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Review

Bioavailable dietary phosphate, a mediator of cardiovascular disease, may be decreased with plant-based diets, phosphate binders, niacin, and avoidance of phosphate additives

Mark F. McCarty B.A. [a,*], James J. DiNicolantonio Pharm.D. [b]

[a] *Catalytic Longevity, Carlsbad, California, USA*
[b] *Wegman's Pharmacy, Ithaca, New York, USA*

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ABSTRACT

Increased fasting serum phosphate within the normal physiological range has been linked to increased cardiovascular risk in prospective epidemiology; increased production of fibroblast growth factor 23, and direct vascular effects of phosphate, may mediate this risk. Although dietary phosphate intake does not clearly influence fasting serum phosphate in individuals with normal renal function, increased phosphate intake can provoke a rise in fibroblast growth factor 23, and in diurnal phosphate levels, and hence may adversely influence vascular health. Dietary phosphate absorption can be moderated by emphasizing plant-based dietary choices (which provide phosphate in less bioavailable forms); avoidance of processed foods containing inorganic phosphate food additives; and by ingestion of phosphate-binder drugs, magnesium supplements, or niacin, which precipitate phosphate or suppress its gastrointestinal absorption. The propensity of dietary phosphate to promote vascular calcification may be opposed by optimal intakes of magnesium, vitamin K, and vitamin D; the latter should also counter the tendency of phosphate to elevate parathyroid hormone.

Serum phosphate as a vascular risk factor

In recent prospective epidemiologic analyses, serum phosphate within the normal physiological range has been found to correlate positively and monotonically with risk for cardiovascular events, new heart failure, and cardiovascular and all-cause mortality [1–8]; an excellent summary of these data in tabular form was provided previously [9]. In the Framingham Offspring Study, cardiovascular risk was 55% higher in the upper quartile of serum phosphate compared with the lower quartile [2]. Remarkably, these associations tend to be strengthened by adjustment for covariant risk factors; hence, there is good reason to suspect that the correlation between serum phosphate and cardiovascular risk is indeed causative [10–13]. In cross-sectional studies, serum phosphate has correlated directly with carotid intima-media thickness, ankle brachial pressure index (a measure of arterial stiffness), left ventricular mass, QT interval, and extent of coronary stenoses [3,14–19]. It has long been known that the excessive serum phosphate levels often seen in chronic kidney failure predict early-onset cardiovascular disease (CVD) and mortality, and are associated with pathologic medial calcification [20,21]. But these new findings link serum phosphate to risk for typical atherosclerosis in individuals with normal kidney function and normal phosphate levels.

Some investigators suspect that high serum phosphate can promote premature aging [22–24]. Klotho is a coreceptor for fibroblast growth factor 23 (FGF23) in the renal tubules and parathyroid gland, enabling FGF23 to promote renal phosphate excretion. Mice bioengineered to lack a functional klotho gene therefore lack proper FGF23 activity and experience chronically elevated serum phosphate. These mice die young and are characterized by a progeroid-like syndrome associated with pathologic calcification, muscle wasting, kyphosis, atherosclerosis, and infertility; remarkably, severe restriction of dietary phosphate largely prevents these abnormalities [22,23,25]. Elevated phosphate is also a feature of the Hutchinson-Gilford progeria

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* Corresponding author. Tel.: +1 760-216-7272; fax: +1 760-704-6379.
E-mail address: Markfmccarty@gmail.com (M. F. McCarty).

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syndrome in humans, and may play a role in their rapid vascular aging—albeit phosphate is not solely responsible for the associated pathology and premature mortality [26].

Possible mediators of the risk

How modest increases in serum phosphate might mediate an increase in vascular risk still requires clarification; multifactorial mechanisms are likely involved. Increased serum phosphate boosts bone production of FGF23, which, like parathyroid hormone (PTH), promotes phosphaturia by reducing membrane expression of sodium phosphate cotransporters in renal tubules [27–30]. FGF23 also acts on the kidneys to decrease expression of 25-hydroxyvitamin D 1 α-hydroxylase (CYP27 B1)—rate-limiting for calcitriol synthesis—while up-regulating expression of 24-hydroxylase (CYP24 A1), which degrades calcitriol [31,32]. The resulting decrease in circulating calcitriol leads to up-regulated production of PTH (albeit this effect is somewhat blunted by a direct action of FGF23 on the parathyroid [33]); this increase in PTH synergizes with FGF23 in promoting phosphaturia [29]. The reduction in calcitriol also diminishes the efficiency of intestinal phosphate absorption by inhibiting expression of a sodium-dependent phosphate cotransporter [34,35]. Thus, high serum phosphate tends to suppress calcitriol—a hormone that promotes intestinal phosphate absorption—while boosting FGF23 and PTH, mediators of phosphaturia.

Unfortunately, this homeostasis may come at a cost: FGF23 and PTH have the potential to act on the vasculature, directly or indirectly, and promote atherosclerosis, endothelial dysfunction, vascular calcification, and ventricular hypertrophy [9]. Increased FGF23 has been correlated with indices of cardiovascular risk, including atherosclerosis and impaired endothelium-dependent vasodilation in individuals with or without renal dysfunction [36–40]. In community-based prospective studies, higher serum FGF23 has been linked to increased risk for cardiovascular events and mortality after adjustment for confounders including serum phosphate and glomerular filtration rate [41,42]. FGF23 can act directly on cardiomyocytes, via a klotho-independent receptor, to promote hypertrophy; not surprisingly, FGF23 has been shown to correlate positively with left ventricular mass in individuals with or without renal disease [37,43]. Elevated levels of FGF23 are independently associated with the progression of chronic kidney disease (CKD), and with cardiovascular events and mortality in predialysis patients with CKD, patients with end-stage renal disease, and kidney transplant recipients [44–46]. Elevated PTH is suspected to be a key mediator of the increased risk for cardiovascular events, atherosclerotic disease, metabolic syndrome (MetS), and ventricular hypertrophy linked to poor vitamin D status [47–54].

In addition to its up-regulatory effect on PTH, the decline in serum calcitriol promoted by increased serum phosphate might increase cardiovascular risk in other ways. In particular, calcitriol suppresses renal secretion of renin [55]. Recent epidemiology points to elevated plasma renin as a risk factor for cardiovascular and total mortality [56–59]—which should not come as a surprise in light of the pro-oxidative effect of renin–angiotensin signaling and the favorable clinical outcomes achieved with drugs that inhibit this signaling. However, whether elevations of serum phosphate or of FGF23 are associated with elevated renin has not been assessed. Additionally, calcitriol can exert anti-inflammatory effects on vascular macrophages; however, calcitriol of autocrine origin (regulated by circulating calcidiol) seems likely to play the chief role in this regard [60–62]. Similarly, whereas serum calcitriol has the potential to decrease risk for cancer in certain vitamin D-responsive epithelia, autocrine calcitriol is thought to make a more important contribution to vitamin D activity in these tissues [63–65]. The possibility that serum calcitriol might modestly modulate cancer risk in the context of poor vitamin D status (and hence low calcidiol levels) requires further evaluation [66]; so far, the effect of serum phosphate on cancer risks has received minimal study. However, it has been argued that the increase in risk for prostate cancer associated with heavy use of dairy products is more reasonably attributed to high phosphate intake than to high calcium intake, owing to the fact that fluctuations in serum phosphate are far greater than those of serum calcium [67].

Increased serum phosphate also may act directly on vascular tissues to mediate risk. In vitro, the high concentrations of phosphate commonly seen in CKD can convert vascular smooth muscle cells to an osteoblast-like phenotype capable of depositing calcium phosphate crystals in an extracellular matrix similar to bone; high phosphate also promotes the deposition of such crystals [9,20,21,68]. Perhaps more pertinent to individuals with normal kidney function is a recent study showing that a meal rich in phosphate (1200 mg) acutely impairs the endothelium-dependent vasodilation in healthy individuals [69]. Studies with cultured endothelial cells suggest that this effect requires intracellular phosphate uptake, and is mediated by activation of protein kinase C, which in turn activates nicotinamide adenine dinucleotide phosphate-oxidase while suppressing the activity of endothelial nitric oxide synthase [69]. At higher concentrations (2.5 mM), phosphate can induce oxidant-associated apoptosis in endothelial cells [70].

In short, elevated serum phosphate, and the homeostatic responses that it provokes—increases in FGF23 and PTH, a decrease in calcitriol—may work in a number of complementary ways to compromise vascular health. Moreover, there is suggestive (although not conclusive) evidence that elevated PTH may increase risk for MetS [50–54]

Why is phosphate decreased in metabolic syndrome?

It is somewhat surprising that serum phosphate tends to be relatively low in individuals with MetS or obesity [10,13]. Does MetS somehow work to suppress phosphate levels—or do low phosphate levels encourage the development of MetS? Or does some third factor suppress both phosphate and insulin sensitivity? There is recent evidence that FGF23 levels tend to be increased in older individuals with MetS [71] (although, somewhat discordantly, FGF23 is reported to correlate inversely with insulin sensitivity in obese adolescents [72]). Moreover, the up-regulation of PTH associated with poor vitamin D status may boost risk for this syndrome [51,52,54,73]. Clearly, increased FGF23 and PTH in patients with MetS would be expected to lower serum phosphate by a phosphaturic effect. Moreover, the increase in sympathetic tone characteristic of MetS can provoke a reduction in serum phosphate, possibly by causing it to shift to intracellular compartments [74–76]. These considerations suggest that the hormonal milieu associated with MetS may be responsible for the relatively low serum phosphate observed in this syndrome. On the other hand, in mice, a diet with only one-third the usual phosphate content led to a marked increase in epididymal fat and a corresponding increase in insulin resistance [77]. So the possibility that severe phosphate deficiency might induce a deterioration of insulin sensitivity in humans merits consideration. Nonetheless, such a phenomenon is hardly likely to be at play in the majority of patients with MetS with modestly reduced serum phosphate. Clinical studies evaluating