The missing link between belly fat and heart disease?

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By now, everyone knows that overweight people have a higher risk of heart attacks, strokes and other problems that arise from clogged, hardened arteries. And people who carry their extra weight around their waist – giving them a “beer belly” or an “apple” shape -- have the highest risk of all.

But despite the impact on human health, the reasons behind this connection between heart disease and belly fat – also known as visceral fat -- have eluded scientists. Now, a new study in mice gives the first direct evidence of why this link might exist – and a tantalizing look at how it might be broken.

In a paper that will be published online today in the journal *Circulation* before print publication in February, a team of University of Michigan Cardiovascular Center scientists reports direct evidence of a link between inflammation around the cells of visceral fat deposits, and the artery-hardening process of atherosclerosis.

The researchers also show that a medication often given to people with diabetes can be used to calm that inflammation, and protect against further artery damage.

Although the scientists caution that it’s far too early to apply their findings to humans with belly fat, they hope that further research in animals and people will reveal more about how this dangerous link comes about, why it begins, how it can be reversed, and perhaps how it

can be diagnosed at an early stage through blood tests.

Until then, the best advice for overweight people who want to reduce their chance of a heart attack or stroke remains the same: Work on losing your belly fat, and your other excess body weight, through a balanced, healthy diet and regular exercise.

The research team is led by Daniel Eitzman, M.D., a cardiologist, laboratory scientist and associate professor in the Division of Cardiovascular Medicine at the U-M Medical School and the VA Ann Arbor Healthcare System.

The discovery came partly by chance. He and his colleagues had been studying mice that lack the gene for leptin, a hormone generated by fat cells that plays a role in appetite and metabolism as well as reproduction. In an effort to get these obese mice to produce some leptin, the team developed a technique to transplant clusters of fat cells from normal mice of the same strain, into the leptin-deficient mice.

The result surprised them. “In addition to producing leptin and preventing obesity, the fat transplants became inflamed, attracting immune cells called macrophages,” Eitzman explains. “Since the mice were genetically identical except for leptin, this shouldn’t have happened. But the inflammation was there, and it was chronic.”

The inflammation occurred around individual fat cells, or adipocytes. Further tests showed it was regulated by the same factors that regulate the inflammation that other researchers have seen in the naturally occurring fat deposits of obese mice – specifically a chemokine called MCP-1.

But because the fat was transplanted, the inflammation could be attributed directly to the fat, and not to overfeeding of the mice, or the

metabolic problems that overfeeding and obesity bring, such as diabetes.

Armed with this discovery, the researchers set out to see what was causing inflammation to occur, and what implications it had. The team included postdoctoral fellow Miina Öhman, M.D., Ph.D., U-M professor Daniel Lawrence, Ph.D., and members of the Eitzman and Lawrence laboratory teams.

They were especially interested to see if there might be any link between the inflammation and atherosclerosis – the formal name for the process by which blood vessels become stiff, narrowed and lined with plaque formations that can trigger the development of blood clots.

This process, which occurs throughout the body, sets the stage for most heart attacks and strokes. Scientists and clinicians now realize that it is based on inflammation – the abnormal reaction of the body's immune system to its own tissue — and in the damage that immune-system cells and molecules can inflict.

Since normal mice don't develop atherosclerosis, the team had to turn to a strain that had been developed to be especially prone to high cholesterol and hardened arteries. These ApoE-negative mice, as they are called, were divided into three groups: two that received fat transplants from normal mice, and one that did not, but that had the same operation that would be used to implant the fat in other mice.

Some of the fat-transplant ApoE-negative mice received transplants of visceral fat, which forms in the belly around the major organs, while others received transplants of subcutaneous fat – the type that's found just under the skin throughout the body.

Sure enough, the mice that received the visceral fat transplants developed atherosclerosis at a much-accelerated rate, and experienced

the same type of inflammation as the leptin-deficient mice had. Meanwhile, those that received subcutaneous fat did not experience an increase in atherosclerosis despite having increased inflammation. The mice that had the “sham” operations developed neither inflammation nor increased atherosclerosis.

“There appeared to be an interaction between the macrophages causing the inflammation in the visceral fat, and the process of atherosclerosis,” says Eitzman, who notes that blood vessels far from the site of the fat transplant developed increased atherosclerosis.

Finally, the team attempted to calm the inflammation and curb the atherosclerosis by treating the mice with pioglitazone – a member of the class of drugs called thiazolidinediones or TZDs that are often used to treat diabetes. While TZD drugs have an impact on metabolism, which makes them useful in diabetes, they also have been discovered to have an anti-inflammatory effect.

And in fact, the drug reduced both the concentration of macrophages and MCP-1, and atherosclerosis, in those mice that received transplants of visceral fat. But the drug had no effect in the other mice.

Now that they have demonstrated the linkage between belly fat, inflammation and hardened arteries, and a potential mechanism for reversing the phenomenon, the team is working on new pieces of the puzzle. Specifically, they’re looking for the factors that might trigger macrophages to invade the area and bring on inflammation, and for blood-borne molecules called biomarkers that might be used as a way to identify early warning signs of atherosclerosis. They’ll also look at other classes of drugs to see if they might have a protective effect, because TZD drugs act on many systems and cause some side effects.

Source: University of Michigan