



Hyperphosphatemia and vascular calcification in chronic kidney disease



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'Over the last decade, mounting evidence has been accumulated indicating that disturbances in bone and mineral metabolism in CKD patients are associated with increased morbidity and mortality.'

Extensive calcification of the arterial wall and soft tissues is a frequent feature of patients with end-stage chronic kidney disease (CKD-5) [1]. Patients on maintenance dialysis evaluated by means of electron beam computed tomography exhibit a degree of calcification fivefold greater than age- and sex-matched individuals with established coronary artery disease but normal kidney function [2]. The presence and extent of vascular calcification (VC) is a sensitive marker of underlying atherosclerotic disease and medial calcification, and is associated with arterial stiffening, systolic hypertension, left ventricular hypertrophy and an adverse cardiovascular prognosis [3]. The great increase in prevalence and extent of VC is poorly explained by traditional cardiovascular risk factors [4] and abnormalities of bone and mineral metabolism likely contribute to its development and progression [5]. A large body of evidence has shown that VC is not solely the result of a passive deposition of crystals of hydroxyapatite in the soft tissues, but is a highly regulated process closely resembling calcium deposition in bone tissue [6]. Nonetheless, there appears to be a relationship between abnormalities of mineral metabolism and VC, as indicated by the fact that elevated blood levels of phosphate are associated with ectopic calcifications and increased risk of calciphylaxis [7]. In addition, *in vitro* studies have demonstrated that calcification of human aortic smooth muscle cells occurs in the presence of high phosphate levels and constant calcium levels in the medium (or the reverse), and that the combination of hypercalcemia and hyperphosphatemia promotes maximum levels of calcification [8].

Therefore, control of serum phosphate in CKD-5 patients becomes crucial in preventing increases in calcium-phosphate product, secondary hyperparathyroidism and ultimately,

VC [9]. We herein analyze the role of phosphate in the pathogenesis of vascular mineralization in CKD-5 patients and examine the new therapeutic tools to prevent VC in humans and animals [10].

Abnormalities in mineral and bone metabolism are very common in end-stage renal disease (ESRD) patients. In this population, parathyroid hyperplasia and enhanced secretion of parathyroid hormone (PTH) characterize secondary hyperparathyroidism [5]. Parathyroid gland enlargement and high circulating levels of PTH are major contributors to increased bone resorption, a feature of renal osteodystrophy. Hypocalcemia, hyperphosphatemia and vitamin D deficiency are the main regulators of hyperparathyroidism secondary to renal failure [5].

Over the last decade, mounting evidence has been accumulated indicating that disturbances in bone and mineral metabolism in CKD patients are associated with increased morbidity and mortality. In fact, cardiovascular events are the most frequent cause of death in patients with chronic renal failure [3]. Calcification of soft tissues and blood vessel walls occurs frequently in dialyzed patients compared with the nonuremic populations [11]. Hyperphosphatemia and increased calcium-phosphate product are important contributors to VC and calciphylaxis in uremic patients and also appear to be associated with increased mortality. The pathogenetic mechanisms of hyperphosphatemia, high calcium-phosphate product and secondary hyperparathyroidism on enhancing VC in CKD, are still poorly understood, although considerable advances have been made.

In the past, the standard treatment for hyperphosphatemia of chronic renal failure consisted of dietary phosphate restriction, dialysis treatment and administration of phosphate-binders (aluminum salts, calcium carbonate or acetate). Recent studies described the limitations of calcium salts as phosphate-binders and the elevated calcium load in patients with advanced renal failure [9]. Moreover, with such a therapeutic approach, more than 50% of patients did not achieve a good control of serum phosphate levels.

Recently, new phosphate binders that do not contain aluminum or calcium and, therefore, lack the side effects associated with calcium-based phosphate binders, opened new perspectives in preventing ectopic calcification in ESRD. Recent studies have shown that new therapeutic tools may be useful in preventing VCs in animals and humans [10].

During the past 10 years, several investigators have been interested in studying the mechanisms responsible for VC. Cardiovascular calcification appears to be due, not only to passive deposition of crystals of calcium–phosphate, but also to an active process of mineralization that resembles bone formation. This process appears to be regulated by genes associated with osteoblastic functions [6]. Moreover, recent studies demonstrated phosphate regulation of VC and have provided some insights into the mechanisms for phosphate-induction of metastatic calcifications. Jono

and colleagues demonstrated that high phosphate levels in the medium (2 mmol/l) induced human aortic smooth muscle cell mineralization of the extracellular matrix [8]. In summary, there are a number of studies to support an active role for phosphate in regulating arterial mineralization, in a manner similar to bone formation.

In conclusion, hyperphosphatemia has been shown to be associated with VC development and progression and is implicated in the pathogenesis of secondary hyperparathyroidism. Tight serum phosphate control will likely reduce the risk of VC and potentially improve outcome. More efficient phosphate removal by dialysis, along with new calcium-free and aluminium-free phosphate binders have been proposed as a means to reach these goals. Nonetheless, additional investigations are necessary to examine the effect of different phosphate binders on mortality and cardiovascular disease in CKD.

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