NEPHROLOGY

Nephrology **22**, Suppl. 2 (2017) 42–46

The role of calcium and non calcium-based phosphate binders in chronic kidney disease

GRAHAME J ELDER[1,2] and JACQUELINE CENTER[2,3]

[1]Department of Renal Medicine, Westmead Hospital, Westmead, [2]Osteoporosis and Bone Biology Division, Garvan Institute of Medical Research, Darlinghurst, [3]Department of Endocrinology, St Vincent's Hospital, Darlinghurst, Australia

KEY WORDS:
calcium, chronic kidney disease, lanthanum, mortality, phosphate binder, sevelamer.

Correspondence:
Professor Grahame Elder. Department of Renal Medicine, Westmead Hospital, Westmead 2145, Australia. Email: g.elder@garvan.org.au

doi: 10.1111/nep.13031

ABSTRACT:

Rising levels of serum phosphate occur late in the course of chronic kidney disease (CKD) and have been easy targets for nephrologists to treat using phosphate binding drugs, as well as fertile ground for the pharmaceutical industry, for meta-analysis and for the earnest pontifications of guideline writers. Unfortunately, the evidence does little to support this focus, which might be better applied to earlier, adaptive hormonal changes, and to phosphate balance rather than serum phosphate levels. Nevertheless, phosphate binders are ubiquitously prescribed to patients on dialysis, and often prescribed to patients with earlier stages of CKD; for which there is no evidence of benefit and some evidence that calcium-based binders (CBBs) and possibly non-CBBs may cause more harm than placebo. For patients on dialysis, observational studies suggest that phosphate binder use may reduce mortality. Meta-analyses report reduced hypercalcaemia for non-CBBs *versus* CBBs, and compared with CBBs sevelamer has been reported to significantly reduce vascular calcification progression and, in some but not all studies, overall mortality. However, limitations include study heterogeneity. For patients on dialysis, CBBs appear to have no advantages over the non-CBBs, apart from lower cost. In general, it seems prudent to avoid prescribing calcium-based drugs to patients who are pre-dialysis, and to use non-CBBs preferentially in CKD stage 5D. Current draft Kidney Disease Improving Global Outcomes guidelines suggest that CBB dosage be minimized in CKD stages 3 to 5D.

INTRODUCTION

Changes associated with the development of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) are often apparent by CKD stage 3 and are universal by the time patients require dialysis. Abnormal values of serum calcium and phosphate are the most commonly measured laboratory features of CKD-MBD, but only occur at later CKD stages. More fundamental and usually unmeasured changes occur early in CKD, and involve endocrine axes controlling mineral homeostasis, and natural inhibitors and potentiators of vascular calcification (VC). Early hormonal changes include a reduction in soluble-Klotho and an adaptive increase in the phosphaturic hormone fibroblast growth factor 23 (FGF23), followed by a reduction in 1,25-dihydroxyvitamin D. The later increase in serum parathyroid hormone (PTH) further reduces tubular reabsorption of phosphate and helps to maintain normal serum phosphate values.

Despite these hormonal adaptations to CKD, serum phosphate values eventually rise, and the solubility limit of calcium and phosphate may be exceeded, at which point crystal development (nucleation) occurs. These crystals have potential to transform and grow into amorphous calcium phosphate and hydroxyapatite that can precipitate, causing damage to blood vessels and other soft tissues. Counterbalancing this process, the serum protein Fetuin-A absorbs small (<1 nm diameter) calcium-phosphate crystals.[1] These molecules of Fetuin-A aggregate to form primary and then secondary calciprotein particles (CPPs), which are colloidal nanoparticles of Fetuin-A with a crystalline core. This process can be interpreted as a defence against potential vascular damage from calcium phosphate crystal deposition in CKD.[2] CPPs inhibit crystal growth, reduce spontaneous crystal precipitation, and can be phagocytosed via scavenger receptors in the liver.[3] However, there are caveats; Fetuin-A is a negative acute phase reactant, and levels fall in patients with CKD. In addition, CPPs are

themselves bioactive ligands that have the capacity to induce VC and renal tubular damage.[4]

Another potent defence against the development of VC involves the vitamin-K2 dependent matrix-Gla protein (MGP). MGP protects against crystal growth in matrix vesicles of vascular smooth muscle cells. The Gla residues of MGP bind strongly to insoluble calcium salts, and MGP also modulates the osteo-inductive properties of bone morphogenic protein-2.[5] However, in patients with CKD, dietary vitamin K2 intake is often low, and patients are frequently treated with warfarin; both of which lead to undercarboxylation and inactivation of MGP. Levels of *inactive* dephosphorylated-uncarboxylated-MGP are high in patients with CKD and increase with dialysis vintage.[6]

Serum phosphate targets

An ability to measure rising serum phosphate levels and the availability of medications to bind dietary phosphate has focussed management strategies on serum phosphate targets. With each progressive stage of CKD, risks of VC, cardiovascular disease (CVD) and mortality increase,[7] and observational data has consistently reported associations of CV risk to levels of serum phosphate[8] rather than to traditional CV risk factors.[9] In addition, laboratory data has established mechanisms by which phosphate can exacerbate hyperparathyroidism,[10,11] and both phosphate and calcium influence VC development.[12,13] Nevertheless, the current focus on *serum* phosphate values is possibly misguided. Instead, interventions that influence phosphate balance, or reduce the risk of early adaptive and homeostatic responses from becoming dysregulated, may have greater impacts on morbidity and mortality.[14,15] Although the consensus view has been that lower serum phosphate values are better, there have been concerns for some time at potential adverse effects of phosphate binders, particularly the toxicity of aluminium. Recent controversy regarding calcium-based phosphate binders (CBBs) has been intensified by reports of increased CV events and mortality associated with calcium supplementation of people with normal renal function.[16]

KDIGO CKD-MBD guidelines

The 2009 Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD guidelines[17] focussed on serum phosphate, and suggested that in CKD stages 3–5 therapy might target normal serum phosphate levels, with the target in CKD stage 5D being a serum phosphate that was 'towards normal' (graded level 2C). Whether calcium or non calcium-based phosphate binders (non-CBBs) were more appropriate to achieve these targets was debated. A systematic review of randomised controlled trials to 2009, including patients with CKD stages 3-5D, concluded that sevelamer was not statistically superior to CBBs for all-cause mortality (10 trials, 3079 patients; RR 0.73; 95 % CI, 0.46 to1.16), although hypercalcaemia occurred more often with CBBs than with sevelamer or lanthanum.[18] Reflecting this, the 2009 guidelines suggested restricting CBB dosage in the presence of hypercalcaemia (graded level 1B), VC and/or adynamic bone disease and/or persistently low serum PTH levels (all graded level 2C). The guidelines emphasized that when VC was identified, no interventions were established that affected hard clinical endpoints and there was no evidence that lowering serum calcium or phosphate to a specific target range lead to improved clinical outcomes. Nevertheless, the suggestion to restrict CBBs in some circumstances appeared justified because of the remarkable prevalence of vascular and valvular calcification in patients with CKD, with coronary artery calcification (CAC) reported in 20% of children on dialysis and 47–83% of adults with CKD stages 3–5, and the heightened risk of CVD among these patients.[17]

Updated analyses

Since 2009 the number of more expensive non-CBBs has increased, as have concerns for the sequelae of long-term positive calcium balance with calcium-based drugs.[19] Nevertheless, observational studies have reported improved patient survival with *any* oral phosphate binder except aluminium salts,[20] although this association is attenuated after adjustment for nutritional status.[21]

Relevant papers since 2009 include a meta-analysis of randomised controlled trials that included 4622 patients.[22] A 22% reduction in all-cause mortality was claimed for the non-CBBs sevelamer and lanthanum *versus* CBBs (relative risk [RR] 0·78, 95% CI 0·61–0·98), which was independent of serum phosphate reduction. Although this paper has not been withdrawn, the validity of some study inclusions and analyses has been questioned.[23] Another meta-analysis, that updated an earlier systematic review[18] to March 2015, compared sevelamer to CBBs, because later lanthanum publications had not included mortality data.[24] Patients treated with sevelamer had a 46% reduction in all-cause mortality (3799 patients; RR 0.54, 95% CI 0.32–0.93), lower total and LDL-cholesterol and a reduced risk of hypercalcaemia, with no significant between-group differences in phosphate lowering. Significant interstudy heterogeneity was predominantly attributable to two outliers; DCOR[25] and INDEPENDENT-HD.[26] Enrolees to these studies differed by age, dialysis duration, diabetes and loss to follow-up, and in INDEPENDENT-HD, baseline characteristics favoured patients allocated to sevelamer. That study reported a dramatic (and controversial) ninefold reduction in CV mortality while DCOR only demonstrated a survival benefit for those ≥65 years of age. Importantly, for predialysis patients, proof is lacking for an advantage of *any* phosphate binder over placebo, and in CKD stages 3b and 4, the combined outcome of therapy with sevelamer, lanthanum carbonate and calcium acetate has been reported to *increase* VC progression, when compared with placebo.[27]

In recent meta-analyses, Wang and colleagues focussed on changes in VC[28] and reported a significant decrease in the rate

of change of CAC and aortic calcification scores and a non-significant reduction in mortality for patients allocated to sevelamer *versus* CBBs. Sekercioglu and colleagues performed a conventional systematic review and a mixed network meta-analysis (NMA) for all-cause and cardiovascular mortality.[29] The seven-node NMA incorporated sevelamer *versus* calcium *versus* lanthanum *versus* iron *versus* phosphate restricted diet *versus* placebo *versus* sevelamer-plus-calcium-plus-magnesium. Both conventional meta-analysis and the NMA suggested higher mortality for CBBs *versus* sevelamer (NMA RR, 1.89 [95 % CI, 1.02 to 3.50]) based on moderate quality evidence (Fig. 1). With an estimated baseline annual mortality of 23 %, this relative effect would translate to an absolute mortality increase with CBBs of 43 per 1000 treated patients (95% CI 23–80). Confidence intervals for all other comparisons indicated no effect that reached statistical significance.

The most recent meta-analysis compared sevelamer and lanthanum to other predominantly calcium-based binders, and reported a non-significant 38% lower mortality for sevelamer (RR 0.62; 95% CI 0.35, 1.08) and a non-significant reduction with lanthanum (RR 0.73 95% CI 0.18–3.00).[30] Hypercalcaemic events occurred three to fourfold less often with non-CBBs and end-of-study calcium values (but not phosphate values) were associated with reduced mortality. Patients treated with CBBs had a greater increase in CAC scores, although this was not associated with mortality. Three included studies that compared sevelamer with iron-based binders for outcomes of serum calcium, phosphate, PTH and adverse events showed no significant differences between treatment groups. Although the newer iron and calcium–magnesium-based phosphate binders are likely to be safe, this cannot be verified without additional study.

Updated KDIGO guidelines

Current draft KDIGO guidelines (http://www.kdigo.org/clinical_practice_guidelines/CKD-MBD%20Update/KDIGO%20CKD-MBD%20Update_Public%20Review_Final.pdf: last accessed 22 January 2017) suggest that hypercalcaemia be avoided (evidence level 2C) and that doses of CBBs be restricted when used in adult patients with CKD stages 3a–5D (graded level 2B). Thus, the current draft guideline is broader than the 2009 guidelines, which only recommended restricted CBB doses in the presence of arterial calcification, adynamic bone disease or persistently low serum PTH levels.

DISCUSSION

General population data suggests caution should be used in prescribing calcium to patients when dietary calcium intake is adequate and in CKD stages 3–4, short-term balance studies indicate that prescribed calcium results in positive calcium balance and does not influence phosphate balance.[19] Patients with CKD stages 3–4 have a high risk of soft tissue calcification, and no phosphate binder has been shown to improve patient-level outcomes over placebo.[27] In the most recent meta-analyses, mortality and progression of VC were significantly lower or lower without statistical significance for sevelamer *versus* CBBs, and non-significantly lower for lanthanum.

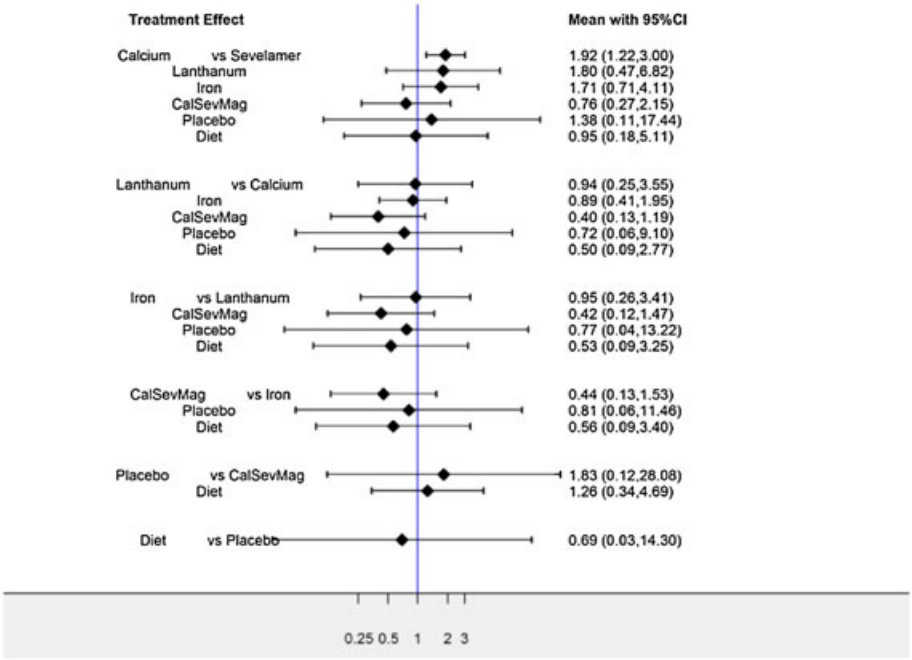

Fig. 1 Comparative effectiveness of phosphate binders in patients with chronic kidney disease; the predictive interval consistency plot from the consistency model of seven-node analysis; outcome: all-cause mortality without a reference standard.[29]

Although this suggests that avoidance of CBBs may improve survival, limitations of these meta-analyses include significant heterogeneity between studies. While pleiotropic effects ascribed to some non-CBBs may have contributed to improved patient outcomes, an avoidance of positive calcium balance is likely to be the principal factor involved. Positive calcium balance appears to influence the initiation or progression of CAC, and may reduce subendocardial perfusion, exacerbate conduction abnormalities and increase CV risk. When comparing risks for CBBs and non-CBBs, it is important to point out that CBBs are not superior to non-CBBs for any patient-level or biochemical outcome, and lower cost remains their only apparent advantage.[31]

A number of issues relating to CBB and non-CBB use require additional research. These include the following:

- Assessing the use of non-CBBs *versus* placebo in patients with pre-dialysis stages of CKD. The current IMPROVE-CKD study of lanthanum *versus* placebo[32] will assist in this discussion.
- Newer iron and magnesium-based phosphate binders should be assessed in CKD stages 3–5 and in CKD stage 5D for VC, CV and mortality endpoints. These studies should address possible advantages of using non-CBBs in patients who are new to dialysis, or who are over 65 years of age with a higher incidence of CV events.
- If funding for further large-scale RCTs is not available, studies should assess surrogate markers that are validated, or highly likely to increase mortality risk. These could include progression of VC, change in pulse wave velocity, and changes in laboratory markers such as FGF23 and the levels of CPPs.
- It would be useful to study the impact of interventions in 'at-risk patients' for outcomes including CV events and mortality. At-risk patients might be those with VC or known CVD, and interventions might include non-CBBs, including magnesium and iron-based drugs, drugs affecting MGP such as vitamin K2, and calcidiol, calcitriol or analogues and calcimimetics.
- Combined approaches using non-CBBs and drugs such as nicotinamide that reduce active phosphate absorption from the gastrointestinal tract are underway.[33] These strategies have greater potential to reduce positive phosphate balance.
- Studies are needed to evaluate dietary intervention in patients with CKD Stages 3–5D, and to identify the presence and degree of phosphate additives in foods and their impact on phosphate metabolism (as suggested by KDIGO).

CONCLUSION

Effective management of hyperphosphataemia in CKD requires a multifaceted approach, of which dietary phosphate restriction and phosphate binders remain important components. The common use of CBBs to achieve normal serum phosphate values in patients who are not on dialysis should be re-evaluated. Current data suggests this practise should be moderated or stopped. Current draft KDIGO CKD-MBD guidelines reflect these concerns, and the possibility that compared with non-CBBs, CBBs may increase risks for VC and mortality in patients with CKD stage 5D.

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