New therapeutic perspectives for vascular and valvular calcifications in chronic kidney disease

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Purpose of review
Vascular and valvular calcification are associated with cardiovascular morbidity and mortality in people with chronic kidney disease (CKD). Uncertainty exists regarding therapeutic strategies to attenuate calcification. This review outlines the pathophysiological mechanisms contributing to vascular and valvular calcification, considers the mechanisms of action of therapeutic interventions, and reports the latest outcomes from interventional studies.

Recent findings
Conventional therapies targeted at CKD-mineral and bone disorder (MBD) modulation have yielded conflicting or inconclusive results. Magnesium and vitamin K supplementation appear to offer attenuation of coronary artery calcification but inconsistent findings justify the need for further studies. Strategies targeting hydroxyapatite formation such as sodium thiosulphate and hexasodium fytate show promise and are worthy of further evaluation. The serum calcification propensity assay (T50) correlates with severity and progression; it holds promise as a potential future clinical tool for screening monitoring calcification risk.

Summary
Whilst knowledge of the pathophysiology of vascular calcification has grown and therapeutic approaches appear promising, as yet no medication has been approved to treat vascular or valvular calcification, or calciphylaxis.

Keywords
calciphylaxis, chronic kidney disease, randomised clinical trial, valvular calcification, vascular calcification

INTRODUCTION

The presence, and severity, of cardiovascular calcification is considered to be a driving factor for morbidity and mortality in people with chronic kidney disease (CKD) [1–3]. As CKD progresses the risk of development and progression of vascular and valvular calcification increases, characterised by low levels (and downregulation) of calcification inhibitors [4]. Vascular and valvular calcification are associated with increased cardiovascular morbidity and mortality [3]. CRIC (Chronic Renal Insufficiency Cohort) data associate a 1 standard deviation log increase in coronary artery calcification (CAC) score with a 40% increased risk of cardiovascular disease, 44% increased risk of myocardial infarction and a 39% increased risk of heart failure [3]. Cardiovascular disease is the leading cause of death in people with CKD and also increases the risk of progression to kidney failure [5,6]. Although it is plausible that interventions to modulate cardiovascular calcification improve survival, to our knowledge no data exists on whether regression of vascular calcification leads to reduced mortality. This review considers the pathophysiological mechanisms contributing to calcification in CKD and presents the findings from key recent papers.

PATHOPHYSIOLOGICAL MECHANISMS

In people with CKD vascular calcification manifests as intimal or medial calcification, calcification of heart valves, or calciphylaxis also known as calcific uremic arteriolopathy (CUA).

The phenotype and pathophysiological mechanisms of vascular calcification (in CKD) are

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KEY POINTS

- Therapeutic interventions including magnesium, vitamin K, sodium thiosulphate and hexasodium fytate show promise (in attenuating calcification) but all require further evaluation in sufficiently powered trials.
- Strict phosphate control may delay progression of coronary artery calcification in patients undergoing maintenance haemodialysis.
- Despite vascular and valvular calcification being associated with an increased risk of cardiovascular morbidity and mortality, currently no data exists on whether regression of vascular calcification leads to reduced mortality.
- To date, no medication has been approved to treat vascular or valvular calcification, or calciphylaxis.
- The serum calcification propensity assay (T50) holds promise as a potential future clinical tool for screening monitoring calcification risk.

described in detail by Dai *et al.* [7]. Far from being a passive process, calcification is an active, chronic and multifaceted process, involving cell-mediated responses as well as deposition of calcium and phosphate complexes in the vasculature. All spurred on by an imbalance between calcification inhibitors and inducers; in part attributed to the down regulation of naturally forming calcification inhibitors such as matrix-Gla protein, pyrophosphate and fetuin-A. As CKD progresses mineral metabolism becomes disturbed and inflammatory processes are triggered; all of which contribute to vascular calcification. The result is a pro-calcific environment which promotes osteogenesis and loss of mineralisation inhibitors, leading to the deposition of an extracellular matrix, creating a nucleation site for hydroxyapatite crystal formation. There has been recent interest in the role of calciprotein particles (CPP) in the pathophysiology of vascular calcification. CPP are circulating complexes of calcium, phosphate and other proteins which develop from primary CPP into secondary CPP which contain hydroxyapatite. Higher levels of circulating CPP have been identified in patients with vascular calcification and CKD [8].

Medial and intimal calcification

Medial calcification is characteristic of arteriosclerosis and considered a consequence of upregulation of osteogenic regulatory genes inducing osteogenic differentiation of mesenchymal cells which results in matrix mineralization, bone, and cartilage formation [7,9]. Intimal layer calcification presents as atherosclerosis largely resulting from the transformation of vascular smooth muscle cells as a result of calcification within advanced atherosclerotic plaques in the vicinity of lipid accumulations [10].

Heart valve calcification

Valvular calcification, less common than vascular calcification, presents distinct physiological and pharmacological differences despite shared risks [11,12]. The pathophysiology of valvular calcification is well described in a comprehensive review by Carrai *et al.* [13]. Although valvular calcification can affect all heart valves, epidemiological data most commonly report aortic valve calcification (AVC) and mitral valve calcification (MVC). AVC being the most frequent cardiovascular disease after coronary artery disease and arterial hypertension [14,15].

Calciphylaxis

Calciphylaxis, also referred to as calcific uremic arteriolopathy (CUA), occurs in the skin as a result of arteriolar calcification of subcutaneous fat and dermis. Whilst rare, calciphylaxis is devastating and has been associated with mortality rates of approximately 50% within a year of diagnosis [16,17]. Although most common in people receiving dialysis, calciphylaxis is also seen in those with CKD in the predialysis stage, including people with an eGFR >60 ml/min/1.73 m^2.[16] Cases have been seen in people with normal kidney function, and warfarin use has been identified as a risk factor [18–20].

THERAPEUTIC INTERVENTIONS

In 2022, the first systematic review of prospective clinical trials on vascular calcification interventions in patients with CKD was published; 77 heterogeneous trials (63 randomised) were included with 6898 participants [21▪▪]. Interventions, including phosphate binders, dialysis manipulation, vitamin D, magnesium, SNF472, bisphosphonates, and statins were assessed noncalcium binders showed conflicting results, while magnesium and sodium thiosulfate (STS), in hemodialysis (HD) participants, showed promise in attenuation of vascular calcification progression. This review underscores the need for further research into effective interventions for vascular calcification in CKD.

Chronic kidney disease-mineral and bone disorder modulation

Hyperphosphatemia, hypercalcaemia and hyperparathyroidism are associated with vascular calcification

however optimal serum levels in CKD patients remain unknown.

Phosphate and calcium

An open-label, multicentre trial, randomised 160 maintenance haemodialysis patients to sucroferric oxyhydroxide or lanthanum carbonate with the aim of reducing serum phosphate to two target levels; strict (3.5–4.5 mg/dl) versus standard (5.0–6.0 mg/dl) for 12 months [22]. No significant difference was seen in the primary end point (percentage change in CAC scores) between the sucroferric oxyhydroxide and lanthanum carbonate groups ($P = 0.481$). However, the strict phosphate group had significantly lower percentage change in CAC scores than the standard phosphate group ($P = 0.006$) suggesting strict phosphate control may delay the progression of CAC.

The LANDMARK Trial randomised 2309 haemodialysis patients (in Japan) to lanthanum carbonate or calcium carbonate (median follow up 3.16 years); there was no significant difference in all-cause mortality or cardiovascular events between treatment groups. Increased cardiovascular death and hyperparathyroidim was reported in the Lanthanum group [23]. A subsidiary study of the LANDMARK trial (129 patients completed) found no between group difference in CAC scores after two years [24]. Limitations in the LANDMARK study mean equipoise continues regarding the calcium versus noncalcium based binder debate; it was a single country study, in a population known to have comparatively low cardiovascular mortality. In addition, possible confounding factors included an increased use of active vitamin D in the lanthanum group and an increased use of sevelamer carbonate in the calcium-based binder group.

Previous, small RCTs (<200 participants), have associated calcium based binders with an increased risk of vascular calcification. Data from calcium balance studies suggest a positive calcium balance occurs with calcium intakes of 1500–2000 mg per day, although what happens to this surplus of calcium (whether it is deposited in the vasculature) remains unclear [25,26]. Evidence relating to calcium based binders and overall calcium intake is reported in detail in a recent European consensus statement titled 'Recommended calcium intake in adults and children with chronic kidney disease'. The publication recommends a total daily calcium intake of 800–1000 mg (upper recommendation 1500 mg) in adults with CKD. Less than 800 mg calcium per day is considered to pose a risk to bone health and more than 1500 mg per day is associated with an increased risk of vascular calcification and mortality [27].

The ideal dialysate calcium concentration remains unproven; current KDIGO guidelines recommend 1.25 or 1.5 mmol/l but acknowledge the paucity of evidence to discriminate between them [28]. OK *et al*. randomised 425 participants with parathyroid hormone (PTH) levels ≤300 pg/ml to received dialysate calcium of 1.25 or 1.75 mmol/l; however, only 284 completed the 48-month study, impacting statistical power [29]. Lower calcium dialysate suggested a trend toward attenuating coronary artery calcification (CAC) progression and improving low bone turnover. The lower calcium dialysate group had higher PTH levels and increased vitamin D usage, both of which may have an indirect role in vascular calcification [30]. The authors concluded 1.25 mmol/l dialysate calcium is preferential in patients receiving HD with moderate secondary hyperparathyroidism (PTH ≤ 300pg/ml) but questions remain regarding applicability to broader HD populations and whether 1.25 mmol/l is superior to 1.5 mmol/l.

PTH and FGF-23

To our knowledge there are no recent trials investigating the impact of PTH targets on vascular calcification. This perhaps warrants further investigation; results from the ADVANCE study indicated the calcimimetic, cinacalcet, attenuates the progression of vascular and valvular calcification in haemodialysis patients with moderate to severe secondary hyperparathyroidism [31]. An upcoming Japanese RCT (trial registry number jRCTs041220126) plans to investigate the impact of early intervention with calcimimetics on CAC in people with secondary hyperparathyroidism [32]. We are not aware of any trials investigating the effect of Fibroblast growth factor 23 on vascular or valvular calcification.

Vitamin K

Vitamin K, existing in two primary forms – K1 (phylloquinone) and K2 (menaquinone), is essential for carboxylation of matrix GLA protein (MGP), an inhibitor of vascular calcification [33]. Vitamin K deficiency, prevalent in CKD, is associated with increased vascular calcification and mortality risk [34]. Deficiency is exacerbated by the use of vitamin K antagonists (VKAs) and may be compounded by dietary restrictions and reduced bioavailability caused by phosphate binders [35]. Consequently, there has been growing interest in correcting vitamin K deficiency to potentially mitigate vascular calcification. There have been a number of intervention trials; the two largest are discussed.

The Valkyrie Study was the first to report the effects of vitamin K status on vascular calcification progression in the chronic HD population [36]. The

study recruited 132 HD patients with atrial fibrillation who were randomised into groups receiving VKAs, rivaroxaban or rivaroxaban plus high dose vitamin K2; 77 patients completed the 18-month follow up. Vitamin K status improved, but did not normalise with VKA removal and vitamin K2 supplementation. There were no differences in coronary artery ($P = 0.73$), thoracic aorta ($P = 0.79$), and cardiac valve ($P = 0.81$) calcium scores, or pulse wave velocity ($P = 0.56$) between treatment arms [36]. The study was extended with patients continuing treatment for a further $\geq$18 months [37]. The primary end point was a composite of fatal and nonfatal cardiovascular events and occurred at a rate of 63.8 per 100 person years in the VKA arm compared with 26.2 and 21.4 per 100 person years in the rivaroxaban and rivaroxaban plus vitamin K2 arms, respectively. There was no difference in death (from any cause) or risk of stroke between treatment groups but symptomatic limb ischemia occurred significantly more frequently, and the risk of major bleeding complications was greater in the VKA group [37].

The Trevasc-HDK study, a larger open label RCT investigated the effects of vitamin K2 supplementation on CAC in people receiving maintenance HD [38▪]. The study randomised 178 HD patients to oral vitamin K2 supplementation (360 mg thrice weekly) or placebo for 18 months; 138 completed follow up and were included in the analysis. Despite effectively reducing plasma levels of uncarboxylated MGP in the vitamin K2 group, there were no significant differences in CAC or aortic valve calcification ($P = 0.45$ and $P = 0.62$, respectively), cfPWV ($P = 0.9$) or clinical outcomes including death [hazard ratio (HR) 0.51, 95% confidence interval (CI) 0.17–1.59, $P = 0.264$].

Randomized controlled trial (RCT) studies investigating the effects of vitamin K1 supplementation have been smaller than the two aforementioned K2 studies and have either shown no differences in CAC progression, or a nonsignificant difference pointing towards vitamin K1 attenuating CAC progression [39,40]. Whilst both vitamin K1 and K2 supplementation appear safe there is currently insufficient evidence to justify routine vitamin K supplementation in these patient populations.

Sodium thiosulphate

Since 2010, sodium thiosulphate (STS) has commonly been used (off licence) for calciphylaxis treatment. STS is considered to reduce calcification by chelating calcium and forming a more soluble compound, calcium thiosulphate, and acting as an antioxidant to improve endothelial function [41]. RCTs investigating STS for the treatment of calciphylaxis have been attempted but none have completed recruitment or reported any results; existing evidence remains limited to data from cohort studies and case reports.

The investigation of effect of STS treatment on vascular calcification is reported in RCTs. A systematic review and meta-analysis published in 2023 assessed the impact of STS treatment on vascular calcification in people undergoing HD; 6 studies were included (5 RCTs) providing 305 participants [42▪]. STS dosage varied from 12.5 to 25 g (per session), administered 2–3 times weekly for intervention periods ranging from 3 to 12 months. There was no statistically significant difference in the calcium volume scores between the groups treated with STS and the control groups. However, a reduced progression of Agatston score was observed in both the coronary and iliac artery regions compared to the control group. Specifically, in the coronary artery group comprising 107 patients, the mean difference was -241.27 (95% CI: −421.50 to −61.03), and in the iliac artery group consisting of 55 patients, the mean difference was −382 (95% CI: −751.07 to −12.93). Gastrointestinal side effects were reported by one in four participants, but no prolonged adverse effects were noted after the completion of STS therapy. STS did not affect bone mineral density (BMD). Results suggest STS may attenuate vascular calcification in patients receiving maintenance HD although larger studies are needed for confirmation.

The same research group published a systematic review and meta-analysis of STS treatment in calciphylaxis [43▪]. Studies were included if their participants were adults diagnosed with CKD and calciphylaxis and if there was a comparator (inclusion of patients treated with and without intravenous STS). No between group difference was found in skin lesion improvement, risk of death or overall survival using time-to-event data [43▪] Further study remains warranted given no RCT data exists. The International BEAT-Calci platform study (Trial registration ID NCT05018221) offers the opportunity to investigate which interventions (including STS) are most favourable in the management of calciphylaxis.

Magnesium

Hypomagnesia predicts cardiovascular and noncardiovascular mortality in people receiving haemodialysis [44]. Magnesium prevents vascular calcification in rats and, in vitro is shown to prevent secondary CPP development [45,46]. It is pivotal in the calcification pathway, downregulating promoters of osteogenic differentiation and upregulating calcification inhibitors in vascular smooth muscle cells [47]. Magnesium also directly inhibits

hydroxyapatite crystal formation, suggesting it may delay progression of vascular calcification [48].

Sakaguchi *et al.* conducted an RCT on 96 people with CKD, investigating magnesium oxide's effect on CAC; the study was terminated early due to efficacy [49]. Two-year follow-up data showed increased serum magnesium in the treatment group, with less CAC progression compared to controls (median; 11.3% vs. 39.5%, $P < 0.001$). The MAGiCAL-CKD trial randomised 148 participants (with CKD) to slow release magnesium hydroxide or placebo for 52 weeks; 135 people completed the trial [50]. Magnesium levels significantly increased in the magnesium group and remained unchanged in the placebo group. The CAC score increased by 31.2% (95% CI, 18.5% to 45.2%, $P < 0.001$) in the placebo group and 33.3% (95% CI, 19.9% to 48.2%, $P < 0.001$) in the magnesium group. The difference between group CAC at week 52 (once adjusted for baseline CAC score, age and diabetes) was only 0.9% (95% CI, −10.2% to 13.4%, $P = 0.438$). Slow recruitment impacted their ability to meet the recruitment target of 250 and therefore, despite being the largest reported RCT to date, the study may not have been statistically powered to detect between group differences in CAC scores.

One way to influence magnesium in the HD population is to alter the magnesium content of dialysate. The Dial-Mag trial (Trial registration ID NCT04079582) is a pragmatic, two-arm, parallel-group, cluster-randomised, open-label, multicentre, trial embedded into routine care across Canada. Centres are randomised to either 0.75 mmol/l or ≤0.5 mmol/l dialysate magnesium concentrations. The primary outcome is cardiovascular-related hospitalization and all-cause mortality. It is anticipated that over 25 000 participants will be included and outcomes are expected from 2028.

It remains unclear whether interventions using magnesium supplementation effect outcomes in CKD; larger, multicentre RCTs are warranted to evaluate the effect of magnesium on hard cardiovascular end points.

HEXASODIUM FYTATE

Hexasodium fytate is a derivative of myo-inoitol hexaphosphate (phytate), which has been developed for the treatment of vascular calcification. Ex-vivo studies indicated that intravenously administered hexasodium fytate was able to bind to hydroxyapatite and prevent further crystal formation. The compound has been evaluated as a novel treatment for vascular calcification in HD populations. The CaLIPSO study enrolled 274 adult patients undergoing maintenance HD with baseline coronary artery calcium (CAC) Agatston scores between 100 and 3500 units [51]. Participants were randomised to receive thrice-weekly infusions of hexasodium fytate at doses of 300 mg, 600 mg, or placebo over 52 weeks. Multidetector computed tomography imaging was conducted at baseline and week 52 to assess CAC volume scores (CACvs). SNF472 significantly reduced CACvs progression compared to placebo, with an 11% reduction in the modified intention-to-treat analysis and an 8% reduction in the per-protocol analysis ($P = 0.016$ and $P < 0.001$, respectively). Subgroup analyses showed consistent treatment effects across all subgroups, with no significant differences in treatment response observed based on patient characteristics. The CaLIPSO study also investigated the effects of hexasodium fytate on total-hip and femoral-neck BMD, using dual-energy X-ray absorptiometry (DXA) scans as part of a prespecified safety evaluation. There were comparable changes from baseline between the combined treatment groups and the placebo but there was greater reduction in BMD in the 600 mg group. The clinical significance of these observations remain uncertain and further studies are needed to evaluate the long-term effects on bone health and fracture risk in this population [52].

The compound was also evaluated in a Phase 2 open label trial in patients with calciphylaxis [53]. This small study of 14 patients reported improvements in pain score, wound healing and health-related quality of life over a 12-week treatment period. A subsequent phase 3 study, CALCIPHYX has completed recruitment and results are awaited [54].

FUTURE BIOMARKERS

Calcification propensity (T50)

The serum calcification propensity assay (T50) developed in 2012 measures the half-transformation time from primary CPP to secondary CPP, reflecting the ability of serum to resist hydroxyapatite crystal formation (the final step in vascular calcification) [55]. A systematic review of 57 publications on serum calcification propensity has recently been published [56]. T50 was not associated with the prevalence and incidence of CAC in CKD, but was associated with CAC severity and progression [57]. The CRIC group reported a one-standard-deviation reduction in T50 was associated with a 28% (95% CI 7–53%) greater risk of CAC progression [57].

T50 is associated with cardiovascular events and all-cause mortality across CKD stages, including

dialysis and transplant recipients. It is also associated with cardiovascular mortality in dialysis and kidney transplant populations [56]. Interventions such as adjusting dialysate composition from acetate-acidified to citrate-acidified, and increasing magnesium dialysate concentration led to a higher T50 [50,58,59]. Oral administration of magnesium (in CKD patients), phosphate binders, etelcalcetide and spironolactone (in hemodialysis patients) was associated with higher T50 levels [56]. While currently limited to research, T50 holds promise as a clinical tool for screening calcification propensity in CKD and monitoring changes in calcification risk over time.

CONCLUSION

Conventional therapies targeted at CKD-MBD modulation have yielded conflicting or inconclusive results. Magnesium and vitamin K supplementation appear to offer attenuation of CAC but findings are not consistent and further studies are warranted. Strategies that target hydroxyapatite formation such as sodium thiosulphate and hexasodium fytate are worthy of further evaluation. Despite our improved understanding of the pathophysiology of vascular calcification, no medication has been approved to treat vascular or valvular calcification, or calciphylaxis.

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