Medical Xpress

Fat in the liver -- not the belly -- is a better marker for disease risk

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New findings from nutrition researchers at Washington University School of Medicine in St. Louis suggest that it's not whether body fat is stored in the belly that affects metabolic risk factors for diabetes, high blood triglycerides and cardiovascular disease, but whether it collects in the liver.

Having too much liver fat is known as nonalcoholic fatty liver disease. The researchers report online in the journal PNAS Early Edition that when fat collects in the liver, people experience serious metabolic problems such as insulin resistance, which affects the body's ability to metabolize sugar. They also have increases in production of fat particles in the liver that are secreted into the bloodstream and increase the level of triglycerides.

For years, scientists have noted that where individuals carried body fat influences their metabolic and cardiovascular risk. Increased fat inside the belly, known as visceral fat, is associated with an increased risk of diabetes and heart disease.

"Data from a large number of studies shows that visceral fat is associated with metabolic risk, which has led to the belief that visceral fat might even cause metabolic dysfunction," says senior investigator Samuel Klein, M.D. "However, visceral fat tracks closely with liver fat. We have found that excess fat in the liver, not visceral fat, is a key marker of metabolic dysfunction. Visceral fat might simply be an innocent bystander that is associated with liver fat."

Klein, the Danforth Professor of Medicine and Nutritional Science, directs the Division of Geriatrics and Nutritional Science and the Center for Applied Research Studies, as well as Washington University's Center for Human Nutrition. He says most of our body fat, called subcutaneous fat, is located under our skin, but about 10 percent is present inside the belly, while much smaller amounts are found inside organs such as the liver and muscle.

This study compared obese people with elevated and normal amounts of liver fat. All subjects were matched by age, sex, body mass index, percent body fat and degree of obesity. Through careful evaluations of obese people with different amounts of visceral fat or liver fat, Klein's team determined that excess fat inside the liver identifies those individuals who are at risk for metabolic problems.

"We don't know exactly why some fats, particularly triglycerides, will accumulate inside the liver and muscle in some people but not in others," says first author Elisa Fabbrini, M.D., Ph.D., assistant professor of medicine. "But our data suggest that a protein called CD36, which controls the transport of fatty acids from the bloodstream into different tissues, is involved."

Fatty acids are the building blocks for making fats, known as triglycerides. Klein, Fabbrini and their colleagues found that CD36 levels were lower in fat tissue and higher in muscle tissue among people with elevated liver fat.

Fabbrini and Klein say changes in CD36 activity could be responsible for diverting circulating fatty acids away from fat tissue and into liver and muscle tissue, where they are converted to triglyceride. Increased tissue uptake of fatty acids could be responsible for metabolic dysfunction.

Klein says those who are obese but don't have high levels of fat in the liver should be encouraged to lose weight, but those with elevated liver fat are at particularly high risk for heart disease and diabetes. He says they need to be treated aggressively to help them lose weight because dropping pounds can make a big difference.

"Fatty liver disease is completely reversible," he says. "If you lose a small amount of weight, you can markedly reduce the fat content in your liver. In fact, even two days of calorie restriction can cause a large reduction in liver fat and improvement in liver insulin sensitivity."

More information: Fabbrini E, Magkos F, Mohammed S, Pietka T, Abumrad NA, Patterson BW, Okunade A, Klein S. Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity. *PNAS Early Edition* (2009), published online Aug. 24, 2009. www.pnas.org/cgi/doi/10.1073/pnas.0904944106

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Korenblat K, Fabbrini E, Mohammed BS, Klein S. Liver, muscle and adipose tissue insulin resistance is directly related to intrahepatic triglyceride content in obese subjects. *Gastroenterology* 134: 1369-1375, 2008.

Kirk E, Reeds DN, Finck BN, Mayurranjan MS, Klein S. Effects of acute and chronic calorie restriction on insulin action in obese men and women. *Gastroenterology* 136: 1552-1560, 2009.

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