Importance of hyperphosphataemia in the cardio-renal axis

William G. Goodman

UCLA Medical Center, Los Angeles, CA, USA

Abstract

Hyperphosphataemia occurs in nearly all patients with end-stage renal disease (ESRD). In the past, the need to manage hyperphosphataemia focused primarily on its role as a contributor to secondary hyperparathyroidism and renal osteodystrophy. There is now widespread recognition that disturbances in phosphorus metabolism and/or the therapeutic measures used to manage it are important risk factors for cardiovascular calcification. This serious complication of chronic kidney disease may contribute to the very high mortality rate from cardiovascular causes in patients undergoing long-term dialysis. New strategies for controlling serum phosphorus levels and for better management of mineral metabolism in general are required to address these issues in patients with ESRD.

Keywords: cardiovascular calcifications; end-stage renal disease; hypercalcaemia; hyperphosphataemia; mineral balance; parathyroid hormone

Introduction

Hyperphosphataemia is a hallmark of end-stage renal disease (ESRD). It results from an imbalance between the amounts of phosphorus absorbed daily from dietary sources by the gastrointestinal tract and the amounts excreted in the urine each day; it occurs when kidney function declines to 25–30% of normal. Phosphorus retention and hyperphosphataemia contribute materially to alterations in vitamin D metabolism and to changes in parathyroid gland function that affect many patients with moderate to advanced chronic kidney disease (CKD), defined recently as stage 3 and stage 4 CKD, respectively. The consequences of hyperphosphataemia thus include secondary hyperparathyroidism and the metabolic bone diseases associated with it, including osteitis fibrosa cystica and mixed renal osteodystrophy. These disorders are common targets for therapeutic interventions, particularly in patients with stage 5 CKD and those undergoing regular dialysis.

It has been recognized for many years, however, that phosphorus retention represents an important risk factor for soft tissue calcification in patients with ESRD. Concern about this complication has grown with the more widespread recognition that the calcification of arteries, the myocardium and cardiac valves is common and often quite extensive in patients with ESRD. Evidence is accumulating that these abnormalities are associated with adverse cardiovascular outcomes and may contribute substantially to the very high mortality rate from cardiovascular causes in the ESRD population [1,2]. Indeed, hyperphosphataemia per se has been reported to increase mortality risk independently in patients receiving haemodialysis (Figure 1) [3].

Common therapeutic strategies for managing phosphorus retention and for controlling hyperphosphataemia include dietary phosphate restriction and the use of phosphate-binding medications to diminish net intestinal phosphorus absorption. Despite such measures, serum phosphorus levels remain elevated in a very high proportion of patients who are treated with dialysis. Dietary indiscretion, failure to adhere to dietary recommendations and either lack of compliance with or improper use of phosphate-binding medications are often invoked to account for such findings. It is increasingly apparent that limitations in the amount of phosphorus that can be removed by conventional dialysis play a major role. Serum phosphorus levels usually revert to normal and phosphate-binding medications are often no longer required in patients treated with alternative dialysis regimens such as daily haemodialysis. Such findings underscore the need for more effective phosphate-binding strategies that include, but are not limited to, the availability of potent, albeit safe, phosphate-binding medications.

Types of cardiovascular calcification

Recent observations indicate that vascular calcification in patients with ESRD is associated with serious adverse clinical outcomes including death. There is
thus considerable interest in clarifying mechanisms that account for the development of vascular calcification in CKD and in better understanding the role of phosphorus retention and/or hyperphosphataemia as potentially important determinants. The process of vascular calcification is not homogeneous, and fundamentally different pathological processes may account for different types of arterial calcification.

There are two distinct types of arterial calcification. One affects primarily the endothelial layer of arteries and the other affects primarily the medial wall or tunica media. The endothelial type of arterial calcification is an integral part of the atherosclerotic process. It occurs within atheromatous plaques together with the localized accumulation of lipids and cellular debris arising from ongoing inflammation. The consequences of atherosclerotic calcification are appreciated widely and include impingement on the lumen of arteries, reductions in blood flow and, in advanced stages, vascular occlusion and thrombosis with tissue ischaemia and necrosis. This type of arterial calcification is largely unrelated to the disturbances in mineral metabolism that occur in CKD, although the calcium content of atherosclerotic plaques has been reported to be greater in patients with ESRD than in persons of the same age without CKD.

The incidence of atherosclerotic vascular calcification increases with age, and its presence provides a legitimate surrogate marker of atherosclerotic burden in persons from the general population who can be assessed by non-invasive techniques such as electron beam computed tomography (CT) and spiral, or helical, CT. The utility of these diagnostic methods has yet to be determined, however, in patients with CKD, particularly for assessing cardiovascular risk.

Medial wall calcification, or Mönckeberg’s sclerosis, has been recognized for many years as a common complication of CKD. This type of arterial calcification involves elastic collagen fibrils within the tunica media of arteries, and the incidence in the general population also increases with age. Medial wall calcification is a prominent finding, however, in many patients with CKD, in those with ESRD who are treated with dialysis and in patients with diabetes. It can occur in relatively young individuals with CKD. Medial wall calcification results in rigid, non-distensible arteries leading to reductions in vascular compliance. Haemodynamic consequences include increases in systolic blood pressure, widening of the pulse pressure and left ventricular hypertrophy. Alterations in mineral metabolism including hyperphosphataemia and the therapeutic use of large oral doses of calcium as a phosphate-binding agent have each been implicated as contributors to this type of arterial calcification in patients with CKD.

**Factors that regulate arterial calcification**

Historically, soft tissue calcification in CKD has been considered to be largely a passive, unregulated process resulting in the accumulation of amorphous deposits of calcium and phosphorus. Elevated serum phosphorus levels and, less frequently, episodes of hypercalcaemia were thought to aggravate soft tissue and vascular calcification by increasing the super-saturated state of plasma with respect to its mineral content. More recently, however, the process of vascular calcification has come to be viewed as a regulated process. Some atherosclerotic lesions contain hydroxyapatite, the crystalline form of calcium found in bone. Certain proteins that are normally involved in bone and mineral metabolism such as osteocalcin, parathyroid hormone (PTH)-related peptide and matrix GLA protein (MGP) are expressed in calcified atherosclerotic lesions. For example, MGP is normally expressed abundantly in cartilage and blood vessels, where it serves to inhibit mineralization in arteries and epiphyseal growth plate cartilages. Mice with inactivating mutations in the gene encoding MGP prematurely calcify growth plate cartilage, resulting in osteoporotic skeletal phenotype, and they develop extensive arterial calcification, leading to death within a few months from aortic and arterial rupture [4]. Other factors, such as citrate and fetuin, function as circulating inhibitors of calcification and appear to modulate or prevent mineral deposition in soft tissues that are continuously exposed to plasma that is super-saturated with respect to

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**Fig. 1.** High serum phosphorus increases relative mortality risk. Reproduced, with permission, from Block et al. [3].
calcium and phosphorus *in vivo*. Such findings suggest numerous pathways that may account for the occurrence of soft tissue and vascular calcification in clinical conditions such as CKD.

Apart from the tissue-specific expression of certain regulatory proteins and the influence of circulating factors, alterations in the phenotypic behaviour of vascular smooth muscle cells (VSMCs) also appear to be involved in the process of arterial calcification. Under selected conditions *in vitro*, VSMCs acquire phenotypic characteristics that are more typical of bone cells. VSMCs have been shown to express a variety of bone-related proteins, and the expression of certain bone-specific proteins such as osteocalcin and Cbfa-1 can be induced *in vitro* by maintaining cells in medium containing high concentrations of phosphorus [5]. Both the levels of protein expression and the extent of calcification *in vitro* were related to the uptake of phosphorus by VSMCs. The results suggest additional mechanisms to account for the local accumulation of mineral within the arterial wall.

**The role of mineral metabolism in calcification**

**Hyperphosphataemia**

As noted previously, hyperphosphataemia has been recognized for many years as a risk factor for the development of soft tissue calcification in patients with CKD. By increasing the mineral content of serum or plasma, the disturbance may diminish the effectiveness of key regulatory factors that serve to maintain mineral in aqueous solution and thus lower the threshold for mineral deposition in blood vessels and other soft tissues. Phosphorus retention and hyperphosphataemia may also induce the transformation of VSMCs into an osteoblast-like phenotype, cells capable of expressing selected bone-related proteins that facilitate or mediate the process of vascular calcification. A better understanding of the mechanisms that account for such changes would be valuable in developing therapeutic strategies to prevent or control this serious complication of CKD.

Phosphorus retention and hyperphosphataemia are only two of several important disturbances in mineral metabolism that contribute to the development of secondary hyperparathyroidism, particularly in patients with ESRD. They are also direct consequences of certain therapeutic interventions designed to control the disorder. Because vitamin D sterols promote intestinal phosphorus absorption, increases in serum phosphorus levels are common and episodes of hyperphosphataemia occur often in patients given vitamin D sterols to lower plasma PTH levels. The benefits and risks associated with conventional approaches to the treatment of secondary hyperparathyroidism are thus being re-evaluated. New therapeutic guidelines have been formulated with an emphasis on safety. It will be important to determine in the future whether such recommendations favourably affect the development and/or progression of vascular calcification in patients with CKD.

**Calcium balance**

In untreated patients with CKD, calcitriol (1,25-dihydroxyvitamin D₃) synthesis by the kidney is diminished, and serum calcitriol levels may be reduced. These changes contribute to decreases in the efficiency of intestinal calcium absorption. Moreover, such patients often ingest diets that have only limited amounts of calcium because the intake of dairy products is restricted in an effort to reduce phosphate intake and prevent phosphorus retention. Untreated patients with CKD thus commonly have serum calcium levels that are modestly reduced or that fall within the lower range of normal.

Total body calcium balance can become quite positive, however, in patients with CKD who are given large oral doses of calcium as a phosphate-binding medication [6]. Passive, vitamin D-independent calcium transport by the intestine increases linearly as a function of load even in those with ESRD. In patients undergoing dialysis, several grams of elemental calcium are usually required to reduce intestinal phosphorus absorption effectively and control serum phosphorus levels. Excess amounts of calcium that are absorbed passively from the gastrointestinal tract may thus be retained in patients with little or no residual kidney function and contribute to the development of soft tissue and vascular calcification.

The problem can be aggravated by the concurrent administration of vitamin D sterols to treat secondary hyperparathyroidism. These agents have biological actions in a wide variety of tissues, and their effects on intestinal calcium and phosphorus absorption can produce dose-limiting increases in serum calcium and/or phosphorus levels.

The potential importance of disturbances in mineral metabolism for the development of vascular calcification has been highlighted by several recent studies. Coronary artery calcification in young adult dialysis patients was associated with the ingestion of very large doses of calcium as a phosphate-binding medication and with greater elevations in the calcium × phosphorus ion product in serum [7]. Guérin *et al.* reported that arterial calcification, as detected by B-mode ultrasound, was associated with the use of relatively larger doses of calcium carbonate and more frequent episodes of hypercalcaemia (Figure 2) [8]. Such findings suggest that very large doses of calcium should not be given to patients with ESRD and that the total daily intake of calcium should be limited to amounts generally recommended for persons in the normal population.

Additional cautionary measures may be needed when calcium-containing compounds are given together with vitamin D sterols to avoid recurrent episodes of hypercalcaemia and hyperphosphataemia. Recent data suggest, but do not prove, that lowering daily
calcium intake by using the calcium-free, phosphate-binding agent sevelamer diminished the rate of progression of coronary artery and aortic calcification in patients undergoing haemodialysis [9]. Whether the use of other calcium-free, phosphate-binding medications will have similar effects on the course of soft tissue and vascular calcification in patients with ESRD is not yet known.

**Calcifications and cardiovascular disease**

Patients undergoing regular dialysis are 10–20 times more likely to die from cardiovascular causes than persons in the general population, and cardiovascular disease accounts for ~50% of deaths in patients with ESRD [10]. The very high prevalence of cardiovascular disease in such patients is due, in part, to an abundance of traditional risk factors, such as older age, hypertension, dyslipidaemia, anaemia and diabetes [10–12]. Nevertheless, cardiovascular calcification represents an additional risk factor for those with ESRD. Calcifications affect the aorta, peripheral arteries, coronary arteries, myocardium and both the mitral and aortic valves [13–15]. Blacher and colleagues have reported recently that survival decreases as the extent of vascular calcification increases in patients undergoing long-term haemodialysis (Figure 3) [16]. Although further work is needed to clarify the role of cardiovascular calcification as a risk factor for cardiovascular morbidity and mortality in patients with ESRD, there is now sufficient evidence to indicate that disturbances in mineral metabolism represent a non-traditional risk for adverse cardiovascular outcomes in patients undergoing dialysis.

**Challenges in preventing calcifications**

Despite conventional approaches to clinical management, 70% of ESRD patients have persistently elevated serum phosphorus levels [3]. In part, the problem is attributable to the use of dialysis strategies that have limited efficacy in achieving weekly total body phosphorus balance. A recent report indicates that ~40% of patients just starting haemodialysis have no evidence of
coronary artery calcification [17]. Such findings differ strikingly from those presented previously in studies of established haemodialysis patients. The results suggest that vascular calcification develops frequently and progresses rapidly during haemodialysis despite current management practices. Innovative measures will be required to reduce the prevalence and severity of this serious complication of ESRD.

Summary

Cardiovascular calcifications are common in patients with ESRD. The causes are numerous, but hyperphosphataemia is a key contributor. High levels of calcium intake in patients with ESRD have been shown to aggravate the process of vascular calcification, and treatment with vitamin D can lead to biochemical changes that may worsen the process. New therapeutic strategies that effectively control serum phosphorus levels and prevent phosphorus retention without aggravating disturbances in calcium metabolism are needed to manage mineral metabolism more safely in patients undergoing long-term dialysis.

References