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: noninimal 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 studies other than control have demonstrated that extracellular phosphate levels attenuate 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 preservative 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 preservative food can lower 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 corn and those given casein (synthetically made) diets is substantial, and the differences also lead to worsened hyperparathyroidism, vascular calcification, and progresive 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 non-compliant when they cannot put it together in a single meal. The differences in the diet sources of protein may also explain why hyperparathyroidism 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.

In long-term studies are needed to show the sustained efficacy of, and increased compliance with, such an approach, but we should not 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.

Sharon M. Moe, MD, is professor of medicine and anatomy & cell biology and director of the division of nephrology at Indiana University School of Medicine.