Lowering High-Normal Phosphate Levels Could Benefit Many, Studies Show

By Timothy O’Brien

Lowering serum phosphate levels may benefit three groups currently not often targeted for phosphate-lowering therapies, studies show. New dialysis patients, patients with early chronic kidney disease (CKD), and possibly even healthy individuals with no clinical evidence of cardiovascular or renal disease may all benefit from reducing their high-normal phosphate levels.

Taking phosphorus binders reduced the risk of death by 25 to 30 percent among dialysis patients in a study reported in the January 2009 *Journal of the American Society of Nephrology*. New dialysis patients with only modest or even no increase in their serum phosphate levels were among those who showed improved survival rates.

Two other reports suggest that high-normal phosphate levels may be tied to a marker of increased cardiovascular risk, not only in patients with moderate CKD but also in apparently healthy young adults.

Taken together, these studies suggest that phosphorus may be less of a bystander and more of an active player in kidney and cardiovascular health.

**Phosphate Binders Lower Mortality in New Dialysis Patients**

“A growing number of publications have suggested that abnormalities of phosphorus metabolism—specifically phosphorus overload—are risk factors for mortality,” said Myles Wolf, MD, of the University of Miami Miller School of Medicine in Miami, Fla. “As a result, many nephrologists believe that lowering serum phosphate levels can improve survival in patients with kidney disease, particularly those on

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Obama Health Plan Would Expand Insurance Coverage

By Eric Seaborg

"Change" was the mantra of President Barack Obama’s campaign, and health care was a main arena he pledged to reform.

"The time has come for affordable, universal health care in America," Obama said when he introduced his health-care initiative at the outset of the campaign. However, most observers agree that his plan would expand the reach of health insurance coverage, but not come close to making it universal. His strategy also includes measures aimed at decreasing costs, improving efficiency, and increasing the focus on chronic diseases.

Some experts believe that the intervening economic crisis will force Obama and his strategists to scale back their plans.

"Big-time health reform is very hard to do and given the budget deficit and economy, it will be even harder to enact something like Obama proposed during the campaign," said Jonathan Oberlander, PhD, associate professor at the University of North Carolina Chapel Hill School of Medicine and School of Public Health. “So during the first year of an Obama administration, especially given the state of the economy, it was a strong chance health reform will be incremental: expanding SCHIP (the State Children’s Health Insurance Program) will be a priority. After that, the administration will have to decide whether to take a risk on ambitious reform that could well fail.”

Oberlander published a side-by-side analysis of the health-care proposals of

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dialysis. However, this therapeutic strategy has been largely based on opinion—no studies have been done to compare survival in dialysis patients receiving phosphate binders versus no treatment.

To address this gap, Wolf and his colleagues compared mortality rates in two groups of new dialysis patients: 3555 patients who started on treatment with phosphorus binders during their first 90 days on dialysis and 5055 who did not.

“This is the group we wanted to study, because if you wait until they've been on dialysis for a long time, just about everybody will develop a high serum phosphorus level leading most of them to be treated," said Wolf. "With new dialysis patients, many will be treated and many will not—that's because their serum phosphorus levels are not yet markedly elevated.”

During the first year on dialysis, patients treated with phosphate binders were at significantly lower risk of death—30 percent—than those not treated. When findings were adjusted for factors that would increase the likelihood of receiving phosphate binders, the protective effect was smaller but still significant at 25 percent.

“The survival benefit was independent of the baseline serum phosphorus level and extended even to patients who didn't have high phosphorus levels at all," said Wolf. "In other words, we found that there may be a beneficial effect in groups that currently are not routinely treated, suggesting that perhaps we should consider treating those patients as well.”

New Links to Vascular Calcification in CKD

Meanwhile, two studies in the February Journal of the American Society of Nephrology sought to determine whether the relationship between serum phosphate levels and cardiovascular risk might appear earlier in the course of kidney disease, or perhaps even in people with no evidence of renal or cardiovascular disease.

Both studies examined associations between serum phosphate levels and coronary artery calcification. Electron-beam or multidetector computed tomography was used to measure calcium in the coronary arteries. The coronary artery calcium (CAC) score, calculated using the Agatston method, provides an accurate indicator of atherosclerosis. The CAC score predicts the incidence of future cardiovascular events in dose-response fashion.

Researchers at the University of Washington measured serum phosphate levels and CAC in 439 patients with moderate CKD and no clinical cardiovascular disease, drawn from the Multi-Ethnic Study of Atherosclerosis. Serum phosphate concentrations were within the normal range—2.5 to 4.5 mg/dL—for 95 percent of patients. The goal was to assess the relationship between phosphate and CAC, focusing on high-normal phosphate levels.

“High serum phosphorus levels within the normal range have been associated with cardiovascular events and premature death in people with CKD," said Bryan Kestenbaum, MD, a University of Washington nephrologist. "Experimental work suggests that phosphorus causes toxicity by promoting calcification of blood vessels.”

The group of patients with moderate CKD had high rates of vascular and valvular calcification. The overall prevalence of coronary artery calcification was 67 percent. Calcification was found in the descending thoracic aorta in 49 percent of patients, the aortic valve in 25 percent, and the mitral valve in 20 percent.

Coronary artery calcification was significantly related to serum phosphate level. For each 1 mg/dL increase in serum phosphate level, there was a 21 percent increase in coronary artery calcification, after adjusting for demographic factors and estimated kidney function. The same phosphate increment was linked to a 33 percent increase in thoracic aorta calcification, a 25 percent increase in aortic valve calcification, and a 62 percent increase in mitral valve calcification.

The association between high-normal phosphate level and CAC was unchanged after adjusting for cardiovascular risk factors or dietary intake. It was stronger among younger patients and among those with better kidney function.

The link between phosphate and CAC was also unaffected by adjustment for 1,25-dihydroxyvitamin D and serum parathyroid hormone levels, both of which could affect phosphate concentration.
Phosphate Levels
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Phosphates Also Linked to Coronary Artery Calcium in Healthy People

The link between high-normal phosphate levels and vascular calcification may extend to healthy people without kidney disease, according to Robert N. Foley, MB, of the United States Renal Data System and the University of Minnesota.

"Among apparently healthy young adults without kidney problems, there is an association between phosphate levels in the normal range and the occurrence of cardiovascular calcification 15 years later," Foley said.

Foley and his colleagues analyzed the relationship between phosphate levels and atherosclerosis in 3,015 healthy young adults, mean age 25 years, from the Coronary Artery Risk Development in Young Adults (CARDIA) study. Almost all those studied were free of kidney and cardiovascular disease when they underwent measurement of serum phosphate level as part of their baseline evaluation.

When these individuals were re-evaluated 15 years later, coronary artery calcification was rated minimal in 3.2 percent of study participants, mild in 4.8 percent, moderate in 1.1 percent, and severe in 0.5 percent. When other risk factors were not taken into account, higher phosphate levels were associated with a lower rate of coronary artery calcification.

But when the findings were adjusted for other cardiovascular risk factors, the relationship between high-normal phosphate levels and CAC became significant. Higher phosphate levels were linked to African-American race, family history of myocardial infarction, and elevated triglycerides. For healthy adults with the highest phosphate levels (greater than 3.9 mg/dL), the risk of coronary artery calcification was increased by 52 percent, compared with those at the lowest level (3.3 mg/dL or less).

High-normal phosphate levels were also linked to some factors considered protective for cardiovascular disease, including younger age, female sex, lower body mass index, higher high-density lipoprotein cholesterol, and lower systolic blood pressure.

The relationship between phosphate and cardiovascular risk is complex. "It’s really a mixed bag of some good risk factors and some bad, and you have to take that into account when you look at the association between phosphate and CAC," said Foley. "High phosphate seems to go with some of the risk factors that you might call metabolic syndrome, but it was inversely related to body mass index and systolic blood pressure," said Vasan S. Ramachandran, MD, of Boston University and the Framingham Heart Study.

So far, it is unknown how these apparently diverse mechanisms work to increase cardiovascular risk in people with high-normal phosphate. "Multiple mechanisms might be operating, partly through metabolic syndrome, or partly through another mechanism tied to phosphate that we don't really understand," Foley said.

Lowering Phosphate Levels in CKD . . . and Before?

The newly discovered links between serum phosphate and CAC suggest a possible benefit of treatments to lower phosphate levels. While there are about 400,000 dialysis patients in the United States, there are estimated to be more than 15 million patients with less severe CKD.

"These patients are typically not considered for treatment with phosphate binders, which are approved by the FDA only for use on dialysis," Wolf said. "If further studies could demonstrate a similar survival benefit of binders in patients with pre-dialysis CKD, the results could have a significant impact on public health."

Interventions to lower the cardiovascular risk associated with high phosphate levels already exist. Wolf said current dietary phosphate binders are "perfectly acceptable choices" for use in CKD patients.

Still, it is too early to infer that phosphorus is a cause of poor outcome in the CKD or the general population, said Kamyr Kalantar-Zadeh, MD, PhD, a nephrologist at UCLA David Geffen School of Medicine and Harbor-UCLA Medical Center.

"High-normal serum phosphorus, in addition to reflecting reduced kidney function, may be a surrogate of unhealthy lifestyle including unhealthy

Framingham Offspring Study. "In our community-based sample, serum phosphate was positively associated with age, female sex, high-sensitivity C-reactive protein, estimated glomerular filtration rate, and total/high-density lipoprotein cholesterol ratio, but it was inversely related to body mass index and systolic blood pressure," said Vasan S. Ramachandran, MD, of Boston University and the Framingham Heart Study.

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Dr. Foley’s study was performed as a
on Amgen-sponsored clinical trials.
resulting fees from Amgen or for work
under a National Institutes
zyme and Ineos.
grant support from Amgen, Inc.
University of Washington research, has
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not necessarily appropriate for a peer-reviewed journal. ASN
Kidney News will also provide a venue to expound upon
scientific and clinical advances, with more commentary
and speculation than a scientific journal can allow.
Since taking on this endeavor, I have been asked a
number of questions by colleagues in the kidney world. Here are ASN Kidney News FAQs:

How will ASN Kidney News be delivered?
The magazine will be a print publication starting in January 2009. The first year it will be mailed every other month. We plan to publish monthly beginning with the January 2010 issue.

Will ASN Kidney News be available online?
For now, a pdf of ASN Kidney News will be available online. Ultimately, a website will supplement rather than duplicate the print publication. Many of our graphics will be available for download. Links to other sources will be considered. Our site will provide a lively forum for discussion of everything kidney!

What is the relationship between ASN Kidney News and Renal Express?
Renal Express, ASN’s electronic newsletter, is undergoing some changes at this time. Its relationship to ASN
Kidney News will be complementary, but has not been finalized as we go to press.

Will I still get ASN Kidney Daily?
These email updates will be unaffected by ASN Kidney News. Some stories may be expanded and updated in the magazine.

How can I contact ASN Kidney News?
Magazine staff can be reached by email at kidneynews@asn-online.org.

Can I contribute to ASN Kidney News?
This magazine belongs to you, the members of the nephrology community. If you have an idea for an article or feature, please contact the magazine staff at kidneynews@asn-online.org. One beautiful thing about a new publication is that we can mold it to be whatever we want!

Who are you?
I am a pediatric nephrologist at the University of Nebraska Medical Center. I have done a bit of everything during my career: patient care, bench and clinical research, education, administration, patient and research advocacy, and editorial work. In short, I’ve experienced what this magazine will cover! I also deal with kidney disease on another level: Our family cat has stage 3 chronic kidney disease (CKD), a leading cause of death in elderly felines. Who knew there were stages of CKD based on estimated glomerular filtration rate for cats! ASN Kidney News will include some regular features, and others may be added at your request. The following will appear regularly in most issues:

Essay and Opinion: Welcome to the kidney soapbox, where controversies and issues can be addressed. Have a strong opinion? Contact us (kidneynews@asn-online.org) and we may give you an audience.

Policy Update: Government regulations affect the care of our patients, the education of our providers, and the funding of our researchers. Conventions for approval of drugs and devices can change as well. Learn about proposed and enacted policies that could alter your world.

Practice Pointers: Delivering excellent care to our patients is everyone’s goal. Sometimes a study or consensus statement will change the standard of care. Others may have developed processes that will improve your practice. Learn ways to improve kidney health care from experts driving the paradigm shifts.

Journal View: Read highlights of cutting-edge biomedical research from the journals of the ASN, as well as other publications. It is impossible for you to read everything in the medical literature, but ASN Kidney News can help you hit the highlights.

Trends in Medical Education: Not just for program directors, this section will include information about maintenance of certification. Issues in fellow education will be included, with contributions from trainees.

Industry Spotlight: Pharmaceutical companies, biomedical supply providers, dialysis units, and even insurance companies employ kidney specialists. Learn more about the issues these people face during the development and delivery of drugs, devices, and clinical care.

The six months we have worked on this inaugural issue have been fast, frightening, and fun. We think you will find this magazine a useful addition to your library. It is a work in progress, and it should be what you, the readers, want and need. Once again, please contact us at kidneynews@asn-online.org with your ideas.

Pascale H. Lane, MD, editor-in-chief of ASN Kidney News, is the Helen Freytag Distinguished Professor of Pediatrics at the University of Nebraska Medical Center.