Progression of vascular calcification in uraemic patients: can it be stopped?

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Introduction

Patients with advanced renal failure may develop several types of soft tissue calcification, including visceral, articular and vascular calcification. Among the latter, the most dramatic form is calciphylaxis, also called 'calcific uraemic arteriolopathy', which generally has an acute course and may be rapidly lethal. In general, more slowly progressive forms prevail which are characterized by either focal, patchy deposits of calcium and phosphate in atheromatous plaques, or by diffuse deposits in the medial layer of the arterial tree. Frequently, the two forms are combined.

Pathogenetic mechanisms

Disturbances of calcium and phosphate metabolism have been shown to play a major role in the pathogenesis of arterial calcification of either type, in association with either hyperparathyroidism or hypoparathyroidism and with vitamin D overload [1,2]. Atheromatous plaques of uraemic patients are more frequently and more intensively calcified than those of non-uraemic subjects [3]. The most marked difference compared with non-uraemic patients does not concern the size, but the composition of the plaque. Like plaque calcification, diffuse medial calcification is also a manifestation of ageing, and in this perspective uraemia can be considered premature and accelerated ageing. Aortic calcification and stiffening account for reduced vascular distensibility and increased vascular resistance in renal failure patients [4].

In addition to classic factors such as advanced age and diabetes mellitus, a predominant role of hyperphosphataemia, hypercalceraemia and elevated serum calcium×phosphate product has been recognized in recent years in the occurrence of coronary and carotid artery calcification as well as cardiac valve calcification [5–7]. Phosphate probably induces soft tissue calcification not only through indirect mechanisms, but also by direct action at specific tissue sites (see below). Of note, coronary artery calcification is inversely correlated with bone mass in dialysis patients [8], as it is in the general population. This could be the consequence, in part, of an imbalance between oxidant and antioxidant factors in chronic renal failure, since oxidative stress has been shown to modulate differentiation of vascular and bone cells oppositely. In this regard, oxidative stress enhanced the differentiation of vascular smooth muscle cells into osteoblast-like cells but resulted in inhibition of differentiation markers in bone osteoblastic cells and marrow stromal cells [9].

In the clinical setting, there is an association between vascular calcification and the dose of oral calcium supplements administered for the control of hyperphosphataemia [4,5]. The noxious effects of high doses of calcium probably play a role in the recently reported association of elevated serum phosphorus and high calcium×phosphate product with increased mortality in dialysis patients [10,11]. Increased coronary calcification, which may impede coronary flow, and increased aortic stiffness, which has been found to be a strong independent predictor of cardiovascular and all-cause mortality, may be possible explanations [12]. Of note, not all ESRD patients with an elevated calcium×phosphate product exhibit progressive vascular calcification. Excessive calcium deposition depends on a complex interaction of several factors. However, the reasonable working hypothesis has been that an optimal control of hyperphosphataemia and hypercalcaemia should reduce the risk of calcification.

Beyond phosphate control: arrest of progressive vascular calcification?

There is increasing awareness that avoiding hypercalcaemia and hyperphosphataemia is beneficial for uraemic patients. Thus, the recent introduction of the non-calcium, non-aluminium containing phosphate binder sevelamer (Renagel®) is considered by the nephrology community as a potentially major step forward. Although its phosphate-binding capacity has
been amply demonstrated in several long-term clinical trials [13–15], its efficacy in terms of controlling the progression of soft tissue calcification had yet to be shown. However, recent data strongly suggest this possibility.

Chertow et al. [16] conducted a randomized clinical trial, comparing sevelamer with calcium-based phosphate binders in a large haemodialysis patient cohort in Europe and the USA. The main study goal was to examine the progression of coronary artery and aortic calcification over a period of 1 year, using the recently introduced quantitative method of electron beam tomography (EBT). Serum phosphorus was equally well controlled in both treatment groups over the 52 weeks of follow-up. However, serum calcium was higher, and serum intact parathyroid hormone (PTH) lower, in the group receiving calcium supplements than in sevelamer-treated patients. The most remarkable result was that at study completion, median coronary artery and aorta calcification scores were unchanged for sevelamer-treated patients, whereas they were significantly increased for calcium-treated subjects. When expressed as relative changes, the coronary artery score increased by 26 vs 6%, and the aorta score by 28 vs 5% in patients receiving calcium-containing binders vs sevelamer, respectively.

These findings are of interest because they clearly show for the first time that it is possible to arrest the progression of vascular calcifications in uraemic patients, a concept which, up to now, has been met with great skepticism. The progression of calcium and phosphate deposition in soft tissues, once initiated, was thought to be irreversible, with the exception perhaps of two particular, relatively infrequent conditions. The first is that of the regression of medial calcification of peripheral small arteries which can be observed occasionally after surgical parathyroidectomy in non-diabetic uraemic patients with severe secondary hyperparathyroidism [1]. The second is tumour-like calcinosis. When associated with elevated plasma PTH levels, it may regress after surgical correction of parathyroid overfunction. However, in association with normal or low bone turnover, its regression has been obtained only in rare instances in haemodialysis patients after their transferral to more intensive treatment schedules with a low-calcium dialysate [17], or after renal transplantation [18].

Open questions

Three questions remain, however, after this treatment success of sevelamer. The first is that of a tempting extrapolation from lower calcium content in coronary arteries to hard clinical end-points, such as decreased progression of coronary artery disease. It is certainly well established that in patients with end-stage renal disease and accelerated vascular calcification, plaque calcium content is markedly greater than that of plaques sampled from non-uraemic patients with atherosclerosis [3]. However, clinical correlates of the extent of calcification in such patients were not clearly identified until recently. A recent study of more than 200 chronic haemodialysis patients who underwent a cross-sectional EBT examination found that coronary artery calcium scores were directly related to the prevalence of myocardial infarction and angina, and the aortic calcium scores were directly related to the prevalence of claudication and aortic aneurysm [6]. Moreover, the extent of coronary calcification was more pronounced with greater age, male gender, white race, diabetes, longer dialysis vintage and, of particular note in the context of this review, with higher serum concentrations of calcium and phosphorus.

However, correlation does not necessarily imply causation [19]. Therefore, the second question that still needs to be solved is whether the arrest of progressive calcification is possibly indicative of reduced progression of atherosclerotic vessel wall injury, or whether this finding mainly reflects reduced progression of medial calcification, with less arterial stiffness and its complications [20]. Conversely, it is also uncertain whether the increase of arterial calcium deposition in the calcium-treated group of dialysis patients should mainly be attributed to medial calcification, atheromatous plaque calcification or both.

The third question, which is more of academic than of practical interest, deals with the underlying mechanisms of the observed effect of sevelamer. This polymer not only allows lowering of serum phosphate but in addition acts as a bile sequestrant and is therefore capable of reducing serum total cholesterol and LDL cholesterol levels [21]. One could imagine that sevelamer’s beneficial effect on arterial calcification, in addition to its main action on plasma phosphate and prevention of calcium overload, is brought about, in part, by its cholesterol-lowering effect. Studies with another family of cholesterol-lowering agents, namely the statins, are presently underway in dialysis patients. It will be interesting to see whether their use leads to a similar arrest of coronary artery calcification or not.

Future directions

For several decades, soft tissue calcification in chronic renal failure has been considered to be a mainly passive event, secondary to elevated extracellular calcium \times phosphate product. However, recent observations of spontaneous arterial calcification in gene knock-out mice [22,23] and in vitro experiments of vascular calcification in cell culture models [24] have provided evidence in favour of the participation of active processes, involving specific cells and proteins. These two intensely studied topics are rapidly evolving at present in the area of general vascular pathology. The transformation of vascular smooth muscle cells to the phenotype of osteoblast-like cells is enhanced by numerous factors, including cyclic AMP, transforming growth factor-β, cholesterol, oxidized lipids and oxidized proteins (AOPP), leptin, AGE-transformed proteins, calcitriol and glucocorticoids [1,24,25].
Of note, organic phosphate is able to transform vascular smooth muscle cells to calcifying cells by a direct action involving the phosphate cotransporter Pit-1, as shown in experiments in vitro [26]. This leads to the local formation of apatite crystals by cells which normally do not favour the deposition of such calcium and phosphate-containing crystals. Chronic inflammatory processes involving monocyte/macrophage infiltration further contribute directly to the calcification process, by cell–cell interaction and production of soluble factors such as TNF-α [27].

The other novel, exciting finding of probably major importance in this field is the identification of proteins with high calcium affinity which exert a protective role against soft tissue calcification, such as matrix-gla protein (MGP) [22], osteoprotegerin [23] and fetuin [28]. A better knowledge of their precise mode of action is not only of theoretical interest since they may become targets for the development of new therapeutic strategies.

These new aspects of the vascular calcification process clearly deserve to be considered specifically for the setting of chronic renal failure. Transformation of vascular smooth muscle cells to a phenotype of osteoblast-like cells clearly also occurs in calcified arteries of dialysis patients. This has been shown in a recent elegant study in which vascular calcification was associated with deposition of several bone matrix proteins, implying again an active, cell-mediated process [29].

Finally, since elevation of the calcium × phosphate product is closely associated with arterial calcification in uraemic patients, the administration of medications which increase this product should be done with caution. Their prescription may have to be combined with that of other drugs known to decrease either plasma calcium, such as the calcimimetics which are still in the development phase [30], or plasma phosphorus, such as sevelamer and other calcium-free, aluminium-free phosphate binders [31]. Another potential approach, which might be worth testing, is to decrease intestinal phosphate absorption by reducing the activity of NaPi cotransporters. The way is paved towards a more effective control of soft-tissue calcifications in patients with chronic renal failure.

References


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