Cause of heart disease spurred by kidney syndrome found, neutralized

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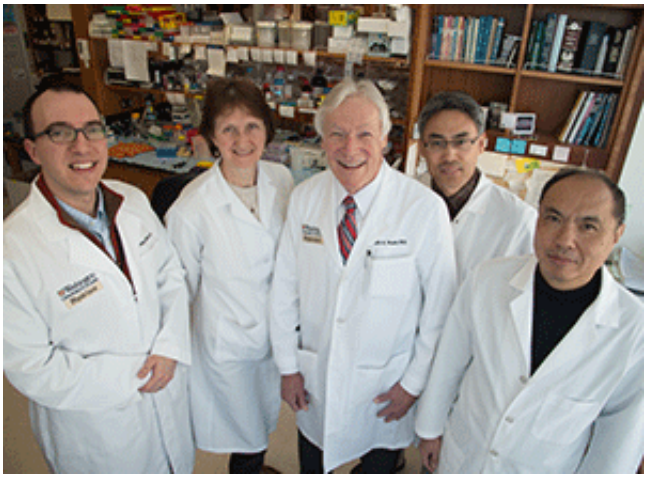

Senior author Keith A. Hruska with other School of Medicine scientists involved in the research. From left, Michael Seifert, MD, Olga Agapova, PhD, Hruska, Toshifumi Sugatani, PhD, DDS, and first author Yifu Fang, MD. Credit: Robert Boston

Chronic kidney disease affects 26 million Americans, but its sufferers are more likely to die of heart disease than kidney problems. However, it hasn't been clear just how kidney disease causes heart disease or what could be done to stop it.

But a new study in mice and people by researchers at Washington University School of Medicine in St. Louis has pinpointed the cause of a kidney-related syndrome also linked to heart disease. Further, they have

discovered how to neutralize a protein produced by the kidney that spurs heart disease, illuminating a new approach to tackling health problems brought on by kidney disease.

The findings one day could improve the health and survival rates of those suffering from chronic kidney disease-mineral bone disorder (CKD-MBD), according to the study's senior author, Keith A. Hruska, MD, a kidney specialist at the School of Medicine.

"We've shown that kidney disease causes diseases of the blood vessels and heart—and has targets that could be used therapeutically to treat associated heart problems," Hruska said. "And this discovery, serendipitously, shows that antibody-based drugs currently in clinical development potentially could be used to reduce deaths from related heart disease, as well as skeletal and other afflictions caused by CKD-MBD."

The research is available online Feb. 27 in the *Journal of the American Society of Nephrology*.

CKD-MBD is a common problem in people with kidney disease. In addition to weakening the bones, CKD-MBD shifts hormone levels in the blood, increasing the risk of heart disease.

To understand the link between kidney disease and heart disease, the researchers set out to see and study CKD-MBD at its inception, early in the course of kidney disease. What they found, in mouse models of diabetes with kidney disease, was that with even a very mild kidney injury CKD-MBD would be initiated.

This would happen because as soon as the kidney detected disease or an injury to itself, it would attempt to repair it, behaving much as it does during embryonic development. But in doing so, it would produce and

circulate proteins that would harm other parts of the body, including the heart, essentially causing far more harm than good.

For example, the researchers found that kidney injury would spur a surge of the kidney protein Dkk1 in the circulation. Left unchecked, the protein can cause the hardening, or calcifying, of blood vessels, eventually leading to heart disease. But when the scientists neutralized the protein with an antibody, they were surprised to find that problems with blood vessels, including vascular calcification, were prevented.

"Neutralizing Dkk1 with an antibody actually corrects the skeletal and vascular disorders associated with kidney disease," said Hruska, a professor of pediatrics, of medicine and of cell biology and physiology.

The researchers also analyzed levels of Dkk1 in 38 patients with mild kidney disease, finding elevated levels of not only Dkk1 and other related proteins but also of the hormone FGF23, an indicator of heart disease onset. This follows the same pattern as seen in the mouse models, supporting the notion that findings in the laboratory could be applied clinically.

When the authors of the study combined the antibody against Dkk1 with phosphate binders—medications that reduce the absorption of harmful phosphates into a patient's blood—they were able to prevent the increase in FGF23 along with preventing vascular disease.

An antibody to Dkk1 currently is being used in clinical trials for multiple myeloma. Hruska wants to see it developed as a therapeutic to treat the heart and skeletal problems associated with CKD-MBD. And there are other antibodies with similar potential to fight kidney disease, he said.

"The fundamental issue here is that kidney disease directly causes cardiovascular disease through this attempt at trying to repair the

injured, diseased kidney," Hruska explained. "And we are hopeful that neutralization of these factors may become a viable therapy for heart disease associated with kidney disease. This could be a significant paradigm shift forward."

More information: Fang Y, Ginsberg C, Seifert M, Agapova O, Sugatani T, Register TC, Freedman BI, Monier-Faugere M, Malluche H, Hruska KA. "CKD-Induced Wingless/Integration1 Inhibitors and Phosphorus Cause the CKD-Mineral and Bone Disorder. "*Journal of the American Society of Nephrology*. Online Feb. 27, 2014.

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