Clinical update

Calcium and phosphate impact cardiovascular risk

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Non-traditional risk factors substantially contribute to cardiovascular (CV) disease. A deranged calcium–phosphate metabolism—first identified as a major non-traditional CV risk factor in patients with chronic kidney disease—may be implicated in development and progression of CV disease even among individuals with intact renal function. This review thus summarizes epidemiological and experimental data on the role of calcium, phosphate, and its major regulating hormones—parathyroid hormone, calcitriol, and fibroblast growth factor 23—in CV medicine.

Keywords
Active vitamin D • Calcium • Calcitriol • FGF-23

Introduction

Despite increased awareness for traditional cardiovascular (CV) risk factors,1 cardiovascular disease (CVD) remains the major cause of death worldwide. It is questionable whether more intense therapy of traditional CV risk factors beyond present treatment targets will reduce CV mortality, since recent large-scale randomized trials failed to provide additional CV benefit by use of combined lipid-lowering agents2 or by more aggressive treatment of hyperglycaemia3 and hypertension.4

Therefore, for residual risk reduction, non-traditional CV risk factors become promising targets. Identification of non-traditional CV risk factors for the general population may start with careful characterization of selected patient cohorts at highest CVD risk, such as chronic kidney disease (CKD) patients, in whom the contribution of non-traditional risk factors to CVD is widely acknowledged.5

Epidemiological and experimental studies identified a deranged calcium–phosphate metabolism as a major non-traditional CV risk factor in CKD patients, as recently summarized.6 Against this background, the present overview discusses how far calcium, phosphate, and their regulating hormones—parathyroid hormone (PTH), active vitamin D (1,25-OH vitamin D or calcitriol), and fibroblast growth factor 23 (FGF-23)—may be implicated in CVD in subjects without advanced CKD; studies primarily focusing on CKD patients will only be mentioned when deemed necessary for proper understanding.

Calcium

Physiological regulation

As the vast majority of total body calcium is located in the bone, only a small fraction of body calcium is present in the plasma. About one half of plasma calcium circulates as free (ionized) calcium, whereas the other half is bound to proteins (mostly albumin) or complexed with citrate, sulphate, or phosphate. Although ionized calcium thus only represents a very small proportion of total body calcium, its level is closely controlled by the interplay of two hormones, namely PTH and calcitriol (Figure 1): decreasing serum calcium levels induce a rapid PTH secretion from parathyroid cells, which in turn stimulates renal hydroxylation of 25–OH vitamin D to calcitriol. While calcitriol triggers intestinal calcium absorption, PTH inhibits renal calcium excretion. Additionally, calcitriol and PTH both stimulate osteoclastic bone resorption, shifting calcium from bone to extracellular fluid. Consequently, serum calcium returns to normal values.7

Conversely, hypercalcaemia inhibits PTH secretion via activation of parathyroid calcium-sensing receptors (CaSR), and directly and indirectly (via reduced PTH levels) lowers calcitriol levels.

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Consequently, intestinal absorption decreases, less calcium leaves the bone, and urinary excretion rises.\(^7\)

**Calcium and cardiovascular disease: clinical evidence**

This tight regulation allows keeping the serum-ionized calcium level within a very narrow range (in the absence of endocrinological disease affecting PTH/calcitriol regulation, malignant conditions, or other severe co-morbidities). Accordingly, measurements of serum-ionized calcium give only poor information on total body calcium homeostasis: calcium overload may occur in the absence of overt hypercalcaemia.

This was impressively illustrated in interventional trials among CKD patients who were randomized to receive either high dosages of calcium salts (acetate or carbonate), or calcium-free medication\(^8,9\) for combating hyperphosphatemia. Patients receiving calcium salts (containing 1.2–2.3 g elemental calcium) had a seemingly minor increase in serum calcium of \(\sim 0.1 \text{ mmol/L}\). Nonetheless, they experienced a much more pronounced progression of vascular calcification.\(^8,9\)

The implications of these studies reach far beyond the field of CKD: in apparently healthy subjects, oral intake of calcium supplements (mostly with a recommended dosage of 500–1000 mg elemental calcium) has been propagated as a remedy against osteoporosis. Given that neutral calcium balance has been calculated to occur at intakes of 741 mg/day in healthy subjects,\(^10\) which is below average dietary intake in western societies,\(^11\) any additional high-dosage calcium supplementation may lead to calcium loading and potentially to tissue deposition in the absence of overt hypercalcaemia.\(^12\)

In line, such intake of calcium supplements for bone protection has recently been claimed to cause excessive myocardial infarction.\(^13\) Conversely, the notion that plasma levels poorly reflect total body calcium balance is further supported by incongruent findings from cohort studies on the association of plasma calcium and future CV events.\(^14\)–\(^16\)

**Calcium and cardiovascular disease: experimental evidence**

Our understanding on the pathophysiological implications of calcium in CVD was revolutionized in the last decade: formerly, it was assumed that, in case of oversaturation, calcium–phosphate crystals were passively disposed in the vessel wall and in the myocardium. In striking contrast, recent evidence clearly demonstrates an active contribution of calcium ions to CVD; first, calcium ions stimulate PiT 1 (a type III sodium-dependent phosphate

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**Figure 1** Physiological regulation of calcium metabolism. Black arrows indicate stimulation; red arrows indicate inhibition.
cotransporter) expression by vascular smooth muscle cells (VSMCs), which may allow phosphate ions to accumulate intracellularly (compare ref.18 for a critical discussion); here, phosphate triggers the development of VSMCs into an osteochondrogenic phenotype (see below). Secondly, calcium induces the release of matrix-vehicle-like structures from viable VSMCs and of apoptotic bodies from apoptotic VSMCs which act as a nucleus for extracellular calcium–phosphate precipitation.19,20 Thirdly, calcium reduces the expression of calcification inhibitors by VSMCs.20 Recent overview articles reviewed calcium and phosphate-mediated vascular calcification in detail.6,18

**Parathyroid hormone**

While a limited body of experimental data suggested direct effects of PTH on myocardial cells (summarized earlier in this journal21), PTH did not induce vascular calcification in experimental studies,22,23 but rather exerted a protective role.24 Epidemiologically, it remains unclear whether PTH has any direct CV effect beyond its role in calcium regulation: following a report on an independent association between PTH and left ventricular (LV) mass in cross-sectional analyses,25 findings from the Uppsala Longitudinal Study of Adult Men claimed that PTH may account for as much as 20% of the population-attributable risk proportion for CV mortality.26 Two subsequent German studies seemingly confirmed a prognostic implication of elevated PTH in cohorts with a high burden of prevalent CVD.27,28 In contrast, adjustments for confounders virtually erased the prognostic impact of PTH on CV mortality among elder commencing-dwelling men in the Osteoporotic Fractures in Men study29 and in the Rancho Bernardo study.30 Associations between PTH and CV death were further challenged by two recent studies among individuals free of CVD at baseline: while elevated PTH predicted incident heart failure31 and malignant arrhythmia32 in the Cardiovascular Health Study, it was neither independently associated with all-cause or CV death, nor with incident myocardial infarction.33 Moreover, a nested case–control study within the Health Professional Follow-Up study failed to identify PTH as a predictor of incident coronary artery disease.33 Of note, the existence of various assays for PTH measurements complicates the comparison between different cohort studies.34

Moreover, in patients with asymptomatic primary hyperparathyroidism, who are chronically exposed to elevated PTH levels, a long-term CV impact of moderately elevated PTH levels has recently been questioned.35 Even among CKD patients, in whom PTH levels are often more than 10-fold higher than in the general population, high PTH failed to independently predict survival in recent large-scale cohort studies.36,37 In line, the Kidney Disease: Improving Global Outcomes (KDIGO) foundation’s 2009 guidelines on chronic kidney disease–mineral and bone disorder (CKD–MBD) defined much wider target ranges for PTH in CKD patients than earlier guidelines.38

Against this background, the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVALVE) study recruited 3883 dialysis patients with secondary hyperparathyroidism, who were randomized to pharmacological PTH lowering by the CaSR-activator cinacalcet, or to placebo treatment,39 for evaluating the effects of cinacalcet on mortality and CV events. Full publication of the study results is scheduled for late 2012; in June 2012, the study’s sponsor pre-announced that cinacalcet failed to improve the CV outcome.

In summary, neither in subjects with intact renal function, nor in CKD patients, firm evidence for a relevant contribution of PTH to CVD exists.

**Vitamin D**

Beyond its fundamental role in bone metabolism and calcium homeostasis, vitamin D may influence various other medical conditions, including CVD. Vitamin D receptors are found in many tissues, and expression of hundreds of genes may be controlled by vitamin D. Since experimental data suggest that vitamin D might exert a wide range of beneficial functions, vitamin D substitution is presently considered a panacea for prevention and treatment of a broad variety of diseases, including malignant, infectious, and CVD. Such an optimistic view is based on the three fundamental assumptions that:

(i) Hypovitaminosis D is a common finding in many industrialized countries.

(ii) Beyond its implication in bone disease and calcium metabolism, hypovitaminosis D substantially contributes to extraskeletal (‘non-skeletal’) co-morbidity.

(iii) Supplementation with vitamin D has important beneficial ‘non-skeletal’ effects beyond calcium and bone metabolism.

All three hypotheses are debatable, and we will critically discuss these assumptions in the context of CVD.

**Is hypovitaminosis D a common finding in industrialized countries?**

Despite its denomination, vitamin D should be considered a hormone rather than a vitamin: the term vitamin, in its strict definition, is chosen for those organic chemical compounds that are not synthesized in sufficient amount by an organism, requiring their dietary intake.

Instead, humans who are regularly exposed to sunlight synthesize adequate levels of vitamin D3 (cholecalciferol), which spontaneously isomerizes to vitamin D3 (cholecalciferol). Thus, vitamin D becomes an essential nutrient only in subjects deprived of exposure to sunlight. Unfortunately, few food components contain sufficient vitamin D, namely fish liver (oils), fatty fish, and egg yolks.40–42

Many individuals are nowadays neither regularly exposed to sunlight nor do they eat adequate amounts of vitamin D-containing food. Therefore, fortification of certain food with cholecalciferol (or alternatively with ergocalciferol (vitamin D2)) was propagated. For certain historic reasons, fortification became more popular in the USA than in many European countries. Both cholecalciferol and ergocalciferol are inactive precursors of active vitamin D (1,25-OH vitamin D; calcitriol), and both require hydroxylation at the 25–carbon and the 1-carbon position. C-25 hydroxylation, which is performed by hepatocytes, is poorly regulated. In
contrast, C-1 hydroxylation, which mainly occurs in the kidney, is highly controlled by various regulators (Figure 2).40,41 Because of their long half-life, measuring of 25-OH vitamin D has become common practice for the assessment of global vitamin D status.43 Unless indicated otherwise, most assays measure 25-OH vitamin D derived from ergocalciferol (25-OH vitamin D2) as well as from cholecalciferol (25-OH vitamin D3). 25-OH vitamin D levels below 20 ng/mL have been defined as vitamin D deficiency, and levels between 20 and 30 ng/mL as vitamin D insufficiency,43 because cohort studies suggested that 25–OH vitamin D levels >30 ng/mL are necessary for adequate suppression of PTH secretion,44 and for optimal intestinal calcium absorption.45 Of note, both assumptions have been questioned recently.42,43,46 Moreover, any such fixed cut-off value inevitably ignores seasonal variation in 25-OH vitamin D levels, and it is completely unknown whether those 25-OH vitamin D levels that are adequate for calcium and PTH regulation may differ from 25-OH vitamin D levels optimal in CV physiology.

The correct definition of hypovitaminosis D is neither trivial, nor purely academic; any definition of an inappropriately high cut-off value will inevitably oversize the dimension of hypovitaminosis D, label millions of individuals around the globe with a misdiagnosis, and potentially expose these otherwise healthy subjects to unnecessary and possibly harmful supplementation.

Collectively, in absence of an unequivocal, biologically, and evidence-based definition of low vitamin D levels, a sound
estimation of the prevalence of true hypovitaminosis D is currently not possible.

**Does hypovitaminosis D substantially contribute to extra-skeletal co-morbidity?**

Vitamin D may have multiple roles in CV physiology, since vitamin D receptors are found in the myocardium as well as in vascular cells. Specifically, vitamin D has been reported to suppress the renin–angiotensin system, 47 to induce insulin secretion 48 and sensitivity, 49 to possess antihypertrophic activity in the myocardium, 50 to block proliferation of VSMCs, 51 to regulate arterial blood pressure, 52 and to inhibit vascular calcification. 53 Moreover, vitamin D may exert immunoregulatory functions, which may further protect against development and progression of atherosclerotic lesions 54 and vascular calcification. 55

However, in clinical cross-sectional studies, low levels of 25-OH vitamin D were neither independently associated with valvular calcification among 1938 Cardiovascular Health Study participants, 56 nor with mean common carotid intima-media thickness in 654 Rancho Bernardo study participants (notably, measurement of internal carotid intima-media thickness yielded discrepant findings). 57

Nevertheless, most large prospective cohort studies found baseline 25-OH vitamin D levels to predict incident CVD, 58,59 CV, 60 and all-cause mortality 60–62 with two notable exceptions. 29,30 Interestingly, the relationship between 25-OH vitamin D and adverse outcome was found to be nonlinear in several cohorts, with very high 25-OH vitamin D levels indicating higher risk rather than optimal protection. 59,62

No observational study can proof causality, and associations of 25-OH vitamin D levels with adverse outcome could reflect residual confounding by unmeasured or poorly measured confounders, despite all efforts of statistical adjustment. Individuals who have lower vitamin D intake to placebo. In these five trials, vitamin D intake ranged from 400 IE daily to 100,000 IE every 4 months, and study size from 191 to 36,282 study participants. Despite their heterogeneity in study design and size, the studies’ results were homogenous: no trial found a significant reduction in CV events among subjects randomized to vitamin D supplementation. 64–68

Vitamin D proponents have argued that vitamin D dosages in most interventional trials were too low to confer CV benefit. In the largest study, participants randomized to vitamin supplementation received 400 IE cholecalciferol daily, keeping many study participants hypovitaminotic despite being randomized to active treatment. 69 Moreover, study participants were not restricted from taking vitamin D supplements on their own, which may have favoured the null hypothesis.

Against this background, two large-scale randomized clinical trials are ongoing that test high-dosage vitamin D supplementation for CVD prevention (Table 1).

Among CKD patients, a single study specifically analysed CV implications of vitamin D treatment: here, despite experimental data on an antihypertrophic myocardial activity of vitamin D, 70 administration of the active vitamin D compound paricalcitol failed to improve myocardial structure and/or function among 227 patients randomized to paricalcitol or placebo. It remains uncertain whether the relatively short treatment period of 48 weeks, and/or a vitamin D-induced increase in FGF-23 (see below) might have masked the hypothesized beneficial effect of vitamin D. 70

In summary, despite a global hype on beneficial non-skeletal effects, convincing data demonstrating that vitamin D therapy improves CV health are currently lacking. Present guidelines from the Endocrine Society recommend that vitamin D intake should primarily be adapted to needs for skeletal health; they suggest against additional vitamin D supplementation for the purpose of preventing CVD, 43 which is in line with a recent scientific statement from the Institute of Medicine.

**Phosphate**

**Physiological regulation of phosphate metabolism**

Average phosphate intake in western societies ranges between 1000 and 1500 mg, depending on food composition. Phosphate-rich nutrition comprises meat, fish, dairy products, and food additives. 71 Intestinal absorption is regulated by calcitriol; in the presence of adequate vitamin D levels, approximately 70% of ingested phosphates are absorbed. 71 To maintain stable serum phosphate levels, urinary phosphate excretion must be adapted to oral intake and intestinal absorption. It is assumed that, by mechanisms which are still incompletely understood, an increase in serum phosphate induces secretion of FGF–23 and PTH, both of which stimulate renal phosphate excretion (Figure 3).

This tight regulation of phosphate homeostasis necessitates intact kidney function. During the course of kidney function decline in CKD, a loss of filtering nephrons may first be compensated by a PTH- and FGF–23 mediated increase in phosphate excretion per single nephron, allowing CKD patients to maintain normal serum phosphate levels until glomerular filtration rate...
Table 1  Future large-scale randomized trials on vitamin D intake

<table>
<thead>
<tr>
<th>Participants</th>
<th>18 000 men ≥ 60 years/women ≥ 65 years</th>
<th>20 000 men ≥ 50 years/women ≥ 55 years</th>
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<tr>
<td>≥</td>
<td>No CVD/malignant disease at baseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>No CVD/malignant disease at baseline&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>Intervention</td>
<td>6000 participants: 1600 IU vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10 000 participants: 2000 IU vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
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<td>6000 participants: 3200 IU vitamin D&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10 000 participants: placebo (patients will additionally be randomized to omega-3 fatty acids or placebo)</td>
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<td>Time frame</td>
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<td>Primary outcome</td>
<td>CVD/cancer</td>
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<td>Supplemental intake of vitamin D/calcium</td>
<td>Vitamin D ≤ 20 μg/day/ calcium ≤ 1200 mg/day</td>
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<td>Estimated study completion: 2019</td>
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<sup>a</sup>Excluding non-melanoma skin cancer.

CVD, cardiovascular disease.

Figure 3  Physiological regulation of phosphate metabolism. Black arrows indicate stimulation, and red arrows indicate inhibition. Dotted lines indicate hypothetical pathways which await final experimental confirmation. Adapted from Heine, Seiler, Fliser, Nephrology Dialysis Transplantation, Oxford University Press, in press.
falls below 30 mL/min.72 Only if CKD progresses further, overt hyperphosphatemia occurs, and CKD patients with highest serum phosphate levels face worst CV outcome.73

Although PTH and FGF-23 prevent overt hyperphosphatemia in the absence of CKD, recent evidence suggests that even high-normal phosphate levels predict adverse outcome, which has first been shown among Cholesterol And Recurrent Events (CARE) study participants (all of whom had prevalent coronary artery disease at study initiation),74 and among Framingham offspring study participants (who were free of CVD at study initiation).15 Within the last years, numerous additional cohort studies confirmed this association.75

An increase in phosphate burden has been associated with cardiac valvular disease,56 with LV hypertrophy (LVH),76 and most notably with vascular calcification. Similarly as discussed before for calcium, phosphate may actively induce calcification by multiple pathophysiologic pathways:

- After its intake into VSMCs, phosphate induces transcription of messenger RNAs encoding proteins involved in matrix mineralization and bone formation, while down-regulating VSMC-specific transcription factors. Vascular smooth muscle cells may subsequently transform from a contractile into an osteochondrogenic phenotype, and release matrix-vesicle (MV) like structures.
- Phosphate may induce apoptosis in VSMCs, which subsequently release apoptotic bodies (AB).
- Matrix-vesicle and AB themselves further trigger extracellular calcium crystallization.
- Phosphate inhibits the transformation of macrophages into vascular osteoclasts, which antagonize vascular calcification by their mineral-resorbing capacity.
- Phosphate induces the expression of FGF-23.

Most of the aspects are discussed in a separate overview article in this Journal,106 and the remaining part of our current manuscript focuses on FGF–23.

**FGF-23**

The phosphatonin FGF-23 is a 251-amino acid protein that is mainly synthesized and secreted by osteoblasts.77 Its secretion may be induced by calcitriol, by PTH, by hyperphosphatemia, and/or by oral phosphate loading.

In the kidney, FGF-23 stimulates phosphaturia by reducing expression and activity of sodium–phosphate (NaPi) co-transporters in the proximal tubules,78 and it lowers calcitriol levels by inhibiting its synthesis and by inducing its degradation. Finally, FGF–23 suppresses PTH synthesis in the parathyroid glands. For exerting these physiological functions, FGF-23 binds to FGF-receptors in the presence of membrane-bound Klotho, which serves as a co-receptor. While FGF-receptors are expressed ubiquitously, membrane-bound Klotho is selectively found in kidneys, parathyroid glands, and in the choroid plexus,79 rendering these organs

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<th>Table 2</th>
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Note: Only studies which did not selectively recruit patients with overt chronic kidney disease are listed. NSSC, nested case–control study; POCS, prospective observational cohort study; CVD, cardiovascular disease; CAD, coronary artery disease; LV, left ventricular; MI, myocardial infarction; CKD, chronic kidney disease; HF, heart failure; TIA, transient ischaemic attack.

Predictive value of FGF-23: −−, no predictive value in univariate analysis; ++, predictive value in univariate analysis; −−, no predictive value after multivariate adjustment; ++, predictive value after multivariate adjustment.

Based on 307 without CKD at baseline.
physiological FGF-23 targets. Similarly to PTH, different assays for measuring FGF-23 exist.\textsuperscript{80}

**Prognostic impact of FGF-23 in cardiovascular disease**

Data on CV implications of FGF-23 first emerged from CKD cohorts: serum levels of FGF–23 progressively rise over the spectrum of CKD, aiming to keep serum phosphate within normal ranges despite low glomerular filtration rate.\textsuperscript{81,82} Indeed, elevated FGF-23 levels may be the earliest\textsuperscript{72} and most pronounced laboratory findings in CKD-MBD.\textsuperscript{83}

At first glance, the increase in FGF-23 might be considered a beneficial compensatory mechanism, protecting CKD patients against phosphate-induced vascular calcification. However, evidence from two large epidemiological studies, the Chronic Renal Insufficiency Cohort (CRIC)\textsuperscript{36} and the Homocysteine in Kidney and End Stage Renal Disease Study (HOST),\textsuperscript{37} stand against this assumption. These two studies followed 4978 CKD patients (not requiring dialysis treatment at baseline) for a medium of 3.5 years\textsuperscript{36} and 2.9 years,\textsuperscript{37} respectively. After adjustment for classical CV risk factors and for traditional CKD–MBD markers, mortality of patients in the higher quartiles of baseline FGF-23 was more than two-fold increased compared with patients with lowest FGF-23.\textsuperscript{36,37} In line, two studies among dialysis patients yielded similar findings.\textsuperscript{83,84} While none of these CKD studies analysed specific causes of death,\textsuperscript{36,37,83,84} data on CV events were gathered in HOST study participants.\textsuperscript{37} Compared with patients with the lowest FGF-23 levels, patients in the highest quartile of baseline FGF–23 had a univariate hazard ratio of 2.58 for future CV events. In multivariate analysis, high vitamin D, calcitriol, and PTH did not.\textsuperscript{37} Similar results were found in two smaller CKD cohort studies.\textsuperscript{85,86}

These impressive findings raised the question whether FGF-23 might have a similar prognostic role among subjects without overt CKD. This issue has been addressed by four prospective studies [namely the Cardiovascular Heath Study (CHS),\textsuperscript{87} Heart and Soul Study,\textsuperscript{88} Health Professionals Follow-up Study (HPFS),\textsuperscript{89} and the Women’s Health and Aging study (WHAS)\textsuperscript{90}], which have been published until July 2012; results from two further studies [the Prevention of Events with Angiotensin Converting Enzyme Inhibition trial (PEACE),\textsuperscript{90} and HOM SWEET HOMe study] are presented at international meetings in 2012.

As summarized in Table 2, these studies showed that elevated FGF-23 levels strongly predicted incident heart failure and CV death among subjects without overt CKD, while atherosclerotic events (namely acute myocardial infarction) were predicted less impressively.

**Is FGF-23 a marker or a mediator of cardiovascular outcome?**

It is controversially discussed in how far FGF-23 actively contributes to CV damage. At first glance, it may be argued that adverse outcome in subjects with elevated FGF–23 may fully be explained by its strong association with impaired kidney function and with systemic phosphate burden. In this scenario, FGF-23 would be an innocent bystander that passively mirrors deleterious implications of kidney damage and systemic phosphate burden on CV biology. Although most epidemiological studies aimed to adjust for kidney function and serum phosphate, residual confounding cannot be ruled out: most cohorts used creatinine-based estimation of glomerular filtration rate for quantifying kidney function,

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**Figure 4** FGF-23 serum levels among HOM SWEET HOMe study participants stratified by left-ventricular function (left columns) and by the presence and degree of coronary artery disease (right columns). P-values from ANOVA with test for trend. Updated analysis after inclusion of all 1309 study participants.
which is somewhat imprecise at early stages of CKD; serum phosphate levels have a large biological variability (a feature shared with other CKD–MBD parameters), and a single phosphate measurement is therefore a poor marker of systemic phosphate burden.

Alternatively, impaired CV outcome in subjects with elevated FGF-23 might result from reduced synthesis and accelerated degradation of calcitriol. However, as stated above, the cardio- and vasculoprotective implications of vitamin D are still under discussion.

Figure 5 Hypothesized interplay of FGF-23 and phosphate in initiation and progression of cardiovascular disease (schematic illustration). (A) An elevated phosphate burden may directly contribute to vascular calcification and to atherogenesis, which impacts cardiac function by increasing left-ventricular afterload and by reducing left-ventricular oxygen supply. Furthermore, an elevated phosphate burden may indirectly contribute to cardiac disease by triggering FGF-23 secretion. FGF-23 induces myocardial hypertrophy, which may predispose to left-ventricular dysfunction. (B–D) Potential implications of therapeutic interventions. While oral phosphate binders decrease both FGF-23 and phosphate burden (Figure 5B), FGF-23 antagonists attenuate FGF-23 signalling on myocardial cells at the expense of reduced renal phosphate excretion, thereby further increasing phosphate burden (Figure 5C). Finally, vitamin D treatment may increase both FGF-23 and phosphate burden, which offsets direct beneficial vascular or myocardial effects of vitamin D (Figure 5D). Black arrows indicate stimulation, and red arrows indicate inhibition. Adapted from Heine, Seiler, Fliser, Nephrology Dialysis Transplantation, Oxford University Press, in press.
In contrast, a direct deleterious effect of FGF-23 on the CV system has long been considered unlikely; although myocardial cells express FGF-receptors, the absence of its co-receptor Klotho seemingly precluded a direct FGF-23 effect. This assumption was recently challenged by Faul et al.,94 who demonstrated in cellular and murine experiments that FGF-23 induced LVH Klotho-independently. Moreover, they reported FGF–receptor blockers to antagonize uraemia-induced LVH. Of note, Shalhoub et al.95 very recently failed to reproduce beneficial effects of FGF-23 inhibition on LVH when using FGF-23 antibodies instead of FGF-receptor blockers.

Expanding findings from cross-sectional studies,96,97 Faul98 supplemented their experimental data with serial echocardiographic studies among CKD patients, in whom elevated FGF-23 levels predicted the development of LVH.

Left ventricular hypertrophy predisposes to development of LV dysfunction and congestive heart failure,99,100 which may link experimental data on FGF-23–induced myocardial hypertrophy with clinical evidence for a predictive role of FGF-23 in incident heart failure.88,90 Further support for an association between elevated FGF-23 levels and LV function comes from our HOM SWEET HOME study, which recruited 1309 patients admitted for elective coronary angiography between May 2007 and June 2010. A total of 1022 out of 1309 patients underwent assessment of LV-function with ventriculography. Cross-sectional data from patients studied before January 2010 were published recently,101 we now updated these results with data from patients recruited afterwards. Confirming our earlier report,101 higher FGF-23 levels were associated with impaired LV function, but not with the presence or severity of coronary artery disease (Figure 4).

**FGF-23 and serum phosphate: partners in crime?**

Upon these experimental and clinical data, we hypothesize an interaction between FGF-23 and phosphate in the pathophysiology of CVD (Figure 5). Chronic kidney disease and/or diet-associated chronic phosphate loading directly induce vascular calcification and atherosclerosis. Via vascular stiffening and a subsequent increase in cardiac afterload, calcification contributes to LVH, while atherosclerosis—when affecting coronary arteries—may reduce myocardial oxygen delivery. Moreover, an elevated phosphate burden triggers secretion of FGF-23, which aims to tackle hyperphosphatemia by Klotho-dependent stimulation of phosphaturia, but in parallel activates cardiomyocytes. This may further contribute to LVH development, which in the long run predisposes to LV dysfunction and congestive heart failure.

Future clinical and experimental studies must test this hypothetical concept, before new therapeutic strategies may be propagated in CVD. Such treatment strategies could comprise oral phosphate binders, FGF-23-blocking agents, or antagonists of FGF-receptors. Among these, only oral phosphate binders are available at present, and their capacity to reduce serum FGF-23 levels has repeatedly been confirmed.102–104 From a pathophysiological viewpoint, oral phosphate binders may confer broader vasculo- and cardio-protection than FGF-23-blocking agents or FGF-receptor antagonists; as depicted in Figure 5, the latter (seemingly more specific) treatment strategies will antagonize myocardial FGF-23 effects at the expense of a reduced urinary phosphate excretion and a subsequent increase in systemic phosphate burden,95 whereas use of phosphate binders tackles both systemic phosphate burden and elevated FGF–23. Notably, different subtypes of FGF-receptors exist, and a better grasp of organ-specific receptor expression might allow to develop selective inhibitors of cardiac FGF-receptors, which may allow combating FGF-23-induced LVH while leaving phosphaturia unaffected.

Finally, this pathophysiological model may help explain why vitamin D did not improve CV outcome in interventional trials; any direct beneficial CV effect of vitamin D supplementation might be offset by an increase in serum phosphate and FGF-23.105

**Summary**

Numerous experimental and clinical data allowed to characterize calcium, phosphate, and their regulating enzymes as emerging CV risk factor. Their role in the initiation and progression of CVD is, however, still insufficiently understood. As all components of calcium–phosphate metabolism are closely intertwined, any interventional modification of a single factor will inevitably affect all other components. Therefore, results from ongoing interventional trials, such as the Finnish Vitamin D Trial and the ‘Vitamin D and Omega-3 Trial’, must be awaited before individual components of calcium–phosphate metabolism may become targets for CVD prevention or treatment in clinical practice.

**Conflict of interest:** G.H.H. has received travel grants and speaker fees from Shire. M.N. has no conflict of interest to declare. D.F. has received speaker fees from Shire, Genzyme, and Amgen.

**References**


Calcium and phosphate impact cardiovascular risk


