Why Do Dialysis Patients Develop a Heart of Stone and Bone of China?

Leena Martola Peter Barany Peter Stenvinkel

Division of Renal Medicine, Department of Clinical Science, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden

Key Words

Adynamic bone disease · Calcification, arteries and heart valves · Calcification process, uremic risk factors · End-stage renal disease · Mineral metabolism disturbances · Osteogenesis · Vascular calcification · Inflammation

Abstract

Vascular calcification is a common complication of end-stage renal disease (ESRD). The mechanisms responsible are complex and have so far been considered to be mainly the result of a passive mechanism due to elevated PO_4 levels and high $\text{Ca} \times \text{PO}_4$ ion product resulting in saturated plasma. However, recent results suggest that also other features, commonly observed in the uremic milieu, such as chronic inflammation, hyperleptinemia and a dysregulation of various mineral-regulating proteins might also contribute to an enhanced calcification process. Moreover, as an inverse relationship between vascular calcification and bone density has been documented in ESRD, it could be speculated that pathologically low bone remodelling (adynamic bone disease) associated with active vitamin D treatment and low parathyroid hormone (PTH) levels may predispose to ectopic calcification of vessels, valves and heart. As patients with vascular calcification have a higher intake of calcium-containing PO_4 binders, novel, non-calcium containing PO_4 binders may diminish the risk of progressive vascu-

lar calcification in this patient group. Further studies are needed to elucidate the respective role of chronic inflammation, hyperleptinemia and PTH-lowering therapies in this fatal complication of ESRD.

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Introduction

No doubt, patients with end-stage renal disease (ESRD) are subjected to a process of accelerated atherogenesis and show a high prevalence of atherosclerotic plaques in their coronary vessels [1]. In fact, as the risk of cardiovascular events in a 30-year-old patient receiving dialysis is more than 100-fold higher than in the general population [2], the mortality of dialysis patients with cardiovascular problems is similar to that of many cancer patients with metastases. As traditional risk factors such as hypertension, dyslipidemia and diabetes mellitus can only partially explain the extent and severity of cardiovascular complications in this patient group, much recent interest has focused on non-traditional risk factors, such as inflammation, oxidative stress, and hyperphosphatemia, all common phenomena in the ESRD population [1].

During the last decade there has been a shift in the perception of the pathogenesis of vascular disease in man [3]. As only about half of patients having an acute coronary event are identified on the basis of traditional Fra-

mingham risk factors, additional risk factors for vascular disease need to be identified. It is therefore of interest that results from various follow-up population studies (e.g., HOPE, ARIC, HOT, and the Framingham Heart Study) indicate that renal insufficiency is a cardiovascular risk factor, independent of hypertension, diabetes mellitus or albuminuria [4]. Moreover, two recent large studies have

demonstrated that even mild renal dysfunction should be considered as a major risk factor for cardiovascular disease (CVD) [5, 6]. This is important new information because almost 10% of a population with low risk and up to 30% of a population with high risk for CVD have signs of moderate renal insufficiency [4]. Both moderate [7] and severe renal insufficiency [8] are associated with an increased prevalence of inflammation, a well-known risk factor for CVD [9].

Fig. 1. A multislice spiral CT of the heart of a 67-year-old male HD patient showing extensive patchy calcifications (indicated by arrows) of coronary vessels, aorta and the main bronchi.

Calcification of Arteries and Heart Valves Are Commonly Observed in ESRD

Vascular calcification is a common phenomenon, increases with age and is present in most subjects aged over 65 years. However, in chronic renal insufficiency, advanced extraosseous calcification is present at a significantly earlier age (fig. 1). Goodman et al. [10] used electron beam computed tomography to demonstrate a high prevalence of coronary artery calcification among young adults receiving dialysis, especially those who had been on dialysis for more than 10 years. Subsequent studies have confirmed these findings and established that vascular calcifications are associated both with clinical symptoms of CVD [11] and cardiovascular mortality [12]. Whereas calcification of mitral and aorta valves occurs in less than 5% individuals in the normal population, the

Fig. 2. Potential causes of vascular calcification in ESRD.

prevalence in dialysis patients is remarkably higher, 45 and 34%, respectively [11]. As in the general population, the degree of cardiac valve calcification predicts cardiovascular morbidity and mortality also in dialysis patients [13]. Vascular calcification in ESRD has for a long time been considered to be the result of a passive process due to elevated PO_4 levels and a high $\text{Ca} \times \text{PO}_4$ ion product. However, recent results suggest that also a number of factors other than disturbances in Ca and PO_4 metabolism promote the deposition of minerals in body tissues (fig. 2).

Vascular Calcification Resembles Osteogenesis

The tunica media of arteries in uremic patients is significantly thicker and lumen considerably smaller (so-called pipe-stem appearance) compared to patients without renal failure [14]. These circumstances are corroborated by animal experiments and may explain why ESRD patients have a high incidence of re-occlusion after coronary angioplasty compared to other patient groups [15]. In gene-modified mice (ApoE knockout mice, which are in particular disposed to CVD) a slight renal insufficiency increases the size of already existing atherosclerotic plaques [16]. Interestingly, the process of vascular calcification in uremic patients seems to be similar to the osteoblastic differentiation in bone development [17]. Thus, bone-related proteins, such as osteopontin (OPN), matrix Gla protein (MGP) and bone morphogenetic protein (BMP), have been identified in calcified arteries [14]. Furthermore, high PO_4 levels promote osteoblastic differentiation in smooth muscle cells in vitro [18]. From these findings it could be hypothesized that the tunica media in arteries of ESRD patients resembles typical bone tissue. It should be noted that osteogenesis also occurs in the heart valves, following basically the same development as seen in vascular calcification [17].

Disturbances in Mineral Metabolism Are Associated with Increased Vascular Calcification

In ESRD patients, disturbed $\text{Ca} \times \text{PO}_4$ balance stimulates the parathyroid glands to produce more parathyroid hormone (PTH). It has been speculated that elevated PTH, by increasing intracellular calcium levels, induces calcification of various tissues [14]. However, the recent data of London et al. [19] does not support the hypothesis

that hyperparathyroidism plays a direct role on the vascular calcification process. Indeed, as two large North American studies have demonstrated, a strong correlation between high PO_4 levels and cardiovascular death, disorders in $\text{Ca} \times \text{PO}_4$ metabolism per se, seems to be capable of increasing the risk for CVD. By analyzing over 6,000 dialysis patients, Block et al. [20] found that over 70% of the patients had high PO_4 levels (>1.6 mmol/l), and mortality increased significantly with serum PO_4 levels >2.1 mmol/l. In this study, the high cardiovascular mortality with hyperphosphatemia was independent of PTH [20]. In an additional registry study from the USA, including almost 13,000 patients, an association of elevated serum PO_4 , high $\text{Ca} \times \text{PO}_4$ product and PTH with cardiac mortality risk was demonstrated in chronic HD patients [21]. It is notable that also in non-renal patients a correlation between hyperphosphatemia and calcification of cardiac valves has been demonstrated [22]. As dialysis patients with vascular calcification have a documented higher daily calcium intake from calcium-based PO_4 binders than patients without calcification [10, 23], it has been suggested that treatment with calcium-based PO_4 binders may actually be a significant risk factor for progressive vascular calcification and premature CVD. As 1,25-dihydroxyvitamin D_3 levels correlate with the extent and progression of vascular calcification [24], vitamin D supplementation may also be a risk factor for vascular calcification. Indeed, Teng et al. [25] observed that paricalcitol (a new vitamin D analogue) treatment in long-term HD patients was associated with a significant survival advantage compared to those receiving calcitriol.

Is Adynamic Bone Disease a Risk Factor for Vascular Calcification?

Lower PTH levels characterize low bone turnover (adynamic bone disease) and as the bone is unable to buffer excess Ca and PO_4 this may allow $\text{Ca} \times \text{PO}_4$ deposition in extrasosseous tissues. Although an inverse relationship between vascular calcification and bone density was demonstrated already 1996 [26], the complex relationship(s) between bone mass and the vascular calcification process has not been extensively studied in uremic patients. In the general population, the progression of atherosclerotic calcification seems to be associated with increased bone loss in women during menopause [27]. As London et al. [28] recently demonstrated that patients with the highest calcification scores had the lowest PTH levels, it could be speculated that this hormone

plays an important role in this scenario. Indeed, in the diabetic LDL receptor-deficient mice, PTH supplementation (teriparatide) inhibited vascular calcification and aortic osteogenic differentiation via direct effects on OPN [29]. Thus, as a low PTH level is associated with vascular calcification [19] and predicts mortality [30, 31], it could be speculated that adynamic bone disease may be a significant risk factor for accelerated atherogenesis in ESRD. This hypothesis is corroborated by findings in dialyzed diabetic patients, a group of patients with extensive vascular calcification (see below), in which impaired PTH secretion is a major mechanism of low bone turnover [32]. Moreover, in a recent study of 515 prevalent dialysis patients, Stevens et al. [33] demonstrated that the combination of low PTH with high $\text{Ca} \times \text{PO}_4$ was associated with the highest risk of mortality. Clearly, as pro-inflammatory cytokines promote both accelerated atherogenesis [34] and bone disease [35], further studies are needed to evaluate the role of persistent inflammation in this scenario. Indeed, it has been hypothesized that uremic cytokines and/or toxic metabolites may contribute to a form of bone disease, indistinguishable from adynamic bone disease, but with increased osteoclastic bone resorption [36].

Inflammation May Promote Vascular Calcification

Although abnormal mineral metabolism may be the most important risk factor for increased vascular calcification in uremia, recent studies suggest that also a chronic inflammatory response stimulates the process of calcification [37]. A cross-sectional study by Wang et al. [38] in CAPD patients indicated that calcification of coronary arteries and cardiac valves are not only associated to age and $\text{Ca} \times \text{PO}_4$ balance, but also to the incidence of malnutrition and inflammation. In addition, correlations between inflammation and diffuse coronary artery calcification [39] and aortic valve alteration [40] have been documented in HD patients. As other chronically inflamed patient groups, such as SLE patients [41], have increased coronary calcification, this also suggests a direct link between vasculopathy and inflammatory activity. Although it is not exactly known how chronic inflammation contributes to increased vascular calcification, various mechanisms have been proposed. Indeed, several of the factors that may promote or inhibit the calcification process are associated to inflammation (table 1). Ketteler et al. [42] have recently presented an interesting hypothesis on how

Table 1. Factors that have been shown to inhibit or promote the calcification process

Factors	Associated to inflammation
<i>Factor-inhibiting calcification</i>	
Osteoprotegerin [48]	+
Osteopontin [50]	+
Bone morphogenic protein-7 [79]	+
Fetuin-A [42]	++
HDL cholesterol [58]	+
Matrix Gla protein [45]	?
<i>Factor-promoting calcification</i>	
Calcitriol [24]	–
Leptin [54]	+
Tumor necrosis factor- α [47]	++
Genetic factors [43]	–
Diabetes mellitus [62]	+

inflammation may promote atherosclerosis in ESRD. They studied circulating plasma levels of α_2 -Heremans-Schmid glycoprotein (fetuin), a negative acute-phase protein preventing calcification process and demonstrated that low levels of fetuin predicted cardiovascular complications in prevalent HD patients. We have recently confirmed these findings in ESRD patients starting dialysis treatment and found that low fetuin levels independently predicted both all-cause and cardiovascular mortality rate [43]. MGP is a fetuin-like compound that serves as a tissue-bound inhibitor of calcification. Like the fetuin-A knockout mice [44], MGP knockout mice also show extreme generalized medial vascular calcification and die of premature vascular disease [45]. Clinical data also support a significant role of MGP. As an example, Jono et al. [46] have documented an inverse relation between MGP levels and severity of coronary artery calcification in 115 patients with coronary artery disease. As the calcification inhibitory effect of MGP is dependent on vitamin K, it has been speculated that warfarin treatment may contribute to an accelerated process of vascular calcification. However, to the best of our knowledge, the putative pro-atherogenic role of warfarin has not yet been evaluated in clinical studies.

As the process of calcification includes monocyte and macrophage infiltration, the release of another pro-inflammatory cytokine, TNF- α , may also take part in vascular calcification by promoting osteoblastic differentiation through the cAMP pathway [47]. Osteoprotegerin (OPG) is another member molecule of the TNF-receptor

family, which may play a central role in the regulation of bone turnover and in calcification processes at extraosseous sites. As OPG knockout animals develop both osteoporosis and significant calcifications of aorta and renal arteries [48], it could be hypothesized that decreased availability of this decoy receptor of RANKL may contribute to extraosseous calcification. On the other hand, as serum OPG levels were significantly elevated in HD patients with a higher aortic calcification index, it could be speculated that increased serum levels of OPG may be a compensatory protective response to the progression of vascular calcification [49]. Moe et al. [50] have demonstrated that vascular calcification of the medial layer of epigastric arteries is associated with deposition of the bone matrix protein OPN in ESRD patients undergoing renal transplantation. These data are corroborated by recent findings by Ström et al. [51] in triple knockout mice (ApoE/LDL receptor/OPN) showing that OPN deficiency reduces atherogenesis.

Role of Other Uremic Risk Factors in the Calcification Process

Leptin, an adipokine often markedly increased in uremic patients [52] and associated to inflammation [53], has also been shown to stimulate the process of calcification [54]. In accordance, a recent study in type-2 diabetic patients demonstrated that plasma leptin levels were associated with coronary atherosclerosis after controlling for both adiposity and CRP [55]. As leptin is a powerful inhibitor of bone formation [56, 57], a reduced bone turnover may be one mechanism by which this adipokine promotes extraosseous calcification. As HDL-cholesterol regulate osteoblastic differentiation and calcification of vascular cells [58], also lipids may play an important role in the calcification process. Oxidative stress is another frequent phenomenon in ESRD which is associated to both inflammation and endothelial dysfunction [1]. Since oxidative stress appears to play an important modulating role in the development of vascular calcification in vitro [59], it is of interest that two placebo-controlled studies have shown a reduction of cardiovascular events in dialysis patients on vitamin E [60] and acetylcysteine [61]. Based on these results, larger trials that are sufficiently powered to assess the effects of antioxidant treatment strategies on mortality appear highly desirable in ESRD patients.

Vascular calcification [62] and adynamic bone disease [63] are particularly common features in patients with

diabetes mellitus – a group of patients having a high prevalence of both inflammation and increased oxidative stress [64, 65]. As the diabetic type of calcification is an active cell-mediated process where smooth muscle cells in blood vessels express a great number of bone matrix proteins regulating the calcification [62], it may be similar to the process observed in ESRD. Although poor control of $\text{Ca} \times \text{PO}_4$ may also be an important contributor of vascular calcification in diabetic ESRD patients, Ishimura et al. [66] have demonstrated that poor glycemic control remains a critical factor. Moreover, since neuropathy seems to be a significant risk factor for the development of vascular calcification in diabetic patients [62], studies are necessary to investigate the role of autonomic neuropathy in the process of uremic calcification.

Prevention and Treatment of Vascular Calcification in ESRD

Although we have now begun to recognize the associations between disturbed mineral metabolism, inflammation and excessive vascular calcification in ESRD, the recommendations given for its treatment are not well recognized. As hyperphosphatemia is an independent risk factor for CVD in this patient group, a main objective should be to adjust PO_4 levels and $\text{Ca} \times \text{PO}_4$ balance. Diet restrictions should be avoided since limitations in PO_4 intake often lead to simultaneous low protein intake and risk of malnutrition. Lower Ca concentration in dialysate could be considered since it can reduce the risk for hypercalcemia, particularly in conjunction with treatment with active vitamin D and/or calcium-based PO_4 binders. Preference may also be given to hemodiafiltration as it removes PO_4 better than routine HD [67]. Daily dialysis may be yet another way of improving PO_4 balance in well-motivated HD patients [68]. Finally, early transplantation in appropriate patient groups should be encouraged as dialysis vintage seems to enhance vascular calcification and mortality [69].

Despite these implements, a majority of dialysis patients will need treatment with PO_4 binders. Ever since nephrologists abandoned the use of aluminium-based phosphate binders during the 1980s (in order to diminish the risk for aluminium accumulation), an assortment of oral calcium salts has been used for the control of hyperphosphatemia. Calcium-based PO_4 binders have been considered to be harmless with only moderate side effects (i.e. moderate hypercalcemia and gastrointestinal problems). However, since these preparations may promote

vascular calcification, new treatment guidelines from the USA (K-DOQI) suggest a radical shift away from calcium usage and recommend that the total Ca intake, including both nutritional Ca as well as calcium-based PO₄ binders, should not exceed 2,000 mg/day [70]. Thus, non-calcium-based binders should be preferred in patients with severe vascular or soft tissue calcifications. The novel non-calcium-, non-aluminium-containing PO₄ binder sevelamer has been shown to diminish the risk for vascular calcification in dialysis patients [71, 72] and may be an alternative for patients with PO₄ retention. Experiments on rats with renal insufficiency have demonstrated that sevelamer is more effective than calcium carbonate to prevent progression of renal insufficiency and the accumulation of calcium in kidneys [73]. Moreover, as sevelamer has favorable effects on lipids [74], it could be speculated that sevelamer, like other lipid-lowering drugs [75], may have anti-inflammatory effects. However, sevelamer is expensive and has relatively moderate PO₄-binding capacity, and sometimes it needs to be combined to various Ca salts in able to reach normal PO₄ levels.

In addition to effective vitamin D analogues controlling PTH production without inducing hypercalcemia, new and more effective, non-calcium-containing PO₄ binders (such as lanthanum chloride and ferric chloride) will soon be introduced for clinical use. The importance of maintenance of some PTH activity (150–300 ng/l), reflecting active bone turnover, should be pointed out since low PTH with high Ca and PO₄ values is associated with higher mortality [30, 31]. As adynamic bone disease may be related to vascular calcification [19], interventions associated with excessive lowering of parathyroid activity (such as parathyroidectomy and treatment strategies that increase the Ca balance) may be a risk factor for excessive arterial calcification. Indeed, one study demonstrated that vascular calcification was more often observed in ESRD patients after parathyroidectomy [28]. In this context the new calcium-receptor-stimulating calcimimetics are of outmost interest, as these drugs seem to have a direct controlling effect on parathyroid gland by adjusting both PTH and Ca × PO₄ product [76]. The role of other potential treatment strategies to prevent vascular calcification in ESRD, such as biphosphonates and calcium channel blockers, have recently been discussed [77].

Since there is clinical evidence suggesting an association between a chronic inflammatory response and widespread vascular calcification, it seems advisable to investigate and treat inflammation aggressively in ESRD patients. Obvious signs of chronic infectious process, such as tooth and foot infections, should be searched for and

properly treated. Other conceivable causes for chronic inflammatory reaction, as rheumatic diseases, hypervolemia, dialysis with bioincompatible membranes, should be considered and, if possible, adjusted. However, from our experience there is seldom any real established reason for chronic inflammation in ESRD patients. It has been suggested that patients with constantly elevated CRP should be evaluated for silent coronary disease [78]. Numerous drugs, which currently have other indications than inflammation, i.e. statins, ACE inhibitors, glitazones and antioxidants, have significant anti-inflammatory effects [1]. Future placebo-controlled studies will show if these medicines and/or targeted anticytokine treatment strategies can be suitable alternatives for the treatment of the inflamed dialysis patient. Finally, as studies on LDL-receptor null mice have shown that BMP-7 (maintains renal tubular differentiation in the adult and is down-regulated in renal failure) is effective in treating vascular calcifications [79], further investigations are needed to demonstrate whether this renal morphogen and cytokine repressor [80] may be a potential future treatment strategy in renal patients with vascular calcification.

In summary, extraosseous calcification of coronary arteries and heart valves is a common phenomenon in ESRD and predicts both cardiovascular events and premature death. Recent evidence suggests that associations exist between disturbed mineral metabolism, chronic inflammation, adynamic bone disease and vascular calcification in ESRD. Hopefully, future studies will reveal if targeted early intervention of these risk factors in dialysis patients may prevent the fatal development of a heart of stone and a bone of China.

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