Phosphate: a novel cardiovascular risk factor

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It has recently been recognized that even in the normal population high normal phosphate concentrations are associated with increased all-cause and cardiovascular mortality. Organic phosphates in unprocessed food items are less efficiently absorbed than food additives in the form of inorganic phosphate salts. This is of relevance because even high normal and even more so elevated phosphate concentrations are correlated with reduced life expectancy and cardiovascular events. The underlying pathophysiology includes endothelial dysfunction, vascular calcification, and cardiac hypertrophy. Phosphate intake and serum phosphate concentrations must be considered as novel cardiovascular risk factors (although the causality of the correlation has not been definitely established).

Serum phosphate as a cardiovascular risk factor in chronic kidney disease and beyond

In patients with chronic kidney disease (CKD), it was recognized some time ago that an elevated serum phosphate concentration is a powerful risk factor for all-cause and cardiovascular mortality.1,2 As a consequence, dietary phosphate restriction is recommended in this population.3 This advice is based on the view that reduction in dietary phosphate intake is associated with a survival benefit.

What is new in this context is the recent observation that the relation between high serum phosphate and survival is not restricted to patients with CKD, but is also seen in patients with cardiovascular disease and even in the normal population: high normal phosphate levels predict coronary calcification even in healthy young men.4 In the Framingham study as well high normal phosphate levels at baseline predicted cardiovascular events.5 Finally, in individuals with cardiac disease and normal renal function, Tonelli et al.6 found a relation between the serum phosphate concentration and the cardiovascular event rate. In this study, the adjusted mortality risk was 22% higher per 1 mg/dL of higher serum phosphate concentration.

New insights into the control of phosphate metabolism

The major determinant of serum phosphate is renal phosphate excretion. In the past, it was thought that the key hormonal determinant of tubular phosphate reabsorption is parathyroid hormone (PTH). This simple view has undergone a major revision with the recent documentation that the master regulator of renal phosphate handling is the fibroblast growth factor (FGF23).7,8 Fibroblast growth factor 23 is a product of osteocytes in bone.7 Fibroblast growth factor 23 is increased dependent on phosphate uptake and levels, and is induced by high levels of calcitriol. The details of FGF23 control are a topic of current evaluation.

Increased FGF23 augments phosphate excretion in the kidney. Fibroblast growth factor 23 interacts at the level of the proximal tubule with a cofactor, i.e. klotho. Apart from causing phosphaturia, FGF23 also suppresses the renal 1-α-hydroxylase and thus the renal synthesis of calcitriol. Klotho, a membrane-bound β-glucuronidase enzyme, is an indispensable part of classical FGF receptor signalling in the kidney that facilitates the renal actions of FGF23 on phosphate handling [by signalling the inhibition of two distinct sodium phosphate transporters (PiT), i.e. NaPi 2a and 2c] and vitamin D synthesis. Klotho knockout in animals replicates the findings in FGF23 deficiency. Of particular interest, however, is the observation that the lack of klotho in knockout mice also reproduces a phenotype of premature senescence.9 Low klotho is associated with high serum phosphate in animal experiments, suggesting that phosphate may be one of the key signalling molecules of ageing.10

The efficacy of the regulation of renal phosphate excretion by FGF23 is illustrated by the observation that in early stages of reduced renal function serum phosphate remains normal at the price of FGF23 elevation (serum phosphate levels only start to rise when >70% of renal function is lost). The complexity of renal phosphate excretion is further increased by the recent documentation of intestinal molecules impacting acutely on renal phosphate handling independently of FGF23 and PTH.7 Fibroblast growth factor 23 acts, apart from the kidney, on other organs as well, e.g. the parathyroids. Of particular interest from the cardiovascular point of view: FGF23 appears to trigger myocardial hypertrophy (Figure 1).
The mechanisms underlying the effects of phosphate on cardiovascular damage

The pathomechanisms underlying the adverse effects of phosphate on cardiovascular organs include vascular calcification, endothelial dysfunction, myocardial hypertrophy, and cardiac malfunction.

Phosphate and cardiovascular calcification

In contrast to the past opinion, cardiovascular calcification is not just the result of passive precipitation of calcium and phosphate. Recent studies documented that high phosphate triggers the differentiation of vascular smooth muscle cells (VSMCs) into osteoblast-like cells, a process that was termed osteogenic transdifferentiation. In the presence of high extracellular phosphate concentrations, phosphate is actively taken up by P1Ts into the cell. This process is a prerequisite to start this transdifferentiation programme. By this pathomechanism VSMCs adopt the expression profile of an osteoblast. Another important additional trigger for this cellular transdifferentiation programme is inflammation.

Phosphate and endothelial dysfunction

Even transient increases of serum phosphate concentrations, e.g. post-prandial hyperphosphataemia, may promote endothelial dysfunction. In the study of Shuto et al. bovine aortic endothelial cells exposed to high phosphate concentrations produced more reactive oxygen species and less NO. Such dysfunction was also triggered by an increased influx of phosphate via sodium-dependent phosphate transporters (inhibitory phosphorylation of eNOS). The human relevance of this effect was documented in volunteers: in a double-blind crossover study a meal containing 1200 mg of phosphate caused a decrease in flow-mediated dilatation at 2 h compared with a meal containing 400 mg of phosphate. Such post-prandial endothelial cell dysfunction may contribute to phosphate-induced cardiovascular morbidity and mortality.

Fibroblast growth factor23 and myocardial hypertrophy/dysfunction

Until recently it was thought that the effects of FGF23 were exclusively mediated via its coreceptor klotho (see above). Experimental data now point to direct, klotho-independent effects of FGF23 on cardiac structure and function, i.e. left-ventricular hypertrophy and malfunction (Figure 1). Elevated FGF23 was found to be
independently associated with left ventricular hypertrophy in patients with CKD, and rat studies documented that FGF23 activates FGF receptors in the heart and induces left ventricular hypertrophy (LVH) via a calcineurin/NFAT signalling pathway, even in the klotho-deficient mice.\textsuperscript{13} Such LVH was attenuated by the administration of an FGF receptor blocker to a hypertensive rat model of CKD, suggesting a blood pressure independent effect of FGF23 on LVH. Given the remarkably strong correlation between serum phosphate concentrations and FGF23, these findings raise the possibility that measures aimed at reducing dietary phosphate could interfere with the genesis of ventricular hypertrophy in renal patients and, perhaps, even in patients without CKD.

**Sources of dietary phosphate**

It makes sense to distinguish natural phosphate sources including phosphoproteins, phospholipids, phosphate esters, or phytates in unprocessed food items, such as milk products, fish, meat, and vegetables, respectively, from phosphate additives. Naturally occurring phosphates are slowly hydrolysed and incompletely as well as slowly absorbed in the GI tract. The proportional absorption of natural phosphates only ranges 30 and 60%.

In contrast, phosphate in the form of sodium phosphate or other phosphate-containing salts are commonly used as additives to food items serving as preservatives, flavour Enhancers, colour stabilizers, sweeteners, antioxidants, or emulsifiers. Such inorganic phosphate is readily absorbed in the gut and may reach uptake proportions of 80 and 100%. Up to 1000 mg of added phosphate, which equals the upper recommended level of daily phosphate intake in CKD patients,\textsuperscript{14} may be found in just one meal of commercial fast food items. Average Western diets provide a daily phosphate intake of 1100–1700 mg.

**Conclusions**

The above findings justify the recommendation to include fasting serum phosphate as a risk predictor in patients with kidney malfunction or cardiovascular disease. In addition, dietary advice to minimize food items containing added inorganic phosphates would constitute a measure for patients with chronic kidney or cardiovascular disease. Therefore, appropriate food labelling seems warranted. Elucidation of the pathogenetic pathways triggered by phosphate will be a fascinating issue in current and future cardiovascular research.

**References**


