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EDITORIAL

Do Serum Metabolites Predict Weight Regain Following Bariatric Surgery?

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The rapid and seemingly inexorable rise of obesity, particularly in developed countries, is a well-recognized threat to human health and longevity [1]. With 39% of the global population overweight and 13% obese, the need for effective treatments represents an urgent healthcare challenge [2]. Bariatric surgery has emerged as the most effective treatment for obesity and its associated metabolic disorders with well-documented long-term durability and effectiveness [3]. Among bariatric procedures, the Roux-en-Y gastric bypass (RYGB) has long been considered the "gold-standard" procedure against which others are compared [4, 5]. Although according to the literature, the exact burden of weight regain after RYGB varies, 10–20% of patients will have significant pathological weight regain [6]. The reason for this treatment failure is still unclear and is likely to be multifactorial. There currently exists no effective method for identifying or predicting which patients will experience this treatment failure.

In recent years, metabolomics has emerged as a popular tool in metabolic and bariatric research [7]. Studying the changing profile of low molecular weight serum metabolites can illuminate how the body responds to changing conditions. While numerous studies have compared the metabolomic profiles of obese patients with and without bariatric surgery, few have specifically investigated those bariatric surgical patients with pathological weight regain. Obesity and bariatric surgery are important drivers of metabolomic changes. Among the pathways most impacted by bariatric surgery are those involved in amino acid metabolism, the tricyclic acid (TCA) cycle, and aminoacyl-tRNA biosynthesis [7]. Nevertheless, less knowledge is available regarding how the post-RYGB metabolomic profile is affected in patients with subsequent weight regain.

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In this issue of *Digestive Diseases and Sciences*, Wasif and colleagues endeavored to answer this question by comparing the metabolomic signatures of patients with and without pathological weight regain following RYGB [8]. They performed an untargeted metabolomic analysis via liquid chromatography/mass spectrometry on three groups of patients: obese patients without bariatric surgery, RYGB patients with sustained weight loss (RYGB-SWL), and RYGB patients with pathological weight regain (RYGB-WR). By including all three groups in their design, the authors attempted to decouple the effects of surgical anatomic rearrangement from weight status. They first showed that independent of weight status, RYGB patients exhibited significant differences in several metabolites associated with amino acid metabolism, suggesting these are related to the anatomic and biologic changes associated with RYGB. They went on to identify 66 metabolites whose levels were uniquely altered in RYGB-SWL patients, correlating them with depletion of fatty acid metabolism (triacylglycerols, diaglycerols, and cholesterol esters) and with elevation of glycine, acetylglycine, and β-hydroxybutyrate. Inversely, weight regain was correlated with elevated fatty acid metabolites and decreased serine, glycine, threonine, phenylalanine, alanine, TCA cycle metabolites, and glutamate metabolism.

These findings invoke several commonalities with those from prior studies. Obesity affects amino acid metabolism, especially branched-chain and aromatic amino acids [2]. Prior work has found decreased levels of glycine and glutamine in obesity and increased glycine levels after bariatric surgery [2, 9]. Other investigators have also suggested that an early increase in hydroxybutyrate levels following RYGB is associated with metabolic improvement after surgery [9]. Interestingly, in this study, the authors found that reduced levels of the amino acid alanine are associated with weight regain. Zheng et al. [10] found that patients with diet-only weight loss had decreased circulating alanine levels when followed out to 2 years. Others have found similarly elevated

alanine levels in obese patients [2]. This apparent discrepancy could suggest that not all weight loss is created equal and that RYGB likely harbors metabolomic ramifications beyond those seen with simple weight loss alone.

Although the field of metabolomics in obesity and bariatric surgery has been growing exponentially in recent years, there has been less work done to specifically examine the potential metabolomic anomalies of bariatric patients who were able to achieve sustained long-term weight loss. This pilot study is an important initial step in addressing this unmet need. The authors were able to identify a set of metabolomic changes that were uniquely observed in post-bariatric patients with sustained weight loss, representing an entry point into a potentially novel diagnostic and therapeutic area for patients who fail to sustain long-term weight loss after surgery.

One possibly interesting question that was not investigated in this study is whether this differential metabolomic signature has any correlation with postoperative glycemic control. One of the drivers fueling the rise in bariatric operations is their remarkable effect on glycemic improvement. More than 60% of RYGB patients with baseline type 2 diabetes experience sustained (> 7 years) remission after surgery [4]. More intriguingly, nearly all of these patients will have significant glycemic improvement shortly after surgery, before any substantial weight loss occurs. Enhanced insulin sensitivity following bariatric surgery has been invoked as a leading hypothesis, although the precise mechanism of this anti-diabetic effect remains elusive [11] and is an area of intense ongoing research. Correlating metabolomic signatures with differential glycemic control following surgery could offer a potentially useful clinical tool to help prognosticate which patients will benefit the most from surgery.

While the results reported here open a tantalizing window into a potentially novel mechanistic understanding of bariatric surgical physiology, caution should be exercised before drawing any generalizable conclusions. First, this was a relatively small study, and by the authors' own power analysis, an adequately powered metabolomic study will require several hundred patients. Second, as the authors noted, several important baseline patient characteristics, such as comorbidities and medications, were not controlled for. Given their potential metabolic impact, this could affect the observed metabolomic signatures. Third, in this study, RYGB-WR group was disproportionately composed of Hispanics. Previous studies have shown that following bariatric surgery, weight loss trajectory is more favorable in whites than in Hispanics or in African-Americans [4]. More efforts are needed to elucidate potential molecular mechanisms underlying this disparity. Finally, the average elapsed time from surgery is significantly longer for RYGB-WR (8.9 years) compared to RYGB-SWL (5 years). This finding is intriguing and unexplained in the present study. It is plausible that this is the result of patient selection bias in a small study, although a larger prospective study will be needed to fully answer this question.

This pilot study will likely lead to new lines of inquiry that will help to place these findings in their proper physiologic context. In particular, the differential metabolomic signatures described herein lack clinically meaningful predictive power, since the data are insufficient to determine whether these metabolomic findings precede weight regain or are simply the consequence of it. Weight regain after bariatric surgery is a challenging clinical entity for which there remain few effective treatment options. A major unmet need in obesity management is the ability to identify patients who are at high risk of weight regain either pre-surgery or before significant weight regain has occurred, which would facilitate personalized management and optimize their outcome.

Future investigations should aim to further elucidate the mechanistic nuances of bariatric surgery in order to harness the potential diagnostic and therapeutic power of the findings reported here. For example, Aron-Wisnewsky and colleagues recently found, in their study of 61 patients undergoing bariatric procedures (RYBG and gastric banding), that decreased gut microbial gene metagenomic richness was associated with increased truncal fat, increased metabolic comorbidities, and altered serum metabolomics [12]. The involvement of the gut microbiome in the metabolic and hormonal regulation of obesity as well as insulin sensitivity is just beginning to be illuminated, adding complexity to our understanding of the mechanism by which bariatric surgery is successful. As current and future work yields greater mechanistic clarity, more precise and less invasive therapeutic options for the obesity epidemic will surely ensue.

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