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Diabetes makes it hard for blood vessels to relax

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One way diabetes is bad for your blood vessels is by creating too much competition for an amino acid that helps blood vessels relax, researchers say.

That amino acid, L-arginine, is broken down by the enzyme arginase to urea, which helps the body eliminate toxins resulting from the proteins we eat. Diabetics have a lot of arginase activity, which means they use a lot more L-arginine, says Dr. Maritza Romero, postdoctoral fellow at the Medical College of Georgia and lead author of the paper published in the current issue of Circulation Research.

It also means too little L-arginine is available to help nitric oxide synthase make nitric oxide, the powerful vasodilator that helps blood vessels relax, says Dr. Romero, who works in the lab of Dr. R. William Caldwell, chair of the MCG Department of Pharmacology and Toxicology and the study's corresponding author.

Researchers also found the amino acid, L-citrulline, as well as statins, compounds known to lower cholesterol, prevent elevation of arginase activity, restoring normal dilation abilities in animal models of type 1 diabetes. In fact, L-citrulline can be recycled into L-arginine.

Now they want to know specific factors and pathways involved in arginase activation and develop pharmaceutical agents to combat excessive arginase activity in diabetes. They also suggest clinical trials of L-citrulline as a supplemental therapy for diabetics with vascular

problems.

Their findings also help explain why L-arginine supplement, marketed to treat hypertension, chest pain, heart failure and more, may not work long term. In the January 4, 2006 issue of the Journal of the American Medical Association, Johns Hopkins researchers reported that a clinical trial of patients taking an L-arginine supplement following a heart attack didn't improve in their vascular tone or their hearts' ability to pump. In fact, more patients died who were taking L-arginine than placebo and the study was closed with the recommendation the supplement not be used by heart attack patients. The supplement still is widely marketed.

"The findings of increased arginase I activity in diabetes may limit other therapeutic approaches proposed for early endothelial dysfunction such as oral L-arginine supplementation," Drs. Thomas L. Luscher and Jan Steffel, of the University of Zurich Cardiovascular Research Institute write in an accompanying editorial. "Although dietary L-arginine supplementation has been shown to exert vascular protective effects in certain clinical settings, this approach is unlikely to be effective in diabetes, if the results of this study can be confirmed by patients in vivo. In fact, the findings of Romera et al may provide a possible explanation for the unexpected neutral or even adverse effects of oral L-arginine in some clinical studies, in particular patients with coronary artery disease and infarction."

A short intravenous course of L-arginine may provide short-term improvement in blood vessel tone, Dr. Romero notes. However most of L-arginine ingested goes directly to the liver to be broken down, not the bloodstream where it can promote relaxation of blood vessels, Dr. Romero says.

Arginase also is associated with vascular problems related to aging, hypertension, sickle cell disease, atherosclerosis and erectile dysfunction,

Dr. Romero says. L-citrulline already is taken by some sickle cell patients to reduce breath-taking fibrosis in their lungs. In addition to helping the body turn toxins into urea that can be safely eliminated from the body, arginase also helps in collagen formation and cell proliferation, but too much can be bad. In fact, Drs. Caldwell and Romero are pursuing studies of how increased arginase activity may harden blood vessel walls.

Source: Medical College of Georgia