Phosphate: Time for a Fresh Look at Dietary Control?

By Sharon M. Moe

Phosphate is a true uremic toxin. Cross-sectional studies in patients undergoing dialysis uniformly demonstrate an increased risk of mortality with increasing phosphate levels. The population-attributable risk of mortality in dialysis patients is markedly greater for phosphate than anemia or urea reduction ratio. Additional cross-sectional studies in patients with and without chronic kidney disease (CKD) who are not yet receiving dialysis have demonstrated that phosphate levels in the upper quartile or tertile within this normal range have increased cardiovascular and/or all-cause mortality. In vitro, animal, and some human studies demonstrate that control of extracellular phosphate levels attenuates the process of vascular calcification. Despite recognition of the importance of this uremic toxin, it remains a clinical challenge to control.

The level of blood phosphate is controlled by three hormone systems—parathyroid hormone, fibroblast growth factor 23 (FGF23)/Klotho, and the vitamin D axis—and each of these systems regulates the others. Despite this complex regulation, there is a fairly wide range of "normal" levels: from 3.0 to 4.7 mg/dL in most laboratories. In patients with CKD, the phosphate level rises with progressive kidney disease because of a failure of this homeostatic system leading to decreased ability to excrete a phosphate load. There is also a normal diurnal variation in phosphate levels, with a peak in the middle of the night and a nadir in the morning, even in CKD. This diurnal variation may also lead to the wide range of "normal" phosphate levels, inasmuch as patients do not get their blood drawn at the same time of day. But three other factors likely play a prominent role in this clinical conundrum.

The first is inadequate dialysis. The majority of total body phosphate is not in the extracellular space, so longer or daily dialysis is required to optimize removal. In the Frequent Hemodialysis Study, a randomized trial of daily versus standard dialysis, survival was greatest and the phosphate was lowest in the daily dialysis arm. Although these findings certainly do not constitute proof that removing more phosphate improves mortality, inasmuch as many other factors were also improved, the study was proof that daily dialysis is an effective therapy for phosphate removal.

The second is food additives—a hidden source of dietary phosphate. Unfortunately, nearly every prepackaged food type, whether in a can, a box, or frozen, has a phosphate-based preservative. The quantity is not shown on the food label, but whatever is eaten is highly bioavailable and therefore is rapidly absorbed. One study has shown that just advising dialysis patients to avoid prepackaged foods can lower blood phosphate levels.

The third is the source of dietary protein. Phosphate is a key component of all proteins. However, in grain-based sources of protein such as soy, and in nuts and beans, the protein is bound to phytate. Humans lack the enzyme phytase and thus cannot metabolize phytate, leading to decreased intestinal bioavailability of those protein sources of phosphate. By contrast, in meat and dairy sources of protein (casein), the phosphate is much more bioavailable, and thus a greater percentage of the phosphate will be absorbed.

In rats with CKD, this difference in phosphate levels between those fed with grain and those given casein (synthetically made) diets is substantial, and the differences also lead to worsened hyperparathyroidism, vascular calcification, and progressive kidney disease.

We recently completed a small pilot crossover trial comparing a vegetarian (nearly vegan except for eggs) diet to a meat diet, each containing 3 g sodium, 80 g protein, and 800 mg phosphate in patients with a mean estimated GFR of 32 mL/min. The vegetarian diet led to a decrease in phosphate levels by 0.3 mg/dL and decreased the FGF23 levels by nearly 30 percent. The first lesson learned from this study was that the estimates of phosphate content from vegetarian sources in the available research databases were very inaccurate. This is not terribly surprising, given that the actual phosphate content of grains depends a lot on the type of grain and the soil and water phosphate content where it was grown. The second lesson learned from this study was that it was nearly impossible to develop a diet incorporating all of the renal diet recommendations, even by experienced research dieticians. And yet, we hand our patients individual lists of different things to avoid and call them noncompliant when they cannot put it together in a single meal. The differences in the dietary sources of protein may also explain why hyperphosphatemia appears to be more common (or more severe) in the Western world than in other cultures.

Perhaps we need a fresh approach to kidney nutrition counseling. And perhaps this can be a simple message: Avoid canned and boxed foods, and eat vegetarian sources of protein. The latter will take some education of patients who are not vegetarian or vegan, but it is likely a much easier educational program than separate handouts for phosphorus, potassium, sodium, and protein. Long-term studies are needed to show the sustained efficacy of, and increased compliance with, such an approach, but we shouldn't give up dietary phosphate restriction. We should also push for the reduction of phosphate-based preservatives—or, at the very least, quantitation of those substances on food labels. Unfortunately, we are what we eat!

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Inhibitors: The Key to Controlling Vascular Calcification

By W. Charles O'Neill

Arterial calcification is a common problem in advanced kidney disease and contributes to the high prevalence of cardiovascular disease. There are two forms: neointimal calcification, associated with atherosclerosis, and medial calcification. The former is not exclusive to renal failure and occurs in anyone with atherosclerosis. It is unclear whether this has any clinical significance other than being a convenient marker of atherosclerosis. Medial calcification is independent of atherosclerosis and is strongly linked with chronic kidney disease (CKD). Recent data based on mammography show that there is a more than threefold risk of medial calcification in ESRD and that this risk may begin as early as stage 3 CKD.

Although disordered phosphate metabolism clearly plays a role in medial arterial calcification, it cannot by itself explain this problem, and strategies other than controlling hyperphosphatemia are needed. A large body of data implicates extracellular pyrophosphate (PPi), an endogenous inhibitor of hydroxyapatite formation, in arterial calcification. Humans lacking the ectoenzyme that produces PPi develop severe arterial calcification in childhood, and mice lacking the same enzyme also develop arterial calcification. Extracellular PPi may also be derived from intracellular PPi, and a mutation in the putative transporter (ANK) leads to ectopic calcification in mice, but primarily of joints rather than vessels.

Plasma levels of PPi are reduced in hemodialysis patients and correlate inversely with arterial calcification. This may be related to another key enzyme in extracellular PPi metabolism, tissue-nonspecific alkaline phosphatase (TNAP), which hydrolyzes PPi and induces arterial calcification when genetically overexpressed in vascular smooth muscle in vitro and in vivo. The activity of TNAP is increased in vessels from uremic rats, suggesting a pathologic role. Currently, little is known about the regulation of TNAP in vascular smooth muscle cells and why it is upregulated in renal failure.

Therapies based on pyrophosphate show promise as potential clinical tools. Both PPi and bisphosphonates (nonhydrolyzable analogs of PPi) inhibit arterial calcification in uremic rats, and recently developed small molecule inhibitors of TNAP can prevent arterial calcification *in vitro*. The doses of bisphosphonates required to inhibit vascular calcification *in vitro* are far greater than those used to inhibit bone resorption in humans. One potential drawback to this approach (and any potential therapy for ectopic calcification) is inhibition of bone mineralization, which requires a high local activity of TNAP to remove inhibitory PPi. Consequently, the nonhydrolyzable bisphosphonates, but not PPi, inhibit bone formation at doses required to prevent arterial calcification in rats.

Two other endogenous inhibitors of arterial calcification, matrix gla protein and osteopontin, also appear to act through direct inhibition of hydroxyapatite formation but probably do not play a primary pathogenic role in the vascular calcification of CKD, inasmuch as both are upregulated in vessels from uremic rats. Matrix gla protein requires vitamin K–dependent γ-carboxylation. Deficiency—either genetic or related to warfarin use—leads to vascular calcification in animals and humans. Osteopontin is, molecule for molecule, the most potent known inhibitor of hydroxyapatite formation, but deficiency does not lead to vascular calcification unless coupled with deficiency of another inhibitor. These proteins have limited therapeutic potential because matrix gla protein is extremely insoluble, and osteopontin has other inflammatory actions. However, vitamin K could be of benefit because patients with advanced renal failure may have vitamin K deficiency. Magnesium also inhibits hydroxyapatite formation and accounts for most of the inhibitory activity in plasma, but its therapeutic potential has not been explored.

Thiosulfate is another compound that can inhibit vascular calcification in vivo and in vitro and is often used to treat calciphylaxis. Although it is present endogenously, the levels are far below those required to inhibit calcification. It is widely assumed that thiosulfate acts by chelating calcium, but recent data indicate that its interaction with calcium ions is extremely weak and that there is no effect on hydroxyapatite formation or dissolution. Thus, its mechanism of action remains to be determined.

It is clear that the arterial wall has a propensity to calcify, even in the absence of altered mineral metabolism, and that endogenous inhibitors, particularly pyrophosphate, are required to prevent this. Thus, arterial calcification must be seen as a failure of these endogenous mechanisms. Although these inhibitors can be the basis for future preventive and therapeutic strategies, their unwanted effects on skeletal mineralization must also be considered.

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