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The Muscle Race After Bariatric Surgery: Ribosomal Proteins Come First

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COMMENTARY

Obesity and its associated cardiometabolic comorbidities, which include type 2 diabetes, have emerged as a global pandemic condition. The global age-standardized prevalence of obesity was 12.0% in 2008, indicating that roughly 500 million adults were obese (1). More recent estimates indicate that, worldwide, the proportion of adults who were overweight or obese in 2013 was 36.9% for men and 38.0% for women (2) and that the number of overweight and obese individuals was 2.1 billion in 2013. As for obesity in children, global estimates also indicate that levels have been rising in recent decades (2,3). If nothing is done to reverse the epidemic, more than 1 billion adults are projected to be obese by 2030 (4).

The use of bariatric surgery to treat obesity has rapidly gained widespread acceptance owing, in part, to greater weight loss and effective treatment of diabetes and other cardiometabolic risk factors. Different types of bariatric surgery such as laparoscopic adjustable gastric banding, Roux-en-Y gastric bypass (RYGB), and biliopancreatic diversion are linked to distinct rates of hyperglycemia remission in patients with type 2 diabetes (5,6). RYGB has emerged as an efficient tool for treating obesity, and it leads to remission in 75% of patients with type 2 diabetes (5,7). The RYGB procedure involves the creation of a stomach pouch out of a small portion of the stomach and attaching it directly to the small intestine, bypassing a large part of the stomach and duodenum. Not only is the stomach pouch too small to hold large amounts of food, but, by skipping the duodenum, fat absorption is substantially reduced (8). Of note, the improvement in glycemic control observed after RYGB occurs within a few days after surgery, and it seems to occur before any significant weight loss or increase in insulin sensitivity (5,9). Early after RYGB surgery, an enhanced insulin secretion rate and enhanced circulating GLP-1 levels have been documented (10,11). However, it takes months before peripheral insulin sensitivity is detected (9,12), which parallels enhanced muscle expression of GLUT4, enhanced mitochondrial respiration, and enhanced phosphorylation of Akt and TBC1D4 (13–15). Transcriptomic profiling performed in skeletal muscle before and 6 months after RYGB has documented a partial normalization of alterations detected in obesity, namely, affecting gene pathways related to lipid metabolism or mitochondria (16). This is in keeping with observations of muscles after biliopancreatic diversion that showed enhanced expression of genes encoding mitochondrial proteins and regulators such as Sirt1, PGC-1α, and PGC-1β (17).

In this issue of *Diabetes*, Campbell et al. (18) provide exciting information on the impact of obesity and RYGB on the skeletal muscle proteome. This study included muscle biopsies obtained from seven obese females before and 3 months after RYGB and from four age-matched lean females. Proteomic analysis identified 2,877 quantifiable proteins. There were 395 differentially expressed proteins (260 downregulated and 135 upregulated) in muscles from the obese women (obtained before surgery) compared with lean control subjects. KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis of the downregulated proteins indicated an enrichment in ribosomal proteins and proteins involved in mitochondrial function (oxidative phosphorylation and Krebs cycle) and muscle contraction. Under these conditions, RYGB surgery caused an increased abundance of 228 proteins and a decreased abundance of 52 proteins in muscles from obese subjects. KEGG pathway analysis of the downregulated proteins after surgery indicated an enrichment of the proteasome pathway, and the analysis of the upregulated proteins revealed ribosome and spliceosome proteins. Transcriptomics performed in obese subjects before and after surgery revealed an enhanced expression of genes involved in the ribosome

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pathway in muscle 3 months after RYGB surgery. The effects of RYGB occurred under conditions in which glucose disposal rate did not improve compared with the presurgery state. Furthermore, a strong correlation between protein and transcript changes for the cytoplasmic ribosome population was documented.

Data from Campbell et al. (18) are important for a number of reasons. This study is the first in which the proteome and transcriptome profiling has been performed in parallel in skeletal muscle from obese patients before and after undergoing RYGB. The study provides evidence that RYGB surgery has a marked impact on the muscle proteome and counteracts some of the effects of obesity. The data are coherent with the following scheme (Fig. 1). In human obesity, skeletal muscle proteome is characterized by reduced expression of proteins involved in ribosome activity, mitochondrial function (oxidative phosphorylation and Krebs cycle), and muscle contraction. This global pattern of changes may explain the susceptibility of some obese subjects to developing sarcopenia (19). RYGB counteracts the effects of obesity by increasing the expression of ribosomal proteins under conditions in which glucose disposal is unaltered compared with the presurgery state (Fig. 1). This indicates that factors linked to surgery such as reduced food intake or enhanced insulin or GLP-1 secretion occurring under these conditions may be relevant in the development of those effects through induction of gene expression processes. It is likely that RYGB generates a second wave of effects linked to improved insulin sensitivity (reported at longer times), which enhances the expression of proteins involved in mitochondrial function and muscle contraction and therefore ameliorates the alterations detected in obesity as reported in transcriptomics (16).

The study by Campbell et al. (18) will require validation by future studies with a greater number of subjects that permits a greater statistical power. It will also be necessary to study the muscle proteome at different

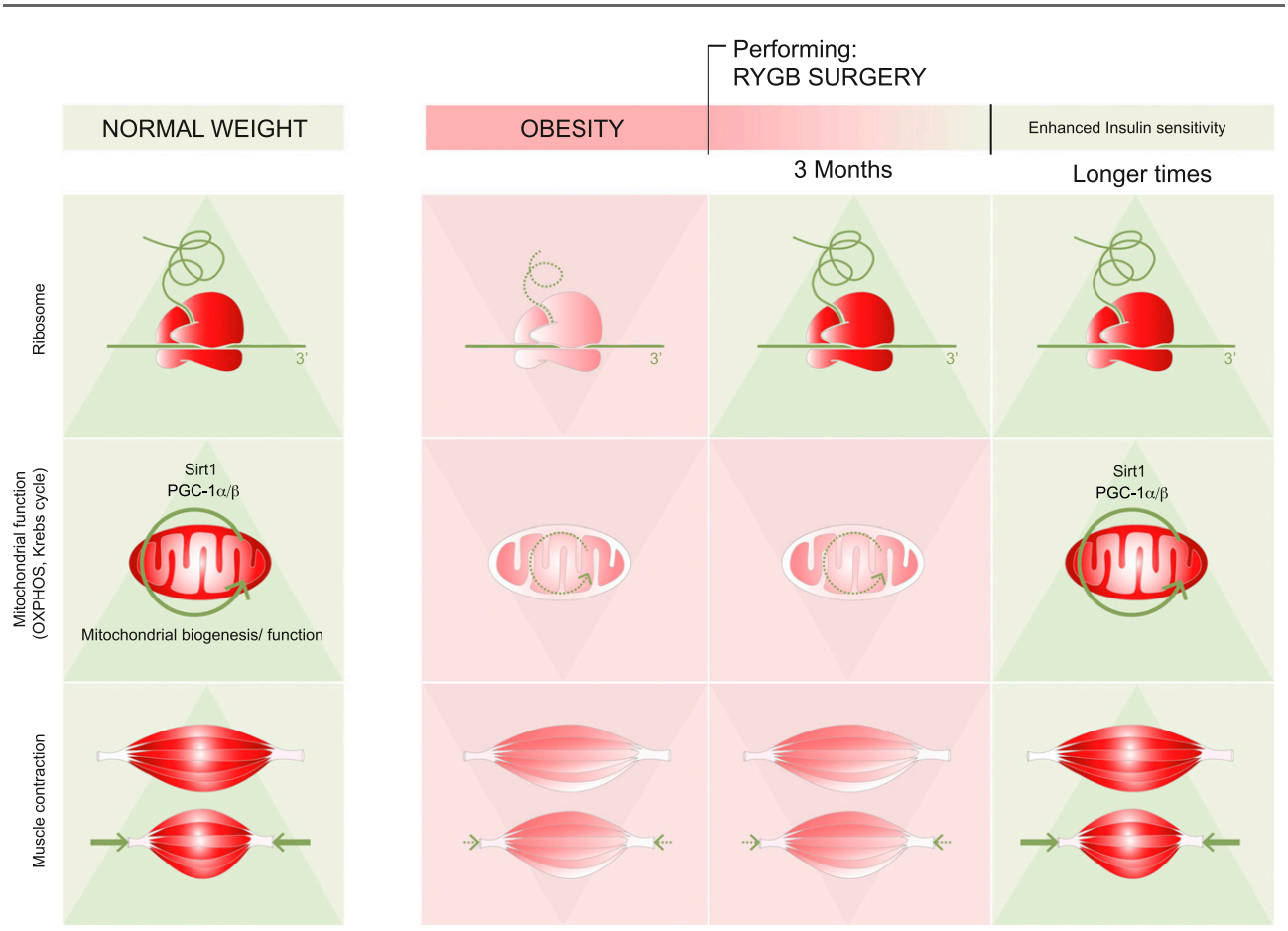

Figure 1—Proposed model for the effects of obesity and RYGB surgery on the skeletal muscle proteome. Under "Obesity," the left panel shows the major inhibitory effects of obesity on the expression of proteins involved in ribosome activity, mitochondrial function, and muscle contraction. The middle panel shows the effects detected 3 months after RYGB, consisting of the normalization of ribosomal proteins in the absence of changes in mitochondrial function or muscle contraction. The right panel speculates on the processes taking place at longer times after RYGB, in which proteins involved in ribosome activity, mitochondrial function, and muscle contraction are normalized in parallel to enhanced insulin sensitivity and expression of factors promoting mitochondrial biogenesis such as PGC-1α, PGC-1β, and Sirt1. OXPHOS, oxidative phosphorylation.

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times after RYGB to identify the different regulatory waves and the link with the metabolic/hormonal cues or the implications of physical activity. Given the relevance of the data and its novelty, Campbell et al. have greatly contributed to a better understanding the metabolic effects of bariatric surgery in muscle. Indeed, the identification of ribosomal proteins as targets of RYGB permits the proposal of such questions as what factors promote these effects in the absence of improved insulin sensitivity and what mechanisms drive these effects. It is also tempting to propose that an early rise in the machinery of protein synthesis will exert a driving force in the recovery of normal muscle capacity upon weight loss.

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