Phosphate in early chronic kidney disease: Associations with clinical outcomes and a target to reduce cardiovascular risk

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KEY WORDS: bone metabolism, cardiovascular risk, chronic kidney disease (CKD), phosphate.

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SUMMARY AT A GLANCE
This review highlights the association between mineral and bone disorders in chronic kidney disease and the extensive burden of cardiovascular disease. A systematic review on the current evidence linking phosphate metabolism and cardiovascular disease, left ventricular hypertrophy, vascular calcification and arterial compliance is presented.

ABSTRACT:
There is an intimate association between mineral and bone disorders in chronic kidney disease (CKD) and the extensive burden of cardiovascular disease (CVD) in this population. High phosphate levels in CKD have been associated with increased all-cause mortality and cardiovascular morbidity and mortality. Observational studies have also shown a consistent relationship between serum phosphate in the normal range and all-cause and cardiovascular mortality, left ventricular hypertrophy (LVH) and decline in renal function. Furthermore, fibroblast growth factor-23 (FGF-23), a phosphaturic hormone, increases very early in the course of CKD and is strongly associated with death and CVD, including LVH and vascular calcification. Few studies have addressed outcomes using interventions to reduce serum phosphate in a randomized controlled fashion; however, strategies to address cardiovascular risk in early CKD are imperative and phosphate is a potential therapeutic target. This review outlines the epidemiological and experimental evidence highlighting the relationship between excess phosphate and adverse outcomes, and discusses clinical studies required to address this problem.

MINERAL METABOLISM IN CKD

Patients with CKD have a disruption in systemic calcium and phosphate homeostasis. As a result of renal damage, progressively higher levels of FGF-23 (released from bone) are required to increase phosphate excretion from residual nephrons. Together with diminished conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (1,25(OH)₂D), these changes affect bone turnover, gastrointestinal absorption of calcium and phosphate, and parathyroid function, with consequences for bone integrity.
and mineral metabolism. Hypersecretion of parathyroid hormone (PTH) is initially appropriate, because it increases calcium and phosphate release from bone and enhances urinary phosphate excretion by reducing its proximal re-absorption. Consequently, PTH and FGF-23 maintain normal calcium and phosphate levels in early stages of CKD, but progressive renal damage results in hyperphosphataemia, increasing FGF-23 levels (up to 1000 times the normal range) and the development of secondary hyperparathyroidism (SHPT) in many patients.

Current management of disordered mineral homeostasis in CKD involves the control of hyperphosphataemia by dietary modification or phosphate binders and the use of calcium, calciferol or active vitamin D compounds to maintain normal PTH levels in CKD stages 1–5. Calcimimetic agents may be added when patients are dialysis dependent and if PTH levels are high or patients have hypercalcaemia thought because of SHPT. Unfortunately, difficulties with phosphate control increase when patients reach CKD stage 5, or patients commence dialysis, and despite dietary restriction and phosphate binder therapy, patients often have poor phosphate control unless they advance to longer dialysis sessions.

**CVD AND MINERAL METABOLISM IN CKD**

Patients with CKD have an excessive burden of CVD and related mortality. Age-standardised rates of all-cause mortality and cardiovascular (CV) events are 5–20 times higher in people with CKD as compared with those with normal kidney function and a collaborative meta-analysis of general population cohorts, consisting of more than 1.2 million people, showed that an estimated glomerular filtration rate (eGFR) of <60 mL/min per 1.73 m² was an independent predictor of all-cause and CV mortality. The risk of CV morbidity and mortality progressively worsened with decline in eGFR. Traditional CVD risk factors (hypertension, older age, hyperlipidaemia and diabetes) are highly prevalent in patients with CKD although they do not explain the heightened CV risk in stages 4–5D. For these patients, ‘non-traditional’ factors, particularly relating to abnormal mineral metabolism, are associated with the increased risk of CVD (Fig. 1).

Recognizing the intimate associations between CVD and abnormalities of bone and mineral metabolism, the term ‘chronic kidney disease-mineral and bone disorder’ (CKD-MBD) was applied, encompassing the disturbances of mineral metabolism, renal bone disease and vascular calcification, together with patient-level outcomes of fracture, CVD and mortality in patients with CKD. Hyperphosphataemia, a key component of CKD-MBD, is strongly associated with adverse outcomes in CKD patients, including CVD, vascular calcification and increased arterial stiffness (Table 1).

The relationship between phosphate and CVD may be explained by several putative mechanisms. The most plausible mechanism concerns the accelerated progression of vascular calcification, which is conceptually linked to the positive phosphate balance seen in CKD (as well as excessive doses of calcium-based phosphate binders). This putative link among hyperphosphataemia, vascular calcification and adverse outcomes has been used to justify the need to better control serum phosphate (and to minimize oral intake of calcium) in patients undergoing dialysis. Hyperphosphataemia may also directly affect vascular health by increasing reactive oxygen species, thereby causing oxidative damage and endothelial dysfunction. Indirectly, hyperphosphataemia increases levels of PTH and FGF-23, both of which have been suggested to have direct pathogenic CV effects, and inhibition of 1,25(OH)₂D synthesis, which is associated with vascular calcification and myocardial disease. Finally, hyperphosphataemia might also identify patients who are less likely to comply with dietary restrictions (and other aspects of their care), which could confer a predisposition to CVD.

**PHOSPHATE AND MORTALITY**

Epidemiological studies show that serum phosphate levels are linearly and independently associated with all-cause and CV mortality in patients on dialysis and pre-dialysis patients with CKD. Block et al. highlighted the association between hyperphosphataemia and mortality in a cross-sectional study of haemodialysis patients using the United States Renal Data System and reported a 17.5% increased population attributable risk from abnormalities of mineral metabolism, largely as a result of high phosphate. Multiple studies have subsequently also reported that high serum phosphate levels are independently predictive of CVD and death in the dialysis population. One study of 3490 non-dialysis CKD patients (veterans in the US) reported that serum phosphate...
Risk, phosphate levels and increased post-transplant mortality show associations of higher pre- and post-transplant serum (CI) 1.12–1.25)). Studies of kidney transplant recipients also show associations of higher pre- and post-transplant serum phosphate levels and increased post-transplant mortality risk, 25,26,43 although this is not a consistent finding with other studies reporting no association. 27,44

Several observational studies have even shown associations between higher serum phosphate levels within the normal reference range and CV events and mortality in people with normal kidney function. 1,13 Tonelli et al. reported a significant association between serum phosphate and all-cause death from a post-hoc analysis of 4127 participants with prior myocardial infarction from the Cholesterol And Recurrent Events (CARE) study, with a hazard ratio (HR) per 1 mg/dL phosphate of 1.27 (95% CI 1.02–1.58). 1

### PHOSPHATE AND CVD

Serum phosphate fulfills many criteria to be defined as a risk factor for CVD. 23,45 Phosphate levels correlate with atherosclerosis in both animal models and humans with advanced CKD, but this relationship also exists among individuals with normal kidney function. A community-based cohort of 3015 healthy young adults from the prospective Coronary Artery

### Table 1

Cross-sectional and longitudinal studies reporting associations between phosphate and cardiovascular disease or clinical outcomes (a) in the general population with normal kidney function and (b) in CKD patients (not on dialysis).

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Outcome measure</th>
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<tbody>
<tr>
<td>(a)</td>
<td></td>
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<tr>
<td>Tonelli 2005 1</td>
<td>4127 patients with prior MI (CARE study)</td>
<td>All-cause mortality: HR 1.27, 95% CI 1.02–1.58 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Dhingra 2007 2</td>
<td>1000 participants (Framingham offspring study)</td>
<td>CV event: HR 1.31, 95% CI 1.05–1.63 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Dhingra 2010 3</td>
<td>3300 participants</td>
<td>Heart failure: OR 1.74, 95% CI 1.17–2.59 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Foley 2009 4</td>
<td>4055 participants</td>
<td>LVH: OR 1.27, 95% CI 1.09–1.47 per 1-SD increase in P</td>
</tr>
<tr>
<td>Foley 2009 5</td>
<td>3015 participants (CARDIA study)</td>
<td>Coronary artery calcification: OR 1.17, 95% CI 1.01–1.34 for 0.5 mg/dL increase in P</td>
</tr>
<tr>
<td>O'Seaghdha 2011 6</td>
<td>2269 participants (Framingham Heart Study)</td>
<td>Doubling of serum Cr: OR 21.4, 95% CI 1.07–4.28 for highest P category (referent group 2.5–3.49 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>13,372 participants (NHANES III)</td>
<td>ESKD: HR 1.27, 95% CI 1.03–1.53 for P ≥ 4 mg/dL compared with P &lt; 4 mg/dL</td>
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<tr>
<td>(b)</td>
<td></td>
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<tr>
<td>Kestenbaum 2005 7</td>
<td>3490 CKD patients (median CrCl 45)</td>
<td>All-cause mortality: HR 1.23, 95% CI 1.12–1.36 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Eddington 2010 8</td>
<td>1203 CKD patients (mean eGFR 32)</td>
<td>All-cause mortality: HR 1.26, 95% CI 1.11–1.5 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Ix 2009 9</td>
<td>1370 (440 with CKD), no CVD (MESA study)</td>
<td>CV mortality: HR 1.50, 95% CI 1.2–2.0 per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Adeney 2009 10</td>
<td>439 CKD patients (MESA study) (mean eGFR 51)</td>
<td>Arterial stiffness: RR 4.6, 95% CI 1.6–13.2 for P &gt; 4 mg/dL compared with P &lt; 3 mg/dL</td>
</tr>
<tr>
<td>Chue 2012 11</td>
<td>208 CKD stage 2–4 patients (mean eGFR 50)</td>
<td>Vascular calcification: RR 1.21 for coronary, 1.33 for thoracic, 1.25 for aortic valve and 1.62 for mitral valve calcification per 1 mg/dL increase in P</td>
</tr>
<tr>
<td>Chue 2011 12</td>
<td>225 CKD stage 2–4 patients (mean eGFR 43)</td>
<td>LVMI: Greater with P &gt; 1.20 mmol/L than P &lt; 1.20 mmol/L (61 vs. 55 g/m2; P = 0.03)</td>
</tr>
<tr>
<td>Landray 2010 13</td>
<td>382 CKD stage 3–5 patients (CRIB study) (mean eGFR 22)</td>
<td>Renal impairment: 0.34 mL/min per month decline in GFR per 1 mmol/L increase in P</td>
</tr>
<tr>
<td>Connolly 2009 14</td>
<td>379 transplant recipients (mean eGFR 53)</td>
<td>ESKD: RR 1.46, 95% CI 1.21–1.77 per 1-SD increase in P</td>
</tr>
<tr>
<td>Moore 2011 15</td>
<td>270 transplant recipients (mean eGFR 40)</td>
<td>All-cause mortality: HR 3.4, 95% CI 1.7–6.6 for P &gt; 1.22 mmol/L (referent range P &lt; 0.92 mmol/L)</td>
</tr>
<tr>
<td>Schaeffner 2007 16</td>
<td>733 transplant recipients (mean eGFR 56)</td>
<td>All-cause mortality: HR 1.21, 95% CI 1.09–1.35 per 0.1 mmol/L increase in P</td>
</tr>
<tr>
<td>Benavente 2012 17</td>
<td>325 transplant recipients (mean eGFR 46)</td>
<td>Graft loss: HR 2.15, 95% CI 1.36–3.40 for highest P quintile (≥1.23 mmol/L) compared with lowest (&lt;0.84 mmol/L)</td>
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</table>

**eGFR expressed in mL/min per 1.73 m²; CrCl expressed in mL/min. CARDIA, Coro- nary Artery Risk Development in Young Adults; CARE, Cholesterol And Recurrent Events; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CRIB, Chronic Renal Impairment in Birmingham; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; NHANES III, the Third National Health and Nutrition Examination Survey; OR, odds ratio; P, phosphate; RR, relative risk; SD, standard deviation.**
Risk Development in Young Adults (CARDIA) study, with 15-year follow-up data, showed baseline phosphate levels were associated with coronary artery calcium assessed by computed tomography (10% of participants experienced significant coronary calcification). A link between phosphate and atheroma was also suggested by a retrospective study of 376 patients undergoing routine coronary angiography, which reported an association between serum phosphate levels and the presence of coronary artery occlusive disease and severe stenosis. The Framingham Offspring Study, which enrolled participants in the general population with no CKD, reported an increased CVD risk (heart attack, stroke, angina, peripheral vascular disease or heart failure) in a continuous fashion with an adjusted HR of 1.31 per 1 mg/dL increase in phosphate (95% CI 1.05–1.63). In the post-hoc analysis of the CARE study, Tonelli et al. also reported a graded relationship, with higher levels of serum phosphate associated with increased risk of new heart failure, myocardial infarction, and the composite of coronary death or non-fatal myocardial infarction.

PHOSPHATE AND LVH

Left ventricular hypertrophy (LVH) is extremely common in CKD patients with a prevalence that increases with declining kidney function and varies from 30–47% in pre-dialysis CKD patients to 41–74% in patients on dialysis. LVH is associated with increased CV events in CKD patients. A recent study of 208 non-diabetic patients with CKD stages 2–4 (mean serum phosphate 1.1 mmol/L) reported an association between increasing serum phosphate and left ventricular mass index (LVMI) measured by cardiac magnetic resonance.

Higher levels of serum phosphate within the normal range are also reported to be associated with increased risk of LVH. One prospective study of 4055 young adults with normal renal function reported an association between phosphate and LVH measured by echocardiography, with odds ratio (OR) per standard deviation (SD) of 1.27 (95% CI 1.09–1.47). Dhingra et al. also reported an association between echocardiographic LVH and phosphate in a prospective study of 3300 participants free of heart failure and CKD. Each 1 mg/dL increment in serum phosphate was associated with a 1.74-fold risk of heart failure (95% CI 1.17–2.59).

PHOSPHATE AND ARTERIAL COMPLIANCE

Arterial stiffness comprises non-occlusive arterial remodelling and represents the functional disturbance of predominantly medial vascular calcification (as opposed to atherosclerotic intimal plaque), leading to reduced compliance of large conductance arteries. As with increased vascular calcification, patients with CKD have greater arterial stiffness than the general population, resulting in the principal consequences of LVH and altered coronary perfusion. Arterial stiffness is an independent predictor of all-cause and CV mortality.

The association between higher serum phosphate and arterial compliance has been reported in several studies. Phosphate is positively associated with pulse wave velocity (PWV), a measure of arterial compliance, and several small studies have shown beneficial effects of non-calcium based phosphate binders with reduction of arterial stiffness in patients on dialysis. One study compared 13 patients on haemodialysis being administered the phosphate binder sevelamer with 13 matched controls and after 11-month follow up reported PWV decreased by 0.83 ± 2.3 m/s in those given sevelamer while it increased by 0.93 ± 1.88 m/s in controls (P = 0.04). Another study of individuals without clinical CVD showed that serum phosphate >1.29 mmol/L was associated with a RR 4.6 (95% CI 1.6–13.2) for a high ankle brachial index compared with participants with phosphate <0.97 mmol/L. Higher phosphate levels in this study were also associated with greater pulse pressure and worse large and small artery elasticity in unadjusted models.

PHOSPHATE AND VASCULAR CALCIFICATION

Vascular calcification is a common complication of CKD and is associated with increased CV and all-cause mortality in both dialysis and pre-dialysis CKD patients. Vascular calcification in CKD predominantly involves the medial arterial layer (whereas atherosclerotic calcification involves the intimal layer), and medial calcification induces arterial stiffness leading to end-organ damage. In vivo studies showed that high extracellular phosphate levels induce vascular smooth muscle cells (VSMC) to transdifferentiate into osteoblast-like cells, which then undergo calcification. Hyperphosphataemia appears to also be involved in a number of other mechanisms that trigger and advance the progression of vascular calcification, including mineralization of VSMC matrix through sodium-dependent phosphate co-transporters, induction of VSMC apoptosis, inhibition of monocyte/macrophage differentiation into osteoclast-like cells, elevation of FGF-23 levels and alteration in klotho expression. Reducing phosphate, for example with phosphate binders, reverses osteoblastic differentiation of vascular cells and vascular calcification.

Many cross-sectional clinical studies have reported an association between serum phosphate and vascular calcification in patients who are pre-dialysis or undergoing dialysis. However, this is not a consistent finding, and calcification is more commonly related to increasing age and dialysis duration. Vascular calcification has intimate interactions with bone mineralization and, as a result of imbalances in mineral metabolism, is associated with both enhanced bone resorption and low or adynamic bone.
Phosphate and cardiovascular risk

PHOSPHATE AND PROGRESSION OF RENAL IMPAIRMENT

Elevations in serum phosphate have been associated with structural changes and renal decline in animal models. In human observational studies, hyperphosphataemia is associated with progression of established CKD and the development of ESKD (end-stage kidney disease) and studies of renal transplant recipients describe an association between serum phosphate levels and structural changes and renal decline in animal models.

One recent study also determined an association between serum phosphate within the normal range and vascular and valvular calcification. This study of 439 young and middle-aged participants from the Multi-Ethnic Study of Atherosclerosis (MESA) with both normal renal function and CKD, and no known CVD, reported that after adjustment for eGFR, each 1 mg/dL increase in serum phosphate concentration was significantly associated with a 21%, 33%, 25% and 62% greater prevalence of coronary artery, thoracic, aortic valve and mitral valve calcification respectively. The CARDIA study, described earlier, also showed that phosphate levels within the reference range were significantly associated with coronary artery calcification.

FGF-23 IN HEALTH AND CKD

FGF-23 is the most potent hormone regulating phosphate homeostasis. In health, FGF-23 is secreted by osteocytes and osteoblasts in response to dietary phosphate intake. FGF-23 suppresses the expression of the type Ia sodium phosphate co-transporter, thus regulating phosphate reabsorption in the renal proximal tubule. FGF-23 also decreases serum concentration of 1,25(OH)2D by inhibiting 1α-hydroxylase and stimulating 24-hydroxylase. Both of these actions of FGF-23 are independent of PTH. Thus, serum phosphate levels remain normal regardless of dietary variability of phosphate intake. FGF-23 binding requires the co-receptor klotho, deficiency of which can cause hyperphosphataemia and heterotopic mineralization.

Serum FGF-23 levels increase with even modest decreases in GFR (60–89 mL/min per 1.73 m2) as a homeostatic response to restore serum phosphate levels and may be the earliest detected serum abnormalities of CKD-MBD. This rise occurs before changes in levels of PTH or 1,25(OH)2D and may contribute to the development of SHPT. As a result of FGF-23 regulation, serum phosphate levels are predominantly maintained within the normal range throughout advancing stages of CKD despite progressive impairment of kidney function. In patients receiving dialysis, FGF-23 levels increase up to 1000-fold that of healthy control levels. At this point FGF-23 is ineffective as a phosphatonin.

FGF-23 AND CLINICAL OUTCOMES IN CKD

Emerging evidence from observational studies in the CKD population suggests a strong association between serum FGF-23 levels and clinically important outcomes, including all-cause mortality and CV events (Table 2). Like serum phosphate, high FGF-23 levels are associated with increased vascular function and calcification. FGF-23 may play a role as it is an independent biomarker of vascular calcification in patients with various CKD stages including early stages.

In one cross-sectional study of 162 patients with CKD stages 3 and 4, increased FGF-23 was associated with increased LVMI (11% increase per 1-SD increase in FGF-23, 95% CI 3–18%) and risk of LVH (OR per 1-SD increase in FGF-23 2.3, 95% CI 1.2–4.2). A study of 3879 CKD patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) also reported an association between FGF-23 and ESKD (HR 1.3 per 1-SD increase in FGF-23, 95% CI 1.04–1.6) for

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participants with eGFR between 30 and 44 mL/min per 1.73 m², as well as an association with increased mortality.⁹¹

Another study of CKD patients also reported an association between higher FGF-23 levels and progression of renal disease.⁹²

Although the associations between LVH and both phosphate and FGF-23 have been reported in observational studies, one recent experimental study showed a direct effect of pathological hypertrophy of isolated rat cardiomyocytes via FGF receptor-dependent activation.⁹⁶ Faul et al. also showed LVH development with intra-myocardial or intravenous injection of FGF-23 in wild-type mice and subsequent treatment with an FGF-receptor blocker attenuated LVH, with no change in blood pressure.⁹⁶ These experiments have thus unveiled a causal role of FGF-23 in the pathogenesis of LVH.

The association between FGF-23 and CV surrogate markers described in Table 2 strongly suggests that the effect of FGF-23 on mortality in CKD is most likely mediated through a CV pathway. A recent clinical study of 200 CKD patients, which highlighted phosphate metabolism associated with vascular and cardiomyocyte dysfunction, also reported that FGF-23 levels were independently associated with the cardiac biomarker troponin-T.⁹³

**RANDOMIZED CONTROLLED TRIALS OF PHOSPHATE BINDERS AND CLINICAL OUTCOMES**

Despite the large body of observational evidence for an association between phosphate and adverse outcomes, very few randomized controlled trials (RCT) have assessed whether therapy with phosphate binders affects significant clinical outcomes. One prospective cohort study of 10 044 incident haemodialysis patients, the Accelerated Mortality of Renal Replacement study, compared all-cause mortality at 1 year among patients either treated or not treated with phosphate binders during the first 90 days of dialysis.⁹⁷ On multivariate analysis, as well as in propensity score-match comparison, this study showed that treatment with phosphate binders was independently associated with decreased mortality compared with no treatment. Another cohort study in non-dialysis patients also showed an association with phosphate binder administration and survival.⁹⁸ This single-centre study of 1188 men with moderate to advanced CKD reported that binders were associated with significantly lower all-cause mortality (HR 0.61 (95% CI 0.45–0.81)). Neither of these studies however were RCT and therefore may have significant potential confounders.

### Table 2 Cross-sectional and longitudinal studies reporting associations between FGF-23 and cardiovascular disease or clinical outcomes in CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Outcome measure</th>
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</thead>
<tbody>
<tr>
<td>Gutiérrez 2008⁷⁷</td>
<td>400 incident ESKD patients on HD</td>
<td>All-cause mortality: Adjusted HR 1.8, 95% CI 1.4–2.4 per unit ↑ in natural log-transformed FGF-23</td>
</tr>
<tr>
<td>Jean 2009⁹²</td>
<td>219 prevalent HD patients</td>
<td>All-cause mortality: HR 2.5, 95% CI 1.3–5 in the highest quartile of FGF-23, reference – the lowest quartile</td>
</tr>
<tr>
<td>Kendrick 2011⁸⁴</td>
<td>1133 patients with pre-dialysis CKD (mean eGFR 18)</td>
<td>All-cause mortality: HR 1.8, 95% CI 1.3–2.4 in 3rd quartile; 2.3, 95% CI 1.7–3.2 in 4th quartile of FGF-23, reference – the lowest quartile</td>
</tr>
<tr>
<td>Seiler 2010⁹⁵</td>
<td>149 pre-dialysis CKD patients (mean eGFR 36)</td>
<td>CV event: Adjusted HR 1.6, 95% CI 1.1–2.3 per unit ↑ in natural log-transformed FGF-23</td>
</tr>
<tr>
<td>Gutiérrez 2009⁹⁶</td>
<td>162 patients with CKD stage 3 and 4</td>
<td>LVMI: 11% ↑ in LVMI per 1-SD ↑ in log-transformed FGF-23, 95% CI 3–18%, P = 0.01</td>
</tr>
<tr>
<td>Mirza 2009⁹⁷</td>
<td>164 CKD patients (mean eGFR 54)</td>
<td>LVH: OR 2.3, 95% CI 1.2–4.2 per 1-SD ↑ in log-transformed FGF-23</td>
</tr>
<tr>
<td>Mirza 2009⁹⁸</td>
<td>27 CKD patients (mean eGFR 52)</td>
<td>LVH: OR 1.8, 95% CI 1.2–2.6 per 1-SD ↑ in log-transformed FGF-23</td>
</tr>
<tr>
<td>Mirza 2009⁹⁸</td>
<td>208 CKD patients (mean eGFR 53)</td>
<td>High atherosclerosis score: OR 5.6, 95% CI 2.8–11.5 in the highest quartile of FGF-23, reference – the lowest quartile</td>
</tr>
<tr>
<td>Kanbay 2010⁹⁶</td>
<td>21 CKD patients with Cockroft-Gault GFR &lt;60</td>
<td>Coronary artery disease: Positive correlation between FGF-23 and Gensini lesion severity score (β = 0.74, P = 0.001)</td>
</tr>
<tr>
<td>Yilmaz 2010⁹⁵</td>
<td>183 CKD patients (mean eGFR 33)</td>
<td>Flow mediated vasodilatation: Positive correlation with FGF-23 (β = −0.30, P &lt; 0.001)</td>
</tr>
<tr>
<td>Isakova 2011⁹¹</td>
<td>3879 CKD patients (mean eGFR 42.8)</td>
<td>All-cause mortality: HR 3.0, 95% CI 1.8–5.1 in the highest quartile of log-transformed FGF-23, reference – the lowest quartile</td>
</tr>
<tr>
<td>Fliser 2007⁹²</td>
<td>177 CKD patients</td>
<td>Progression of renal impairment: HR 1.11, 95% CI 1.08–1.15 per 10 μg/mL ↑ in FGF-23. Mean FGF-23 levels were 35 ± 28 versus 69 ± 70 pg/mL in non-progressors (n = 112) versus progressors (n = 65) after median 53 months</td>
</tr>
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</table>

eGFR expressed in mL/min per 1.73 m². CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; FGF-23, fibroblast growth factor-23; HD, haemodialysis; HR, hazard ratio; LVH, left ventricular hypertrophy; LVMI, left ventricular mass index; OR, odds ratio; SD, standard deviation.
Several RCT have assessed the effect of phosphate binders on vascular calcification (coronary and aortic) in dialysis and pre-dialysis CKD patients. These studies however have all involved comparisons between calcium-based binders and non-calcium based binders, with most suggesting that non-calcium based binders contribute less to the development of vascular calcification. A meta-analysis of eight RCT (collective sample size 2873 participants), however, showed no benefit of using non-calcium over calcium-based phosphate binders on mortality (RR 0.68, 95% CI 0.41–1.11) or in CV events (two RCT, over calcium-based phosphate binders on mortality (RR 0.85, 95% CI 0.35–2.03).

The only RCT to directly address the impact of phosphate binders on survival as a primary end-point was also a comparison between calcium-based binders and sevelamer. The Dialysis Clinical Outcomes Revisited (DCOR) study was a multicentre, randomized, open-label trial comparing the different binders on all-cause and cause-specific mortality. Unfortunately despite 2103 patients initially randomized to treatment, only 1068 patients completed the study in which the primary end-point was negative. The Renagel in New Dialysis (RIND) study, an 18-month RCT comparing sevelamer versus calcium-based binders, also addressed mortality as pre-specified secondary end-point. In 127 new haemodialysis patients baseline coronary artery calcification score was a predictor of all-cause mortality, and patients randomized to sevelamer had improved survival. A more recent RCT in 212 Italian CKD patients (CKD stages 3–4) reported that those randomized to sevelamer versus calcium carbonate also had lower all-cause mortality, although the event rate was higher than would be expected for a pre-dialysis population. Current clinical guidelines vary on when and how aggressively to manage biochemical parameters of CKD-MBD, and intervention to address phosphate levels frequently does not occur until compensatory mechanisms (increased PTH and FGF-23) fail; generally when the GFR drops below 20 mL/min. The international KIDIGO (Kidney Disease: Improving Global Outcomes), the National Kidney Foundation K/DOQI (Kidney Disease Outcomes Quality Initiative) and CARI (Caring for Australasians with Renal Impairment) guidelines recommend monitoring and maintaining serum phosphate within the normal range with dietary restrictions and binders, initiated in CKD stages 3 and 4 as required, whereas the recent NICE guidelines suggest phosphate should only be monitored in CKD stages 4 and 5. No guideline suggests intervention should commence before the development of hyperphosphataemia or SHPT.

**EFFECT OF PHOSPHATE-LOWERING THERAPY ON FGF-23 IN CKD**

Most evidence linking phosphate and FGF-23 with vascular calcification, arterial stiffness and LVH comes from cross-sectional studies. It is not known whether FGF-23 is just a biomarker or plays a causative role. A limited number of poor quality RCT have studied the effect of phosphate-lowering therapy on FGF-23 (Table 3). However, the results of these RCT are severely limited by small sample size, short follow up, single-centre design, lack of adequate blinding and unclear allocation concealment.

### DIETARY INTERVENTIONS

In theory, a low phosphate diet for individuals with CKD stages 3 and 4, even in the setting of normal serum phosphate levels, may prevent the development of hyperphosphataemia, SHPT or elevations in FGF-23. Dietary restriction of phosphate however is difficult because of the high phosphate content of the typical Western diet and the absence of phosphate on food labelling. In the Western diet, phosphate is ingested primarily as protein and dairy products, as well as preservatives and additives. Several studies have described regulation of FGF-23 concentrations by dietary phosphate intake. A recent cross-sectional study of 1261 participants of the Health Professionals Follow-up Study, most with preserved kidney function, reported that higher phosphate intake was associated with higher FGF-23, which the authors concluded may contribute to the link between FGF-23 and CVD. In community-based participants without CVD (MESA cohort, n = 4494), each 20% greater dietary phosphate intake was associated with an estimated 1.1 g greater LVMI (95% CI 0.5–1.6). However, analysis of the NHANES III data did not show any association between high dietary phosphate intake and FGF-23.

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Table 3 Randomized controlled trials evaluating the effect of phosphate binders on FGF-23

<table>
<thead>
<tr>
<th>RCT</th>
<th>Participants</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isakova 2011</td>
<td>16 CKD patients (mean eGFR 54)</td>
<td>No effect of lanthanum or placebo on serum FGF-23 levels after 2 weeks</td>
</tr>
<tr>
<td>Oliveira 2010</td>
<td>40 CKD patients (mean CrCl 35)</td>
<td>Sevelamer, but not calcium acetate, reduced the serum FGF-23 levels from 107 pg/mL to 54 pg/mL, P &lt; 0.05 after 6 weeks</td>
</tr>
<tr>
<td>Gonzalez-Parra 2011</td>
<td>18 CKD patients (mean CrCl 42)</td>
<td>Lanthanum reduced FGF-23 levels, median per cent change from baseline –21.8% (interquartile range –4.5%, –30%), P &lt; 0.05 after 4 weeks</td>
</tr>
<tr>
<td>Yilmaz 2012</td>
<td>100 CKD patients (mean eGFR 23)</td>
<td>Sevelamer, but not calcium acetate, increased FMD from 6.1% to 7.1%, P &lt; 0.001 after 8 weeks. Changes were associated with reduction in FGF-23 levels –27.1% (–33.2%, –8.8%) with sevelamer</td>
</tr>
</tbody>
</table>
and mortality in 1105 CKD patients (HR 0.98 per 100 mg/dL increase (95% CI 0.93–1.03)).

Few clinical trials have looked at lowering dietary phosphate absorption in participants with normal phosphate levels to prevent the complications of CKD-MBD. An experimental study using a rat model of CKD-MBD reported animals with reduced GFR fed a grain-based diet, compared with standard synthetic casein animal diets, had lower serum phosphate, urinary phosphate excretion and serum levels of FGF-23. The same investigators conducted a cross-over trial in nine patients (mean eGFR 32 mL/min) and compared vegetarian and meat diets. They reported decreased urine phosphate excretion, lower serum phosphate and decreased FGF-23 levels with a vegetarian diet after 1 week. This study also highlighted that higher dietary phosphate intake was associated with increased FGF-23.

Dietary phosphate counselling for CKD patients can be complex and patients are often confused by the multitude of recommendations. Simplifying the approach by asking them to eat more grains and less meat and less pre-prepared or packaged foods may potentially lead to increased dietary adherence and subsequent improved phosphate homeostasis. One study educating ESKD patients on dialysis to avoid phosphate-containing food additives resulted in modest improvements in hyperphosphataemia. However, further dietary studies are required in CKD patients as additives are increasingly being added to processed and fast foods and the effect of dietary modifications on serum phosphate levels in early CKD is unclear.

**FUTURE CLINICAL TRIALS**

Despite the rapidly growing body of literature suggesting phosphate dysregulation is associated with increased morbidity and mortality in CKD, what remains to be established is whether early intervention to prevent phosphate retention can impact on the development of the adverse clinical outcomes associated with CKD-MBD. To date, there has not been an adequately powered, placebo-controlled, multicentre RCT evaluating the effects of phosphate-lowering therapy on reduction of CVD burden in CKD patients.

One of the first questions to help design an RCT addressing phosphate homeostasis in early CKD would be to determine the trigger for intervention or the abnormality that one should aim to correct. Hyperphosphataemia occurs late in CKD, at which point arterial or ventricular function may be impaired, so the approach should probably be to intervene before this occurs. Rising phosphate levels within the normal range maybe both a trigger for intervention and its target, but phosphate levels undergo circadian and dietary variation and fasting levels may also be uninformative, so this approach may not prove valuable. An alternative trigger or target may be rising levels of PTH or, earlier than that, FGF-23 as shown in the CRIC study. FGF-23 is appealing because levels correlate to mortality at the initiation of dialysis and PTH is less appealing because few data confirm its association to morbidity or mortality, except at extreme levels.

Even having decided upon a trigger for intervention, it is unclear how to evaluate efficacy, except by using data on morbidity, mortality and adverse events that would require large numbers of trial participants. Some surrogate outcomes proposed include changes to levels of urinary phosphate excretion, FGF-23, PTH or PWV and other markers of arterial stiffness or calcification. However, the interpretation of biochemical responses should incorporate the effects of phosphate lowering on intestinal phosphate transport as well as on signalling between the intestine and kidney! Low phosphate diets (or the use of phosphate binders) may result in a reduction of phosphate excretion (assessed as TmPO4/GFR) because of intestine to kidney feedback, so that ‘phosphate flux’ remains unchanged and FGF-23 levels may not shift. However, when levels do rise, FGF-23 is reported to reduce intestinal phosphate uptake, in keeping with its role to maintain phosphate homeostasis. Additionally, lowering dietary phosphate may upregulate intestinal sodium-phosphate co-transporters to increase phosphate absorption. All of these factors complicate study design.

Despite these difficulties, there are currently several ongoing placebo-controlled trials assessing the impact of phosphate-lowering in CKD using different phosphate binders. These studies have used CKD stage (eGFR) as the trigger for intervention, rather than levels of phosphate, PTH or FGF-23; although FGF-23 levels are almost uniformly elevated by CKD 3–4. Biochemical indices, surrogate CV markers such as arterial stiffness, vascular calcification and LVH, and progression of CKD are being evaluated and these data will provide valuable information on the early pathogenesis of CKD-MBD. The Phosphate Normalization in CKD Trial (PNT) in the USA has studied the effect of calcium-based binders, sevelamer and lanthanum on arterial stiffness and coronary artery calcification among 90 participants with CKD (eGFR 20–45 mL/min per 1.73 m²) in an open-label study. The Chronic Renal Impairment in Birmingham (CRIB-PHOS) Study from the UK is studying the effect of sevelamer on LVMI and arterial stiffness among 120 participants with CKD stage 3 in a double-blind RCT. Another larger study, the IMPROVE-CKD (IMpact of Phosphate Reduction On Vascular End-points in CKD) study, has just commenced recruiting in Australia and New Zealand and will be enrolling 488 participants in a placebo-controlled RCT evaluating the impact of lanthanum carbonate on arterial stiffness and aortic calcification over 24 months in CKD stages 3b and 4.

**CONCLUSION**

There is a plethora of emerging observational evidence showing a strong association of phosphate and FGF-23 with increased all-cause mortality and CVD burden. Moreover,
FGF-23 is emerging as the most potent phosphate-regulating hormone and, like phosphate, could be a promising novel therapeutic target in the CKD-MBD pathway. However, it is not known whether elevated levels of phosphate and FGF-23 are mere biomarkers of CVD or mortality or play a causative role in the pathogenesis. The epidemiological data are bolstered by many laboratory studies that show a role of phosphate to induce vascular calcification and endothelial dysfunction. These data make a compelling argument for testing whether phosphate reduction strategies can mitigate renal and non-renal risk in patients with CKD, although there is limited evidence on the effects of phosphate-lowering therapy on clinical outcomes and study design is complicated by the multiple mechanisms that are aimed to maintain phosphate homeostasis when GFR is normal or minimally compromised. Large randomized controlled trials are urgently needed to prove or disprove the benefits, risks and potential economic impact of introducing phosphate-lowering therapy before patients develop ESKD.

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