**Twins Study Offers Clues to Metabolically Healthy Obese**

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A new, unique study of 16 identical twin pairs, where each has 1 lean and 1 obese twin, has yielded some important clues as to the mechanisms behind metabolically healthy obesity.

In half the twin pairs, the obese twins turned out to be as metabolically healthy as their lean counterpart, with low levels of liver fat and little sign of chronic inflammation in their adipose tissue, according to the research [published online](http://www.diabetologia-journal.org/files/Naukkarinen.zip) October 6 in *Diabetologia*. But the remaining 8 obese twins had the classic hallmarks of unhealthy obesity, with marked insulin resistance, dyslipidemia, and a fatty liver, as well as upregulation of chronic inflammation in their fat tissue.

"Our results suggest that metabolically healthy obesity is characterized by an adipose tissue that maintains normally functioning mitochondria, remains free of inflammation, and is able to handle the excess energy by making more fat cells and not just bigger fat cells," lead author Jussi Naukkarinen, MD, PhD, from the Obesity Research Unit, University of Helsinki, Finland, wrote in an email to *Medscape Medical News*.

"In this milieu, the liver seems to be spared from fattening and, as a consequence, the metabolic consequences usually associated with obesity can be avoided," he added.

While no medication currently exists for the specific purpose of preventing adipose tissue inflammation or to promote mitochondrial health for efficient processing of food into energy, it is possible that such treatments could be developed, the researchers say.

**Two Distinct Subgroups of Obese Twins Emerge**

Not all individuals who are obese display the metabolic disturbances commonly associated with the condition, and this concept of metabolically healthy obesity is [now becoming more widely recognized by clinicians](http://www.medscape.com/viewarticle/810325).

The current research used a rare monozygotic obesity-discordant twin-pair design to control for confounding factors seen in other human studies into metabolically healthy obesity — which include genetic factors, early development and environment, age, and sex.

In the 16 weight-discordant identical twin pairs (aged 22 to 35 years old with a mean difference in weight between twin pairs of approximately 17 kg), the researchers examined detailed characteristics of metabolic health, including subcutaneous, intra-abdominal, and liver fat (as measured by magnetic resonance imaging or spectroscopy), as well as oral glucose tolerance, lipids, adipokines, and C-reactive protein. They also assessed transcriptomic pathways related to mitochondrial function and inflammation in subcutaneous adipose tissue.

Two distinct subgroups of twins emerged from the examinations. Half of the obese twins had percentages of liver fat that closely matched their lean twin, while the other half had more than a 7-fold increase in liver fat compared with their lean twin (718% increase, *P* = .012).

The obese metabolically unhealthy twins also had significantly greater insulin production in response to an oral glucose tolerance test, greater levels of C-reactive protein (CRP), higher levels of low-density lipoprotein (LDL) cholesterol, and lower levels of high-density lipoprotein (HDL) cholesterol than their lean twin, as well as a tendency toward hypertension. In contrast, the metabolically healthy obese twins and their lean twins had similar glucose and insulin-sensitivity profiles, as well as similar levels of CRP and blood lipids.

Other findings included:

* The metabolically healthy obese twins had 11% more fat cells than their lean twins (*P*=0.069) vs 8% less (nonsignificant) for the non–metabolically healthy twins compared with their lean counterpart.
* Intrapair differences in plasma leptin concentrations were smaller in the metabolically healthy obesity group, suggesting that circulating leptin levels were disproportionately higher in the non–metabolically healthy obese twins.
* The obese metabolically healthy twins exhibited significantly less activity in the chronic inflammatory response pathway than the other obese twins.

"Our results suggest that maintenance of high mitochondrial transcription and lack of inflammation in subcutaneous adipose tissue are associated with low liver fat and metabolically healthy obesity," the researchers conclude.

**Findings Likely Generalizable, Possibility of Therapy**

Limitations of the study include the small sample size, because young adult obesity-discordant monozygotic twins are rare, and the lack of biopsies for visceral adipose tissue and liver. Nevertheless, the authors consider that their results are probably generalizable to other populations.

"There is no reason to believe that these findings regarding mitochondria and adipose tissue inflammation shouldn't be generalizable to the broader population," Dr. Naukkarinen said.

"What is unknown, however, is how the metabolically healthy status is maintained as the individuals age. While it is possible that they remain healthy, it could also turn out to be a trait that slowly disappears as the 'exposure' to obesity becomes longer," he explained.

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Both groups of twins developed overweight at a similar age, however, which would suggest, at least in this age range, that it is a persistent phenomenon, he noted.

And with regard to potential future treatments, "an interesting finding on the inflammation side of the story is that individuals with long-term use of anti-inflammatory medications — to treat, for example, rheumatoid arthritis — have been shown to be relatively protected from obesity-associated diabetes," he explained.

"This gives reason to believe that, in the future, drugs [could target] the known chronic adipose tissue inflammation [that] characterizes the 'usual,' metabolically harmful obesity," he concluded.

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