Readily available treatment could help prevent heart disease in kidney patients

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The estimated 19 million Americans living with chronic kidney disease (CKD) face a high risk of death from cardiovascular disease. Recent studies have shown that a main source of this cardiovascular risk is CKD patients' high levels of blood phosphate.

Now researchers at Washington University School of Medicine in St. Louis have demonstrated that high blood phosphate directly stimulates calcification of blood vessels and that phosphate-binding drugs can decrease vascular calcification. That means drugs that reduce phosphate levels could help protect CKD patients from cardiovascular disease, according to the authors of the study, which is available online in advance of print publication in the *Journal of the American Society of Nephrology*.

"One of the kidney's functions is to help maintain a constant balance of phosphate in the bloodstream," says senior author Keith A. Hruska, M.D., director of the Division of Pediatric Nephrology and professor of pediatrics, of medicine and of cell biology and physiology. "When kidney failure occurs, an excess of serum phosphate develops. It turns out that high phosphate serves as a signal that stimulates cells within blood vessel walls to become bone-forming cells and to deposit calcium crystals. That produces vascular stiffness that is a cause of cardiovascular mortality."

Phosphate-binding drugs are already on the market, and based on evidence in this study and others like it, the Food and Drug

Administration has recently decided to extend the label of such drugs. As a result, calcium acetate (PhosLo), sevelamer (Renagel) and lanthanum carbonate (Fosrenol) will be labeled to indicate they are approved for treatment of high serum phosphate levels in patients with CKD.

Hruska, Suresh Mathew, M.D., instructor in pediatrics, and colleagues studied mice with CKD and atherosclerosis — calcified plaques in the arteries. They gave the mice phosphate-binding agents, which prevent phosphate in the diet from entering the bloodstream. This therapy decreased arterial calcification in the mice. The treatment also diminished the activity of a genetic program that stimulates blood vessel cells to become bone-forming cells.

Skeletal turnover normally allows the bones to assimilate excess phosphate, but in people with CKD, bone turnover is inhibited and excess phosphate stays in the bloodstream. There it can induce the differentiation of blood-vessel-wall cells into bone-forming cells.

Scientists previously identified a growth factor called BMP-7 (bone morphogenic factor-7) that increases skeletal bone formation. In addition to demonstrating the beneficial effect of phosphate-binding drugs, Hruska and colleagues found that giving BMP-7 to CKD mice also reduced phosphate in their bloodstreams and decreased the calcification of blood vessels.

"BMP-7 restores the ability of the skeleton to serve as a reservoir for phosphate, and in the walls of blood vessels it blocks the process of differentiation into bone-forming cells," Hruska says. "It's possible that BMP-7 also could someday be developed into a therapy for patients with CKD and have the added advantage of restoring normal skeletal function and protecting the normal physiology of blood vessels."

Hruska indicates that large-scale population studies have demonstrated that serum phosphate levels may be as important as serum cholesterol levels in predicting cardiovascular problems. The mechanism described in the study, in which the skeleton cannot absorb excess phosphates, is also present in elderly people with osteoporosis. In addition, diabetes can lead to kidney damage and high serum phosphate.

"There's a huge segment of the population affected by these problems," Mathew says. "Elderly osteoporosis patients and people with diabetes have high rates of cardiovascular disease and high levels of vascular calcification. So our findings may have importance even beyond patients with CKD."

Because the data in this study strongly suggest serum phosphate reduction could be highly effective for reducing cardiovascular risk in CKD patients, Hruska and Mathew have begun the process of establishing a clinical trial of phosphate reduction in CKD. "We're working to design a multicenter study to demonstrate that control of phosphate balance in CKD decreases cardiovascular events and increases survival," Hruska says.

Source: Washington University School of Medicine

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