Cardiovascular calcification in end-stage renal disease

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Abstract
Cardiovascular diseases are common in patients with end-stage renal disease (ESRD) and cardiovascular morbidity and mortality among dialysis patients are substantially higher than in the general population. The reasons for this high incidence are multiple. They include traditional factors such as hypertension, diabetes, dyslipidaemia, sodium overload, and elevated homocysteine levels as well as disturbances of mineral metabolism, specifically abnormalities in phosphorus and calcium homeostasis. This review will describe the specific cardiovascular complications related to calcifications in ESRD, the implications of the abnormalities of mineral metabolism in its pathogenesis and the current imaging techniques available for the detection of cardiovascular calcifications. Excess of calcium load contributes to the development of cardiac calcifications; therefore, alternative strategies to diminish exogenous calcium load should be considered in patients with ESRD.

Keywords: cardiovascular calcification; end-stage renal disease

Introduction
Cardiovascular diseases are common in patients with end-stage renal disease (ESRD). Cardiovascular morbidity and mortality among dialysis patients are substantially higher than in people with normal kidney function [1–5], and cardiovascular disease accounts for almost half of all deaths among dialysis patients [1,2,6]. Moreover, cardiovascular mortality among dialysis patients is higher than would be predicted simply from concurrent risk factors such as diabetes, hypertension, and elevated cholesterol levels [8]. Lesions of cardiovascular calcification are also seen in dialysis patients at a much younger age than in the general population [4,9]. Even adults less than 30 years of age on dialysis have a high incidence of coronary artery calcification and these lesions progress at a relatively rapid rate [4]. A retrospective autopsy study of paediatric ESRD patients also found a high incidence of soft-tissue and vascular calcification [9].

The reasons for this high incidence of cardiovascular disease are multiple. There are a number of traditional risk factors such as hypertension, diabetes, dyslipidaemia, sodium overload, elevated homocysteine levels, and water overload that are commonly seen in the ESRD population [7,10–16]. In addition, there are factors specific to ESRD that contribute to the high incidence of cardiovascular calcification in the dialysis population, such as disturbances in mineral metabolism, and specifically abnormalities in phosphorus and calcium homeostasis [3,4,17–24].

Cardiovascular complications and consequences in patients with ESRD
Calcifications of the myocardium, coronary arteries, and cardiac valves are frequently observed in patients with ESRD [3,17,25–28]. Vascular calcification is also associated with increased aortic stiffness, which is predictive of cardiovascular mortality in these patients [17].

Cardiovascular calcification lesions can lead to the development of a number of clinically significant complications, including myocardial ischaemia, myocardial infarction, impaired myocardial function, congestive heart failure, cardiac valve insufficiency, and cardiac arrhythmias [18–20,26,29,30]. Thus, cardiovascular lesions in the ESRD patient are associated with substantial morbidity and mortality risks [6,29].

Mitral valve calcification has been correlated with left ventricular dilatation and reduced left ventricular systolic function (ejection fraction) in patients treated with peritoneal dialysis [27]. Another study found aortic valve calcification was associated with rapid development of functional aortic stenosis and subsequent morbidity and mortality [18]. Myocardial calcification can impair left ventricular function [26].

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and calcification of the cardiac conduction system can cause death [25]. Thus, these studies clearly demonstrate that the development of cardiovascular complications is relatively frequent in patients treated with long-term dialysis therapy.

**Detection of calcific cardiovascular lesions**

Over the last several years, technical advances in medical imaging have led to the detection and quantification of calcification in the major arteries. Techniques such as ultrasound and electron beam computed tomography (EBCT) have been utilized to monitor the presence and progression of vascular calcifications. Using EBCT, coronary artery calcification was detected in 88% of young adult haemodialysis patients [4]. Goodman et al. also found that coronary artery calcium scores almost doubled over an 18–24 month period, indicating a relatively rapid progression of this lesion [4]. Another study found that chronic haemodialysis patients had coronary artery EBCT calcium scores that were 2.5- to 5-fold higher than non-dialysis patients with known or suspected coronary artery disease [3]. This study also found significant progression of coronary artery calcification, as measured by EBCT calcium scores, over a period of less than 1 year in the haemodialysis patients [3]. Both of these studies found that coronary artery calcification is common and rapidly progressive in dialysis patients.

Likewise, calcification of coronary valves is commonly seen in dialysis patients [3,18,20,27,28]. Ribeiro et al. reported aortic valve calcification in 52% and mitral valve calcification in 45% of chronic haemodialysis patients assessed by echocardiography [20]. Braun et al. found aortic valve calcification in 55% and mitral valve calcification in 59% of chronic haemodialysis patients [3]. There was also significant progression of the valvular calcification over approximately 1 year [3]. In addition, abnormalities in large arterial wall motion, thickness, and calcifications were detected by arterial ultrasound in patients with ESRD [17].

**Abnormalities in mineral metabolism—role in cardiovascular disease**

Phosphorus and calcium abnormalities appear to contribute to soft-tissue calcification, accelerated cardiovascular calcification, and overall mortality in ESRD [4,17,20,21,31,32]. Indeed, elevated serum phosphorus levels are associated with an increased risk of death in such patients [21,23,31], particularly from coronary artery disease [23]. Similarly, there is a strong association between increased calcium–phosphorus (Ca×P) product and cardiac calcification or risk of death [4,9,17,20,21,23,26,27,32].

Among two large national samples of chronic haemodialysis patients, serum phosphorus levels above 6.5 mg/dl (2.10 mmol/l) and Ca×P products above 72 mg²/dl² (5.81 mmol²/l²) were associated with an increased adjusted relative risk of death [21]. The association between elevated serum phosphorus levels and increased mortality risk was independent of parathyroid hormone (PTH) levels [21].

The presence of coronary valve calcification has been associated with Ca×P values as low as 55 mg²/dl² (4.46 mmol²/l²) in chronic dialysis patients [27]. Goodman et al. found that young adult dialysis patients with coronary artery calcification had higher serum phosphorus levels, as well as higher Ca×P values, than those without coronary artery calcification on EBCT [4]. A sample of adult dialysis patients had greater myocardial calcium content than control subjects, and this increased myocardial calcium content was significantly associated with elevated Ca×P products and vascular calcification [26].

Administration of vitamin D to treat secondary hyperparathyroidism increases intestinal absorption of calcium and phosphorus, and raises serum calcium and phosphorus levels [19,22,32]. Soft-tissue and vascular calcification were associated with a history of vitamin D therapy, particularly calcitriol, in a study of autopsy material in paediatric patients with ESRD [9]. Thus, ESRD patients may have been exposed to a variety of factors that elevate serum calcium and phosphorus levels and the Ca×P product and, therefore, increase the risk for development of vascular calcifications.

The current therapeutic approach with the use of calcium-containing phosphate binding agents is associated with a net positive calcium balance. Furthermore, the dialysate calcium concentration plays an additional role in the development of a positive calcium balance as there is a positive calcium flux from the dialysate solution with the standard dialysate calcium concentration [33]. Thus, the use of calcium-containing binders and the dialysate calcium concentration play a major role in the persistence of a positive calcium balance and contribute to the exogenous calcium load [33–35].

Goodman et al. found that young adult dialysis patients with coronary artery calcification ingested almost twice as much calcium from calcium-based phosphate binders as those patients without arterial calcification [4]. In another recent study, the amount of calcium in the prescribed dose of calcium-based phosphate binders was associated with the extent of arterial wall stiffness [17]. Patients who received higher doses of calcium-based phosphate binders experienced hypercalcaemic episodes more frequently [17,36].

**Management strategies and goals to reduce risk**

The importance of controlling serum phosphorus levels and Ca×P values is widely recognized. More recently it has been suggested that values considered safe
previously may not be optimal for avoiding the risk of vascular calcification [22].

Dietary phosphate restriction is important, but this alone is not typically adequate for controlling serum phosphorus levels in patients with renal failure. Furthermore, the long-term acceptability of such a diet is impractical, because of its taste and the fact that it will not provide adequate protein intake [37]. Dialysis provides some removal of excess phosphorus, but this is limited by the intracellular inorganic phosphorus fraction. The amount of phosphorus removed weekly by typical haemodialysis or peritoneal dialysis regimens is far less than the normal weekly phosphorus intake [33]. Therefore, almost all ESRD patients require some type of phosphate binder.

In the past, aluminum-containing phosphate-binding agents have been the primary drugs used to control hyperphosphataemia in patients with advanced renal failure and those treated with maintenance dialysis. It is well recognized, however, that such drugs are a major factor for the development of aluminum intoxication. Therefore, several calcium-containing compounds have been used to reduce intestinal phosphorus absorption [36]. However, the doses required for effective phosphorus control also provide a large dose of calcium, and hypercalcaemia is one of the major side effects with the long-term use of calcium salts with or without vitamin D therapy. Indeed, it has been shown in a prospective study by Salusky et al. that serum calcium levels were higher when calcium carbonate was used as a phosphate binder as compared with when aluminum hydroxide was used as a phosphate binder in patients treated with dialysis [36]. Furthermore, intestinal absorption of calcium may be further increased by the use of calcitriol or other vitamin D compounds, which are used to treat secondary hyperparathyroidism in patients with ESRD treated with dialysis.

The factors discussed above can all contribute to the excess calcium load common in dialysis patients. Thus, it is important to explore alternative methods to achieve adequate control of serum phosphorus levels in long-term dialysis patients and to avoid the consequences of the exogenous calcium load that can place dialysis patients at higher risk for cardiovascular calcification and disease.

There are several newer phosphate binders that are free of aluminum and calcium. Aluminum-free, calcium-free phosphate binders include: (i) sevelamer hydrochloride (Renagel® capsules and tablets), an ion-exchange resin, shown to be effective in reducing serum phosphorus while concurrently reducing serum cholesterol and low-density lipoprotein cholesterol levels among dialysis patients in short- and long-term studies [38–41]; (ii) stabilized polynuclear-iron hydroxide and ferric–polymaltose complex, iron-containing compounds shown to be effective in short-term clinical studies [42,43]; and (iii) lanthanum chloride hydrate, which is currently undergoing clinical trials [44]. Of these aluminum-free, calcium-free phosphate binders, only sevelamer is currently approved in the US and Europe to control hyperphosphataemia in renal disease.

Treatment of secondary hyperparathyroidism generally requires the administration of vitamin D compounds. The availability of newer, less-calcaemic vitamin D analogues such as doxercalciferol or paricalcitol may help to avoid common complications of calcitriol therapy such as hypercalcaemia and hyperphosphataemia [45–47]. However, long-term studies are still needed to answer this important question.

Conclusion

It appears that long-term exposure to abnormalities in mineral metabolism and prolonged dialysis treatment contribute to the development of coronary artery calcification, even in young adults treated with maintenance haemodialysis.

Phosphate retention and excess calcium load in ESRD appear to increase the risk of soft-tissue and cardiovascular calcification, as well as subsequent cardiovascular disease and death [4]. Thus, maintaining normal calcium and phosphorus balances remains a primary goal in the management of patients with ESRD treated with dialysis. Chronic exposure to large doses of calcium in patients with minimal renal function—especially when serum phosphorus levels are also high—appears to be associated with the development of arterial calcification. This is seen even in relatively young patients who do not have other cardiovascular risk factors.

Greater efforts should be made to improve the clinical management of ESRD and mineral homeostasis, even in young adults and children, to avoid the development of mineral imbalances that may contribute to cardiovascular disease and death. Recently, Block and Port recommended the following target levels: serum calcium, 9.2–9.6 mg/dl (2.3–2.4 mmol/l); serum phosphorus, 2.5–5.5 mg/dl (0.81–1.78 mmol/l); Ca×P product, <55 mg²/dl² (<4.46 mmol²/l²), and intact PTH, 100–200 pg/ml [22]. Whether these recommendations will have an impact on the rate of vascular calcifications remains to be prospectively evaluated.

Acknowledgements. This work was supported in part by grants from the Public Health Service (DK-35423, DK52905 and RR-00865) and by funds from the Casey Lee Ball Foundation.

References


