Disorders in mineral homeostasis and bone are recognized today as having a fundamental role in the cardiovascular complications of chronic kidney disease (CKD). This syndrome has been named ‘CKD-mineral bone disorder’ (CKD-MBD) [1]. The current understanding of the initial mechanisms involved in the pathogenesis of CKD-MBD is focused on very early increases in the skeletal hormone, FGF23, as a sign of disturbed skeletal function [2], loss of skeletal anabolism, hyperphosphataemia, decreased calcitriol and secondary hyperparathyroidism (sHPT). In the later stage, vascular calcification develops.

Four different sites of ‘vascular calcification’ have been described in CKD patients: arterial intimal calcifications, arterial medial calcifications, calcification of the cardiac valves and calcific uraemic arteriopathy [3]. The calcification process in the intima and media shares several common osteogenic mechanisms but also differs in several etiological aspects. Intima atherosclerotic calcifications are typical for advanced common atherosclerosis. Calcium accumulation in the media of arteries is characteristic for CKD but is also observed in diabetes.

The mechanism of vascular calcification is linked to transformation of the phenotype of vascular smooth muscle cells (VSMC) from contractile cells to secretory cells, expressing markers of osteoblastic lineage cells. Expression of these markers, osteopontin, osteocalcin, alkaline phosphatase, bone morphogenic proteins and the osteoblast-specific transcription factors, RUNX2 and osterix, has also been demonstrated in the calcified vasculature of uraemic patients. This is due to the fact that, unlike skeletal and cardiac muscle cells, VSMCs do not terminally differentiate but retain the capacity to dedifferentiate and proliferate [3].

Another major mechanism in the calcification cascade in the vasculature is disturbed regulation of extracellular matrix mineralization, including loss of local and circulating calcification inhibitors, such as matrix gla protein, pyrophosphate and fetuin-A, which are also reduced in CKD patients.

‘Hyperphosphataemia’ in a CKD is a very important factor for development of vascular calcifications. High extracellular phosphorus and calcium might directly affect VSMCs. In vitro, it has been shown that phosphorus can act as a signalling molecule and induce phenotypic changes in the VSMCs via the sodium-dependent phosphate cotransporter, Pit-1. Likewise, elevated calcium levels might enhance mineralization by increasing Pit-1 messenger RNA and regulating the sensitivity of VSMCs to phosphorus [4].

Several studies on the vascular effects of ‘vitamin D’ have demonstrated that calcitriol and its analogues can stimulate vascular calcification, indirectly by increasing intestinal calcium and phosphorus absorption and by contributing to the induction of adynamic bone disease or directly, as documented for calcitriol in vitro [5]. In a translational model of vascular calcification, where uraemia, diabetes and hyperphosphataemia were induced in low density lipoprotein receptor-deficient mice, a beneficial effect of low doses of calcitriol and paricalcitol was found, while high doses of the sterols aggravated calcification [6]. In other studies, it was shown that the different active vitamin D sterols had different effects on vascular calcification in uraemic rats [7,8]. A protective effect of calcimimetics on the vitamin D-induced vascular calcifications was demonstrated in an animal model, where the vascular calcifications were induced by uraemia and high doses of calcitriol or paricalcitol and where concomitant treatment with calcimimetics prevented calcifications [9,10].

The calcium-sensing receptor (CaR) is located in a number of organs and is the main focus for the treatment of sHPT with ‘calcimimetics’, which, besides reducing parathyroid hormone (PTH) levels, also induces a slight fall in the serum levels of calcium and phosphate. A functional CaR is also found in the VSMCs [11,12] and it has clearly been shown experimentally that calcimimetics reduce the accumulation of calcium and phosphorus in the aorta [10,13] and delay the development of both vascular calcification and atherosclerosis in uraemic mice [12]. This effect
might be indirect due to lowering of serum calcium and phosphate levels and ameliorating high bone turnover or directly via CaR in the vascular walls.

This latter possibility is supported by a large body of *in vitro* evidence. Although in animal studies an effect of large doses of calcimimetics on blood pressure has been described, it should be pointed out that in human clinical studies, no evidence for an effect of calcimimetics mediated via changes in blood pressure has been reported.

Some new important factors are under investigation. One is ‘klotho’, which was originally identified as an aging suppressor [14]. Klotho is closely related to mineral homeostasis, exerts a phosphaturic effect and controls the 1α-hydroxylase activity, which might affect extraskeletal calcifications in a uraemia. CKD is a state of klotho deficiency. Recently, it was found that klotho deficiency caused vascular calcification in CKD and that klotho in *vitro* had a direct effect on preservation of the phenotype of VSMCs, despite high extracellular phosphate [15]. In clinical studies, it is observed that established calcification has a tendency to progress (as also shown in the ADVANCE study) and cannot be completely arrested or reversed except in a few casuistic reports after parathyroidectomy of patients with severe sHPT [16]. It is therefore worth while to mention an interesting model on klotho-deficient mice, carrying inducible transgene depending on zinc water feeding for klotho expression. In this model, supplementation with klotho reversed already established arteriosclerosis and calcifications [17]. Untreated animals developed the phenotype of klotho-/- inclusive of vascular calcifications and were rescued when klotho expression was induced by zinc feeding.

Careful experimental studies point toward a role of the ‘skeleton’ in phosphate homeostasis and in the development of vascular calcifications [18]. Both low and elevated rates of skeletal remodeling contribute to hyperphosphataemia in CKD, due to excess bone resorption uncoupled to bone formation. Proper management of CKD-MBD would include maintenance of normal skeletal remodeling. In uraemia, the physiological levels of PTH are insufficient to maintain skeletal remodelling due to a complex phenomenon of skeletal resistance to the action of PTH. Therefore, PTH levels above the, ‘normal range’ should be accepted, however, clearly avoiding severe sHPT [19].

In the clinical practice, we should pay careful attention to the calcium, phosphate, vitamin D, PTH and FGF23 status of our dialysis patients and make every effort to prevent or correct major changes in these parameters. The advances in the basic science of these serum factors and their interactions and changes in CKD Stage 5 are a source of great scientific interest. The transfer of laboratory knowledge to the clinic has been rapid, always with more on the horizon. The use of the parent vitamin D, calcitriol, or its analogues, a variety of oral phosphorus binders and calcimimetics acting directly on the parathyroid CaR, has provided with a sense of security and wisdom indicating that we have something to offer the patients, who are persuaded to accept our advice and adhere to treatment. We would be even more secure in our advice if we knew that the advice that we were proposing was based on solid comparative outcome studies. These have been slow in coming and those that have appeared are often confounded by the idiosyncrasies of a population with multiple complications and diseases and a high mortality.

A major contributor to the high mortality in CKD Stage 5 is vascular calcification, and Raggi et al. [20] have been brave enough to institute a randomized controlled trial, the ADVANCE study, on the effects of a calcimimetic with a low dose of calcitriol or a vitamin D analogue (paricalcitol, doxercalciferol or alfacalcidol) compared to the effect of flexible doses of calcitriol analogue alone, as used to treat sHPT. They enlisted 360 patients (235 completed the study) at 90 sites on three continents. There are 12 authors, but probably as many investigators and assistants involved in the study as patients.

![Fig. 1. Impact of treatment with calcimimetics and active vitamin D sterols on vascular calcifications in CKD.](https://academic.oup.com/ndt/article-abstract/26/4/1117/1884773)
The main end point of the ADVANCE trial was negative. Was it anyway worth the effort? Yes it certainly was. Patients who received cinacalcet together with a fixed low dose of calcitriol or an analogue had significantly less progression of their aortic valve calcification than patients given the vitamin D analogues in flexible doses alone. These drugs were administered in addition to their calcium-based phosphorus binders. This significant effect of the calcimimetic with the calcitriol analogue is impressive and even more so when considering the nonsignificant tendency to less calcification in this group at the coronary arteries, mitral valve and thoracic aorta. The calcimimetic low-fixed dose vitamin D group had, as expected, lower levels of serum PTH, calcium, phosphate and calcium–phosphate product (Figure 1). These are accepted major factors in the pathogenesis of vascular calcification and mortality. However, in this 1-year study, mortality was not an end point. For this, we must wait for the much larger and longer EVOLVE study, which is presently in progress.

So where do we stand now and has the ADVANCE study helped us increase our confidence how we treat our patients? The answer again is yes. It is an important contribution, and we must rely on the surrogates of serum factors and now vascular calcification. However, we should not lower our guard because we do not know the results on patient outcome. That said, the investigators have performed a further service in that they studied test compounds not against a placebo but rather against an accepted current therapy—a more formidable task.

There are other questions that we would like to have been asked in this large study. What were the effects on serum FGF23 levels? This is particularly relevant considering the correlation of high FGF23 levels with mortality in CKD patients [21,22]. The finding that PTH acts on bone cells to increase FGF23 expression raises the possibility that judicious use of calcimimetics with low-dose vitamin D compounds may prevent the high FGF23 levels in CKD [23] despite the effect of vitamin D itself to increase FGF23 [24]. Those and other questions remain for the future, but in the meantime, the ADVANCE study does advance our knowledge, which may or may not evolve into concrete indications for therapy in the long-awaited EVOLVE study.

Conflict of interest statement. None declared.

(See related article by Raggi et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 2011; 26: 1327–1339)

References


Received for publication: 20.12.10. Accepted in revised form: 31.12.10