More evidence that 'healthy obesity' may be a myth

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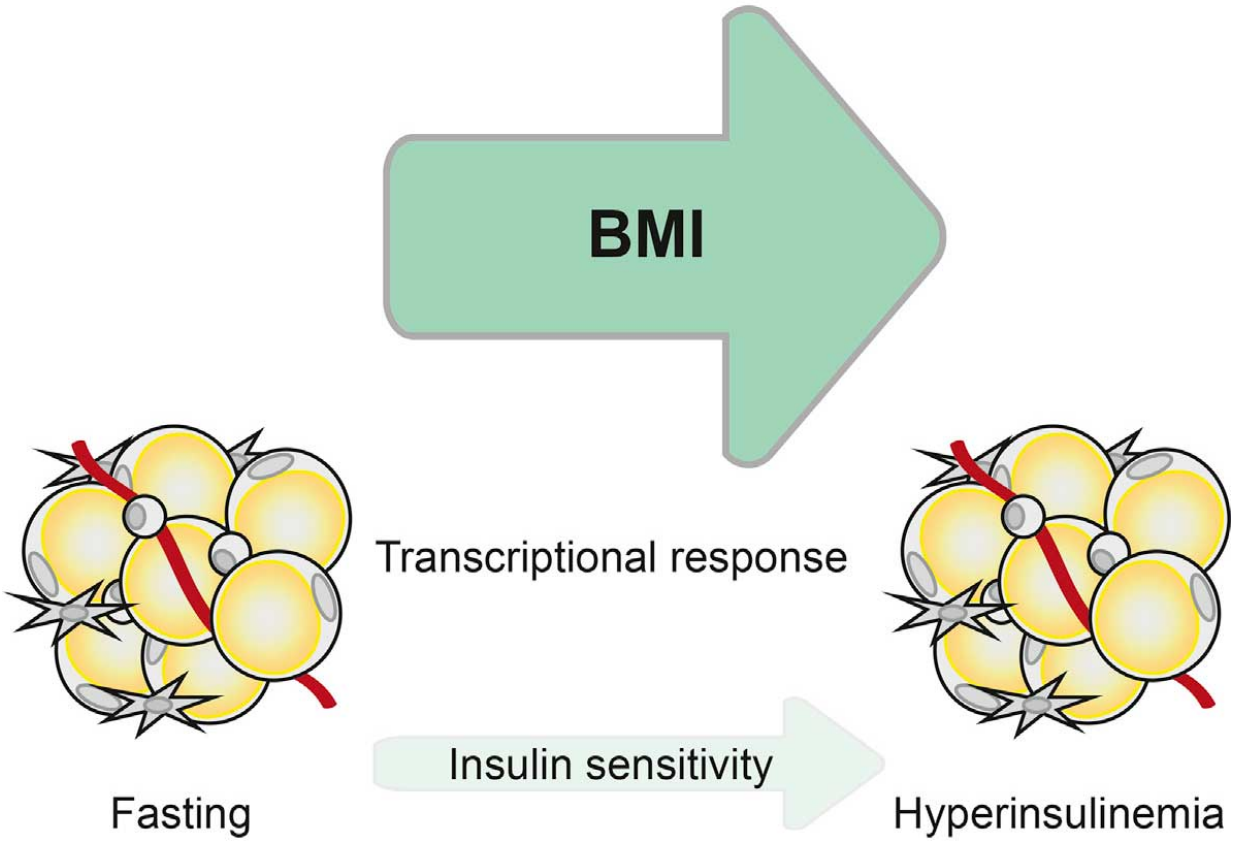

This graphic abstract represents the findings of Ryden et al, who performed transcriptomicprofiling in adipose tissue from nonobeseand obese subjects discordant ininsulin sensitivity. The transcriptionalresponse to hyperinsulinemia was similaramong obese subjects and differed fromthat in non-obese subjects. The twoobese groups differed only in a limited setof genes, thereby challenging the notionof healthy obesity. Credit: Ryden et al./*Cell Reports* 2016

The term "healthy obesity" has gained traction over the past 15 years, but scientists have recently questioned its very existence. A study published August 18 in *Cell Reports* provides further evidence against the notion of a healthy obese state, revealing that white fat tissue samples from obese individuals classified as either metabolically healthy or unhealthy actually show nearly identical, abnormal changes in gene expression in response to insulin stimulation.

"The findings suggest that vigorous health interventions may be necessary for all obese individuals, even those previously considered to be metabolically healthy," says first author Mikael Rydén of the Karolinska Institutet. "Since obesity is the major driver altering gene expression in fat tissue, we should continue to focus on preventing obesity."

Obesity has reached epidemic proportions globally, affecting approximately 600 million people worldwide and significantly increasing the risk of heart disease, stroke, cancer, and type 2 diabetes. Since the 1940s, evidence supporting the link between obesity and metabolic and cardiovascular diseases has been steadily growing. But in the 1970s and 80s, experts began to question the extent to which obesity increases the risk for these disorders. Subsequent studies in the late 90s and early 2000s showed that some obese individuals display a relatively healthy metabolic and cardiovascular profile.

Recent estimates suggest that up to 30% of obese individuals are metabolically healthy and therefore may need less vigorous interventions to prevent obesity-related complications. A hallmark of metabolically healthy obesity is high sensitivity to the hormone insulin, which promotes the uptake of blood glucose into cells to be used for energy. However, there are currently no accepted criteria for identifying

metabolically healthy obesity, and whether or not such a thing exists is now up for debate.

To address this controversy, Rydén, Carsten Daub, and Peter Arner of the Karolinska Institutet assessed responses to insulin in 15 healthy, never-obese participants and 50 obese subjects enrolled in a clinical study of gastric bypass surgery. The researchers took biopsies of abdominal white fat tissue before and at the end of a two-hour period of intravenous infusion of insulin and glucose. Based on the glucose uptake rate, the researchers classified 21 obese subjects as insulin sensitive and 29 as insulin resistant.

Surprisingly, mRNA sequencing of white fat tissue samples revealed a clear distinction between never-obese participants and both groups of obese individuals. White fat tissue from insulin-sensitive and insulin-resistant obese individuals showed nearly identical patterns of gene expression in response to insulin stimulation. These abnormal gene expression patterns were not influenced by cardiovascular or metabolic risk factors such as waist-to-hip ratio, heart rate, or blood pressure. The findings show that obesity rather than other common risk factors is likely the primary factor determining metabolic health.

"Our study suggests that the notion of metabolically healthy obesity may be more complicated than previously thought, at least in subcutaneous adipose tissue," Rydén says. "There doesn't appear to be a clear transcriptomic fingerprint that differentiates obese subjects with high or low insulin sensitivity, indicating that obesity per se is the major driver explaining the changes in gene expression."

One limitation of the study is that it examined gene expression profiles only in subcutaneous white fat tissue, not other types of fat tissue or other organs. Moreover, all of the obese subjects were scheduled to undergo bariatric surgery, so the findings may only apply to individuals

with severe obesity.

In future research, Rydén and his collaborators will track the study participants after bariatric surgery to determine whether weight loss normalizes gene expression responses to insulin. They will also look for specific genes linked to improved metabolic health in these individuals.

In the meantime, the study has an important take-home message. "Insulin-sensitive obese individuals may not be as metabolically healthy as previously believed," Rydén says. "Therefore, more vigorous interventions may be necessary in these individuals to prevent cardiovascular and metabolic complications."

More information: *Cell Reports*, Rydén et al.: "The Adipose Transcriptional Response to Insulin Is Determined by Obesity, Not Insulin Sensitivity" www.cell.com/cell-reports/full … 2211-1247(16)31014-2 , DOI: 10.1016/j.celrep.2016.07.070

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