Restoring this enzyme's function protects against heart disease in lupus and beyond

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Dr. Jim Oates (left) and Dr. Joy Buie (right) of the Medical University of South Carolina. Credit: Sarah Pack, Medical University of South Carolina

Patients with lupus, an inflammatory disease in which the body's immune system attacks its own tissues, are on average seven to nine

times more likely to develop heart disease than the general population. Younger women with lupus are 50 times as likely to develop the disease as young women without the disease.

The endothelium—the single layer of cells lining blood vessel walls—is thought to protect against heart disease. It does so in part by producing nitric oxide.

A research team at the Medical University of South Carolina has shown that the enzyme responsible for nitric oxide production stops working properly when exposed to serum from lupus patients. They also showed that its ability to produce nitric oxide can be restored by administration of L-sepiapterin. Their findings are published in an article published ahead of print by *Lupus Science & Medicine*.

The article provides proof of concept that the enzyme could be a therapeutic target for heart disease in lupus. Restoring the enzyme's function could also help protect lupus patients against kidney disease. The same inflammatory forces are at work there but the damage occurs much more quickly.

The findings also suggest that restoring the protective function of endothelial cells could be a strategy for treating heart disease more broadly.

"Our study demonstrates that therapies directed towards restoring the function of the enzyme that makes nitric oxide might be effective in restoring the function of the endothelium," explains Jim C. Oates, M.D., senior author on the article. Oates is director of the Division of Rheumatology & Immunology and vice chair for research at MUSC.

"So it's a proof of concept that allows us to move forward in studying the enzyme, nitric oxide synthase, or restoring its function as a target for

vascular disease in lupus," continues Oates.

"This is a first step in a long process of trying to identify therapeutics that might be useful for preventing this accelerated phenotype of cardiovascular disease in lupus patients," says Joy Buie, Ph.D., MSCR, a postdoctoral fellow at MUSC and the first author on the article.

For the study, the team collected serum samples from a cohort of African American patients, specifically Gullah patients, with lupus who have been followed since 2003. The South Carolina Clinical & Translational Research Institute at MUSC helped the research team collect study samples from control volunteers, process study samples from both study patients and control volunteers, and securely store collected data.

The MUSC team showed that exposing endothelial cells to serum from patients with lupus caused the enzyme that produced nitric oxide to quit working properly. That enzyme is known as endothelial nitric oxide synthase.

Instead of producing the protective nitric oxide, it began producing superoxide, which promoted damaging inflammation.

In essence, the enzyme lost its power to protect against heart disease and instead promoted conditions that could lead to it. A co-factor needed for the proper function of the enzyme had been rendered unusable by exposure of the endothelial cells to the serum of lupus patients.

Administering L-sepiapterin to the cells restored the enzyme's ability to produce nitric oxide by providing a new and more reliable source of that co-factor.

"If you try to give the co-factor itself, it's rapidly oxidized by the same

process that leads to the dysfunction of the enzyme," explains Oates. "So giving L-sepiapterin, a precursor to the co-factor, makes it less susceptible to that rapid breakdown."

L-sepiapterin is not currently approved for administration in humans. However, it is under investigation for the treatment of a number of diseases, including diabetic gastroparesis. Before it can be administered to patients, much further testing, both in animal models and in clinical trials, will be necessary to confirm its efficacy and safety profile.

But these findings point to a whole new way of understanding, preventing, and treating heart disease, one that is not limited only to patients with lupus.

"Many people focus on controlling cholesterol to protect against heart disease," explains Buie. "Our study focuses the attention on making endothelial cells happy and functional. It identifies therapeutic targets on endothelial cells as being important."

That's not to say that controlling cholesterol and other lifestyle changes aren't important. They too can affect how well the endothelium protects against heart disease.

"Lifestyle modifications can affect the endothelium. The Western diet—characterized by highly processed foods that are high in saturated and trans fat and low in good oils like omega-3 fatty acids—contributes to heart disease in everybody, not just lupus patients," explains Oates. "So changing to a healthy diet and becoming more active goes a long way."

But these findings suggest that pharmaceutically restoring endothelial function deserves further study as an additional therapeutic approach for patients with lupus and others at high risk of heart disease.

More information: Joy N Jones Buie et al, L-sepiapterin restores SLE serum-induced markers of endothelial function in endothelial cells, *Lupus Science & Medicine* (2019). DOI: 10.1136/lupus-2018-000294