Precision Medicine in Bariatric Procedures

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KEYWORDS

• Precision medicine • Bariatric surgery • Bariatric endoscopy • Genetics
• Epigenetics • Obesity

KEY POINTS

- Precision medicine uses a variety of factors including deep phenotyping, omics assays, and environmental factors to devise practices that are individualized to subsets of patients.
- There are wide variations in clinical response to bariatric procedures, and hence individualized approaches to treatment and prediction of outcomes are very pragmatic.
- Precision approaches to bariatric procedures developed thus far include genetic, epigenetic, metabolomic, microbiomic, clinical quantitative traits, and energy balance phenotypes.

INTRODUCTION

The prevalence of obesity in the United States is greater than 40% currently and is estimated to reach nearly 50% by 2030.[1,2] This enormous burden of the disease leads to a heavy strain on the health care system, with $172.74 billion of annual expenditures relating to obesity and related comorbidities in the United States.[3] Obesity has a multifactorial and complex pathophysiology, including environmental factors, genetic and epigenetic factors, microbiome-related disruption, and socioeconomic factors.[4,5] Management options for obesity are evolving, and include lifestyle and behavioral modifications, antiobesity medications, and bariatric procedures (metabolic and bariatric surgery [MBS] and endoscopic bariatric therapies [EBT]).

Bariatric procedures cause significant and sustained weight loss and are the most effective therapeutic option for obesity. Additionally, there are ample data showing

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significant improvement of obesity-related co-morbidities and overall mortality with MBS.[6–8] Contemporary techniques of MBS include laparoscopic sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), and adjustable gastric banding. RYGB is considered the most effective option, albeit with the highest rate of major adverse events.[9] Recent years have seen the evolution of EBT, with procedures like intragastric balloons (IGB) and endoscopic sleeve gastroplasty (ESG) gaining global popularity and FDA approval. Overall, bariatric procedures are getting increasingly popular, although they faced a small dip during the coronavirus disease 2019 pandemic. The American Society for Metabolic and Bariatric Surgery estimates close to 200,000 bariatric procedures are performed annually in the United States.[8,9]

Obesity mediates tissue injury in various ways. Excessive lipid accumulation in obesity overwhelms the body's lipid metabolism pathways. This leads to malfunctions in the endoplasmic reticulum and mitochondria, increasing levels of reactive oxidative species, free fatty acids, and intermediates like ceramide. These free fatty acid intermediates trigger various proinflammatory kinases, leading to an increase in inflammatory adipokines and infiltration by immune cells like macrophages and type 1 T helper (TH1). Additionally, these intermediates and the ensuing inflammatory environment activate nuclear factor κB, altering gene transcription. These alterations impact insulin signaling in several ways, including changes in insulin receptor phosphorylation and function, and cause tissue damage, especially when ectopic fat accumulates in the liver and vascular structures. These various changes are likely contributors to both localized and systemic inflammation[5] (**Fig. 1**).

Precision medicine is a practice wherein prevention and treatment strategies take individual variability into account.[10] Most current prevention and treatment approaches are formulated and based on the average patient, and hence less than optimal for many patients. Precision medicine steps away from this one-size-fits-all approach. It involves using a variety of factors including deep phenotyping using clinical, physiologic, and behavioral characteristics, omics assays (eg, genomics,

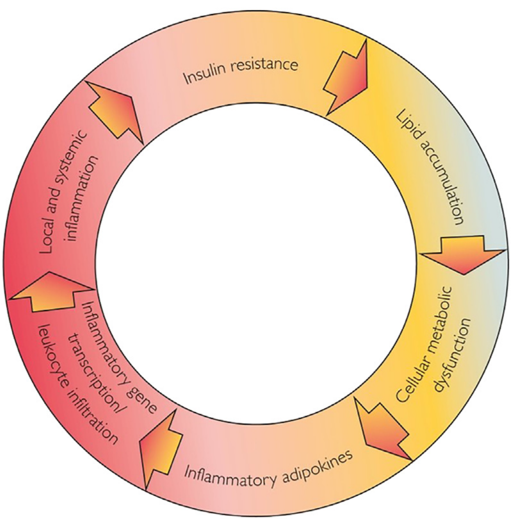

Fig. 1. Obesity-related tissue dysfunction. (*Reproduced from* Busebee B, Ghusn W, Cifuentes L, Acosta A. Obesity: A Review of Pathophysiology and Classification. Mayo Clin Proc. 2023;98(12):1842-57.)

epigenomics, transcriptomics, and microbiomics among others), and environmental factors to devise practices that are individualized to subsets of patients.[11] The Precision Medicine Initiative started in the United States in 2015 generated much excitement in the medical community and has been driving impetus for research and development in this arena.[12] Although much of this focus has been in the realm of oncology, precision medicine is increasingly being considered for the management of other chronic diseases like obesity.

Precision medicine for obesity is an evolving field. Obesity is a multi-factorial disease that is influenced by genetic, epigenetic, and environmental factors. Hence, incorporating elements like omics assays and clinical phenotyping can help with the clinical stratification of patients with obesity based on the underlying pathophysiology. In turn, this may help treat patients in an individualized and targeted manner. This is crucially important to optimize outcomes in bariatric surgery. It is well known that despite the efficacy of bariatric surgery and EBT, these procedures have a heterogenous response among patients. A study using the Longitudinal Assessment of Bariatric Surgery (LABS) database showed that there are distinct trajectories of weight loss among different patients in both the initial and long-term follow-up.[10] Even controlling for follow-up and patient compliance, the authors see variations in clinical response to bariatric procedures. Personalizing the therapeutic modality to the individual can lead to enhanced effectiveness and tolerability. Hence, precision medicine has untapped potential and enormous implications for use in bariatric procedures. The authors review advances in precision medicine made in the field of bariatrics and discuss future avenues and challenges.

GENETICS

Genes play an important role in obesity, with genetic factors accounting for 40% to 70% of an individual's predisposition to obesity.[13] Large genome-wide association studies have identified more than 300 loci in which single nucleotide polymorphisms (SNPs) are associated with development of obesity.[13] Simulation studies have shown that currently known SNPs do not account for more than 20% of variance in body mass index (BMI). However, there are likely many SNPs influencing obesity yet to be described. Polygenic risk scores have been developed that have the ability to predict BMI and obesity-related comorbidities with good accuracy.[14,15] Monogenic obesity (developed due to mutations or deficiencies in a single gene) and syndromic obesity (severe obesity associated with additional phenotypes and other organ abnormalities) are relatively uncommon, accounting for less than 5% of all severe obesity. Several genes and mechanistic pathways have been implicated in monogenic obesity, including the leptin-melanocortin pathway (LMP) and syndromes such as Bardet-Biedl syndrome, Alstrom syndrome, and Carpenter syndrome.[16]

As described previously, weight loss after bariatric procedures is extremely varied. Data suggest that a component of this variability may be attributed to strong genetic determinants. A study evaluating heritability of weight loss to RYGB showed that first-degree relative pairs had a similar response to surgery, which was not seen with cohabitating or unrelated individuals.[17,18] These genetic determinants seem to play a more dominant role in combination restrictive/malabsorptive procedures, rather than purely restrictive procedures like gastric banding.[19] Different weight-loss trajectories have been ascribed to genetic markers in 4 obesity genes: the mass and obesity-associated (FTO), insulin-induced gene 2 (INSIG2), melanocortin 4 receptor (MC4R), and proprotein convertase subtilisin/kexin type 1 (PCSK1) genes.[20] A recent systematic review and meta-analysis on this topic demonstrated that uncoupling protein (UCP) variant rs660339 and FKBP5 have been consistently associated with greater and lesser weight loss after bariatric surgery, respectively.[19] It did note that studies evaluating other genes like FTO and MC4R have been inconsistent with their association with outcomes after bariatric surgery. However, multiple studies have shown that in the short term, weight loss outcomes after bariatric surgery have been found to be similar in patients with and without variants in LMP.[21,22] Patients with variants in LMP have been found to have progressive and significant weight regain in the mid term and long term after RYGB.[23] This has been attributed to initial strong changes in neuroenteric hormone signaling being able to work through an impaired LMP and produce an effective short-term weight loss, but not being able to sustain this in the long term. Through a study of the Mayo Clinic biobank, the authors have also shown that patients with variants in LMP have weight recurrence after endoscopic transoral outlet reduction for RYGB[24] (**Fig. 2**).

Heritability of obesity traits is complemented by the interaction of genes and the environment, including unfavorable dietary, activity, and lifestyle factors. Keeping this in mind, multiple genetic risk scores have been developed, which incorporate SNPs along with variations in multiple anthropometric traits based on demographic and environmental characteristics. Several studies have evaluated several genetic risk scores examining weight loss from 12 to 96 months after bariatric surgery and found them to be predictive of outcomes.[24–26] With further development, longer study periods, and external validation, these risk scores may be a valuable tool in our armamentarium of predicting outcomes after surgery and personalizing therapeutic modalities.

Therapeutic opportunities are being explored for patients with known genetic predisposition to obesity. Setmelanotide is an MC4 receptor agonist developed for the treatment of obesity arising from proopiomelanocortin, PCSK1, or leptin receptor deficiency.[25,26] Use of phentermine-topiramate extended release in patients with a "hungry brain" phenotype, which may include patients with variants in the LMP, has been shown to superior results compared to usual care.[27]

Overall, genetic profiling of patients prior to bariatric procedures presents an exciting avenue to influence outcomes. Firstly, if preoperative evaluation reveals a high genetic score for obesity, they may benefit from a lower criteria threshold for receiving procedures, and may benefit from more aggressive, combination

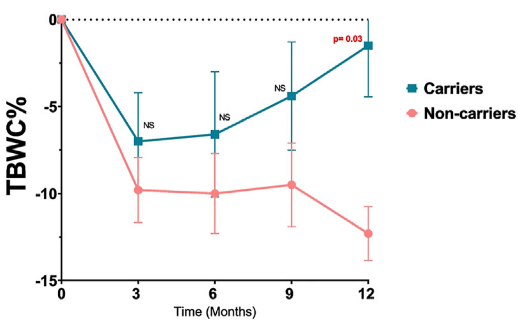

Fig. 2. Effects of heterozygous variants in the leptin-melanocortin pathway on transoral outlet reduction after roux-en-Y gastric bypass: a case–control study and review of literature. (Gala, K., Ghusn, W., Fansa, S. et al. Effects of Heterozygous Variants in the Leptin-Melanocortin Pathway on Transoral Outlet Reduction After Roux-en-Y Gastric Bypass: A Case–Control Study and Review of Literature. OBES SURG 33, 1284–1288 (2023). https://doi.org/10.1007/s11695-023-06462-0.)

restrictive/malabsorptive procedures. Secondly, genetic risk scoring can help with predicting outcomes. Lastly, using a combination of appropriate pharmacotherapy may help patients with high genetic risk achieve optimal weight loss outcomes after bariatric procedures.

EPIGENETICS

Epigenetic changes interact with the DNA or transcript without changes to the nucleotide sequence and alter gene expression.[28] The epigenome can be altered by the effect of external environmental factors, providing a dynamic response by the organism in a short time. Distinct epigenetic patterns have been identified in patients with obesity and metabolic diseases. Additionally, there is a growing body of literature that suggests that epigenetic modifications could be involved in the mechanisms underlying the response to bariatric surgery. It is well known that bariatric surgery has several effects on metabolism apart from weight loss, including improved insulin sensitivity, improved risk of cardiovascular disease and cancer, and resolution of the chronic inflammatory state induced by obesity.[29] It is hypothesized that bariatric surgery could influence epigenetic changes and gene expression, leading to these improvements in metabolism.[30] These modifications are best evaluated using epigenetic markers, which include DNA methylation, histone post-translational modification (PTM), and non-coding RNAs (ncRNAs) including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs).[31]

DNA methylation is the most widely studied epigenetic marker in relation with obesity. Large, epigenome-wide association studies have showed the correlation between changes in DNA methylation and excess adiposity.[32,33] Changes induced by bariatric surgery have been shown to be different, and generally more prominent, compared to those induced by diet/lifestyle modifications.[31] These changes are so significant that a study showed durable and detectable changes even in the subsequent offspring methylome and transcriptome of a mother who underwent RYGB.[34] Data suggest that bariatric surgery modifies the DNA methylation profile of the specific genes, measured in both specific tissues like liver, adipose tissue, and skeletal muscle as well as peripheral blood.[35] Changes in methylation of specific genes have been demonstrated, including PGC1A, PDK4, and SORBS3.[36] Analysis of skeletal muscle has shown that bariatric surgery leads to hypermethylation at CpG shores and exonic regions close to transcription start sites, hence potentially influencing the epigenome.[37] Additionally, there are changes reported in the methylation of specific genes belonging to inflammatory pathways, such as SERPINE-1, interleukin (IL)-6, tumor necrosis factor-alpha (TNF-A), IL-1B, and polycystic kidney disease-4 (PKD4).[38] Studies have shown changes in methylation patterns can be predictive of weight outcomes; for instance, a study demonstrated that patients with greater weight loss after RYGB had lower SERPINE-1 methylation levels 6 months after surgery.[39]

Other epigenetic changes and markers after bariatric surgery are being investigated. A recent study showed pilot data on the use of microRNA (miRNA) to predict weight loss outcomes after bariatric surgery. They reported 6 different miRNA that had previously been implicated in regulation of fatty acid biosynthesis, adipocyte proliferation, type 2 diabetes, and obesity that had the potential for discriminating between the high and low weight loss groups after surgery.[26] Liu and colleagues studied differentially expressed genes for subcutaneous adipose tissue after bariatric surgery and used integrated bioinformatics analyses to identify hub genes and associated pathways affected after bariatric surgery.[24] Several animal models have studied changes in the expression of lncRNAs after bariatric surgery, and have identified potential targets for prediction of outcomes after surgery.[30]

The next steps in this field need to be made in establishing the clinical significance of methylation and other epigenetic variations. Defining these changes in the epigenome can help prognosticate and even serve as therapeutic targets for the weight-loss and metabolic outcomes to bariatric surgery.

METABOLOMICS

Metabolomics represents the systematic identification and quantification of metabolites in a target organism or sample. It signifies a global metabolic profiling of organisms in relation to other variables including genetic variation or external stimuli.[40] Metabolites constitute of intermediate or end-product of metabolism low-molecular weight molecules (<1 kD).[41]

MBS and EBT contribute to a decreased body weight, with a significant effect on glycemic control,[42] cardiovascular disease risk,[43] and other metabolic parameters.[44,45] To better understand this metabolic effect, a significant effort was put to study metabolomics in patients after bariatric procedures. Importantly, MBS alters metabolic profiles compared to non-surgical procedures, when controlling for same weight loss outcomes.[46,47] Hence, MBS has a distinctive metabolic signature that might play a critical role in weight loss and associated improvement in metabolic comorbidities. Although there still have not been reliable preoperative models to predict weight loss, metabolomic analyses can aid in detecting biomarkers that reflect precise preoperative prediction of metabolic and surgical outcome after bariatric procedures.[48]

The most studied procedures in the metabolic field are RYGB (54%) and LSG (29%), followed by other less commonly explored procedures (eg, duodenal-jejunal endoluminal bypass, laparoscopic gastric banding, IGB, ESG).[49] Multiple metabolic pathways are altered after bariatric procedures. These pathways include the amino acids derivatives, bile acids, endocannabinoids, TCA cycle-related metabolites, lipid derivatives, microbiota-related metabolites, and other pathways.[48]

Amino Acids Derivatives

Branched chain amino acids (BCAAs) (ie, valine, leucine, and isoleucine) are known to be upregulated in obesity and type-2 diabetes mellitus (T2DM).[50] This might be due to regulation of BCAA aminotransferase, elevated gut microbiome BCAA synthesis,[51] and/or decreased microbial BCAA uptake and catabolism.[52] In fact, elevated BCAAs reflect a strong biomarker for insulin resistance. Similarly, aromatic amino acids (ie, phenylalanine, tyrosine, and tryptophan) are also upregulated in diseases such as obesity and T2DM. The rise in phenylalanine and tyrosine is attributed to a decrease in tyrosine aminotransferase function caused by insulin resistance and elevated specific metabolites including cysteine and alpha-hydroxybutyrate.[50] As for tryptophan, its metabolic pathways are altered in patients with obesity which is correlated with obesity-related systemic inflammation.[53]

Bariatric surgeries have been demonstrated to decrease the levels of BCAAs and aromatic amino acids in multiple studies.[54,55] These changes might enhance and explain the improvement in metabolic pathways and disease after bariatric surgeries. However, Kramer and colleagues showed that blocking the surgical effect on BCAAs does not alter the potent effects of bariatric surgeries on weight loss and glucose tolerance.[56]

LSG was shown to increase the serum concentration of serine and glycine.[57] Circulating levels of glutamate were also shown to decrease.

Lipid Derivatives and Bile Acids

Among the lipid derivatives, several metabolites were thoroughly studied in patients who underwent bariatric procedures. These include free fatty acids, acylcarnitines (AC), bile acids, and phospholipids. Studies have shown that short-chain AC derived from BCAA decrease after MBS,[47,58] while other short-chain AC increase rapidly and remain elevated for 6 to 12 months.[59,60] Long-chain ACs transiently increase before decreasing in the long term.[59,61]

Unsaturated, long-chain saturated, and non-esterified fatty acids demonstrate a decrease after bariatric surgery in most studies.[59,62] However, medium-chain saturated fatty acids increase after these bariatric surgeries.[63,64] Regarding phospholipids, most sphingomyelins decreased biliopancreatic diversion.[65] However, in RYGB, saturated sphingomyelins decrease while unsaturated increase.[66,67] As for bile acids, bariatric procedures with malabsorption component (eg, RYGB) seem to increase fasting and secondary circulating bile acids[65,68] while restrictive procedures resulted in inconsistent results in the literature.[69]

MICROBIOME

The human microbiota is made up of the 10 to 100 trillion symbiotic microbial cells harbored primarily in the gut of all humans; the human microbiome consists of the genetic material harbored by these cells. Changes in microbiota content are significantly associated with acute and chronic diseases, like obesity, type 2 diabetes, atopic diseases, inflammatory bowel disease, and atherosclerosis.[70]

The gut microbiota of obese patients has significant changes, including an increased Firmicutes/Bacteroidetes ratio at the phylum level, and decrease in Christensenellaceae and the genera Methanobacteriales, Lactobacillus, Bifidobacteria, and Akkermansia.[71] In essence, the gut microbiota regulates energy absorption, central appetite, fat storage, chronic inflammation, and circadian rhythms. It is thus not surprising that there are significant changes in the gut microbioata after MBS. Mechanisms driving these changes include malabsorption status, changes in the metabolism of bile acids, changes in gastric pH, and changes in the metabolism of hormones.[72] There are significant taxonomic changes after surgery, with reports demonstrating an increase in bacterial species richness after surgery, relating to an improved host metabolic profile.[73] There are also data suggesting an increase in functional annotations associated with amino acid utilization, sugar metabolism, and fatty acid utilization after bariatric surgery.[74,75] These changes are likely a major contributor to weight loss and improvements in glycemic and metabolic control. Hence, many new molecular targets and small molecules of microbial origin in the host may be used for prognostication of outcomes, as well as targets for obesity treatment. Although the translation of these findings is in its infancy, the microbiota represents an exciting opportunity for precision medicine in the realm of bariatric procedures.

CLINICAL QUANTITATIVE TRAITS AND PREDICTIVE MODELS

Several clinical tools have been developed to help guide the use of bariatric procedures in patients with obesity. Some scores have been built to predict diabetes remission in patients with T2DM.[76] Other clinical classifications have also demonstrated a possible utility in MBS and EBT.[77,78] Such clinical measurements are of significant importance for physicians treating patients with obesity and related comorbidities (eg, T2DM).

T2DM is one of the major comorbidities that is associated with obesity. In fact, obesity represents the most common risk factor for T2DM.[79] Around 80% to 90% of patients with T2DM have overweight or obesity.[80] Importantly, patients with T2DM are associated with higher all-cause mortality rates related to multiple complications of this disease including cardiovascular disease, respiratory diseases, cerebrovascular disease, cancer, kidney diseases, specific infectious diseases, and other diseases.[81] T2DM was reported to be among the top 10 causes of death in 2019.[82] In addition, its economic burden continues to be rising to reach $245 billion in 2012[83] and $327 billion in 2017.[84] Bariatric surgeries have been shown to be effective in achieving T2DM remission. However, there is a notable heterogeneity in disease remission in patients with T2DM, ranging between 24% and 84%.[76] This wide difference can be attributed to various factors including type of procedure, baseline metabolic parameters, T2DM remission definition, and other contributors. Hence, multiple predictive models have been validated to help evaluate disease remission in patients with T2DM.

One of the most widely used and validated metrics for T2DM remission is the Individualized Metabolic Surgery (IMS) Score constructed by Aminian and colleagues. This is an evidence-based scoring system to select MBS (ie, RYGB and LSG) depending on T2DM severity, predicting disease remission.[85] In a cohort of 659 patients and an external validation cohort of 241 patients, patients were categorized into 3 stages of diabetes severities based on 4 different parameters. This score is based on preoperative variables like number of diabetes medications, insulin use, duration of diabetes (years), and glycemic control (HbA1c <7%). Depending on the score, patients can be classified either into the mild category: score 0 to 25; moderate category: 25< Score ≤95; and severe category: greater than 95. Patients with mild and severe scores may benefit equally from RYGB and SG in terms of T2DM remission. In fact, both procedures significantly improve T2DM for patients in mild category. However, a severe score, which reflects a limited functional β-cell reserve, denotes a similar low efficacy in both procedures for T2DM remission. As for the moderate severity, RYGB demonstrated better remission rates compared to SG, attributing to a more pronounced neurohormonal effect. Hence, this score provides an applicable model to help select bariatric procedures. Although more recent studies show similar efficacy of RYGB and SG in the intermediate group, there remains a clear trend in higher remission rates with lower IMS scores.[86–88]

Another score that was created by Robert and colleagues included multiple predictive factors of T2DM remission at 1 year after MBS. In this cohort, there was no significant difference in T2DM remission between RYGB, SG, and LAGB, with a trend of better outcomes in patients who have undergone RYGB (RYGB: 74%; SG: 50%; LAGB: 50%). Patients with higher scores have a higher chance of T2DM.[89]

The DiaRem score represents an algorithm that predicts T2DM remission rates over 5 years.[90] Based on this score, patients are divided into 5 groups representing different T2DM remission ranges. The Ad-DiaRem score is another model used to predict T2DM remission after RYGB surgeries. It was created with a test cohort of 213 patients and validated in 2 independent cohorts in France (n = 134) and Israel (n = 99). A higher score represents a lower T2DM remission rate after bariatric surgery.[91] Lastly, the ABCD score was initially developed in an Asian population of patients with T2DM (N = 63) who had undergone RYGB and has been validated in a prospectively collected cohort of 176 patients. With the increase in this score, the higher remission rate is expected.[92]

ENERGY BALANCE AND OBESITY PHENOTYPES

Emerging studies highlight the importance of individual variations in energy intake and expenditure in obesity pathophysiology and management plan.[5,27] Energy intake is influenced by both homeostatic mechanisms, which regulate hunger and fullness, and hedonic factors, which are influenced by emotional states. Quantifiable traits such as satiation and satiety, assessed through calorie consumption and gastric emptying rates, respectively, are linked to obesity and can shed light on individual differences in weight gain.[27] In addition, energy expenditure can decrease in response to calorie restriction or weight loss, and this reduction can predict future weight gain. A persistent decline in energy expenditure can even continue years after initial weight loss.[5,93]

A new classification system based on phenotypes related to eating behaviors and energy expenditure seeks to stratify obesity more precisely. This system identifies 4 phenotypes: abnormal satiation, abnormal satiety, emotional eating behavior, and abnormal resting energy expenditure.[27,94] Treatments tailored to these phenotypes have shown better weight loss outcomes than non-specific approaches.[5,27,95] Medications like phentermine-topiramate and GLP-1 agonists have been effective in managing specific phenotypes by reducing energy intake and modulating gastric emptying.[27] Further work in this arena may provide insights into the application of bariatric surgery and EBTs, indicating a promising direction for individualized obesity management.

PRECISION MEDICINE IN ENDOSCOPIC BARIATRIC THERAPIES

Endoscopic bariatric therapies (EBTs) are minimally invasive alternatives to bariatric surgery that have emerged over the past few years. These include space-occupying devices like IGBs and TransPyloric Shuttle, and gastric remodeling techniques, such as ESG and primary obesity surgery endoluminal 2.0 (POSE 2.0).[96] Research on precision medicine and omics in these modalities is lacking.

Moreover, the authors' group has explored the use of physiologic predictors of outcomes after EBTs. In a prospective feasibility study, 32 patients who underwent placement of IGBs had their gastric emptying time measured at baseline and 3 months following the procedure.[97] Patients who had a delay in gastric emptying had significantly higher weight loss compared to those who had no change in their gastric emptying. A meta-analysis also showed that IGBs cause delayed gastric emptying, correlating to weight loss.[98] One study showed that IGBs cause a delay in emptying of solid foods only.[99] This has also been explored in patients undergoing ESG, who also experienced delayed gastric emptying, correlating with short-term weight loss, as well as changes in gastric accommodation.[78] When comparing modalities, it has been shown that IGBs cause more significant delay in gastric emptying compared to ESG, with these changes having a greater effect on weight loss.[77] Overall, these differences in physiologic responses have been predictive of response to therapy, and could be used to select interventions.

SUMMARY

Precision medicine-based studies are paving the way for personalized treatment of obesity and outcomes after bariatric procedures. The traditional approach of "one size fits all" does not take into account the remarkable heterogeneity of obesity while positioning treatments for patients, and hence results in underwhelming responses to therapies. This includes bariatric procedures, which have a high rate for reversal of obesity and metabolic syndrome if used in the right patient. Using personalized approaches with high-resolution technologies based on "omics profiling" will help optimize treatment approaches and outcomes. Although in early stages, precision medicine has a tremendous potential in the management of obesity and related diseases.

CLINICS CARE POINTS

- Precision medicine is a practice in which prevention and treatment strategies take individual variability into account.
- Significant data in the realm of genetics shows that response to MBS is affected by underlying genetic determinants.
- Areas like epigenetics and metabolomics are in their infancy for use in bariatric procedures.
- Clinical quantitive tools and predictive models for prediction of outcomes after bariatric procedures are evolving.

DISCLOSURES

A. Acosta and Mayo Clinic hold equity in Phenomix Sciences Inc. and are inventors of intellectual property licensed to Phenomix Sciences Inc. A. Acosta served as a consultant for Rhythm Pharmaceuticals, General Mills, Amgen, Bausch Health, RareStone; has contracts with Vivus Inc, Satiogen Pharmaceutical, and Rhythm pharmaceutical. The remaining authors have nothing to disclose.

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