REVIEW ARTICLE

Management of type 2 diabetes with bariatric surgery and the role of precision medicine. Narrative review

Manejo de la diabetes tipo 2 con cirugía bariátrica y el papel de la medicina de precisión. Revisión narrativa

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ABSTRACT

Bariatric surgery has become the best treatment for morbid obesity. It has been documented that it achieves higher remission rates of the associated comorbidities when compared with medical treatment. Our objective with this review is provide information about the remission rates of such metabolic alterations with an emphasis on type 2 diabetes mellitus (T2DM), and mainly about how the research on the mechanisms that explain these results have evolved. Initially, the remission mechanisms of conditions such as T2DM were focused on studying the immediate as well as long-term changes of glucose metabolism and the physiology of incretins and hormones of the appetite-satiety axis, concluding that early changes were weight independent and that chronic changes were consequential to sustained weight loss. The possibility of obtaining tissues during the surgery has incorporated the histological, functional, molecular, and genetic study of biopsies from the liver, subcutaneous, and visceral adipose tissue, among others. These new approaches have been combined with methods based on systems biology, to integrate the genetics, transcriptomics, metabolomics, and microbiota with the histological, functional, and molecular findings and their relationship with clinical outcomes. This will likely combine bariatric surgery with precision medicine, favoring a better selection of patients and a more accurate prediction of outcomes.

Key words: Bariatric surgery. Precision Medicine. Systems biology. Type 2 diabetes.

RESUMEN

La cirugía bariátrica se ha convertido en el mejor tratamiento para la obesidad y se han documentado tasas de remisión de comorbilidades superiores a las obtenidas con el tratamiento médico. Esta revisión tiene como objetivo proporcionar información sobre la remisión de dichas alteraciones metabólicas con énfasis en la diabetes tipo 2 (DM2), y sobre todo en cómo ha evolucionado el estudio de los mecanismos que explican estos resultados. Inicialmente, el estudio de los mecanismos por los cuales es posible remitir condiciones como la DM2, se concentraron estudiar los cambios hormonales inmediatos y, a largo plazo, los cambios en el metabolismo de la glucosa y la fisiología de las incretinas y las hormonas del eje apetito-saciación, concluyéndose que los cambios tempranos son independientes del peso y los tardíos dependen del mantenimiento del peso perdido. La posibilidad de obtener tejidos de difícil acceso durante la cirugía ha incorporado el estudio histológico, funcional, molecular y genético a través de la obtención de biopsias de hígado, tejido adiposo subcutáneo y visceral, entre otros. Estos nuevos enfoques se han combinado con abordajes basados en biología de sistemas, con el fin de integrar la relación del genoma, la transcriptómica, la metabolómica y el microbioma con estudios histológicos, funcionales, moleculares y con los desenlaces clínicos. Esto acercará la cirugía bariátrica a la Medicina de precisión para tener una mejor selección de pacientes y predicción de resultados.

Palabras clave: Cirugía bariátrica. Medicina de precisión. Biología de sistemas. Diabetes tipo 2.

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INTRODUCTION

Obesity, mainly defined as body mass index $>30 \text{ kg/m}^2$, is a heterogeneous, chronic and progressive non-communicable disease that represents an important economic and health burden in México, where more than one-third of the population has obesity¹. Remarkably most patients with type 2 diabetes (T2D) have obesity, while a lower percentage of diabetes is diagnosed in patients with obesity. Nonetheless, early abnormalities on glucose metabolism and insulin action such as hyperinsulinemia are commonly present.

The presence of T2D reduces the threshold for prescribing bariatric surgery, in such a case is named metabolic surgery and can be practiced in patients with overweight and Grade 1 obesity².

Bariatric surgery is a metabolic surgery since it can improve and, even induce the remission of T2D and other metabolic conditions. The essential difference between metabolic and bariatric surgery is that the former is focused on reversing T2D while the latter is directed to weight loss³.

The four more practiced surgical procedures are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), laparoscopic gastric banding, and biliopancreatic diversion (BPD), all of them have different effects on gastrointestinal hormones and weight⁴. Describing these techniques are beyond the scope of this revision.

THE CLASSICAL APPROACH TO EVALUATE THE EFFECTS OF BARIATRIC SURGERY ON T2D

One of the first reports that highlighted the benefits of bariatric surgery in T2D was published by Pories et al., where they demonstrated that blood sugar and the need for insulin diminished significantly within 24 h after RYGB, the quick onset of these biological effects

permitted to speculate that the mechanisms were related to neurohormonal changes and were independent of weight loss⁵. After that, several authors started to describe cases where most patients presented remission of hyperglycemia after BPD and RYGB⁶⁻¹⁰.

The classical approach for assessing the effect of metabolic surgery in T2D has been to evaluate its efficacy in terms of remission rates or the potential mechanisms behind remission. The predictors for T2D remission depend on factors like the type of surgery, accepting that procedures that induce malabsorption such as BPD and RYGB are more effective than those which are only restrictive. The other important predictors rely on subjects' characteristics, for example, age, diabetes duration, and insulin needs¹¹⁻¹³. The remission rate also depends on the definition of remission used, studied population, and timeframe, with remission rates ranging from $>90\%$ after the 1st year of surgery to $<30\%$ after 10 years. The more extensively studied cohort, the Swedish Obesity Study cohort reported a remission rate of 74.2% after year 2 and 30% after 15 years¹⁴. The long-term benefits regarding remission of T2DM reported by different cohorts are described in Table 1¹⁴⁻²⁴.

Finally, the mechanisms of action have been attributed to factors like an increase in incretins secretion, the composition of bile acids (BA), changes in the microbiota, and weight loss magnitude. Some changes such as insulin sensitivity are explained by weight loss magnitude and are independent of the type of surgery or medical intervention. Other effects occur early, which suggests they independent of weight loss²⁵. The hormones implicated in this acute response are the incretins. Incretins are gut hormones that promote insulin secretion, decrease gastric emptying, and promote satiety²⁶. It has been reported that incretins are significantly reduced within the 1st days after surgery and show an significant increase 1 month after²⁷. This increase is sustained,

TABLE 1. Remission rate of type 2 diabetes after bariatric surgery

Author, year	Population	Surgery	Follow up	FU rate	Remission rate of T2DM	Excess weight loss
SOS Swedish Cohort 2014 ¹⁴	1158	RYGB	15 years	41	Diabetes 30.4 %	25%
2012 Adams et al. ¹⁵	418	RYGB	6 years	92.6%	62%	27.7%
STAMPED group 2017 ¹⁶	97	RYGB SG	5 years	90%	29%	23%
Adams et al. 2017 ¹⁷	418	RYGB	12 years	90%	Diabetes: 51%	35 kg
SOS Swedish Cohort 2012 ¹⁸	343	RYGB	2 years	81%	Diabetes 72.4%	23%
Angrisani 2013 ¹⁹	51	LAGB RYGB	10 years	85%	100%	24%
STAMPED group 2014 ²⁰	97	RYGB SG	3 years	91%	62%	24%
Cheng et al. 2015 ²¹	52	SG RYGB	5 years	97%	36%	21%
Inge et al. (Cincinatti) 2016 ²²	228	RYGB	3 years	78%	97%	27%
Gulliford 2016 ²³	449 153 220	RYGB SG LAGB	6 years	13	30%	NR
Chen et al. 2016 ²⁴	173	RYGB	10 years	45%	52.6%	66%

RYGB: roux en-y gastric bypass; SG: sleeve gastrectomy; LAGB: laparoscopic adjustable gastric banding; FU: follow-up, NR: no reported; SOS: Swedish obesity study.

improves insulin secretion, and reduces appetite and gastric emptying favoring a better control of glycemia. Regarding BA, Patti et al. demonstrated in a group of patients who underwent gastric bypass, that the concentration of BA increased significantly after surgery 8.9 ± 4.84 versus 3.86 ± 1.95 (compared with a control group with extreme obesity). They also identified relevant changes in the composition of BA, with subfractions of taurochenodeoxycholic, taurodeoxycholic, glycocholic, glycochenodeoxycholic, and glycodeoxycholic acids being higher in the GB groups when compared to the overweight group. In addition, the concentration of BA showed an inverse correlation with the 2-h post-meal glucose and fasting triglycerides and a positive correlation with adiponectin and GLP-1, suggesting that altered bile acid levels and their composition could contribute to improved glucose and lipid metabolism²⁸. Dutia et al. demonstrated temporary changes in BA levels with a reduction during the 1st month after

surgery in the fasted state followed by an increase 2 years after. Significant correlations between BA, FGG19, body weight, incretin effect, and peptide YY were found as well, suggesting that BA may be involved in the improvement of T2DM after gastric bypass²⁹. Numerous studies in animal models and small-sample clinical studies have suggested that components of microbiota rapidly suffer changes as a result of the starvation state induced by surgery as well as the restructuration of the gastrointestinal tract after a gastric bypass³⁰.

NOVEL APPROACHES FOR THE STUDY OF BARIATRIC SURGERY AND POTENTIAL MECHANISMS BEHIND WEIGHT LOSS AND T2D REMISSION

In the past decade, the aforementioned classical approach for studying the effects of bariatric-

metabolic surgery has evolved to include “omics” mechanisms such as genetics, transcriptomics, and microbiome as well as the physiological and histological study of tissues from the liver, the visceral and subcutaneous adipose tissue (SAT), among others³¹. Bariatric surgery is an excellent opportunity to have access to tissues and biological samples for a better understanding of the pathophysiology of obesity and diabetes, its interaction with the environment, the genes, and the mechanisms involved in the remission and the relapse of these conditions. With the integration of these data, it is possible to practice precision medicine, which uses advanced knowledge in molecular biology, genomics, and bioinformatics to develop individualized prevention and treatment programs for improving the effectiveness of these treatments³². In the next lines, we will briefly describe interesting findings in these fields and their interaction with obesity and T2D.

Genetics

Some authors have identified genetic predictors of weight loss with bariatric surgery. For example, in 2011, Still et al. demonstrated in a group of 1001 patients who underwent gastric bypass a high allelic burden of four obesity SNPs (in *FTO*, in the insulin-induced gene 2 *INSIG2*, in the melanocortin receptor *MC4R*, and in the proprotein convertase subtilisin/kexin type 1 *PCSK1*). In addition, through a linear mixed regression analysis, they described significant differences in postoperative weight loss trajectories across groups with low, intermediate, and high numbers of obesity SNP alleles ($p < 0.0001$)³³. Matzko et al. demonstrated in a subgroup of 37 patients who underwent Roux-en-Y surgery that weight loss trajectories were significantly different using an additive model for two SNPs in the promoter region of ghrelin and that patients homozygous for the rs490683 CC genotype exhibited the most weight

loss³⁴. Other genes associated with obesity and with predicting outcomes after bariatric surgery are: *TMEM160*, *PTBP2*, *NUDT3*, *TFAP2B*, *ZNF608*, *MAP2K5*, *GNDAD2*, and *MTCH2*. These findings have made it possible to develop genetic scores to predict weight loss in patients who undergo bariatric surgery³⁵.

Other genetic approaches to predict weight loss after bariatric surgery focus on microRNA (miRNA). For example, Doyon et al., using miRNA techniques, identified that 6 and 12 months after the surgery, there are seven miRNA profiles that differentiate patients with the greatest and lowest body weight, concluding that specific miRNAs were associated with differences in weight loss outcomes after RYGB or SG.

Regarding genetics and its contribution to clinical outcomes related to glucose metabolism, genetic knockout models have been used to test potential mechanisms for explaining the metabolic benefits of bariatric surgery. Models with GLP-1-R knockout mice have shown that this deletion did not attenuate the benefit of the surgery on glucose tolerance suggesting that other mechanisms compensate for the absence of GLP-1³⁶⁻³⁸. In contrast, leptin appears to be required for improving glycemic control after RYGB in mice, as ob/ob mice who underwent bariatric surgery failed to improve glucose tolerance, insulin sensitivity, and hyperinsulinemia despite losing weight³⁹. These types of studies are not feasible in humans but provide insight into the mechanisms of glucose control.

ADIPOSE TISSUE, HISTOLOGY, PHYSIOLOGY, AND TRANSCRIPTOMICS

The adipose tissue in adults is typically divided into visceral adipose tissue (VAT) and SAT the latter

being under the skin and being easily accessible to obtain samples for research. The VAT includes omental, retroperitoneal, and mesenteric depots. Hyperplasia, hypertrophy, and dysfunction of VAT and SAT have been documented in people with obesity. Significant reductions of both adipose tissues have been extensively documented few months after bariatric surgery⁴⁰. Several authors have demonstrated diminution of the size of the adipocytes from SAT without changes in their number after bariatric surgery⁴¹⁻⁴³. The adipocyte diameter correlates inversely with adiponectin and directly with leptin; therefore, bariatric surgery improves both adipokines.

Mitochondrial function in SAT may be an important contributor to this effect by responding to the energy balance changes following weight loss. Mitochondrial oxidative metabolism is diminished in obesity and some authors have reported that mitochondrial oxidative pathways are downregulated in diet-induced weight-loss, which in turn, could impair sustained weight-loss^{44,45}. In contrast, an increased SAT mitochondrial capacity has been reported after surgically induced weight loss. Van der Kolk et al. investigated how the SAT transcriptional capacity for mitochondria changed following diet and surgical interventions in four independent, European weight-loss studies using a standardized set of bioinformatics analysis. They showed that mitochondria-related gene expression is regulated in opposing directions following diet versus surgically induced weight loss. Specifically, surgery induced weight loss by upregulating mitochondrial oxidative metabolism. The strongest effects were observed in mtDNA-encoded mRNA transcripts. This finding suggests that bariatric surgery favors an appropriate mitochondrial function in SAT that may associate with a lower rate of weight regain⁴⁶.

LIVER

Bariatric surgery offers the opportunity for extensively studying the liver because, during de surgery, biopsies can be collected. That has provided the opportunity for studying alterations commonly seen in obesity and T2DM like nonalcoholic fatty liver disease (NAFLD). With extreme obesity, virtually all patients have some degree of fat infiltration in the liver. Luo et al. demonstrated that patients with NAFLD undergoing bariatric surgery show significant decreases in liver volume and steatosis, with 83% of patients achieving resolution of steatosis, no differences between SG and RYGB were identified⁴⁷. Microarray technology has been used in the liver of NASH patients who underwent bariatric surgery, this technique is an essential tool to illustrate gene expression patterns in different tissues and can help to understand the molecular mechanism of the disease^{48,49}. Using this method, Chen et al. obtained hepatic gene expression data and histologic NASH status, at baseline and 1 year after RYGB surgery. Differentially expressed genes (DEGs) were identified by comparing gene expression before and after surgery. They identified 130 common DEGs (29 upregulated and 101 downregulated) between the GSE106737 and GSE83452 datasets. They also found that mineral absorption, IL-17 signaling pathway, osteoclast differentiation, and TNF signaling pathway were significantly enriched, globally the study described a change in gene expression in the liver of NASH patients with a bioinformatic method⁵⁰.

MICROBIOME

The microbial community in the intestine plays an important role in the pathogenesis of obesity. Studies in humans and animal models have shown that

RYGB restructures the gut microbiota, prompting the hypothesis that some of the effects of RYGB are caused by altered host-microbial interaction⁵¹.

Recent studies have found that obesity has distinct metabolomic fingerprints associated with a shift in the microbiome-derived metabolites. Weight loss surgeries modify this obesity-related metabolomic fingerprint in a way that mimics the metabolome and microbiome associated with healthy or lean persons⁵².

Zhang et al. examined 184,094 sequences of microbial 16S rRNA genes from PCR amplicons using the 454-pyrosequencing technology in nine subjects (normal weight, extreme obesity, and post-gastric bypass). They demonstrated that Firmicutes were dominant in normal-weight and obese persons but significantly decreased after bypass surgery patients who had a proportional increase of Gammaproteobacteria. Using real-time PCR they detected significantly higher numbers of H₂-utilizing methanogenic Archaea in obese persons than in normal or post-gastric bypass individuals leading to the hypothesis that the interspecies H₂ transfer between bacterial and archaeal species is a contributing mechanism for increasing energy uptake by the human large intestine of obese persons. They concluded that the bacteria population shift observed in the patients who underwent surgery may reflect the double impact of the gut alteration caused by the surgical procedure and the consequential changes in food ingestion⁵³.

Later, Liou et al. studied the microbiome after RYGB using a mouse model. The s16S ribosomal RNA gene sequencing of murine fecal samples collected after RYGB surgery revealed that alterations to the gut microbiota after RYGB are conserved among humans, rats, and mice, resulting in a rapid and sustained increase in the relative abundance of

Gammaproteobacteria (*Escherichia*) and Verrucomicrobia (*Akkermansia*). These changes were more prominent in the distal gut below the surgical manipulation site. Interestingly, transfer of the gut microbiota from RYGB-treated mice to non-operated, germ-free mice resulted in weight loss and decreased fat mass in the recipient, potentially due to altered microbial production of short-chain fatty acids.

Shen et al. studied the microbial diversity and composition by 16S rRNA sequencing, putative bacterial pathways, and targeted circulating metabolites in 26 individuals, before and at 3, 6, and 12 months after RYGB or SG. They reported a tendency to increase alpha diversity and a significantly altered beta diversity which were reverted after 1 year. They also found an association between these changes in the microbiome with decreased circulating biomarkers of inflammation, increased BA and products of choline metabolism, and other bacterial pathways suggesting that the microbiome partially mediates the observed metabolic improvement within the 1st year after bariatric surgery⁵⁴.

Recently, Chaudhari et al. showed in a murine model, that the selective transport of a microbial metabolite, litholytic acid, from the gut to the liver after a SG activates hepatic Vitamin D receptor, thereby inducing expression of bile acid sulfotransferase SULT2A, which produce the antidiabetic molecule CA7s. The CA7s is a gut-restricted TGR5 agonist with antidiabetic properties⁵⁵.

COMBINING BOTH APPROACHES FOR TRANSITIONING INTO PRECISION MEDICINE

Metabolic surgeries are complex multi-step, multi-disciplinary interventions for treating chronic

non-communicable multifactorial diseases. Therefore, it is not surprising that elucidating the relative contribution of the multiple mechanisms that have been proposed for explaining its benefits is challenging. Despite the great advancements in this field, some very relevant questions remain unanswered which still prevents advancing toward a more personalized prescription of bariatric surgery.

First, it is important to recognize that some of the already identified genetic predictors may be ethnic-specific and that other relevant genetic predictors may be unknown yet. Therefore, more population-specific genetic studies are needed.

On the other hand, since hormonal and microbiome changes are acutely influenced by the diet, it would also be important to standardize diet in the perioperative period. It could be possible that some of the magnitudes of the reported changes arise from the differences between pre-surgical and post-operative diets and not from the surgery itself. What is more, it is also possible that some peri-operative dietary interventions improve the safety or the efficacy of this procedure. For example, it would be interesting to explore if perioperative dietary interventions that favor Firmicutes improve the efficacy of these surgeries.

In summary, methodologically standardized studies that simultaneously assess the effect of dietary, medical, and surgical interventions throughout the perioperative period and encompassing multiple “omic” levels, are warranted.

Finally, all medical interventions require careful patient selection to be successful. Since personalized medicine recently known as precision medicine is, in essence, personalized benefit-risk assessments, it would be useful to standardize the definitions of clinical outcomes (such as remission and relapse)

and to standardize time and adherence restrictions for them. For example, it would be unfair to conclude a gastric bypass surgery was unsuccessful if a patient regains weight after 3 years but with only 12 months of proper follow-up. Conversely, it would be questionable to attribute to a surgical procedure the success of the remission of a disease that was fully or mostly achieved by pre-surgical dietary interventions. Unquestionably, bariatric surgeries are life-saving and life-changing interventions; however, since non-surgical dietary interventions have also proved to achieve weight loss and the remission of diabetes and NAFLD⁵⁵, the availability of these alternatives should be mentioned and pondered during patient selection.

CONCLUSIONS

The obesity epidemic has imposed significant changes in the management and understanding of this disease, recognizing that bariatric surgery is the best available treatment for achieving weight loss and inducing the remission of some of the metabolic alterations that are related to adiposity. The remission of diabetes has been one of the most thoroughly studied clinical outcomes after bariatric surgery and the incorporation of the systems biology has enabled the study of the mechanisms behind the observed physiologic changes (classically studied *in vivo* with dynamic tests to evaluate differences in incretin, ghrelin, glucose, and insulin among others) in patients who underwent to these procedures. The unique opportunity for accessing tissues during the surgery made it possible to deepen the study of obesity. The incorporation of data from the “omic” studies and their interaction with the environment as well as with the hormones that regulate glucose, appetite, and satiety after bariatric surgery, will help to improve our understanding of the mechanisms that regulate weight loss, weight

regains, remission, and the relapse rates of these comorbidities. This will allow advancing the prescription of bariatric surgery into precision medicine to improve the selection and prognosis of candidates for bariatric surgery.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

ETHICAL DISCLOSURES

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

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