REVIEWS

CALCIUM BALANCE AND NEGATIVE IMPACT OF CALCIUM LOAD IN PERITONEAL DIALYSIS PATIENTS

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Like hemodialysis patients, peritoneal dialysis (PD) patients are facing an excessively increased burden of vascular and valvular calcification. According to some surveys, more than 80% of prevalent PD patients are complicated with vascular calcification, and more than one third have heart valve calcification.

Dysregulated phosphate metabolism is well recognized to play an important role in inducing vascular calcification, but increasing evidence is suggesting that dysregulated calcium metabolism also promotes vascular calcification and might in fact be more potent than phosphate in inducing that calcification. Growing evidence from randomized controlled trials shows more progression of vascular calcification and higher mortality among chronic kidney disease (CKD) patients receiving calcium-based phosphate binders than among those receiving non-calcium-containing phosphate binders. Those results raise important safety concern about the use of high-dose calcium-based phosphate binders in the CKD population, including both non-dialysis and dialysis patients (especially anuric dialysis patients), who have markedly reduced urinary calcium excretion. To prevent calcium overload, this review recommends restricting the dose of calcium-based phosphate binders in CKD patients, especially those who are elderly, who have increased cardiovascular risk, who already have baseline vascular or valvular calcification, or who have low intact parathyroid hormone and adynamic bone disease.

KEY WORDS: Calcium balance; calcium-based phosphate binders; vascular calcification.

Vascular calcification is a highly prevalent complication in patients with chronic kidney disease (CKD). The prevalence has been estimated to range from about 50% in non-dialysis CKD patients (1), to more than 60% in incident dialysis patients (2), and to more than 80% in prevalent hemodialysis (HD) (3) and peritoneal dialysis (PD) patients (Wang AY, Lo WK, Cheung SC. Unpublished observation). The prevalence of cardiac valve calcification is estimated to be close to 30% in dialysis patients (4). The presence of vascular (5) and valvular calcification (6) is a powerful predictor of mortality and cardiovascular death in dialysis patients, including patients receiving PD. In most dialysis patients, vascular calcification is progressive in nature, especially in those with pre-existing calcification (7). According to an earlier analysis by Russo and co-workers (1), the coronary artery calcification score was higher by at least 50% in CKD patients compared with patients having calcification and normal renal function during a mean follow-up of 2 years.

This review briefly discusses calcium balance in patients with CKD, especially those receiving PD therapy, and the negative effects of calcium in human vascular smooth muscle cells. More importantly, it reviews recent evidence demonstrating the negative impact of calcium loading in the healthy population as well as in CKD patients.

Perit Dial Int 2014; 34(4):345–352 www.PDIConnect.com
epub ahead of print: 04 Feb 2014 doi: 10.3747/pdi.2013.00177

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Received 8 July 2013; accepted 14 August 2013

DYSREGULATED MINERAL METABOLISM IN CKD

Derangements in mineral metabolism have been regarded a key contributing factor to vascular and valvular

SERUM CALCIUM: A POOR MARKER OF TOTAL BODY CALCIUM LOAD

Calcium exists in the body either as free ions or bound complexes. More than 99% of total body calcium is present in the skeleton as calcium-phosphate complexes, primarily hydroxyapatite, which is the main constituent of bone. Non-bone calcium represents less than 1% of total body calcium, and the various calcium pools (including intracellular, interstitial, and serum calcium) are in constant and rapid exchange. Serum calcium accounts for only 0.025% of total body calcium (14). Thus, serum calcium is not a reliable marker of total body calcium load. Nevertheless, an analysis based on a large US population cohort demonstrated that, compared with an adjusted serum calcium between 9 mg/dL and 9.5 mg/dL, a high adjusted serum calcium (9.5 mg/dL or more) was associated with increased mortality risk in HD patients (17). In another prospective analysis including more than 1000 incident HD and PD subjects, high adjusted serum calcium, calcium-phosphate product (CaxP), and PTH were associated with mortality immediately before an event (18). Thus, hypercalcemia represents a very extreme situation of calcium overload and is associated with a greatly heightened mortality risk in dialysis patients, including those on PD.

EFFECTS OF CALCIUM ON VASCULAR SMOOTH MUSCLE CELLS

Dysregulated phosphate metabolism is well recognized to play an important role in inducing vascular calcification in CKD (19,20), but there is experimental evidence suggesting that calcium may be a more potent inducer of vascular calcification than phosphate (21). In response to changes in extracellular calcium concentration (as with changes in phosphate concentration), human vascular smooth muscle cells undergo phenotype change, with release of matrix vesicles, apoptosis, and vesicle calcification (22,23). Using an *ex vivo* culture model of human vessel rings, calcification was shown to be induced more potently by serum calcium than by serum phosphate at an equivalent CaxP. The effects of elevated calcium and phosphorus in inducing vascular calcification appear synergistic (21). Calcium and phosphate share common pathways in inducing osteogenic differentiation of vascular smooth muscle cells, increasing vesicle calcium loading, apoptosis, and extracellular matrix degradation, resulting in extracellular matrix mineralization (20). Notably, the degree of calcification was accentuated in vessel rings from CKD patients on dialysis compared with vessel rings from non-dialysis CKD patients (21), suggesting that uremia itself contributes to the process of vascular calcification.

RISK OR BENEFIT WITH CALCIUM SUPPLEMENTATION IN INDIVIDUALS WITH NORMAL KIDNEY FUNCTION

Current dietary reference intakes recommend a dietary calcium intake of 1000 – 1500 mg daily in healthy individuals, depending on age. The reference intakes were derived from calcium balance studies in various age groups and represent the minimum amount of calcium needed to optimize bone mass during peak bone growth in childhood, to promote bone consolidation in adulthood, and to minimize bone loss in old age (14). Calcium supplements with or without vitamin D have long been used to slow bone loss and reduce osteoporosis in adults, especially elderly individuals whose dietary intake may frequently be insufficient to meet the dietary reference intakes (24). However, some recent analyses failed to demonstrate a conclusive benefit of calcium supplementation in the prevention of non-vertebral and hip fractures in the general population (25–27). In addition, concerns have been raised about the cardiovascular safety of calcium supplementation. A large randomized clinical trial in healthy postmenopausal women reported an important association between calcium supplementation at a dose of 1000 mg daily and increased rates of myocardial infarction (28). In a recent meta-analysis that pooled seven studies, calcium supplementation was clearly associated with an increased risk of acute myocardial infarction and also a trend toward an increased risk of stroke, death, and sudden death (29). Those data constitute important evidence for a reconsideration of the potential adverse effects of calcium supplementation even in the healthy non-CKD population, especially elderly individuals.

IMPACT OF CALCIUM LOAD ON PATIENTS WITH CKD MINERAL BONE DISEASE

A study by Goodman and co-workers (30) observed a doubling of the coronary artery calcification score within a relatively short period of follow-up in a cohort of young dialysis patients. The progression of coronary artery calcification was associated not only with age, duration of dialysis, and serum phosphorus, but also with the dose of calcium-based phosphate binder. Guerin *et al.* (31) reported a similar significant relation for the dose of calcium-based binder and hypercalcemia with the severity of plain radiography-derived calcification score. Those data alerted, for the first time, the potential risk for increased vascular calcification in the dialysis population from long-term calcium use and calcium loading. Indeed, calcium loading is associated with progressive coronary artery and aortic calcification, especially when mineral metabolism is not well controlled (32).

Furthermore, in determinations of the risk of vascular calcification, bone activity appears to show a significant interaction with the dose of calcium-based phosphate binder. Calcium loading had a significantly more negative impact on aortic calcification and stiffening in patients with adynamic bone disease than in those with active bone. Independent of other factors, including the dose of calcium-based phosphate binders, adynamic bone was associated with more vascular stiffness (33), suggesting important crosstalk between bone and vasculature.

The relationship between dialysate calcium concentration and the risk of vascular calcification is poorly studied in both HD and PD. Some preliminary data suggest a positive relation between dialysate calcium concentration and vascular stiffening in HD and PD patients alike (34,35). Use of high-calcium (compared with low-calcium) dialysate has also been associated with significantly more arterial stiffening (34,35). However, randomized controlled trial data are needed to determine whether a dialysate calcium concentration of 2.5 mEq/L might be of benefit in lowering the calcium burden and reducing the progression of vascular calcification in PD patients.

In line with the observational data, a number of randomized controlled trials demonstrated that use of non-calcium-containing phosphate binder, namely sevelamer, was associated with significantly less progression of coronary artery and aortic calcification in dialysis patients. In the Treat-to-Goal study in HD patients, use of sevelamer was associated with phosphate control similar to that achieved with calcium-based phosphate binder, but with less hypercalcemia, lower levels of PTH, and significantly less progression in coronary artery and aortic calcification (3). In another 18-month study, Block and co-workers (7) reported a similar finding that progression of coronary calcification was more rapid with the use of calcium-based phosphate binder than with the non-calcium-containing sevelamer. The extended 5-year follow-up in the same cohort of HD patients observed a significant survival benefit associated with the use of non-calcium-containing sevelamer compared with calcium-based phosphate binder (36).

In another multicenter, randomized open-label parallel-design study, the DCOR trial, in which HD patients were randomized to receive either non-calcium-containing (sevelamer) or calcium-based phosphate binder. The primary endpoint was mortality; secondary endpoints included cardiovascular mortality and hospitalizations. During a follow-up period of more than 36 months, no significant differences were observed in the all-cause mortality rate, the cause-specific mortality rate, or hospitalizations. However, a significant age interaction with treatment effect was observed, in that

a significant survival benefit of sevelamer treatment was seen in the subgroup of patients more than 65 years of age (37). Those data suggest that, in older patients, treatment with sevelamer may be associated with lower overall cardiovascular-related mortality. However, the DCOR study had several limitations related to an extremely high drop-out rate of nearly 50%. Furthermore, the fact that subjects who discontinued early (within 90 days) were followed might raise criticisms of an introduction of bias because of cross-over to the alternate therapy. Thus, findings from DCOR can be regarded only as preliminary; further research is needed for confirmation.

Preliminary data suggest that other non-calcium-containing phosphate binders such as lanthanum carbonate may also slow the progression of vascular calcification in HD patients (38,39). In a rat model of uremia, serum phosphate levels were effectively controlled and aortic calcification was reduced during treatment with the non-calcium-containing phosphate binders sevelamer and magnesium carbonate compared with calcium-based phosphate binder (40). Taken together, the data consistently demonstrate that non-calcium-containing phosphate binders might slow the progression of vascular calcification in CKD. So far, no similar randomized controlled trials have been conducted in PD patients to examine differences in the progression of vascular calcification and other hard endpoints in relation to the use of calcium-based compared with non-calcium-containing phosphate binders. Nevertheless, it might be possible to take support from the studies in HD patients, whose results might be expected to be applicable to PD patients.

In pre-dialysis CKD patients, similar data suggest less progression in coronary artery calcification with non-calcium-containing sevelamer compared with calcium-based phosphate binder (41). In a recent randomized open-label trial (42), 212 CKD patients (stages 3 – 5) were randomized to receive either sevelamer or calcium carbonate for 36 months. Serum phosphorus was maintained between 2.7 mg/dL and 4.6 mg/dL for patients with stage 3 or 4 CKD and between 3.5 mg/dL and 5.5 mg/dL for patients with stage 5 CKD. Sevelamer-treated patients had a significantly lower adjusted risk of reaching the primary composite endpoint of death and dialysis start. In the subgroup of patients with a coronary artery calcification score higher than 0, regression of coronary artery calcification was demonstrated in significantly more of those being treated with sevelamer than of those being treated with calcium. Furthermore, the cumulative incidence of *de novo* onset of coronary artery calcification was significantly higher in the calcium-treated patients than in the sevelamer-treated patients (81.8% vs 12.8%).

Taken together, these randomized trial data in the CKD population add to the growing evidence linking increased development of new-onset vascular calcification and increased progression of vascular calcification with the use of calcium-based phosphate binder compared with non-calcium-containing binder. The data clearly raise concerns about the potential hazards of long-term calcium use and calcium overload in CKD patients. They also provide important evidence for avoiding excessive use of calcium in the CKD population, and especially in dialysis patients who have markedly impaired urinary calcium excretion and in nearly all anuric dialysis patients.

A recent prospective study randomized 148 CKD patients with normal or near-normal levels of serum phosphorus to receive calcium acetate, lanthanum carbonate, sevelamer carbonate, or placebo, and showed that treatment with phosphate binders significantly lowered serum and urinary phosphorus and attenuated the progression of secondary hyperparathyroidism, and yet promoted the progression of vascular calcification. Those findings raise some uncertainty about the safety and efficacy of phosphate binders in CKD. However, the study suffered from several major limitations—specifically, its very small sample size and single-center nature, and the fact that a variety of phosphate binders were grouped for comparison against placebo (43). The results are not generalizable at this stage and will require further investigation.

HOW MUCH ELEMENTAL CALCIUM CAN BE SAFELY PRESCRIBED IN PD PATIENTS?

So far, no data on calcium balance in PD patients have been developed. Thus, a safety limit for an elemental calcium dose in PD patients is currently uncertain. According to a recent calcium balance study conducted in late-stage 3 and 4 CKD patients and normal subjects, a high calcium diet (2000 mg elemental calcium daily) fed to CKD patients was clearly associated with a significantly more positive calcium balance than was seen with an 800-mg calcium diet fed to control subjects and CKD patients (44). Normal subjects and CKD patients being fed the 800-mg calcium diet were in slightly negative to neutral calcium balance. Another very recent placebo-controlled calcium balance study suggested that stage 3 and 4 CKD patients are already in neutral calcium balance when consuming a diet adequate in calcium (957 mg calcium daily). Taking 1500 mg additional calcium from calcium carbonate daily would result in positive calcium balance in stage 3 and 4 CKD subjects who are already consuming a diet adequate in calcium (45). Those findings have important implications, suggesting that the

daily elemental calcium dose given to late-stage 3 and 4 CKD patients as phosphate binder should likely be kept within 800 mg or even lower. Additional calcium loading in CKD patients may pose a risk of positive calcium balance. For dialysis patients, including those on PD, it is anticipated that the maximal daily elemental calcium dose should be even lower because of a further reduction in urinary calcium excretion; however, that hypothesis will require further confirmation. Whether the maximal daily elemental calcium dose may differ for PD patients with and without residual kidney function also warrants investigation. Before more clinical evidence is available, my personal opinion is that caution should be used in prescribing calcium-containing phosphate binders in CKD patients. The maximal additional elemental calcium given daily in the form of calcium-containing phosphate binder should be kept to no more than 800 mg to avoid calcium overload.

WHAT SHOULD BE THE CALCIUM CONTENT OF DIALYSATE USED BY PD PATIENTS?

Given that the clinical goal is to maintain neutral calcium balance, I believe that a dialysate calcium concentration of about 2.5 mEq/L (1.25 mmol/L) might help to avoid a positive or negative calcium balance (46). The Kidney Disease Improving Global Outcomes (KDIGO) 2007 CKD mineral bone disease guideline suggested the use of a dialysate calcium concentration between 2.5 mEq/L and 3.0 mEq/L (47). A recent kinetic modeling study in HD patients (48) indicated that a dialysate calcium concentration of less than 2.5 mEq/L would be required to prevent long-term calcium accumulation in a significant proportion of HD patients. According to the kinetic modeling study, more than 500 mg calcium might be transferred during a single dialysis session and that, on average, 76% of the calcium flux is from the miscible calcium pool rather than the plasma pool. Furthermore, kinetic modeling of intestinal calcium absorption shows strong dependence on the dose of vitamin D analogs and weaker dependence on calcium intake. In contrast, others have argued against dialysis using a calcium concentration of less than 2.5 mEq/L to create a negative calcium balance that allows room to use oral calcium-based phosphate binders and vitamin D analogs to create a positive calcium balance. Dialysis with a calcium concentration of less than 2.5 mEq/L might result in a reduction in plasma calcium concentration if the rapidly exchangeable calcium pool in bone cannot release calcium fast enough. Indeed, there have been reports that dialysate calcium concentrations of less than 2.5 mEq/L might be associated with an increased

incidence of hypotension, cardiovascular events, and death during dialysis. Furthermore, a dialysate calcium concentration of less than 2.5 mEq/L might stimulate PTH secretion and worsen secondary hyperparathyroidism (16). However, a previous study showed that, even though a dialysate calcium concentration of 2.5 mEq/L might be associated with a temporary increase in PTH level in PD patients, the PTH level was well maintained within the recommended level in long-term follow-up (49). There are also suggestions from a number of nonrandomized studies that progressive deterioration in arterial stiffening is less with the use of low-calcium (or, more properly termed, “physiologic” calcium) dialysate in PD and HD patients alike (34,35).

Table 1 summarizes the risks and benefits potentially associated with the use of low-calcium dialysate compared with standard calcium dialysate in PD patients. Given the current controversies, prospective randomized studies will be needed to determine the optimal dialysate calcium concentration and whether use of a dialysate calcium concentration of 2.5 mEq/L might confer benefit by lessening the progression of vascular calcification and arterial stiffening, and by improving outcomes in PD patients.

KDIGO RECOMMENDATION FOR CALCIUM USE AND CALCIFICATION DETECTION IN PD PATIENTS

For PD patients, KDIGO recommend restricting the dose of calcium-based phosphate binder or the dose of calcitriol or vitamin D analogs in the presence of persistent or recurrent hypercalcemia, arterial calcification, persistently low PTH, and adynamic bone disease in PD patients with hyperphosphatemia (47). Furthermore, for

the detection of calcification burden, commonly available imaging modalities such as lateral plain abdominal radiography for vascular calcification and echocardiography for valvular calcification are suggested. Patients with known vascular or valvular calcification are to be considered at the highest cardiovascular risk, and it is reasonable to use that information to guide the management of CKD mineral bone disease (47).

CONCLUSIONS

Recognition that calcium is an important inducer of vascular calcification in CKD is increasing. However, serum calcium is a poor reflection of total body calcium load. The use of calcium-based phosphate binder has been associated with more *de novo* vascular calcification and more rapid progression of vascular calcification in patients with CKD. In a number of studies, adverse clinical outcomes are more often associated with use of such binders than with the use of non-calcium-containing binders.

To avoid the risk of further perpetuating vascular calcification, calcium loading should be avoided in patients with persistent or recurrent hypercalcemia, arterial calcification, and persistently low PTH or adynamic bone disease. In addition, based on currently available evidence, caution should be taken with respect to the use of high-dose calcium in patients at risk of cardiovascular events or having baseline vascular or valvular calcification, and in elderly patients. I believe that the optimal dialysate calcium for PD patients is one that will maintain a neutral calcium balance; however, more studies are required to definitively answer that important question.

TABLE 1
Potential Benefits and Risks Associated with the Use of Low-Calcium and Standard- or High-Calcium Dialysate in Peritoneal Dialysis Patients

	Ca ⁺⁺ content of dialysate	
	Low (1.25 mmol/L or 2.5 mEq/L)	Standard or high (1.75 mmol/L or 3 mEq/L)
Calcium balance	Neutral or slightly negative	Positive
Serum calcium	↓	More hypercalcemia
Serum phosphate	Variable	Variable
Intact PTH	Short-term ↑	↓
Arterial properties	Reduces arterial stiffening	Increases arterial stiffening
Vascular calcification	?	?
Bone mass and histology	?	?
Mortality and CVEs	?	?

PTH = parathyroid hormone; CVEs = cardiovascular events.

DISCLOSURES

The author has received grants and speaker honoraria from Sanofi, Baxter and Fresenius Kabi, and has served as an advisory board member for Sanofi.

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