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Managing phosphate retention: is a change necessary?

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Introduction

Cardiovascular disease accounts for half the deaths in adults treated with maintenance dialysis, and mortality from cardiovascular causes is far higher than that in the general population [1,2]. Contributing factors include sodium and water overload, hypertension, diabetes mellitus, alterations in lipid metabolism and elevated levels of homocysteine in serum [3–8]. Despite considerable progress over the last two decades in the management of these and other traditional cardiovascular risks, the mortality rate from cardiovascular causes has not diminished in patients with end-stage renal disease (ESRD) [9]. Indeed, cardiovascular mortality for those treated with dialysis continues to far exceed that predicted from the combined risks attributable to age, sex, systolic blood pressure, left ventricular hypertrophy, serum total and HDL cholesterol, cigarette smoking and diabetes mellitus [10]. Other factors are likely, therefore, to account for the high incidence of cardiovascular death in those undergoing long-term dialysis.

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Disturbances of calcium and phosphate metabolism and cardiovascular morbidity

Evidence is accumulating that disturbances in mineral metabolism contribute to the development of cardiovascular disease and to overall mortality in patients with ESRD [11–15]. Block *et al.* reported that elevated serum phosphorus levels were an independent risk factor for death in adults undergoing dialysis even after adjusting for established cardiovascular risks and other co-morbid conditions [11]. The mechanisms that underlie this association remain uncertain, but hyperphosphataemia has long been recognized as an important determinant of soft tissue and vascular calcification in patients with chronic renal failure. Several recent studies suggest that vascular calcification, due at least in part to hyperphosphataemia and/or the measures used to manage phosphate retention, represents one

pathway by which alterations in mineral metabolism can adversely affect clinical outcomes both in adult and in paediatric patients with ESRD [12–14,16,17].

Soft-tissue calcifications in patients with renal failure

Vascular calcification in patients with chronic renal failure was first described by Virchow [18]. The overall prevalence of the disorder is not known, but Tatler *et al.* found that 27% of patients with advanced renal disease had evidence of vascular calcification when treatment with dialysis was first begun [19]. The percentage of those with evidence of vascular calcification rose to 80% after 9 years of maintenance dialysis therapy [19]. Others have reported that vascular calcifications are present in 20–55% of the general dialysis population. Calcification of the myocardium and cardiac valves also occurs in patients with ESRD [20]. Together, these abnormalities are likely to contribute to myocardial ischaemia, impaired myocardial function, cardiac valve insufficiency and cardiac arrhythmia in patients undergoing long-term dialysis.

Calcification of atherosclerotic plaques

Arterial calcification is an integral component of atherosclerosis, and 80–90% of advanced atherosclerotic vascular lesions contain calcium [21]. The presence of calcium within atherosclerotic plaques may be a particularly important determinant of plaque fragility, leading to plaque rupture and thrombosis. Although the relationship between vascular calcification and the atherosclerotic process is not fully understood, certain factors that are integrally involved in mineral metabolism are known to influence the process of arterial wall calcification [22–25].

Calcium deposits in atherosclerotic plaques can contain hydroxyapatite, which represents the crystal phase of calcium and phosphorus in fully mineralized bone. In some cases, advanced atherosclerotic lesions have fully formed bone elements within them, including trabeculae, lacunae and areas resembling marrow spaces. Potential mediators of bone formation within the arterial wall included developmental retention of pluripotent cells or osteoblastic immigration with loss of regulatory control [23,26]. Studies using *in situ* hybridization in calcified human atherosclerotic lesions have demonstrated expression of the bone-related proteins osteopontin and bone morphogenic protein type 2 (BMP-2) [23,27]. It has also been shown that smooth muscle cells can calcify under certain *in vitro* cell culture conditions [28], and vitamin D has been suggested to play a role in the development of vascular calcifications [29].

Despite these findings, the relationship between arterial calcification in chronic renal failure and the process of calcification within atherosclerotic lesion remains uncertain. It is possible that the abnormalities of mineral metabolism that result from chronic renal failure aggravate the deposition of calcium and phosphorus within existing atherosclerotic plaques. Alternatively, the two processes may be distinct and unrelated to one another. Considerable additional work is required to resolve this matter.

Arterial calcifications in dialysis patients and the role of oral calcium intake

In a recent issue of *Nephrology, Dialysis and Transplantation*, Guerin *et al.* provided additional evidence implicating certain components of the clinical management of patients with ESRD in the development of cardiovascular pathology [14]. These investigators used B-mode ultrasonography to measure wall stiffness in the common carotid artery, in the femoral artery and in the aorta of patients treated with haemodialysis. They found that wall stiffness was directly related to the presence and extent of arterial calcification. Factors associated with increases in arterial wall rigidity were age, duration of dialysis, serum fibrinogen levels and the prescribed dose of calcium that was used as a phosphate-binding agent [14]. In the present issue of this journal, Eifinger and colleagues reported evidence of coronary artery calcification as determined by electron beam computed tomography (EBCT) in children and young adults who were treated with maintenance dialysis. Such findings, together with other recently presented data [13], extend to younger persons the observations made originally by Braun *et al.* who noted that 65% of adult haemodialysis patients between the ages of 29 and 72 years had EBCT evidence or coronary artery calcification [30]. The results of three independent studies demonstrate that the extent of coronary calcification is substantially greater in patients with ESRD than that observed in patients of the same age and gender in the general population, including those with angiographically documented coronary artery disease [13,30,31].

The observations by Guerin and co-workers [14] and by Eifinger *et al.* are consistent with data reported recently by Goodman and colleagues in young adults treated with dialysis [13]. Nearly 90% of patients between the ages of 20 and 30 had EBCT evidence of coronary artery calcification [13]. In contrast, only three of 60 volunteers of the same age with normal renal function had any coronary artery calcification that was detectable by EBCT [13]. Patients with positive scans were older, and they had been treated with dialysis for much longer than those with negative scans. As such, the proportion of young adults with coronary artery calcification increased as a function of the duration of treatment with dialysis [13]. Coronary artery calcification scores nearly doubled when EBCT were repeated 18–24 months later.

Compared with those without EBCT evidence of coronary artery calcification, young adult with positive EBCT scans had higher serum phosphorus levels and higher values for the calcium–phosphorus ion product

in serum. Both factors have previously been implicated in the development of cardiac valve calcification in older adults with ESRD [20]. Perhaps more important, however, was the finding that young adult dialysis patients with coronary artery calcification were ingesting nearly twice as much calcium in the form of calcium-containing, phosphate-binding agents than those without detectable calcium deposits [13]. Together with the recent observations of Guerin and co-workers [14], the results suggest that the most widely used method for controlling serum phosphorus levels in patients undergoing dialysis can aggravate cardiovascular disease as manifested by arterial calcification and diminished arterial wall compliance. It is quite possible, therefore, that protracted exposure to large oral doses of calcium in patients with little or no residual renal function, particularly those with persistently high serum phosphorus levels, can lead to the development of coronary artery calcification even in younger patients who do not harbour traditional cardiovascular risks.

Importance of controlling phosphate retention

The use of phosphate-binding agent is unavoidable in nearly all patients with ESRD [32,33]. Dietary phosphate restriction alone is only moderately effective in controlling serum phosphorus levels, and further decreases in dietary phosphorus content compromise overall nutrition, particularly protein intake [34]. Phosphate removal during dialysis is limited largely due to the intracellular location of most inorganic phosphorus. The amounts removed either by thrice-weekly haemodialysis, ~800 mg/treatment or 2400 mg/week, or by daily peritoneal dialysis, 300–400 mg/treatment or 2100–2800 mg/week, are far less than that ingested by most patients, 800–1200 mg/day or 5600 9600 mg/week [35]. The inadequacy of current haemodialysis regimens for controlling serum phosphorus levels is underscored by the finding that patients treated with daily nocturnal haemodialysis have normal serum phosphorus levels and often do not require oral phosphate-binding medications [36].

The use of phosphate-binding agents

During the first two decades of treatment with maintenance dialysis in patients with end-stage renal disease, aluminium-containing compounds were used predominantly as phosphate-binding agents. Subsequently, the use of these compounds was associated with the development of aluminium toxicity because patients with renal failure cannot excrete aluminium that is absorbed from the gastrointestinal tract [37,38]. As a result, calcium-containing compounds have been widely used for the past decade as phosphate-binding agents both in adults and in children undergoing regular dialysis [39–42]. Unfortunately, quite large oral doses of calcium are needed to effectively diminish intestinal phosphorus absorption. Indeed, the doses required far exceed the 1500 mg of elemental calcium that is recommended for persons with normal renal function to prevent age-related bone loss [43,44]. Calcium intake in dialysis patients often ranges from 5 to 8 g per day [39–41]. A portion of the calcium ingested is absorbed via the passive vitamin D-independent pathway, which increases directly as a function of the amount of ingested [45]. The concurrent administration of 1,25-dihydroxyvitamin D or other vitamin D sterol further increases the risk of developing hypercalcaemia and/or hyperphosphataemia [46,47].

Potential value of new aluminium- and calcium-free phosphate binding agents and vitamin D derivatives

In this context, alternative methods for managing hyperphosphataemia in patients undergoing long-term dialysis that do not entail the use of very large oral doses of calcium should be implemented. Dietary calcium intake should be maintained at levels that are sufficient to satisfy daily requirements, but the use administration of additional calcium as calcium-containing phosphate-binding agents should be avoided.

The new phosphate-binding agent, sevelamer (Renagel®), approved by the Food and Drug Administration (FDA) in the United States, is an ion exchange resin that binds phosphorus in the intestinal lumen and prevents its absorption. It does not contain either calcium or aluminium, and it has been shown to be effective in managing phosphate retention both in short-term and long-term studies of patients undergoing haemodialysis [48–51]. The cholesterol lowering properties of this compound also make it an appealing therapeutic alternative for use in a subgroup of patients who are known to be at risk for developing cardiovascular disease [52].

In addition to sevelamer, there are other iron-containing compounds in different phases of drug development, such as stabilized polynuclear iron hydroxide and ferric polymaltose complex, have been shown to be effective in controlling serum phosphour levels in short-term studies in adults and rats with chronic renal failure [53,54]. Another agent, lanthanum chloride hydrate, also decreases intestinal phosphorus absorption in experimental animals, and clinical trials using this compound are currently underway [55].

When the treatment of secondary hyperparathyroidism with vitamin D sterols is necessary, the use of new vitamin D analogues that putatively have less of an effect in raising serum calcium and phosphorus levels should be considered to diminish the chances of developing hypercalcaemia and/or hyperphosphataemia. These are often complications of calcitriol therapy, and their occurrence limits the dose of calcitriol that can be safely given [47]. The new vitamin D analogues that are available for clinical use in the United States

include 19-nor-1,25-dihydroxyvitamin D_2 or paricalcitol, and 1-alpha-hydroxyvitamin D_2 or doxercalciferol. Both compounds have been shown to effectively lower serum PTH levels with only modest changes in serum calcium and/or phosphorus levels in haemodialysis patients with secondary hyperparathyroidism [56,57]. The frequency of episodes of hypercalcaemia and hyperphosphataemia during treatment with these agents has not, however, been directly compared with that observed during treatment with calcitriol. Such information is needed to determine whether the use of paricalcitol or doxercalciferol provide safe alternatives to calcitriol for controlling excess PTH secretion in patients with ESRD.

Whether the more stringent control of serum phosphorus levels and the avoidance of hypercalcaemia using recently developed therapeutic strategies, as recently advocated by Block *et al*., will favourably affect the development and progression of vascular calcification and cardiovascular disease in the ESRD population remains to be determined [58]. Evidence is accumulating, however, to prove that phosphate retention and/or the conventional therapeutic interventions aimed at managing this consequence of chronic renal failure can aggravate soft tissue and vascular calcifications [13,14]. As such, maintaining serum calcium and phosphorus levels, and values for the calcium-phosphorus ion product in serum, within the ranges seen in persons with normal renal function rather than at the higher levels previously considered to be acceptable in those with chronic renal failure seem prudent. There is less available information about the suitable target range for of values of serum PTH that diminishes or minimizes the risks of soft tissue and vascular calcification. The continued high risk of cardiovascular death in patients with ESRD demands that serious consideration be given to fundamental changes in the clinical management of abnormalities in bone and mineral metabolism in such patients, particularly when certain aspects of treatment have been implicated as contributors to vascular calcification and overall in adult patient mortality. Such factors should also be considered in the management of paediatric patients with end-stage renal disease [16].

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Editor's note

Please see also Letter to the Editor by F. Eifinger *et al*. pp. 1892–1894.