Vascular Calcifications: Pathogenesis, Management, and Impact on Clinical Outcomes

Jorge B. Cannata-Andía, Minerva Rodríguez-García, Natalia Carrillo-López, Manuel Naves-Díaz, and Bernardino Díaz-López

Bone and Mineral Research Unit, Instituto Reina Sofía de Investigación, Hospital Universitario Central de Asturias, Universidad de Oviedo, Asturias, Spain

The predisposition to vascular calcifications in patients with chronic kidney disease (CKD) has gained great interest in recent years as many studies have described its likely impact on morbidity and mortality. The mechanism by which the process of vascular calcification is produced is complex, and it does not consist in a simple precipitation of calcium and phosphate but is instead an active and modifiable process. Several “modifiable and nonmodifiable” factors that are able to promote vascular calcification are extremely frequent in patients with CKD. Most of the present strategies to decrease vascular calcifications are based in the control of the more prevalent modifiable risk factors. Unfortunately, the extremely important nonmodifiable risk factors, which are highly prevalent, such as older age, time on dialysis, and diabetes, are not under one’s control. Recent studies also have shown that vascular calcifications in some localizations were associated with increased osteoporotic fractures not only in dialysis patients but also in the general population, and interestingly, mortality also was associated significantly and positively with vascular calcifications and nontraumatic bone fractures. Despite that new strategies may improve the management of vascular diseases and specifically have a positive impact on the high prevalence of vascular calcifications, still the best possible control of the bone metabolic and inflammatory parameters are in the primary line. The horizon of the coming decade looks promising, but solid clinical and epidemiologic data are needed to manage better the bone- and cardiovascular-related disorders in patients with CKD.


The predisposition to vascular calcifications in patients with chronic kidney disease (CKD) was mentioned for the first time in the 19th century when Virchow described the appearance of metastatic calcifications in patients with kidney failure. However, this complication of CKD has been neglected because its impact on patient outcome was poorly known until recently. The subject has gained great interest in recent years as many studies described that a high percentage of patients with CKD show vascular calcifications, including those who are younger than 30 yr (1–5), stressing also its likely impact on morbidity and mortality (6,7). The various types and localizations of vascular calcifications have an impact on cardiac mortality not only by increasing and complicating coronary atherosclerosis but also by increasing the stiffness of the main arteries, which in turn affects heart function and risks the perfusion and oxygenation of the heart (8–11).

The high prevalence of vascular calcification has been studied, and it is known better in the setting of patients with stage 5 CKD. However, a high prevalence of vascular calcifications also has been demonstrated in the earliest phases of CKD. A recent study showed that 40% of patients (mean age 52 yr) with CKD and a mean GFR of 33 ml/min showed 40% of coronary artery calcifications compared with 13% in control subjects of similar age with no renal impairment (12).

Vascular calcifications are not an exclusive finding of patients with CKD. In a recent study that was carried in a subgroup of the randomly selected cohort of the European Union-supported European Vertebral Osteoporosis Study (EVOS) Study that comprised patients who were >50 yr old (mean 68 yr) and had normal renal function or a minor degree of renal insufficiency as a result of age, aortic calcifications were observed in 54.2% of men and 43.1% of women (7; Naves et al., submitted). The prevalence of aortic calcifications of normal subjects, which is discussed later in this review, was significantly lower than the prevalence of aortic calcification that was observed in patients who were of the same age, gender, and region and undergoing dialysis (7; Naves et al., submitted).

The differences between the vascular calcifications that are observed in the normal population and in patients with CKD are not only the type and the localizations of the calcifications but also the early age at which vascular calcification begin in patients with CKD (5). This fact, together with the influence of several risk factors, will have a great impact on the rate, extension, and severity of the vascular calcifications and also in mortality, which is known to increase according to the number and the severity of vascular calcifications (6) and is almost 20 times higher in patients with CKD than in general population.
Types, Mechanisms, and Risk Factors of Vascular Calcification: The Equilibrium between Promoters and Inhibitors of Calcification

Calcification in the vessel walls occurs in two sites: The intima and the media. The medial calcifications are a consequence of the inflammation and calcification of the atherosclerotic plaques; their presence is associated with atherosclerotic burden, and it is initiated early in life and progresses. They frequently are localized in two functionally relevant arteries, such as the aorta and the coronaries. The medial calcification occurs in the elastic lamina of large- and medium-small size arteries; they are frequent in patients with CKD, but diabetes and age also are associated with an increase of medial calcification. Both types of calcification are present in patients with CKD, but the complications of these two types of vascular calcifications are different: The former is mainly associated with occlusion of the vessels, and the latter is associated with vascular stiffness. In the end, both count, and they are partly responsible for the increase of mortality in patients with CKD (7,10,11).

The mechanism by which the process of vascular calcification is produced is complex, and it does not consist of a simple precipitation of calcium and phosphate but is instead an active and modifiable process in which, step by step, the vascular smooth cells undergo apoptosis and vesicle formation changes the phenotype of smooth vascular cells into osteoblast-like cells, inducing matrix formation and also attracting local factors that are involved in the mineralization process. Uremic vascular calcification may be interpreted as the result of the dysregulation of the current equilibrium between promoters and inhibitors, in which several uremic factors—with phosphorus at the top of the list—may induce the phenotypic modifications mentioned before.

In humans and other mammals, serum concentrations of calcium and phosphate exceed the calcium-phosphate solubility product by several times, but intravessel precipitation does not take place. This fact clearly stresses the important role played by the physiologic inhibitors of the calcification that counterbalance the widely known effect of the promoters of calcifications. The list of promoters and inhibitors of the calcification process is large, and it increases every year (13–20). However, the main interest has been put in those that are known as “modifiable factors,” which can act as promoters of calcification. Some of them are closely associated with the mortality rates, such as phosphorus, calcium, vitamin D, parathyroid hormone (PTH), dyslipidemia, and other markers of inflammation and nutrition such as C-reactive protein, homocysteine, fibrinogen, and albumin. From this large list, some factors recently have drawn special attention, such as matrix GLA protein, osteoprotegerin, pyrophosphates, and fetuin A (11,13,17,18).

From all of these risk factors, the best known are those that are related to mineral metabolism. Table 1 summarizes the more prevalent modifiable and nonmodifiable risk factors. Most of the present strategies to decrease vascular calcifications are based in the control of the more prevalent modifiable risk factors. Unfortunately, the extremely important nonmodifiable risk factors, which are highly prevalent, such as old age, time on dialysis, and diabetes cannot be modified. From this list of modifiable risk factors, high serum phosphorus needs to be highlighted as the risk factor that has been associated more strongly with increased vascular calcifications and mortality (21–24). Today, it is widely accepted that high phosphorus is a potent stimulus that turns on the differentiation of smooth vascular cells into osteoblast-like cells, triggering signals that will end in mineralization (14–16). The final product is a vascular calcification in the media of vessels that resembles the structure of bone tissue.

Also, the use of calcium-containing phosphate-binding agents, serum PTH levels, and the high dosage of vitamin D metabolites have been associated with increased vascular calcifications (14–16). For all of these risk factors, the experimental and clinical evidence is less strong than for phosphorus. It seems clear that high serum calcium may increase vascular calcification and, it can have an impact on mortality as it has been shown recently by us and others (21–24). However, the role of low serum calcium still remains controversial (22,24). Something similar happens with the serum PTH levels. Both high and low PTH levels have been associated with a higher risk for cardiovascular events and mortality (22–24). The role of vitamin D as a risk factor merits particular attention because high dosages of vitamin D metabolites have been associated, experimentally and clinically, with an increase in vascular calcifications and mortality, whereas nontoxic current administration of vitamin D metabolites has been associated with greater survival (25,26).

Vascular Calcifications, Bone Mass, Nontraumatic (Osteoporotic) Bone Fractures, and Mortality

Patients with CKD show vascular calcification almost in all localizations, from high-caliber arteries, such aorta, where the prevalence is extremely high, to medium- and small-size ves-
sels, including coronary arteries. Also, calcification of the cardiac valves represents a high risk for cardiovascular dysfunction (27). Recent studies also have shown that vascular calcifications in some localizations were associated with increased risk for having vertebral fractures (7). Furthermore, preliminary data that are discussed in this review suggested that the presence of severe vascular calcifications are positively associated with an increase in the incidence and the prevalence of any kind nontraumatic fractures in both the general population and dialysis patients (7,28; Naves et al., submitted).

The EVOS surveyed more than 15,000 randomly selected European individuals of both genders; it showed a high prevalence of vertebral fractures in men (20%) and women (20%). A recent study, as part of this cohort, also showed a high prevalence of aortic vascular calcifications in both genders (Figure 1). In addition, as expected, with age, bone mass decreased and

Figure 1. (A) Prevalence of aortic calcifications in men and women from the Oviedo cohort of the European Vertebral Osteoporosis Study (EVOS). Effect of age on vitamin D levels (B), femoral neck bone mineral density (C), intact parathyroid hormone levels (PTH; D), and prevalence of vertebral fractures (E) in men (□) and women (□) from the Oviedo cohort of the EVOS.
nontraumatic vertebral fractures increased in both genders. In EVOS, the serum levels of 25-hydroxy vitamin D [25(OH)D3], the prevalence of secondary hyperparathyroidism, the bone mass, and the prevalence of nontraumatic vertebral fracture and aortic calcifications showed associations. The lower the serum 25(OH)D3 and bone mass, the greater the prevalence of secondary hyperparathyroidism and nontraumatic vertebral fractures (Figure 1).

The progression of aortic vascular calcifications (new calcifications or increase in the size of preexisting calcifications) was significantly higher in patients who had a previous aortic calcification independent of the grade of severity (mild, moderate, or severe; \( P < 0.001 \), age adjusted). In addition, patients with severe aortic calcifications showed a higher prevalence and incidence of all nontraumatic fractures (age adjusted). It is interesting that after 8 yr of follow-up, mortality also was significantly and positively associated with the rate of severe vascular calcifications in men and with the rate of nontraumatic bone fractures in women (7; Naves et al., submitted).

Similar results were obtained recently in patients who had CKD and were on hemodialysis. As in other previous studies (4,6), we found a high prevalence of vascular calcifications in several localizations, such as aorta, pelvis (utero-sperm, femoral, iliac), and hands (digital, palm arch, radial). Comparing the data from hemodialysis patients with EVOS (age- and gender-matched population), the risk for aortic calcifications was significantly higher in both men (odds ratio [OR] 7.7; 95% confidence interval [CI] 3.7 to 16.1) and women (OR 9.0; 95% CI 3.8 to 21.0) who were on hemodialysis (Figure 2). In addition, women who were on hemodialysis and had severe vascular calcifications (any localization) showed a high mortality risk (OR 8.1; 95% CI 1.7 to 37.7, after all adjustments including age). Similarly, women who died during the 2-yr follow-up period had a prevalence of vertebral fractures three times higher (58.8 versus 19.3%) than those who were alive at the end of the observational period (OR 6.0; 95% CI 1.6 to 22.1, adjusted for the same variables; Figure 3) (29). Age and diabetes were strongly associated with vascular calcifications, but other widely known modifiable risk factors, such as serum PTH, calcium and phosphorus levels, vitamin D, calcium-containing phosphate binder intake, dyslipidemia, hypertension, and smoking, were not associated with the prevalence, severity, or progression of the vascular calcifications. In summary, after 2 yr of follow-up, vascular calcifications and bone fractures both were associated with higher mortality rate (7,28). If we combine the clinicopediomilogic data and the described associations between serum 25(OH)D3 levels, vascular calcifications, bone mass, and nontraumatic bone fractures, we can speculate that all of them might be linked by factors that are beyond aging.

Strategies to Reduce Vascular Calcifications: Clinical and Experimental Experience

So far, despite the large list of widely known risk factors, in daily practice, there is a reduced list of modifiable factors that can be controlled adequately in patients with CKD. The final part of this article reviews some aspects that are related to possible interventions to reduce vascular calcifications. Some of them are available already, and others still are in the experimental area.

Because of the high prevalence of hyperphosphatemia in patients with CKD stage 5 (still approximately 40 to 70% in most large series) and the implications of high phosphate in vascular events and mortality and its implications in the pathogenesis of secondary hyperparathyroidism, most strategies have concentrated on the control of serum phosphorus. Despite great efforts, still poor results have been obtained to bring serum phosphorus to safe values in the majority of dialysis patients. In addition, few studies have demonstrated the benefits of reducing serum phosphorus on vascular calcifications and mortality.

A recent study demonstrated that long-term treatment with sevelamer in rats decreased renal calcification and also slowed the progression of renal failure compared with untreated rats or rats that received calcium carbonate (29). This effect seems to be at least partly independent of serum phosphorus control, suggesting that other mechanisms play an important role. In addition, a recent clinical trial showed that sevelamer, at 6 and 12 mo, reduced the progression of both coronary and aortic calcifications, measured by electron beam computed tomography, compared with calcium carbonate (30). As in the experimental study quoted, this effect...
was seen independent of serum phosphorus control because both treatments, sevelamer and calcium carbonate, were effective in controlling hyperphosphatemia.

Regarding the relationship between vitamin D metabolites, vascular calcifications, cardiovascular outcomes, and mortality, this is a challenging area that still remains controversial. Although it is widely known that a high dosage of vitamin D metabolites favors the onset and progression of vascular calcifications and its complications, several recent studies demonstrated a long-term beneficial effect of vitamin D metabolites on proliferative, cardiovascular, and immune disorders and also on survival rates. Also, some differential effects of the vitamin D metabolites and analogues were shown (25,26,31–33). In addition, clinical and epidemiologic studies have already shown in various populations a negative relationship between serum levels of calcitriol and/or calcidiol, within normal serum value ranges, and cardiovascular events or vascular calcifications (Figure 1, A and B), suggesting that maintaining high-normal serum values of these two metabolites may have positive implications in clinical outcomes (34).

Regarding calcimimetics and its likely effect on calcification, recent experimental studies using the calcimimetic R568 demonstrated that it did not induce vascular calcification. On the contrary, the concurrent administration of R568 with calcitriol significantly reduced the aortic calcifications that were induced by a high dosage of calcitriol and also reduced mortality in that group of rats (35).

Bisphosphonates may have a potential future role in the management of vascular calcifications. Bisphosphonates can increase bone mass effectively and reduce bone nontraumatic fragility fractures in women and men of the general population and also in transplant patients (36–38). Also, bisphosphonates have been shown to reduce vascular calcifications in experimental models (39), but until recently, no data were published regarding their effect in patients with CKD. A recent report in a reduced group of hemodialysis patients demonstrated that etidronate reduced and even reversed the progression of coronary artery calcifications after 6 mo of treatment (40). We should consider these positive and interesting results with caution, because we still need more data and more studies to confirm and to translate the use of bisphosphonates in the daily clinical practice in patients with CKD.

Similarly but in an even less advanced experimental phase, the osteoprotegerin (OPG)/receptor activator of NF-κB ligand (RANKL)/receptor activator of NF-κB (RANK) system may play a role in the future treatment of vascular diseases (14). In fact, it is known that after menopause, there is greater bone loss, but there also is an increase in vascular calcifications. Estrogen stimulates OPG production in osteoblasts and decreases bone resorption, but OPG also can be a mediator of the estrogen action in smooth vascular cells. Some preliminary findings have shown that long-term estrogen treatment in rats not only significantly decreased the eroded bone surface but also significantly increased the OPG expression in the aorta (41), suggesting that OPG may play a role in the pathogenesis of vascular calcification and might have a role in the future as a therapeutic agent.

Despite new strategies that may improve the management of vascular diseases and specifically have a positive impact on the high prevalence of vascular calcifications, still our best available tools are related to the best possible control of the bone metabolic and inflammatory parameters. Recent preliminary data from the Control de la Osteodistolía Renal en Sudamérica (CORES) study showing that sustained control (at least 2 yr) of bone metabolic parameters according to Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines may have a positive impact on morbidity and mortality are encouraging (42). To evaluate the impact of guidelines and the effect of new therapeutic options, prospective studies that concentrate on clinical outcomes, such as Current Management of Secondary Hyperparathyroidism: A Multicenter Observational Study (COSMOS) (43), are needed. The horizon of the coming decade looks promising, but we need solid clinical and epidemiologic data to manage better the bone- and cardiovascular-related disorders in patients with CKD.

Acknowledgments

The clinical and epidemiologic studies that are related to secondary hyperparathyroidism, vascular calcifications (VC), and outcomes and the experimental studies that are related to the study of the differential expression of genes and proteins in secondary hyperparathyroidism and VC and the effect of phosphorus and vitamin D in VC have been supported by EVOS, European Community (1991 to 1993); by European Prospective Osteoporosis Study (EPOS), European Community BIOMED 93 to 95. BMHL-CT-0182 (1993 to 1997); Fondo de Investigaciones Sanitarias (FIS) 94/1901-E, FIS 98/787, FIS 02/0613, FIS 04/1576, Fundación pasa el Fomento en Arterias de la Investigación Cientifica Aplicada y la Tecnología (FICYT) IB05-060 and Fundación Renal Iñigo Alvarez de Toledo.

References

risk in end-stage renal disease. **Hypertension** 38: 938–942, 2001


