Review Article

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

NIGEL D TOUSSAINT,[1,2,3] EUGENIE PEDAGOGOS,[1] SVEN-JEAN TAN,[1,3] SUNIL V BADVE,[4] CARMEL M HAWLEY,[4] VLADO PERKOVIC[5] and GRAHAME J ELDER[6,7]

[1]The Royal Melbourne Hospital, Parkville, Victoria, [2]Western Health, Footscray, Victoria, [3]Department of Medicine, The University of Melbourne, Melbourne, Victoria, [4]Princess Alexandra Hospital, Brisbane, Queensland, [5]George Institute for Global Health, Camperdown, New South Wales, [6]Westmead Hospital, Westmead, New South Wales, and [7]Osteoporosis and Bone Biology Program, Garvan Institute for Medical Research, Sydney, New South Wales, Australia

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.

High serum phosphate is a major risk factor for death, cardiovascular disease (CVD) and vascular calcification among patients with and without chronic kidney disease (CKD).[1–5] Even serum phosphate levels within the normal range are associated with increased mortality, CVD and renal disease progression.[1–3,6] Mechanisms by which increased phosphate leads to adverse outcomes are not fully understood, but evidence suggests a direct effect of phosphate on vascular calcification and endothelial dysfunction as well as modulation of key hormones such as fibroblast growth factor-23 (FGF-23). There is increasing observational data linking phosphate excess and high FGF-23 with CVD and mortality, and therapies that effectively reduce serum phosphate concentration are of tremendous contemporary interest as putative therapeutic agents to reduce the CVD burden in CKD.

However, no clinical trials have been conducted to establish a causal relationship between phosphate and adverse outcomes.

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.[7] Consequently, PTH and FGF-23 maintain normal calcium and phosphate levels in early stages of CKD,[8] 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.[9]

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.[10,11] 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[12] 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 m^2 was an independent predictor of all-cause and CV mortality.[13] The risk of CV morbidity and mortality progressively worsen 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).[14,15]

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.[16] 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).[29,30]
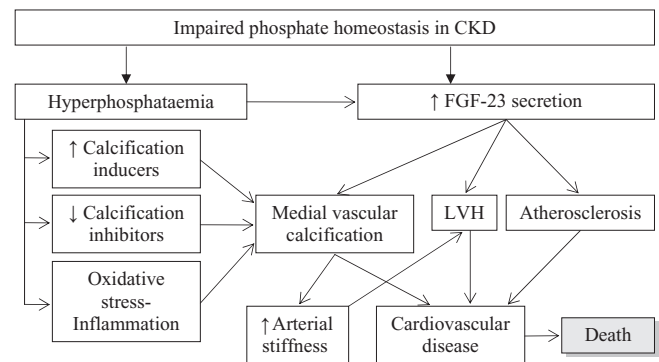
Fig. 1 The role of CKD-MBD in the pathogenesis of cardiovascular disease in CKD. CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; FGF-23, fibroblast growth factor-23; LVH, left ventricular hypertrophy.

The relationship between phosphate and CVD may be explained by several putative mechanisms.[31–34] 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).[32,35] 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.[36] Hyperphosphataemia may also directly affect vascular health by increasing reactive oxygen species, thereby causing oxidative damage and endothelial dysfunction.[33,34,36] 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[4] and pre-dialysis patients with CKD.[2] 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.[4] Multiple studies have subsequently also reported that high serum phosphate levels are independently predictive of CVD and death in the dialysis population.[37–42] One study of 3490 non-dialysis CKD patients (veterans in the US) reported that serum phosphate

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)

Study	Participants	Outcome measure
(a)		
Tonelli 2005[1]	4127 patients with prior MI (CARE study)	*All-cause mortality*: HR 1.27, 95% CI 1.02–1.58 per 1 mg/dL increase in P
Dhingra 2007[3]	1000 participants (Framingham offspring study)	*CV event*: HR 1.31, 95% CI 1.05–1.63 per 1 mg/dL increase in P
Dhingra 2010[17]	3300 participants	*Heart failure*: OR 1.74, 95% CI 1.17–2.59 per 1 mg/dL increase in P
Foley 2009[18]	4055 participants	*LVH*: OR 1.27, 95% CI 1.09–1.47 per 1-SD increase in P
Foley 2009[19]	3015 participants (CARDIA study)	*Coronary artery calcification*: OR 1.17, 95% CI 1.01–1.34 per 0.5 mg/dL increase in P
O'Seaghdha 2011[6]	2269 participants (Framingham Heart Study)	*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)
	13,372 participants (NHANES III)	*ESKD*: RR 1.90, 95% CI 1.03–3.53 for P ≥ 4 mg/dL compared with P < 4 mg/dL
(b)		
Kestenbaum 2005[2]	3490 CKD patients (median CrCl 45)	*All-cause mortality*: HR 1.23, 95% CI 1.12–1.36 per 1 mg/dL increase in P
Eddington 2010[15]	1203 CKD patients (mean eGFR 32)	*All-cause mortality*: HR 1.26, 95% CI 1.1–1.5 per 1 mg/dL increase in P
		CV mortality: HR 1.50, 95% CI 1.2–2.0 per 1 mg/dL increase in P
Ix 2009[20]	1370 (440 with CKD), no CVD (MESA study)	*Arterial stiffness*: RR 4.6, 95% CI 1.6–13.2 for P > 4 mg/dL compared with P < 3 mg/dL
Adeney 2009[21]	439 CKD patients (MESA study) (mean eGFR 51)	*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
Chue 2012[22]	208 CKD stage 2–4 patients (mean eGFR 50)	*LVMI*: Greater with P > 1.20 mmol/L than P < 1.20 mmol/L (61 *vs.* 55 g/m^2; $P = 0.03$)
Chue 2011[23]	225 CKD stage 2–4 patients (mean eGFR 43)	*Renal impairment*: 0.34 mL/min per month decline in GFR per 1 mmol/L increase in P
Landray 2010[24]	382 CKD stage 3–5 patients (CRIB study) (mean eGFR 22)	*ESKD*: RR 1.46, 95% CI 1.21–1.77 per 1-SD increase in P
Connolly 2009[25]	379 transplant recipients (mean eGFR 53)	*All-cause mortality*: HR 3.4, 95% CI 1.7–6.6 for P > 1.12 mmol/L (referent range P < 0.92 mmol/L)
Moore 2011[26]	270 transplant recipients (mean eGFR 40)	*All-cause mortality*: HR 1.21, 95% CI 1.09–1.35 per 0.1 mmol/L increase in P
Schaeffner 2007[27]	733 transplant recipients (mean eGFR 56)	*Graft loss*: HR 2.15, 95% CI 1.36–3.40 for highest P quintile (≥1.23 mmol/L) compared with lowest (≤0.84 mmol/L)
Benavente 2012[28]	325 transplant recipients (mean eGFR 46)	*Graft loss*: HR 1.27, 95% CI 1.07–1.51 and HR 1.34, 95% CI 1.14–1.57 per 0.1 mmol/L increase in P at 6 and 12 months respectively

eGFR expressed in mL/min per 1.73 m^2, CrCl expressed in mL/min. CARDIA, Coronary 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.

>3.5 mg/dL (1.13 mmol/L) was associated with a significantly increased risk for death, with the mortality risk increasing linearly with each subsequent 0.5 mg/dL increase in phosphate.[2] A meta-analysis of 47 cohort studies ($n = 327\,644$) also supported the evidentiary basis for an association between higher serum phosphate and mortality in CKD patients.[5] In this study the risk of death increased 18% for every 1 mg/dL (0.32 mmol/L) increase in serum phosphate (relative risk (RR) 1.18 (95% confidence interval (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.[1,3] 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 fulfils many criteria to be defined as a risk factor for CVD.[35,45] 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

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).[19] 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.[46]

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).[3] 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.[1]

PHOSPHATE AND LVH

Left ventricular hypertrophy (LVH) is extremely common in CKD patients with a prevalence that increases with declining kidney function[47] and varies from 30–47% in pre-dialysis CKD patients to 41–74% in patients on dialysis.[47–49] LVH is associated with increased CV events in CKD patients.[48,50,51] 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.[22]

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).[18] 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.[17] 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.[52–54]

The association between higher serum phosphate and arterial compliance has been reported in several studies.[20,30,55–58] Phosphate is positively associated with pulse wave velocity (PWV),[30,55] 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.[56,57] 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 ($P = 0.04$).[56] 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.[20]

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.[53,59] 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.[60] 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.[61–63] Reducing phosphate, for example with phosphate binders, reverses osteoblastic differentiation of vascular cells and vascular calcification.[35]

Many cross-sectional clinical studies have reported an association between serum phosphate and vascular calcification in patients who are pre-dialysis or undergoing dialysis.[64–66] However, this is not a consistent finding, and calcification is more commonly related to increasing age and dialysis duration.[67] 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

turnover. The presence of hyperphosphataemia, an imbalance of inducers and inhibitors of calcification, and inflammation and oxidative stress, contribute to the pathogenesis of medial calcification in CKD. Whether vascular calcification can be prevented or reversed with strategies aimed at maintaining phosphate homeostasis is as yet unknown.

One recent study also determined an association between serum phosphate within the normal range and vascular and valvular calcification.[21] This study of 439 young and middle-age 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 calcium levels in a young healthy adult population.[19]

PHOSPHATE AND PROGRESSION OF RENAL IMPAIRMENT

Elevations in serum phosphate have been associated with structural changes and renal decline in animal models.[68] In human observational studies, hyperphosphataemia is associated with progression of established CKD and the development of ESKD (end-stage kidney disease)[23,69–71] and studies of renal transplant recipients describe an association between higher serum phosphate and renal allograft loss.[27,28] Serum phosphate levels in the upper-normal range have also recently been reported to be associated with an increased risk of developing incident CKD and ESKD.[6,24] One study involving 2269 participants from the Framingham Heart Study showed that those in the highest phosphate category had an increased risk of CKD with OR 2.14 (95% CI 1.07–4.28) when compared with the reference group with serum phosphate 2.5–3.49 mg/dL.[6] The same study also analysed 13 372 participants from the Third National Health and Nutrition Examination Survey (NHANES III) and reported that phosphate ≥ 4 mg/dL was associated with an increased risk of incident ESKD (RR 1.90 (95% CI 1.03–3.53)).

Zoccali et al. recently evaluated the relationship between baseline serum phosphate, disease progression and response to angiotensin-converting enzyme (ACE) inhibition in 331 patients with proteinuric CKD in the prospective Ramipril Efficacy In Nephropathy (REIN) trial.[72] Phosphate levels in the highest two quartiles were significantly associated with faster progression to both ESKD and to a composite endpoint of doubling of serum creatinine or ESKD compared with patients with phosphate levels below the median. Therefore, with higher serum phosphate levels the renoprotective effect of ramipril decreased, despite adjustment for potential confounders such as GFR and urinary protein. This

suggests that phosphate may potentially modify the protective effect of the only real therapeutic class of agents used in CKD.

FGF-23 IN HEALTH AND CKD

FGF-23 is the most potent hormone regulating phosphate homeostasis.[73] In health, FGF-23 is secreted by osteocytes and osteoblasts in response to dietary phosphate intake. FGF-23 suppresses the expression of the type IIa sodium phosphate co-transporter, thus regulating phosphate reabsorption in the renal proximal tubule.[73,74] FGF-23 also decreases serum concentration of $1,25(OH)_2D$ by inhibiting 1α-hydroxylase and stimulating 24-hydroxylase.[74] 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.[75]

Serum FGF-23 levels increase with even modest decreases in GFR (60–89 mL/min per 1.73 m^2) as a homeostatic response to restore serum phosphate levels[76] and may be the earliest detected serum abnormalities of CKD-MBD.[77] This rise occurs before changes in levels of PTH or $1,25(OH)_2D$,[8,18,78] and by accentuating $1,25(OH)_2D$ deficiency[76] may contribute to the development of SHPT.[79] 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.[8] 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.[80,81] Recent studies have reported elevated FGF-23 levels to be associated with increased CVD and mortality in patients on dialysis[81,82] and in patients with coronary artery disease who had both preserved renal function and mild to moderate CKD.[83]

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 impaired vascular function and calcification.[89,90,93] FGF-23 may play a role as it is an independent biomarker of vascular calcification in patients with various CKD stages including early stages.[94,95] 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).[86] 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

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

Study	Participants	Outcome measure
Gutiérrez 2008[77]	400 incident ESKD patients on HD	*All-cause mortality*: Adjusted HR 1.8, 95% CI 1.4–2.4 per unit ↑ in natural log-transformed FGF-23
Jean 2009[82]	219 prevalent HD patients	*All-cause mortality*: HR 2.5, 95% CI 1.3–5 in the highest quartile of FGF-23, reference – the lowest quartile
Kendrick 2011[84]	1133 patients with pre-dialysis CKD (mean eGFR 18)	*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 *CV event*: HR 1.9, 95% CI 1.2–3 in 3rd quartile; 2.3, 95% CI 1.4–3.8 in 4th quartile of FGF-23
Seiler 2010[85]	149 pre-dialysis CKD patients (mean eGFR 36)	*CV event*: Adjusted HR 1.6, 95% CI 1.1–2.3 per unit ↑ in natural log-transformed FGF-23
Gutiérrez 2009[86]	162 patients with CKD stage 3 and 4	*LVMI*: 11% ↑ in LVMI per 1-SD ↑ in log-transformed FGF-23, 95% CI 3–18%, $P = 0.01$ *LVH*: OR 2.3, 95% CI 1.2–4.2 per 1-SD ↑ in log-transformed FGF-23
Mirza 2009[87]	164 CKD patients (mean eGFR 54)	*LVH*: OR 1.8, 95% CI 1.2–2.6 per 1-SD ↑ in log-transformed FGF-23
Mirza 2009[88]	27 CKD patients (mean eGFR 52)	*High atherosclerosis score*: OR 5.6, 95% CI 2.8–11.5 in the highest quartile of FGF-23, reference – the lowest quartile
Mirza 2009[89]	208 CKD patients (mean eGFR 53)	*Arterial stiffness (change in reflection index)*: Standardized β 0.26, 95% CI 0.12–0.4, $P < 0.001$ 1-SD ↑ in log-transformed FGF-23
Kanbay 2010[94]	21 CKD patients with Cockroft-Gault GFR <60	*Coronary artery disease*: Positive correlation between FGF-23 and Gensini lesion severity score (β = 0.74, $P = 0.001$).
Yilmaz 2010[90]	183 CKD patients (mean eGFR 33)	*Flow mediated vasodilatation*: Positive correlation with FGF-23 (β −0.30, $P < 0.001$)
Isakova 2011[91]	3879 CKD patients (mean eGFR 42.8)	*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. *End-stage kidney disease*: HR 1.3, 95% CI 1.04–1.6 per 1-SD ↑ in log-transformed FGF-23 for patients with eGFR 30–44
Fliser 2007[92]	177 CKD patients	*Progression of renal impairment*: HR 1.11, 95% CI 1.08–1.15 per 10 rU/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

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.

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.[63]

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

RCT	Participants	Results
Isakova 2011[111]	16 CKD patients (mean eGFR 54)	No effect of lanthanum or placebo on serum FGF-23 levels after 2 weeks
Oliveira 2010[112]	40 CKD patients (mean CrCl 35)	Sevelamer, but not calcium acetate, reduced the serum FGF-23 levels from 107 pg/mL to 54 pg/mL, $P < 0.05$ after 6 weeks
Gonzalez-Parra 2011[113]	18 CKD patients (mean CrCl 42)	Lanthanum reduced FGF-23 levels, median per cent change from baseline −21.8% (interquartile range −4.5%, −30%), $P < 0.05$ after 4 weeks
Yilmaz 2012[114]	100 CKD patients (mean eGFR 23)	Sevelamer, but not calcium acetate, increased FMD from 6.1% to 7.1%, $P < 0.001$ after 8 weeks. Changes were associated with reduction in FGF-23 levels −27.1% (−33.2%, −8.8%) with sevelamer

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FGF-23, fibroblast growth factor-23; FMD, flow mediated dilatation; LVH, left ventricular hypertrophy; RCT; randomized controlled trial.

Several RCT have assessed the effect of phosphate binders on vascular calcification (coronary and aortic) in dialysis and pre-dialysis CKD patients.[99–103] 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, $n = 153$, RR 0.85, 95% CI 0.35–2.03).[104]

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.[105] 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.[106] 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.[103]

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 KDIGO (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,[107–109] whereas the recent NICE guidelines suggest phosphate should only be monitored in CKD stages 4 and 5.[110] 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[111–114] (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.[115,116] 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.[117] 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).[118] However, analysis of the NHANES III data did not show any association between high dietary phosphate intake

and mortality in 1105 CKD patients (HR 0.98 per 100 mg/dL increase (95% CI 0.93–1.03)).[119]

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.[120] 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.[121] 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.[122] 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.[123] FGF-23 is appealing because levels correlate to mortality at the initiation of

dialysis[15,93,124] 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 $TmPO_4$/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.[125–127] 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 m^2) in an open-label study.[125] 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.[126] 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.[127]

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 and 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.

ACKNOWLEDGEMENTS

REFERENCES

1. Tonelli M, Sacks F, Pfeffer M *et al*. Relationship between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 2005; **112**: 2627–33.
2. Kestenbaum B, Sampson JN, Rudser KD *et al*. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J. Am. Soc. Nephrol.* 2005; **16**: 520–8.
3. Dhingra R, Sullivan L, Fox S *et al*. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch. Int. Med.* 2007; **167**: 879–85.
4. Block G, Hulbert-Shearon T *et al*. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am. J. Kidney Dis.* 1998; **31**: 607–17.
5. Palmer SC, Hayen A, Macaskill P *et al*. Serum levels of phosphorus, parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease: A systematic review and meta-analysis. *JAMA* 2011; **305**: 1119–27.
6. O'Seaghdha CM, Hwang SJ, Muntner P, Melamed ML, Fox CS. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. *Nephrol. Dial. Transplant.* 2011; **26**: 2885–90.
7. Berndt T, Kumar R. Phosphatonins and the regulation of phosphate homeostasis. *Annu. Rev. Physiol.* 2007; **69**: 341–59.
8. Levin A, Bakris GL, Molitch M *et al*. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. *Kidney Int.* 2007; **71**: 31–8.
9. Cunningham J, Locatelli F, Rodriguez M. Secondary hyperparathyroidism: Pathogenesis, disease progression, and therapeutic options. *Clin. J. Am. Soc. Nephrol.* 2011; **6**: 913–21.
10. Weiner DE, Tighiouart H, Amin MG *et al*. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: A pooled analysis of community-based studies. *J. Am. Soc. Nephrol.* 2004; **15**: 1307–15.
11. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kidney Dis.* 1998; **32**: S112–19.
12. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N. Engl. J. Med.* 2004; **351**: 1296–305.
13. Chronic Kidney Disease Prognosis Consortium; Matsushita K, van der Velde M, Astor BC *et al*. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: A collaborative meta-analysis. *Lancet* 2010; **375**: 2073–81.
14. Muntner P, He J, Astor BC *et al*. Traditional and nontraditional risk factors predict coronary heart disease in chronic kidney disease: Results from the atherosclerosis risk in communities study. *J. Am. Soc. Nephrol.* 2005; **16**: 529–38.
15. Eddington H, Hoefield R, Sinha S *et al*. Serum phosphate and mortality in patients with chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2010; **5**: 2251–7.
16. Moe SM, Drueke T, Lameire N *et al*. Chronic kidney disease – mineral and bone disorder: A new paradigm. *Adv. Chronic Kidney Dis.* 2007; **14**: 3–12.
17. Dhingra R, Gona P, Benjamin EJ *et al*. Relations of serum phosphorus levels to echocardiographic left ventricular mass and incidence of heart failure in the community. *Eur. J. Heart. Fail.* 2010; **12**: 812–18.
18. Foley RN, Collins AJ, Herzog CA *et al*. Serum phosphate and left ventricular hypertrophy in young adults: The coronary artery risk development in young adults study. *Kidney Blood Press. Res.* 2009; **32**: 37–44.
19. Foley RN, Collins AJ, Herzog CA *et al*. Serum phosphorus levels associate with coronary atherosclerosis in young adults. *J. Am. Soc. Nephrol.* 2009; **20**: 397–404.
20. Ix JH, De Boer IH, Peralta CA *et al*. Serum phosphorus concentrations and arterial stiffness among individuals with normal kidney function to moderate kidney disease in MESA. *Clin. J. Am. Soc. Nephrol.* 2009; **4**: 609–15.
21. Adeney KL, Siscovick DS, Ix JH *et al*. Association of serum phosphate with vascular and valvular calcification in moderate ckd. *J. Am. Soc. Nephrol.* 2009; **20**: 381–7.
22. Chue CD, Edwards NC, Moody WE *et al*. Serum phosphate is associated with left ventricular mass in patients with chronic kidney disease: A cardiac magnetic resonance study. *Heart* 2012; **98**: 219–24.
23. Chue CD, Edwards NC, Davis LJ, Steeds RP, Townend JN, Ferro CJ. Serum phosphate but not pulse wave velocity predicts decline in renal function in patients with early chronic kidney disease. *Nephrol. Dial. Transplant.* 2011; **26**: 2576–82.
24. Landray MJ, Emberson JR, Blackwell L *et al*. Prediction of ESRD and death among people with CKD: The Chronic Renal Impairment in Birmingham (CRIB) prospective cohort study. *Am. J. Kidney Dis.* 2010; **56**: 1082–94.

25. Connolly GM, Cunningham R, McNamee PT *et al*. Elevated serum phosphate predicts mortality in renal transplant recipients. *Transplantation* 2009; **87**: 1040–44.

26. Moore J, Tomson CR, Tessa Savage M, Borrows R, Ferro CJ. Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation. *Clin. Transplant.* 2011; **25**: 406–16.

27. Schaeffner ES, Födinger M, Kramar R, Sunder-Plassmann G, Winkelmayer WC. Prognostic associations of serum calcium, phosphate and calcium phosphate concentration product with outcomes in kidney transplant recipients. *Transpl. Int.* 2007; **20**: 247–55.

28. Benavente D, Chue CD, Moore J, Addison C, Borrows R, Ferro CJ. Serum phosphate measured at 6 and 12 months after successful kidney transplant is independently associated with subsequent graft loss. *Exp. Clin. Transplant.* 2012; **10**: 119–24.

29. Jung HH, Kim S-W, Han H. Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis. *Nephrol. Dial. Transplant.* 2006; **21**: 1915–20.

30. Toussaint ND, Lau KK, Strauss BJ *et al*. Associations between vascular calcification, arterial stiffness and bone mineral density in chronic kidney disease. *Nephrol. Dial. Transplant.* 2008; **23**: 586–93.

31. Shuto E, Taketani Y, Tanaka R *et al*. Dietary phosphorus acutely impairs endothelial function. *J. Am. Soc. Nephrol.* 2009; **20**: 1504–12.

32. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int.* 2009; **75**: 890–7.

33. Amann K, Tornig J, Kugel B *et al*. Hyperphosphatemia aggravates cardiac fibrosis and microvascular disease in experimental uremia. *Kidney Int.* 2003; **63**: 1296–301.

34. Chue CD, Townend JN, Steeds RP, Ferro CJ. Arterial stiffness in chronic kidney disease: Causes and consequences. *Heart* 2010; **96**: 817–23.

35. Mathew S, Tustison KS, Sugatani T *et al*. The mechanism of phosphorus as a cardiovascular risk factor in CKD. *J. Am. Soc. Nephrol.* 2008; **19**: 1092–105.

36. Tonelli M, Pannu N, Manns B. Oral phosphate binders in patients with kidney failure. *N. Engl. J. Med.* 2010; **362**: 1312–24.

37. Block GA, Klassen PS, Lazarus JM *et al*. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J. Am. Soc. Nephrol.* 2004; **15**: 2208–18.

38. Young EW, Albert JM, Satayathum S *et al*. Predictors and consequences of altered mineral metabolism: The Dialysis Outcomes and Practice Patterns Study. *Kidney Int.* 2005; **67**: 1179–87.

39. Kalantar-Zadeh K, Kuwae N, Regidor DL *et al*. Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. *Kidney Int.* 2006; **70**: 771–80.

40. Wald R, Sarnak MJ, Tighiouart H *et al*. Disordered mineral metabolism in hemodialysis patients: An analysis of cumulative effects in the Hemodialysis (HEMO) Study. *Am. J. Kidney Dis.* 2008; **52**: 531–40.

41. Tentori F, Blayney MJ, Albert JM *et al*. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am. J. Kidney Dis.* 2008; **52**: 519–30.

42. Floege J, Kim J, Ireland E *et al*. Serum iPTH, calcium and phosphate, and the risk of mortality in a European heamodialysis population. *Nephrol. Dial. Transplant.* 2011; **26**: 1948–55.

43. Sampaio MS, Molnar MZ, Kovesdy CP *et al*. Association of pretransplant serum phosphorus with posttransplant outcomes. *Clin. J. Am. Soc. Nephrol.* 2011; **6**: 2712–21.

44. Roodnat JI, van Gurp EA, Mulder PG *et al*. High pretransplant parathyroid hormone levels increase the risk for graft failure after renal transplantation. *Transplantation* 2006; **82**: 362–7.

45. Hruska K, Mathew S, Lund R, Fang Y, Sugatani T. Cardiovascular risk factors in chronic kidney disease: Does phosphate qualify? *Kidney Int.* 2011; **79** (Suppl 121): S9–13.

46. Narang R, Ridout D, Nonis C, Kooner JS. Serum calcium, phosphorus and albumin levels in relation to the angiographic severity of coronary artery disease. *Int. J. Cardiol.* 1997; **60**: 73–9.

47. Verma A, Anavekar NS, Meris A *et al*. The relationship between renal function and cardiac structure, function, and prognosis after myocardial infarction: The VALIANT Echo Study. *J. Am. Coll. Cardiol.* 2007; **50**: 1238–45.

48. Eckardt KU, Scherhag A, Macdougall IC *et al*. Left ventricular geometry predicts cardiovascular outcomes associated with anemia correction in CKD. *J. Am. Soc. Nephrol.* 2009; **20**: 2651–60.

49. Patel RK, Oliver S, Mark PB *et al*. Determinants of left ventricular mass and hypertrophy in hemodialysis patients assessed by cardiac magnetic resonance imaging. *Clin. J. Am. Soc. Nephrol.* 2009; **4**: 1477–83.

50. Boner G, Cooper ME, McCarroll K *et al*. Adverse effects of left ventricular hypertrophy in the reduction of endpoints in NIDDM with the angiotensin II antagonist losartan (RENAAL) study. *Diabetologia* 2005; **48**: 1980–7.

51. Weiner DE, Tighiouart H, Vlagopoulos PT *et al*. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. *J. Am. Soc. Nephrol.* 2005; **16**: 1803–10.

52. London G, Guerin A, Marchais S *et al*. Arterial media calcification in end-stage renal disease: Impact on all-cause and cardiovascular mortality. *Nephrol. Dial. Transplant.* 2003; **18**: 1731–40.

53. Blacher J, Guerin AP, Pannier B *et al*. Impact of aortic stiffness on survival in end-stage renal disease. *Circulation* 1999; **99**: 2434–39.

54. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 2010; **55**: 1318–27.

55. Ferro CJ, Chue CD, Steeds RP, Townend JN. Is lowering phosphate exposure the key to preventing arterial stiffening with age? *Heart* 2009; **95**: 1770–2.

56. Othmane TEH, Bakonyi G, Egresits J *et al*. Effect of sevelamer on aortic pulse wave velocity in patients on hemodialysis: A prospective observational study. *Hemodial. Int.* 2007; **11**: S13–21.

57. Takenaka T, Suzuki H. New strategy to attenuate pulse wave velocity in haemodialysis patients. *Nephrol. Dial. Transplant.* 2005; **20**: 811–16.

58. Mitsnefes MM, Kimball TR, Kartal J *et al*. Cardiac and vascular adaptation in pediatric patients with chronic kidney disease: Role of calcium-phosphorus metabolism. *J. Am. Soc. Nephrol.* 2005; **16**: 2796–803.

59. Chiu Y-W, Adler SG, Budoff MJ *et al*. Coronary artery calcification and mortality in diabetic patients with proteinuria. *Kidney Int.* 2010; **77**: 1107–14.

60. Jono S, McKee MD, Murry CE *et al*. Phosphate regulation of vascular smooth muscle cell calcification. *Circ. Res.* 2000; **87**: e10-7.

61. Kendrick J, Chonchol M. The role of phosphorus in the development and progression of vascular calcification. *Am. J. Kidney Dis.* 2011; **58**: 826–34.

62. Giachelli CM. Vascular calcification: *In vitro* evidence for the role of inorganic phosphate. *J. Am. Soc. Nephrol.* 2003; **14**: 5300–4.

63. Li X, Yang HY, Giachelli CM. Role of the sodium-dependent phosphate co-transporter Pit-1, in vascular smooth muscle cell calcification. *Circ. Res.* 2006; **98**: 905–12.

64. Shigematsu T, Kono T, Satoh K *et al*. Phosphate overload accelerates vascular calcium deposition in end-stage renal disease patients. *Nephrol. Dial. Transplant.* 2003; **18** (Suppl 3): iii86–9.

65. Goodman WG, Goldin J, Kuizon BD *et al*. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N. Engl. J. Med.* 2000; **342**: 1478–83.

66. Ford ML, Smith ER, Tomlinson LA, Chatterjee PK, Rajkumar C, Holt SG. FGF-23 and osteoprotegerin are independently associated with myocardial damage in chronic kidney disease stages 3 and 4. Another link between chronic kidney disease-mineral bone disorder and the heart. *Nephrol. Dial. Transplant.* 2012; **27**: 727–33.

67. McCullough PA, Sandberg KR, Dumler F, Yanez JE. Determinants of coronary vascular calcification in patients with chronic kidney disease and end-stage renal disease: A systematic review. *J. Nephrol.* 2004; **17**: 205–15.

68. Neves KR, Graciolli FG, dos Reis LM *et al*. Adverse effects of hyperphosphatemia on myocardial hypertrophy, renal function, and bone in rats with renal failure. *Kidney Int.* 2004; **66**: 2237–44.

69. Voormolen N, Noordzij M, Grootendorst DC *et al*. High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. *Nephrol. Dial. Transplant.* 2007; **22**: 2909–16.

70. Norris KC, Greene T, Kopple J *et al*. Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. *J. Am. Soc. Nephrol.* 2006; **17**: 2928–36.

71. Schwarz S, Trivedi BK, Kalantar-Zadeh K *et al*. Association of disorders in mineral metabolism with progression of chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2006; **1**: 825–31.

72. Zoccali C, Ruggenenti P, Perna A *et al*. Phosphate may promote CKD progression and attenuate renoprotective effect of ACE inhibition. *J. Am. Soc. Nephrol.* 2011; **22**: 1923–30.

73. Shimada T, Hasegawa H, Yamazaki Y *et al*. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J. Bone Miner. Res.* 2004; **19**: 429–35.

74. Saito H, Kusano K, Kinosaki M *et al*. Human fibroblast growth factor-23 mutants suppress Na+-dependent phosphate co-transport activity and 1α,25-dihydroxyvitamin D3 production. *J. Biol. Chem.* 2003; **278**: 2206–11.

75. Ix JH, Shlipak MG, Wassel CL, Whooley MA. Fibroblast growth factor-23 and early decrements in kidney function: The Heart and Soul Study. *Nephrol. Dial. Transplant.* 2010; **25**: 993–7.

76. Shigematsu T, Kazama JJ, Yamashita T *et al*. Possible involvement of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism associated with renal insufficiency. *Am. J. Kidney Dis.* 2004; **44**: 250–6.

77. Gutiérrez OM, Mannstadt M, Isakova T *et al*. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N. Engl. J. Med.* 2008; **359**: 584–92.

78. Gutiérrez O, Isakova T, Rhee E *et al*. Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J. Am. Soc. Nephrol.* 2005; **16**: 2205–15.

79. Larsson T, Nisbeth U, Ljunggren O *et al*. Circulating concentration of FGF-23 increases as renal function declines in patients with chronic kidney disease, but does not change in response to variation in phosphate intake in healthy volunteers. *Kidney Int.* 2003; **64**: 2272–9.

80. Razzaque MS, Lanske B. The emerging role of the fibroblast growth factor-23-klotho axis in renal regulation of phosphate homeostasis. *J. Endocrinol.* 2007; **194**: 1–10.

81. Craver L, Marco MP, Martínez I *et al*. Mineral metabolism parameters throughout chronic kidney disease stages 1–5 – achievement of K/DOQI target ranges. *Nephrol. Dial. Transplant.* 2007; **22**: 1171–6.

82. Jean G, Terrat J-C, Vanel T *et al*. High levels of serum fibroblast growth factor (FGF)-23 are associated with increased mortality in long haemodialysis patients. *Nephrol. Dial. Transplant.* 2009; **24**: 2792–6.

83. Parker BD, Schurgers LJ, Brandenburg VM *et al*. The associations of fibroblast growth factor 23 and uncarboxylated matrix Gla protein with mortality in coronary artery disease: The Heart and Soul Study. *Ann. Int. Med.* 2010; **152**: 640–8.

84. Kendrick J, Cheung AK, Kaufman JS *et al*. FGF-23 associates with death, cardiovascular events, and initiation of chronic dialysis. *J. Am. Soc. Nephrol.* 2011; **22**: 1913–22.

85. Seiler S, Reichart B, Roth D *et al*. FGF-23 and future cardiovascular events in patients with chronic kidney disease before initiation of dialysis treatment. *Nephrol. Dial. Transplant.* 2010; **25**: 3983–9.

86. Gutiérrez OM, Januzzi JL, Isakova T *et al*. Fibroblast growth factor 23 and left ventricular hypertrophy in chronic kidney disease. *Circulation* 2009; **119**: 2545–52.

87. Mirza MA, Larsson A, Melhus H *et al*. Serum intact FGF23 associate with left ventricular mass, hypertrophy and geometry in an elderly population. *Atherosclerosis* 2009; **207**: 546–51.

88. Mirza MA, Hansen T, Johansson L *et al*. Relationship between circulating FGF23 and total body atherosclerosis in the community. *Nephrol. Dial. Transplant.* 2009; **24**: 3125–31.

89. Mirza MA, Larsson A, Lind L, Larsson T. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. *Atherosclerosis* 2009; **205**: 385–90.

90. Yilmaz MI, Sonmez A, Saglam M *et al*. FGF-23 and vascular dysfunction in patients with stage 3 and 4 chronic kidney disease. *Kidney Int.* 2010; **78**: 679–85.

91. Isakova T, Xie H, Yang W *et al*. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA* 2011; **305**: 2432–9.

92. Fliser D, Kollerits B, Neyer U *et al*. Fibroblast growth factor 23 (FGF23) predicts progression of chronic kidney disease: The Mild to Moderate Kidney Disease (MMKD) Study. *J. Am. Soc. Nephrol.* 2007; **18**: 2600–8.

93. Nasrallah MM, El-Shehaby AR, Salem MM *et al*. Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. *Nephrol. Dial. Transplant.* 2010; **25**: 2679–85.

94. Kanbay M, Nicoleta M, Selcoki Y *et al*. Fibroblast growth factor 23 and fetuin A are independent predictors for the coronary artery disease extent in mild chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2010; **5**: 1780–6.

95. Desjardins L, Liabeuf S, Renard C *et al*. FGF23 is independently associated with vascular calcification but not bone mineral density in patients at various CKD stages. *Osteoporos. Int.* 2011 [Epub ahead of print].

96. Faul C, Amaral AP, Oskouei B *et al*. FGF23 induces left ventricular hypertrophy. *J. Clin. Invest.* 2011; **121**: 4393–408.

97. Isakova T, Gutiérrez OM, Chang Y *et al*. Phosphorus binders and survival on hemodialysis. *J. Am. Soc. Nephrol.* 2009; **20**: 388–96.

98. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K. Outcomes associated with phosphorus binders in men with non-dialysis-dependent CKD. *Am. J. Kidney Dis.* 2010; **56**: 842–51.

99. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int.* 2002; **62**: 245–52.

100. Russo D, Miranda I, Ruocco C *et al*. The progression of coronary artery calcification in predialysis patients on calcium carbonate or sevelamer. *Kidney Int.* 2007; **72**: 1255–61.

101. Block GA, Spiegel DM, Ehrlich J *et al*. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int.* 2005; **68**: 1815–24.

102. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG. Reduction of aortic calcification with lanthanum carbonate vs calcium-based phosphate binders in haemodialysis – A randomized controlled trial. *Nephrology* 2010; **16**: 290–8.

103. Di Iorio B, Bellasi A, Russo D *et al*. Mortality in kidney disease patients treated with phosphate binders: A randomized study. *Clin. J. Am. Soc. Nephrol.* 2012; **7**: 487–93.

104. Jamal SA, Fitchett D, Lok CE *et al*. The effects of calcium-based versus non-calcium-based phosphate binders on mortality among patients with chronic kidney disease: A meta-analysis. *Nephrol. Dial. Transplant.* 2009; **24**: 3168–74.

105. Suki WN, Zabaneh R, Cangiano JL *et al*. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int.* 2007; **72**: 1130–7.

106. Block GA, Raggi P, Bellasi A *et al*. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int.* 2007; **71**: 438–41.

107. The Kidney Disease: Improving Global Outcomes (KDIGO) Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int.* 2009; **113**: S1–130.

108. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am. J. Kidney Dis.* 2003; **42** (Suppl 3): S1–201.

109. Elder G, Faull R, Branley P *et al*. The CARI guidelines. Management of bone disease, calcium, phosphate and parathyroid hormone. *Nephrology (Carlton)* 2006; **11**: S230–61.

110. National Collaborating Centre for Chronic Conditions. *Chronic Kidney Disease: National Clinical Guideline for Early Identification and Management in Adults in Primary and Secondary Care*. London: Royal College of Physicians (UK), 2008. (NICE Clinical Guidelines, No. 73).

111. Isakova T, Gutiérrez OM, Smith K *et al*. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. *Nephrol. Dial. Transplant.* 2011; **26**: 584–91.

112. Oliveira RB, Cancela ALE, Graciolli FG *et al*. Early control of PTH and FGF23 in normophosphatemic CKD patients: A new target in CKD-MBD therapy? *Clin. J. Am. Soc. Nephrol.* 2010; **5**: 286–91.

113. Gonzalez-Parra E, Gonzalez-Casaus ML, Galán A *et al*. Lanthanum carbonate reduces FGF23 in chronic kidney disease Stage 3 patients. *Nephrol. Dial. Transplant.* 2011; **26**: 2567–71.

114. Yilmaz MI, Sonmez A, Saglam M *et al*. Comparison of calcium acetate and sevelamer on vascular function and fibroblast growth factor 23 in CKD patients: A randomized clinical trial. *Am. J. Kidney Dis.* 2012; **59**: 177–85.

115. Antoniucci DM, Yamashita T, Portale AA. Dietary phosphorus regulates serum fibroblast growth factor-23 concentrations in healthy men. *J. Clin. Endocrinol. Metab.* 2006; **91**: 3144–9.

116. Burnett SM, Gunawardene SC, Bringhurst FR, Juppner H, Lee H, Finkelstein JS. Regulation of C-terminal and intact FGF-23 by dietary phosphate in men and women. *J. Bone Miner. Res.* 2006; **21**: 1187–96.

117. Gutiérrez OM, Wolf M, Taylor EN. Fibroblast growth factor 23, cardiovascular disease risk factors, and phosphorus intake in the health professionals follow-up study. *Clin. J. Am. Soc. Nephrol.* 2011; **6**: 2871–8.

118. Yamamoto KT, Robinson-Cohen C, de Oliveira MC *et al*. Dietary phosphorus is associated with left ventricular mass: The Multi-Ethnic Study of Atherosclerosis. American Society of Nephrology Kidney Week 2011, Oral Presentation SA-OR351, Philadelphia, PA.

119. Murtaugh MA, Filipowicz R, Baird BC, Wei G, Greene T, Beddhu S. Dietary phosphorus intake and mortality in moderate chronic kidney disease: NHANES III. *Nephrol. Dial. Transplant.* 2012; **27**: 990–6.

120. Moe SM, Chen NX, Seifert MF *et al*. A rat model of chronic kidney disease-mineral bone disorder. *Kidney Int.* 2009; **75**: 176–84.

121. Moe SM, Zidehsarai MP, Chambers MA *et al*. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin. J. Am. Soc. Nephrol.* 2011; **6**: 257–64.

122. Sullivan C, Sayre SS, Leon JB *et al*. Effect of food additives on hyperphosphatemia among patients with endstage renal disease: A randomized controlled trial. *JAMA* 2009; **301**: 629–35.

123. Isakova T, Wahl P, Vargas GS *et al*. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int.* 2011; **79**: 1370–8.

124. Wolf M. Forging forward with 10 burning questions on FGF23 in kidney disease. *J. Am. Soc. Nephrol.* 2010; **21**: 1427–35.

125. Block GA, Persky MS, Ketteler M *et al*. A randomized double-blind pilot study of serum phosphorus normalization in chronic kidney disease: A new paradigm for clinical outcomes studies in nephrology. *Hemodial. Int.* 2009; **13**: 360–2.

126. Chue CD, Townend JN, Steeds RP, Ferro CJ. Evaluating the effects of sevelamer carbonate on cardiovascular structure and function in chronic renal impairment in Birmingham: The CRIB-PHOS randomised controlled trial. *Trials* 2011; **12**: 30.

127. Australian New Zealand Clinical Trials Registry website. ACTRN12610000650099. [Cited 23 May 2012.] Available from URL: http://www.anzctr.org.au/trial_view.aspx?ID=335812