Do not be misguided by guidelines: the calcium × phosphate product can be a Trojan horse

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In recent years, it has become increasingly evident that the dramatic cardiovascular mortality of end-stage renal disease (ESRD) patients is connected with disturbances in calcium and phosphate homeostasis. While for decades the manifestations of secondary and tertiary hyperparathyroidism were largely regarded as particular forms of bone disease, it is now common sense that extrasosseous and especially cardiovascular calcifications may develop as a consequence of an increased extracellular availability of calcium and phosphate ions in this setting. This ‘paradigm shift’ with regard to renal osteodystrophy led to the publication of the K/DOQI guidelines in October 2003 which, in addition to defining target levels of intact parathyroid hormone (iPTH) in different stages of kidney failure, now recommend target levels for serum phosphate (P), serum calcium (Ca) and the Ca × P product [1]. While these guidelines represent a major step forward to improved cardiovascular prevention in ESRD patients, we wish to advise and explain in this article that some caution may be necessary in the interpretation of serum Ca and P levels.

Deranged Ca and P homeostasis as a cardiovascular risk factor

The one side of the coin

It has long become clear that traditional risk factors such as arterial hypertension or hypercholesterolaemia do not explain the excess cardiovascular mortality of patients on dialysis. The observation that low blood pressure and low serum levels of low-density lipoprotein (LDL)-cholesterol actually were associated with a worse outcome in the dialysis population led to the term ‘reverse epidemiology’ in an attempt to describe this seemingly paradoxical phenomenon [2]. While searching for the key determinants of survival in ESRD patients, several large registry studies indicated that hyperphosphatemia and an increased Ca × P product represent independent risk factors for the survival of dialysis patients [3–5]. In a recent study, >40,000 patients of the FMC North America Patient Statistical Profile system exhibited, after adjustment for multiple variables, a 25% increase of mortality at serum phosphate levels of 6.0–7.0 mg/dl and a 100% increase of risk when phosphate levels exceeded 9 mg/dl [5]. The predictive value of the Ca × P product was similar, while increased serum Ca levels were a weaker, though still significant risk predictor.

Hyperphosphataemia and an increased serum Ca × P product were also found to be associated with the presence or magnitude of vascular and valvular calcifications in some, but not in all studies. For example, Goodman et al. observed in young patients on dialysis a correlation of the degree of coronary artery calcifications with the degree of serum Ca × P product elevation and the oral Ca load (i.e. intake of Ca-containing phosphate binders), but not with serum Ca levels or hyperphosphataemia alone (borderline significance for the latter: \( P = 0.06 \)) [6]. Similar results were obtained by Wang et al., namely a significant correlation between valvular calcifications and Ca × P product in patients on peritoneal dialysis [7]. Since the magnitude of vascular and valvular calcifications is a strong predictor of mortality in dialysis patients (reviewed in [8]), preventive measures should certainly aim at such obvious progression factors.

The other side of the coin

The ‘Treat-to-Goal’ study may serve to demonstrate the potential difficulties in interpreting the effects of Ca load and the role of the Ca × P product measured in the context of uraemic cardiovascular calcifications. This study compared the impact of sevelamer vs Ca-containing phosphate binders (calcium acetate or carbonate) on the progression of coronary and aortic calcifications in dialysis patients [9]. Calcifications progressed in patients treated with Ca-containing phosphate binders, while sevelamer therapy was associated with a halt in progression. In the context of the present discussion, it is noteworthy that at the end of the study, both patient groups had similar serum calcium and phosphate levels, while Ca levels were marginally lower in the sevelamer group (2.3 vs 2.4 mmol/l) during the course of the study and associated with a lower incidence of hypercalcemic episodes (8 vs 17%) as compared with the Ca-containing phosphate binder group. Consequently, these laboratory data do not adequately reflect the fact that patients in the Ca-containing phosphate binder group ingested ~500 g more elemental Ca during 1 year than the sevelamer-treated patients. While it could be argued that most of this excess Ca was probably excreted in the stools, it appears reasonable to estimate that a significant proportion underwent intestinal absorption—facilitated by the concomitant vitamin D treatment in close to 60% of the patients included in the study.

Another clinical example to demonstrate the difficulty of relating a high Ca × P product to extrasosseous calcifications is calcific uraemic arteriolopathy (calciphylaxis), which is characterized by extensive calcifications of cutaneous arterioles leading to tissue ischaemia, ulceration and secondary superinfection. Affected patients usually exhibit severe calcifications of larger arteries as well. Whereas initial reports suggested a link between calciphylaxis and hyperparathyroidism, hypercalcaemia and hyperphosphataemia, it was increasingly reported that many cases occurred in the presence of apparently normal serum Ca, P and iPTH levels, and some even following parathyroidectomy. Interestingly, in some cases, an increased Ca load...
appears to have triggered or aggravated calciphylaxis, as beneficial effects of lowering the dialysate Ca and cessation of Ca carbonate therapy were reported [10]. In our own experience in eight calciphylaxis patients, mean serum Ca levels (2.4±0.2 mmol/l), serum P levels (1.79±0.25 mmol/l) and the Ca×P product (4.3±0.8 mmol²/l²) were also relatively low and only three of the patients had a Ca×P product above the K/DOQI target level [11].

Extraosseous calcification: why are we all ‘metastable’?

Recently, it became evident that vascular calcification is not just a passive precipitation process due to Ca and P levels exceeding their solubility product in the extracellular space. Indeed, even normal serum Ca and P concentrations in serum exceed their solubility product in an aqueous solution by many orders of magnitude (H₂O, 2.1×10⁻³⁴ vs extracellular body fluid: 1.8×10⁻⁶). Body temperature, pH and the ionic strength (especially Na⁺ and Cl⁻ ions) in the extracellular environment compensate in large part for that difference, but serum still remains a ‘metastable’ solution concerning Ca and P precipitation and requires calcification inhibitors to prevent extraosseous calcifications. This has become clear by experiments in genetically manipulated mice, which demonstrated that deletion of individual genes caused extensive soft tissue and/or vascular calcifications (reviewed in [12]) rendering these genes ‘operational’ calcification inhibitors including fetuin-A, matrix Gla protein, osteoprotegerin, ank and klotho. For the sake of clarity, we would like to restrict the term ‘inhibitor’ to referring to kinetic inhibition of the calcification reaction, which adequately characterizes the properties of fetuin-A. The absence of some of the other genes is associated with soft tissue calcification as well, but their products never participate in precipitation reactions as chemical or biochemical ‘inhibitors’ in the kinetic sense.

Deficiencies of kinetic calcification inhibitors may be additional and critical determinants of the initiation and progression of calcification processes in patients with chronic kidney disease. Our recent cross-sectional study showing that deficiency of the circulating calcification inhibitor fetuin-A was associated with impaired all-cause and cardiovascular survival in ESRD patients can be regarded as indirect in vivo evidence in humans that a lack of calcification inhibition may indeed impose a risk to patients on dialysis [13]. In addition, in the eight calciphylaxis patients mentioned above, in whom serum Ca and P levels were not significantly deranged, we consistently observed very low fetuin-A serum levels [11]. Deficiencies of calcification inhibitors such as fetuin-A may thus increase the risk of extraosseous calcification even at relatively normal Ca and P concentrations.

Lessons from uraemic calcification-prone mice

In order to gain a better understanding of the relationship between uraemia, mineral load and calcification inhibitor deficiencies, we recently performed an experimental study in fetuin-A-deficient (Ahsg⁻⁻) mice [14]. These studies were performed in mice carrying the C57BL/6 genetic background, because these animals require exogenous stimuli to develop extraosseous calcifications, in contrast to Ahsg⁻⁻ mice on a DBA/2 background, which calcify spontaneously [11]. The C57BL/6-Ahsg⁻⁻ mice allowed us to combine variably in vivo fetuin deficiency, renal insufficiency and high dietary phosphate load. A total of eight groups of mice were investigated. Wild-type mice with or without renal insufficiency (induced by 5/6 nephrectomy) and on either normal or high phosphate diet were compared with fetuin-A⁻⁻ mice exposed to the same interventions. We then evaluated the influence of these interventions on extraosseous calcifications and the Ca×P product amongst the groups.

In none of the groups with normal renal function and in none of the groups with normal phosphate intake did extraosseous calcifications develop, and in all of them Ca×P product remained normal. The key findings of this experimental study related to the two groups with renal insufficiency plus a high phosphate intake. If combined with a wild-type, i.e. fetuin-sufficient, background, no tissue calcifications (except for the kidneys) occurred, although the serum Ca×P product increased significantly (to 10.1±0.24 mmol²/l²). In contrast, if combined with a fetuin-A-deficient background, widespread calcifications of the myocardium, lungs and heart valves were detected, although the Ca×P product in serum remained normal (5.9±0.8 mmol²/l²).

What do the above observations imply? First, a high Ca×P product may be compensated, at least temporarily, by adequate calcification inhibitor levels that maintain the solubility of Ca and P ions in the serum. Secondly, and more importantly, in the presence of severe calcification inhibitor deficiencies, calcium and phosphate appear to precipitate and deposit in tissues so rapidly that a rise in serum Ca and P concentrations is no longer detectable. Consequently, in this situation, serum Ca and P may be a misleading source to assess the risk of calcification.

Is a high Ca×P product in serum always harmful?

The answer is probably: yes, at least in most of the cases and certainly in those in whom there is a persistent elevation of the Ca×P product. Experimentally, if a high Ca×P product is persisting for prolonged times in the presence of renal insufficiency, calcifications will develop even in association with normal fetuin-A levels [15]. Secondly, it is an old clinical observation that in dialysis patients with extremely elevated Ca×P
products, massive soft tissue calcifications spontaneously sometimes develop within a few days [8]. Thirdly, in dialysis patients, in addition to the registry studies cited above [3–5], Stevens and co-workers recently showed in >500 study subjects that a high Ca × P product predicted an impairment of cardiovascular survival especially if associated with either very low or very high iPTH serum levels [16]. These observations may point to another very important determinant when interpreting the role of an increased Ca × P product in dialysis patients, namely that of the ‘bone buffer’. In patients suffering from adynamic bone disease as well as in patients with severe high-turnover bone disease, the bone is unable to buffer available extracellular Ca and P ions, leading to an increased extraosseous Ca and P pool. Consistent with this observation, Braun et al. noted an inverse relationship between bone density and coronary calcification in dialysis patients [17].

Finally, when considering the Ca × P product, serum Ca and P levels should always be also judged separately. Both hyperphosphataemia and hypercalcaemia may directly induce biological processes such as osteogenic differentiation of vascular smooth muscle cells, immediately pathophysiologically relevant to progressive vascular calcification in addition to just increasing the Ca × P product [18–20]. However, while hyperphosphataemia regularly indicates a real extracellular phosphate overload, the interpretation of hypercalcaemia appears more complicated, since protein-binding, vitamin D-dependent intestinal absorption and the state of bone turnover all rapidly regulate the serum levels. Further, potentially dangerous serum calcium peaks cannot be reliably detected by occasional measurements. In accordance, registry data point much more clearly to the importance of hyperphosphataemia as an independent mortality risk predictor in dialysis patients than to a role of hypercalcaemia [5]. Measurements of ionized serum Ca levels may be at least a partially better way to overcome such difficulties, but will be hard to implement in clinical practice. Given the available evidence, the cumulative Ca load administered to patients should therefore be assessed in addition to measurements of serum Ca levels in order to better predict individual hypercalcaemia-associated cardiovascular risks [6]. The Ca load should be limited according to the recommendations of the current K/DOQI guidelines (i.e. maximum elemental Ca intake by Ca-based P binders, <1.5 g/day; maximum total elemental Ca intake, <2.0 g/day) [1].

**Conclusion**

Based on a large amount of experimental and clinical data, an increased Ca × P product must still be regarded as a predictor of cardiovascular risk and calcification in the majority of dialysis patients. However, in some uraemic individuals, a ‘guideline-conform’ normal Ca × P product may be misleading, since it may result from an impaired capacity of serum to keep Ca and P ions in solution, leading to a rapid deposition of Ca and P within extraosseous calcifications. Based on the above, we require refined tools to identify individuals at high risk for progressive cardiovascular tissues. Ideally, future treatment recommendations should be extended to incorporate measurements of fetuin-A, the major systemic calcification inhibitor. Since fetuin-A is regulated as a negative acute-phase reactant, elevated C-reactive protein levels might serve as a surrogate marker until fetuin-A measurements become more widely available. This more complete assessment hopefully will be able to avoid situations in which the Ca × P product becomes a true ‘Trojan horse’, i.e. a formally appropriate product suggesting a well-controlled situation, when in fact matters are out of control.

**Conflict of interest statement.** None declared.

**References**


