Potential option for treating chronic kidney disease

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People with chronic kidney disease often have an overactivation of the sympathetic nervous system, which contributes to increased risk for cardiovascular events such as heart attack and stroke.

New clinical research indicates the drug tetrahydrobiopterin may be able to dial back this overactivation, leading to positive effects on the sympathetic nervous system and some measures of arterial stiffness.

The findings were published in *American Journal of Physiology* (*Regulatory, Integrative and Comparative Physiology*).

"We want to find some new options for patients with chronic kidney disease," says Jeanie Park, MD, assistant professor of medicine (renal division) at Emory University School of Medicine and Atlanta Veterans Affairs Medical Center.

"Currently, doctors use drugs such as beta blockers and clonidine in an effort to treat high blood pressure and sympathetic nervous activation. However, these drugs often have intolerable side effects, and long-term studies have hinted that those drugs may not improve future cardiovascular disease risk."

Tetrahydrobiopterin, also known as BH4, is a cofactor for the enzyme that synthesizes nitric oxide, which regulates blood vessel function. BH4 is normally synthesized and recycled by the body. In 2007, BH4 was approved by the FDA as a non-dietary treatment for the inherited

metabolic disorder phenylketonuria. It has been previously studied at Emory by Arshed Quyyumi, MD and colleagues as a treatment for hypertension.

It is estimated that more than 20 million people in the United States have impaired kidney function; its main causes are hypertension and diabetes. Previous research has shown that people with chronic kidney disease tend to have lower BH4 levels and lower levels of nitric oxide availability, making BH4 supplementation a potential remedy, Park says.

The study participants were 36 male veterans with hypertension and "mild to moderate" chronic kidney disease: not at or close to the stage where they would need dialysis. They received tetrahydrobiopterin (200 mg twice daily) or a placebo for 12 weeks.

Muscle sympathetic nerve activity—the study's "primary endpoint,",measured in bursts per minute—was assessed by inserting an electrode into the peroneal nerve in the leg, before and after the course of BH4 treatment.

"One way to think of muscle sympathetic nerve activity is that it reflects elevated adrenaline levels," Park says.

Researchers also measured patients' blood pressure, arterial stiffness and the ability of blood vessels to relax (flow-mediated dilatation). Muscle sympathetic nerve activity declined 7.5 bursts per minute in the BH4-treated group, from a baseline of 47 bursts per minute. In comparison, the placebo group rose 3.2 bursts per minute. This effect was seen both in patients who were taking common blood pressure medications (ACE inhibitors/angiotensin receptor blockers) and those who were not.

The researchers observed positive effects on augmentation index, a

measure of arterial stiffness, but not pulse-wave velocity, another measure of arterial stiffness. Park hypothesizes that the discrepancy may come from a difference in effect on large vs. small blood vessels. The team saw a small effect on blood pressure, which was not statistically significant but could be investigated in a larger study, and no significant changes in ability of blood vessels to relax.

Park says her team's next step is to analyze tetrahydrobiopterin's effects on exercise intolerance in chronic kidney disease. People with chronic kidney disease tend to have an exaggerated increase in blood pressure and muscle sympathetic nerve activity in response to physical exercise, which contribute to exercise intolerance.

"These findings warrant larger studies investigating the effects of BH4 on blood pressure and other cardiovascular risk factors in chronic kidney disease," Park says.

More information: *American Journal of Physiology*, ajpregu.physiology.org/content … 1/ajpregu.00409.2014

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