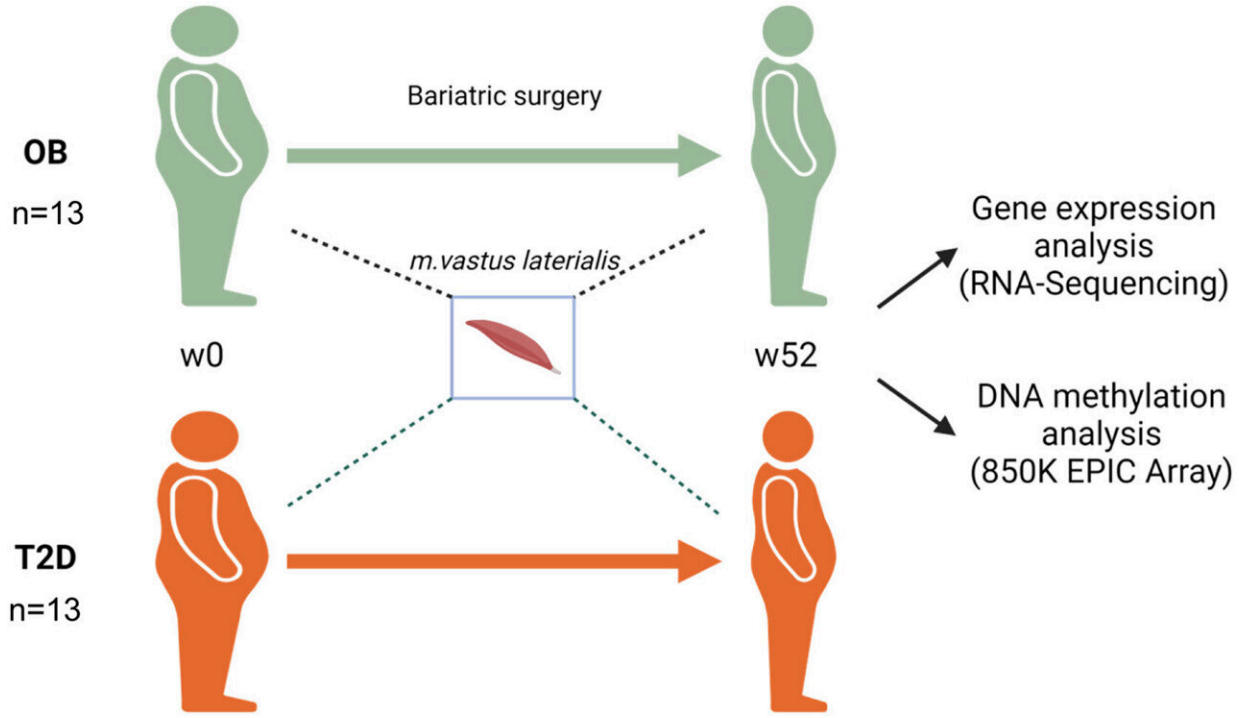
New molecular insights into bariatric surgery's impact on obesity and type 2 diabetes

August 13 2024, by Susann-C. Ruprecht



Study design. Skeletal muscle biopsies were obtained from OB and T2D individuals before (w0) and one year after (w52) bariatric surgery. The samples were then subjected to gene expression and DNA methylation analyses. Credit: *Diabetes & Metabolism* (2024). DOI: 10.1016/j.diabet.2024.101561

Researchers from the German Institute of Human Nutrition Potsdam-

Rehbruecke (DIfE) and the German Center for Diabetes Research (DZD) have published a study in *Diabetes & Metabolism* that sheds light on the molecular adaptations occurring in skeletal muscle following bariatric surgery, particularly in individuals with and without type 2 diabetes.

Bariatric surgery is a widely recognized intervention for obesity management. The medical intervention alters the digestive system to limit the amount of food that can be eaten or absorbed or affect hunger via the incretin system, thereby promoting significant and sustained weight loss. Bariatric surgery is typically considered for individuals who have not achieved long-term weight loss through diet and exercise.

It is known that during the development of type 2 diabetes (T2D), epigenetic alterations (DNA methylation and hydroxymethylation) occur in skeletal muscle, a key tissue taking up glucose in response to insulin. However, it is unclear to what extent these alterations are reversible through interventions such as bariatric surgery.

Linking clinical outcomes to transcriptome and epigenome

Therefore, an interdisciplinary DZD team including the researchers Leona Kovac, Annette Schürmann and Meriem Ouni from the DIfE as well as Sabine Kahl and Michael Roden from the German Diabetes Center (DDZ) investigated the effects of surgically induced weight loss on metabolic, transcriptional, and epigenetic adaptations in skeletal muscle of obese individuals with and without T2D by using a comprehensive bioinformatic approach.

Additionally, multidimensional links between molecular and metabolic changes induced by bariatric surgery were explored. These links aimed

at identifying novel prominent candidates associated with weight loss and improved muscle function.

The examined individuals were a subset of participants from the BARIA_DDZ cohort study, which closely monitors individuals through detailed metabolic characterization both before and over five years following bariatric surgery.

The study described here focused on the metabolic and molecular outcomes achieved during the first year. In total, 13 male participants with obesity (OB) and 13 participants with OB and T2D underwent an extensive anthropometric and metabolic investigation including a muscle biopsy and detection of tissue-specific insulin sensitivity before and one year after surgery.

Perturbed epigenetic flexibility

DZD researchers found distinct molecular responses in skeletal muscle following bariatric surgery between obese individuals and those with additional T2D. Before surgery, obese T2D participants exhibited higher fasting glucose and insulin levels alongside lower insulin sensitivity compared to OB. Following surgery, improvements in metabolic health were more pronounced in OB, reflected by differential gene expression patterns related to insulin signaling, intracellular signal transduction, and oxidative phosphorylation.

In contrast, obese T2D participants showed alterations only in genes associated with ribosome and spliceosome pathways, with less pronounced changes in DNA methylation, potentially linked to altered expression of one of the T2D risk genes involved in the demethylation processes.

Tailoring of individual therapies

These findings underscore the importance of understanding molecular adaptations in skeletal muscle post-bariatric surgery, particularly in individuals with type 2 diabetes. "Our study suggests that epigenetic mechanisms play a crucial role in mediating these responses and predicting the health outcome," states Dr. Ouni.

"Our future research will investigate the molecular mechanisms underlying changes in DNA hydroxymethylation and its potential function in skeletal muscle post-surgery. Furthermore, we aim to validate specific candidates identified by the bioinformatic approach as potential therapeutic targets in muscle," emphasizes Prof. Dr. Schürmann, Head of the Department of Experimental Diabetology at DIfE. In this manner, approaches for individuals with different metabolic profiles could be tailored.

More information: Leona Kovac et al, Different effects of bariatric surgery on epigenetic plasticity in skeletal muscle of individuals with and without type 2 diabetes, *Diabetes & Metabolism* (2024). DOI: 10.1016/j.diabet.2024.101561

Provided by Deutsches Institut für Ernährungsforschung Potsdam-Rehbrücke

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