

High Phosphate, Mortality Risk in CKD Linked

Serum phosphate may increase mortality risk by contributing to vascular calcification.

REVIEWED BY BRYAN KESTENBAUM, MD

Elevated phosphate levels may be linked to an increased risk of death in people with chronic kidney disease (CKD). "Elevated serum phosphate levels have been linked with vascular calcification and mortality among dialysis patients," wrote Bryan Kestenbaum, MD, and colleagues from the University of Washington, Seattle, in the *Journal of the American Society of Nephrology*.

Hyperphosphatemia has also been independently linked with calcification of the coronary arteries, aorta and cardiovascular and all-cause mortality in the setting of end stage renal disease (ESRD), they said.

The link between serum phosphate levels and mortality in patients not on dialysis with CKD had not previously been explored, Dr. Kestenbaum said. He and colleagues studied a cohort of US veterans from the Pacific Northwest with CKD, which was defined by two continuously abnormal outpatient serum creatinine measurements at least 6 months apart, between 1999 and 2000.

PREVIOUSLY MEASURED

From the eligible population of 95,619 veterans, 7,021 met the definition of CKD. Patients who received chronic dialysis and those with a present or previous renal transplant were excluded. After exclusions, 6,370 patients with CKD were available for analysis; 3,490 had a previous serum phosphate measurement within 18 months.

The researchers reported the primary endpoint was all-cause mortality, the secondary endpoints were acute myocardial infarction (MI) and the combined endpoint of MI plus death. Patients were an average of 71 years, and many had medical problems such as heart disease or diabetes.

After adjustment, serum phosphate levels >3.5 mg/dL were associated with a significant increased risk for death. This level is high, but in the normal range for healthy people. Mortality risk increased linearly with each subsequent 0.5 mg/dL increase in serum phosphate levels. At levels over 3.5 mg/dL, the risk of death increased steadily – about 23% for each additional 1 mg/dL in phosphate level. Risk of acute MI increased by 35% per 1 mg/dL increase in phosphate.

The risk continued over a few years, according to an

American Society of Nephrology news release. By 3 years, 56% of patients with the highest phosphate levels were alive versus 67% in the middle levels and 72% in the lowest level.

"Although this study was not designed to identify the causative role of phosphate in mortality risk, several plausible mechanisms might explain our findings," Dr. Kestenbaum wrote. "For example, cultured smooth muscle cells respond to inorganic phosphate concentrations of 1.4 mmol/L by expressing bone markers core binding factor-1 and osteocalcin, with subsequent mineralization of the extracellular matrix."

The investigators also suggested that serum phosphate may increase mortality risk by contributing to vascular calcification, and excessive phosphate may also increase mortality and cardiovascular risk by increasing circulating PTH or decreasing 1,25-Dihydroxy vitamin D levels.

Dr. Kestenbaum pointed out that the study had limitations. Although the analyses were adjusted for creatinine and other risk factors, it is still possible that high phosphate levels are a marker of worsening renal disease because creatinine levels are a relatively insensitive measure of renal function, he said. He also told *Diabetic Microvascular Complications Today* that the study population was predominantly older, white men with extensive cardiovascular morbidity. "It is unclear whether similar results would be found among different patient populations."

Investigators said that results suggest that an elevated phosphate level is an important danger sign in CKD. It remains to be seen if high phosphate levels are a causative factor or merely a warning sign of complications, especially cardiovascular disease. If causative, then treatments to lower phosphate levels may help reduce the risk of death in people with CKD. ■

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Kestenbaum B, Sampson JN, Rudser KD, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol*. 2005;16: published as doi:10.1681.