Calcimimetics, parathyroid hormone, and vascular calcification in chronic kidney disease

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Vascular calcification (VC) occurs frequently in chronic kidney disease, contributing to cardiovascular mortality. Numerous risk factors have been identified, including renal osteodystrophy and bone turnover, with low turnover as a main determinant. Other reports support high turnover as a factor in VC. Calcimimetics, which lower serum parathyroid hormone, and parathyroidectomy each prevented VC induced by five-sixths nephrectomy in rats. These results favor increased bone turnover due to hyperparathyroidism, instead of low turnover, as a factor in VC in uremia.


Vascular calcification (VC) in uremic patients has become an important area of research in the past decade and has been related, at least in part, to the frequent occurrence of cardiovascular death in patients with chronic kidney disease. It is now known that most patients with various degrees of renal insufficiency will never reach dialysis treatment, as they are destined to die before end-stage renal disease as a result of cardiovascular disease. One important factor in cardiovascular death in uremic subjects has been recognized in arterial calcifications and stiffening. Calcification of the arteries is due to calcium deposits in atherosclerotic plaques of the intima and in the media layer. Rigidity of main arteries is a cause of myocardial hypertrophy and dilatation and is due partly to calcification, but also to change in the structure of the arterial wall with loss of the elastic lamina.

The study of arterial and coronary calcification has been improved by the introduction of imaging techniques such as electron beam computed tomography and, lately, multislice computed tomography. Many risk factors for arterial calcium deposits have been identified. Among these are age, dialysis vintage, and male gender. Increased serum phosphate levels have been proposed as an important factor in cardiovascular mortality in hemodialysis patients. At the same time, increased serum phosphate was found to be an important risk factor for arterial calcifications. Giachelli et al. have provided evidence that hyperphosphatemia may affect vascular smooth muscle cells, promoting their differentiation into osteoblast-like cells, which are able to synthesize a number of proteins that favor the calcification of the artery. Among these, collagen type I, osteocalcin, osteopontin, and alkaline phosphatase are of paramount importance. Therefore, the occurrence of arterial calcification in uremic patients is now thought of not as due to a passive precipitation mechanism but as a well-structured event in which cell activity and differentiation are able to induce a process resembling the calcification occurring in bone tissue. Further studies have provided more information on the complexity of the equilibrium between calcification-favoring factors, such as plasma supersaturation of calcium and phosphate, and inhibitory factors, able to prevent calcium deposits in the arteries. Several animal models have shown the importance of fetuin-A, matrix GLA protein, and osteoprotegerin in preventing calcium deposits and how these factors can be modulated by other conditions, such as inflammatory states, malnutrition, and lipoprotein derangements. Additional risk factors for vascular calcifications have been hypothesized, such as bone status of uremic patients, in whom different types of bone disease, ranging from low to increased turnover, may be present (Figure 1). Even in non-uremic patients, a possible linkage exists between bone and vascular tissue, as an association was found between osteoporosis and vascular calcium deposits.

The relationship between bone turnover and VC in hemodialysis patients is still a matter of controversy. The current opinion is that an association exists between low bone turnover and increased risk of VC in hemodialysis patients. This opinion is supported by the concept of bone tissue as a calcium- and phosphate-buffering compartment. Restriction of this compartment in adynamic bone has been studied and confirmed by Kurz et al. with calcium tracers. However, clear evidence of this inverse association between bone turnover and VC in uremic subjects is lacking. The major contribution was provided by the study by London et al., based on a cohort of dialysis patients subjected to bone biopsy for histomorphometric study and semiquantitative evaluation of arterial calcium deposits by means of ultrasonography and X-rays of main arteries. The study revealed evidence of low bone activity and adynamic bone in patients with major arterial calcium deposits. However, the parameter bone formation rate (BFR/BS), the best indicator of bone turnover, was not evaluated. Moreover, this interesting report was questionable because a large number of previously parathyroidectomized patients were part of the cohort, with calcifications...
presumably formed before parathyroidectomy. In addition, many of the patients were severely aluminium loaded, with consequent decreased bone activity and lower serum parathyroid hormone (PTH) levels. Patients with more severe calcium deposits had received more calcium carbonate as a chelating agent. Therefore, low bone turnover may have been caused by excessive calcium loads, rather than aluminium deposition, triggering vascular calcium deposits.

In contrast, experimental studies in rats have shown the importance of increased bone turnover as a risk factor for VC in uremia. Price et al.⁵ have shown in uremic rats that high bone turnover is accompanied by a wider extent of medial artery calcification; this can be prevented by a dose of ibandronate, which inhibits bone resorption. The authors concluded that medial artery calcification is linked to bone resorption. There is a fetuin–mineral complex in the blood of rats in which extensive calcification of the artery media is induced. This complex is generated in the bone remodeling compartment and is inhibited by bisphosphonates or osteoprotegerin. However, the existence of this complex in humans has so far not been confirmed.

Another interesting experimental study, by Neves et al.,⁵ explored the possible contribution of PTH to cardiovascular calcifications in uremic rats. Parathyroidectomy was performed in five-sixths nephrectomized rats and a continuous infusion of PTH started. All rats on PTH replacement developed extensive aortic calcification, and some animals also presented coronary calcifications. These findings were apparently unrelated to differences in dietary phosphorus and to the serum levels of calcium and phosphate. Calcifications were also observed in rats with normal levels of these ions. The authors suggested that high PTH levels induce elevated bone turnover and medial calcification, as in Mönckeberg’s sclerosis. In line with these results are the data published by Coen et al.⁵ Among 197 patients on hemodialysis, multislice computed tomography showed a significant increase in coronary calcification scores in the patients with high serum PTH levels, known to be associated with elevated bone turnover, while in the patients with lower PTH values (0–150 pg/ml), mainly associated with low bone turnover and adynamic bone, calcification scores were higher than normal but significantly lower than in the groups with high serum PTH levels.

In the study by Kawata et al.⁷ (this issue), the matter of the rate of bone turnover as a possible factor in VC in the uremic subject has been dealt with by a different approach. This experimental study is an important contribution to a better insight into the mechanism of VC, despite the limits in interpreting animal models and translating their conclusions to clinical understanding. The authors examined the effects of calcimimetic administration on aortic and heart calcification in five-sixths-nephrectomized rats, on a diet sufficiently rich in phosphate and calcium. The calcimimetic drug was administered for 41 days, and the results were compared with those in control nephrectomized rats not receiving the drug. In addition, to further elucidate the role of PTH, Kawata et al. studied the effects of parathyroidectomy on the development of aortic and heart calcification. Both groups of animals with suppression of serum PTH levels, due to calcimimetic administration or total parathyroidectomy, did not develop VC, whereas calcifications were found in control animals. A decrease of bone turnover associated with calcimimetic administration was also suggested by the fall in serum osteocalcin. In nephrectomized cinacalcet-treated rats, there was no mRNA expression of osteoblastic markers such as osteocalcin, osteopontin, and RunX2, in contrast to nephrectomized vehicle-treated rats. A mild reduction in serum phosphate and CaxP product induced by cinacalcet administration or by parathyroidectomy could have played a role in the suppression of VC. The rats did not receive vitamin D and calcitriol, and their serum levels were not considered to be calcification factors. In other studies,⁸ calcimimetics were found to counteract the VC effect of calcitriol. Calcitriol administration to uremic rats induced VC in spite of a decrease of serum PTH levels. This calcitriol-induced calcification was prevented by the administration of calcimimetics. It is worth mentioning that a clinical control trial to evaluate cinacalcet or standard therapy with VC as primary end point is in progress.

A possibility remains that calcimimetics might have a direct protective effect on vascular tissue against calcification induced either by calcitriol and vitamin D receptor activators or by the uremic state itself, acting independently of the suppressed bone turnover. A study by Molostvov et al.⁹ evaluated the expression of CaSR mRNA and protein in human aortic smooth muscle and endothelial cells in large and small arteries. The expression of the CaSR was lower in end-stage renal disease. Therefore, a direct effect of calcimimetics on the arterial wall inducing protection from the calcification process cannot be ruled out. Further studies in this direction are required.

**Figure 1** | Mechanisms of vascular calcification in chronic kidney disease. MGP, matrix GLA protein; OPG, osteoprotegerin.
Extracorporeal removal (ECR) techniques used for clearance of toxins may be critical in the management of chemical or drug poisoning. The use of these techniques for removal of toxins can be justified if there is evidence of severe toxicity and if the total-body elimination of the toxin can be increased by 30% or more by the extracorporeal technique. Large randomized controlled trials of ECR in toxicology are hard to come by and, for obvious reasons, difficult to perform.

Specific extracorporeal techniques and their indications remain a matter of debate. Application of extracorporeal modalities requires a thorough knowledge of drug pharmacokinetics and of the techniques available. The technology of choice for the removal of a particular toxin, however, may not be immediately available to physicians in clinical practice.

Holubek et al. (this issue) describe trends in the use of ECR for removal of toxins in the United States over a 21-year period of poison-center data recorded in the Toxic Exposure Surveillance System (TESS) database from 1985 to 2005. TESS is a uniform data set of cases reported from poison centers in the United States. Categories of information include the patient, caller, route of exposure, substance or substances, clinical picture, treatment, and medical outcomes. The trend was an increase in hemodialysis (HD) use with a decrease in hemoperfusion (HP) over the final 10 years. This may be attributed to a change in the technology itself as well as a change in the profiles of drugs causing overdose. Improvement in HD technologies over the years, with use of newer synthetic membranes at greater blood flow rates, has resulted in drug elimination rates similar to that achieved through HP. HP cartridges are expensive and have limited shelf life, and some require sterilization. It is technically more difficult to perform, cannot correct the acid–base fluid and electrolyte abnormalities associated with intoxications, and can cause thrombocytopenia, leukopenia, and hypocalcemia.

According to TESS data from 2004, only 27 of the almost 2.5 million exposures reported to United States poison control centers were managed with charcoal HP. Shalkham et al. reported the availability of charcoal HP cartridges in only approximately one-third of hospitals receiving emergency patients in New York City, and only three in-hospital HD units had performed HP in the past five years, on three cases. The use of theophylline and barbiturate drugs, which were traditionally removed by HP, has declined, leading to a decline in the use of HP for their elimination.

The role of continuous renal replacement therapy (CRRT), available since the late 1970s, in the treatment of poisoning is still under debate and is not currently reported in the TESS database. The use of continuous veno-venous hemofiltration (CVVH) and continuous veno-venous hemodiafiltration (CVVHD) have been reported in poisonings with salicylates, barium, lithium, carbamazepine, phe- nobarbital, methanol, iodine, pilsicainide, mercury, metformin, valproic acid, and tetramine. CVVH and CVVHD are considered continuous therapies because they are applied for a longer time (24–48 hours) than HD (usually 4–6 hours). An advantage of CVVH and CVVHD is that they are better tolerated than HD in hemodynamically unstable patients. CVVH achieves solute clearance by convection (solvent drag effect) through the membrane, with pore dimensions larger...