellitus, and/or glucose intolerance, are thought to contribute to both atherosclerotic calcification and medial wall calcification (Table 1). Disturbances in lipid metabolism, male sex, and hypertension aggravate the atherosclerotic process, but there is little evidence that these represent risk factors for medial wall calcification. Indeed, the relationship between medial wall calcification and blood pressure is a reciprocal one. Elevations in blood pressure are a result rather than a cause of medial wall calcification.

Inflammation is now recognized as an integral component of atherosclerosis and may aggravate its severity. Because inflammation reduces fetuin-A synthesis, any of a variety of systemic

inflammatory processes may facilitate vascular and soft-tissue calcification by lowering the serum concentrations of this important circulating factor, which serves to maintain the solubility of calcium in plasma.³⁸⁻⁴⁰ Recent evidence suggests that abnormalities in calcium and phosphorus metabolism, including therapeutic interventions that affect total body calcium balance, influence the development and progression of medial wall calcification in patients with CKD.^{12,13} Treatment with vitamin D sterols may aggravate vascular calcification, but it is uncertain whether this is due solely to increases in serum calcium and/or phosphorus concentrations or possibly to localized tissue-specific actions.⁵⁸ A role for parathyroid hormone (PTH) as a cause of medial wall calcification remains uncertain.

Race and/or genetic factors may also influence the development of arterial calcification. The disorder is less prevalent in blacks than in whites both in the general population and in those with CKD. Polymorphisms in the genes for MGP and perhaps for fetuin-A, OPN, osteoprotegerin (OPG), ank, and Npps represent potential mechanisms to account for such differences, but much additional work will be required to address these issues adequately.⁵⁹⁻⁶¹

WHAT WE NEED TO KNOW. . .

Recent observations linking disturbances in calcium and phosphorus metabolism to adverse clinical outcomes emphasize the need to better understand the impact of current therapeutic strategies for renal osteodystrophy on mineral metabolism in patients with CKD.^{7,12,20,32,62,63} Although much is known about the physiology and regulation of intestinal calcium transport, additional information about the efficiency of intestinal calcium absorption at various stages of CKD is needed. More specifically, the relative importance of passive, diffusion-dependent intestinal calcium transport versus active, vitamin D-dependent intestinal calcium absorption at different stages of renal functional impairment should be determined. The impact of large oral doses of calcium on net intestinal calcium absorption in patients undergoing dialysis has not been characterized adequately, particularly during the concurrent administration of vitamin D sterols. The effect of intermittent vitamin D dosage regimens, which are now employed widely, on the effi-

ciency of intestinal calcium absorption has not been studied systematically, especially in comparison to treatment with daily oral doses of calcitriol. More information is needed about new vitamin D sterols and their role as modifiers of intestinal calcium transport.

Because it contributes to vascular calcification and serves as an independent risk factor for death in patients treated with dialysis, hyperphosphatemia and its management represent major challenges for clinical management. The design and implementation of new therapeutic strategies that can normalize serum phosphorus levels and prevent phosphate retention in patients with stage 5 CKD will be important. Equally important is the determination of whether such interventions favorably affect the development and progression of vascular calcification, cardiovascular outcomes, or mortality rates in this high-risk population. Alternative dialysis regimens such as daily nocturnal hemodialysis or short-duration hemodialysis that is done 6 days per week represent 2 promising approaches to more optimally manage phosphorus retention in those who require renal replacement therapy.^{64,65} However, the need is ongoing to identify, develop, and introduce more effective phosphate-binding agents if current dialysis strategies are to be continued.¹¹

The evolution of each type of arterial calcification needs to be characterized further in patients with CKD using reliable, objective measurement techniques. The relationships between atherosclerotic and medial wall calcification and specific cardiovascular outcomes should be determined. Careful assessments of patients with CKD who do not develop arterial calcification may be useful in identifying demographic, biochemical, and/or genetic characteristics that protect against arterial calcification.

Imaging methods such as EBCT and spiral computed tomography are valuable for detecting vascular calcification in preliminary studies and in a few clinical trials.^{12,18,21} Nevertheless, the utility of EBCT measurements of coronary artery calcification as a marker of the severity of vascular disease, as judged by angiographic and/or autopsy studies, or as a predictor of adverse cardiovascular outcomes has yet to be demonstrated in patients with CKD. The limited availability of EBCT and spiral computed tomogra-

phy, together with their high costs, render them less useful as practical tools for the routine management of large numbers of patients with CKD. Techniques that are affordable and widely available should be evaluated thoroughly to determine their value in detecting the presence and monitoring the progression of arterial calcification in routine clinical practice.

For certain clinical syndromes that are encountered less often, such as calciphylaxis (calcific uremic arteriolopathy), establishing clinical registries may be useful. This formalized structure would provide mechanisms to better characterize the disorder and its progression, to identify additional risk factors that contribute to its development, and to assess objectively the efficacy of various therapeutic interventions.

WHAT WE SHOULD DO WITH WHAT WE KNOW. . .

The extraordinary risk of cardiovascular disease and the prominent role of vascular calcification as a component of it argue strongly that measures be implemented to detect vascular calcification in patients undergoing dialysis as well as in those with less advanced kidney disease. Some have suggested that these assessments be done annually in all patients with CKD, stages 2 to 5. The primary objectives of such screening are to offer a preliminary assessment of risk for individual patients and to heighten awareness among clinicians about the importance of vascular calcification as a cause of adverse clinical outcomes. There is insufficient information currently to justify specific therapeutic interventions based solely upon the results of screening. Evidence of vascular calcification should, however, prompt patients and clinicians alike to review current management approaches, to identify factors that may aggravate vascular calcification, and to implement corrective measures designed to limit or reduce overall cardiovascular risk. The data generated by the regular screening of patients for vascular calcification would provide an opportunity to identify factors that affect disease progression and would offer a framework to evaluate the effectiveness of interventions designed to modify its course.

To be feasible in the context of clinical practice, the methods employed to assess vascular calcification should be widely available and rela-

tively inexpensive. Calcifications of the aorta and iliac arteries can be detected readily by standard radiographs, and they have been shown to be a reliable marker of the extent of arterial calcification in persons from the general population. Echocardiography is a sensitive method for detecting cardiac valve calcification, and the necessary technical expertise for such examinations is widespread.⁶⁶ Calculated values of pulse pressure that are obtained from conventional blood pressure measurements are easily obtained, and they provide information about the hemodynamic consequences associated with medial wall calcification as discussed previously. We suggest that these three simple, noninvasive techniques be used to develop a numeric cardiovascular calcification index (CCI) for initial risk assessment and longitudinal follow-up.

Initial efforts should determine the reliability and reproducibility of the CCI and examine the relationship between such values and those obtained by other more precise techniques for measuring arterial calcification such as EBCT and vascular ultrasound. Validation of such an approach, if forthcoming, would expand opportunities for epidemiological research, longitudinal studies, and clinical trials.

Experimental models using genetically modified animals hold considerable promise in this rapidly developing field of research. They provide an opportunity to more carefully examine the impact of CKD and the disturbances in bone and mineral metabolism associated with it on selected putative molecular mediators of arterial calcification. Mice with inactivating mutations of the genes for MGP, OPN, OPG, and fetuin-A represent only a few examples among many experimental models that should be informative.

An ongoing effort should be undertaken to educate clinicians in general and nephrologists in particular about the types of arterial calcification that develop in patients with CKD and the serious consequences associated with them. A greater awareness of the relationships among renal bone disease, mineral metabolism, arterial calcification, and cardiovascular disease may ultimately lead to more cohesive therapeutic strategies that maximize benefit while limiting risk.

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