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New link between high-fat 'Western' diet and atherosclerosis identified

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Columbia University Medical Center (CUMC) researchers have found that a diet high in saturated fat raises levels of endothelial lipase (EL), an enzyme associated with the development of atherosclerosis, and, conversely, that a diet high in omega-3 polyunsaturated fat lowers levels of this enzyme. The findings establish a "new" link between diet and atherosclerosis and suggest a novel way to prevent cardiovascular heart disease. In addition, the research may help to explain why the type 2 diabetes drug rosiglitazone (Avandia) has been linked to heart problems.

The study, conducted in mice, was published in the October 4 online edition of *Atherosclerosis, Thrombosis, and* Vascular Biology.

Like other lipases, EL plays a role in the metabolism of blood lipoproteins, which are complexes of lipids (fats) and proteins. EL, which is secreted by macrophages (a type of white blood cell) and other cells in arteries, was discovered in 1999. Studies have shown that elevated EL is associated with atherosclerosis and inflammation. Until now, however, little was known about how dietary fats might affect this enzyme, said study leader Richard Deckelbaum, MD, the Robert R. Williams Professor of Nutrition professor of pediatrics and of epidemiology and director of the Institute of Human Nutrition at CUMC.

In the current study, a strain of mice susceptible to atherosclerosis was fed a normal diet enriched with either palmitic acid (a common saturated fat) or eicosapentaenoic acid (an omega-3 fatty acid, or polyunsaturated

fat, found in fish oil, among other foods). After 12 weeks, the mice's aortas were examined for changes in the expression of EL and inflammatory factors. Aortas of mice fed the saturated fat diet showed a significant increase in EL and detrimental changes in inflammatory factors, while those of mice fed the polyunsaturated fat diet showed a significant decrease in EL and beneficial changes in inflammatory factors. Studies in cultured macrophages showed similar results.

"Our study identifies a new way in which the high-saturated-fat Western diet could lead to the development of atherosclerosis, though, of course, these results need to be confirmed in human studies," said Dr. Deckelbaum. "The findings might also explain some of the cardiovascular benefits that have been attributed to omega-3 fatty acids."

The researchers also found, in cell culture studies, that macrophages fed saturated fat showed increased expression of PPAR-gamma, a cell signaling molecule that plays a role in regulating lipid metabolism and inflammatory responses. This increase was blocked when the cells were fed an omega-3 fatty acid.

"These findings are intriguing, because we know that the diabetes drug rosiglitazone (sold under the brand name Avandia) is a strong PPAR-gamma activator and that it has been associated with an increased risk of heart disease," said Dr. Deckelbaum. "So we hypothesized that if rosiglitazone activates ppar-gamma, it might also activate EL, which would explain its effects on the heart."

In fact, when the macrophages were given rosiglitazone, the expression of EL increased markedly. The addition of omega-3 fatty acids to the cells blocked this increase. "This would suggest that besides raising LDL cholesterol levels, rosiglitazone can raise the risk of cardiovascular disease by increasing EL," said Dr. Deckelbaum. "In addition to its potential role in increasing arterial inflammatory responses, EL increases

the anchoring of LDL to cell surfaces, which could be associated with increased LDL accumulation in coronary arteries."

Use of Avandia was severely restricted in 2010, when the drug was linked to the development of heart disease.

More information: The paper is titled, "Fatty acids regulate endothelial lipase and inflammatory markers in macrophages and in mouse aorta: a role for PPARγ."

Provided by Columbia University Medical Center

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