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Bariatric metabolic surgery outcome and the genetic makeup of the patients: a review

Susmit Kosta[1]✉, Mohit Bhandari[2], Winni Mathur[2], Mal. Fobi[2]

Bariatric Metabolic Surgery (BMS) can shrink waistline but a new studies show it can cause surprising changes in genes. Combined with environmental influences, genes are up to 70% responsible for body's weight. BMS may be the only effective way to alter these genetically predetermined body processes. In this review we analysis and interpretation of recent literature regarding to the different genetic forms of obesity and its implications in the BMS practice. The identification of genes involved in monogenic, syndromic and polygenic obesity, has improved our understanding about the mechanisms of its development as well as the potential effect of these genes over the outcome of BMS. There are no reports in the literature about the effect of BMS in monogenic obesity. Surgery has demonstrated discreet results in patients with syndromic obesity in comparison whit normal obese individuals. Regarding polygenic obesity there are some reports of certain single nucleotide polymorphisms (SNPs) associated with a greater weight-loss in the postoperative. Genetics have a considerable contribution to the development of different forms of obesity. Similarly, several and different BMS techniques used for weight-loss have demonstrated to be effective but variable on their results. For this reason, we strongly recommend surgeons to be aware of the potential genetic aspects and it's applications of this field for better selection and treatment of obese patients.

INTRODUCTION

Metabolic diseases including obesity are highly heritable. In combination with environmental effects; genes are up to 70% responsible for body's weight [1]. Obesity is the most urgent epidemic of the modern age, both in the United States and globally [2]. Obesity is understood to be a pathologic process resulting in excess body fat. It is the result of the interaction of inherited genetics and the environment mediated by epigenetic changes in those genes or their expressed proteins. Sixty-seven percent of variability in body mass index (BMI) is attributable to inheritance. Of the total variability, 40% is due to genes that control food intake, 12% is due to metabolic rate, 5% to fat oxidation and 10% to spontaneous physical activity [3]. Morbid obesity can cause systemic arterial hypertension and type 2 diabetes mellitus both of which are also influenced by genetics. While acute and chronic changes in body-weight or obesity-related co-morbidities are heavily influenced by environmental factors, there are still strong genomic modifiers and regulator genes which account for variability in baseline traits and inter subject response to interventions.

Obesity and genetics are directly related [4] and auspiciously nowadays, bariatric metabolic surgery (BMS) is the most effective long-term treatment for morbid obesity [5]. It results in a significant reduction in body weight, accompanied by improvement of several risk factors for cardiovascular disease [6,50]; however, patients do not all lose the same percentage of weight or enjoy the same clinical benefits after surgery. Outcomes after BMS can vary widely partly due to the genetic component. BMS might be the only effective way to alter these genetically predetermined body processes.

There have been BMS outcomes that indicate that the amount of weight-loss after BMS can be predicted in part by a DNA sequence variation found on chromosomes [7]. These findings explain why the success of gastric bypass surgery varies so widely and could help clinicians identify those who would benefit the most from this type of surgery. To identify and classify specific genetic factors that might play a role, researchers examined the genomes of more than thousand individuals undergoing gastric bypass surgery. Hatoum *et al.*, found that individuals with two copies of a specific variant on chromosome15 lost on average about 39% of their body weight, whereas those without a copy of this variant lost less than 30% of their body weight [7]. Moreover, the activity of the gene located closest to this variant also predicted weight-loss. This is the first instance where a GWASs search has identified genetic predictors of weight-loss after gastric bypass surgery. Although clinical, demographic, psychological, and surgical predictors, such as age, sex and baseline have been used for predicting the variation of the therapeutic effects of surgery, these phenotype factors explain only a small part of the variation and fall short of identifying patients with good efficiency [8,9]. There has been consensus in academia that not only the phenotype but also the genotype should be used for customized treatment. Through growth in the understanding of the genetics and epigenetics of obesity, various studies have been carried out to identify the association between outcomes and treatments in order to implement further personalized therapeutic options. Thus, this review is intended to provide an up-to-date overview of our current understanding of genetic influences on obesity, with

[1]Central Research Lab, Sri Aurobindo Medical College and PG Institute Indore, Madhya Pradesh, India; [2]Department of Bariatric Surgery, Mohak Bariatric and Robotic Surgery Centre, Indore, Madhya Pradesh, India

✉*Corresponding Author*: Dr. Susmit Kosta; Central Research Lab, Sri Aurobindo Medical College and PG Institute, Indore, Madhya Pradesh, India; Email: susmitkosta@gmail.com

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emphasis on GWASs and influence of candidate genes studies on BMS responses to intervention. We begin by reviewing how candidate genes can influence the outcomes of different BMS process. We will pay particular attention to the genetic risk score predicting the clinical outcome of BMS with how genetic variants can influence obesity. Finally, we will discuss the outlook in what way the field of BMS can leverage knowledge of molecular mechanism that could mediate the control of epigenetics modifiers to adopt a personalized medical approach for optimal outcomes across this widespread and diverse patient population.

INFLUENCE OF CANDIDATE GENES ON THE OUTCOMES OF DIFFERENT BMS PROCESS

The effect of different polymorphisms after BMS is an interesting area of investigation. Gene variants may determine the outcomes of obesity treatment. As Laparoscopic gastric banding (LGB), Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy (LSG) and One Anastomosis Gastric Bypass (OAGB) are the major BMS procedures; we will begin our review according to the different types of surgery.

LGB is a therapeutic method of inducing a durable weight-loss in obese patients [10]. Some studies have focused on whether genetic factors of body weight homeostasis could account for differences in the therapeutic effects of LGB. One study of 167 unrelated obese subjects, with a six-month follow-up, showed that carriers of the G-174G IL-6 genotype had lost more weight than those with G-174C or C-174C. Carriers of the A866A uncoupling protein two genotype lost more weight after LGB than those with G866G; however, the researchers did not observe that, after LGB, there was any statistically significant difference in subjects with obesity carrying the Gly972Arg polymorphism of the insulin-receptor-substrate-1 (IRS1) gene and Pro12Ala polymorphism of the peroxisome-proliferator-activated-receptors (PPARs) gene, when compared with non-carriers [11]. Another study showed similar effects [12]. Sarzynski *et al.* tested the association of SNPs in 11 obesity candidate genes, including ADIPOQ, BDNF, FTO, GNB3, LEP, LEPR, MC4R, NR3C1, PPARs, PPARGC1A and TNF, with weight-loss and weight-regain; among the 11 SNPs, only FTO rs16945088 was associated with maximum weight-loss after gastric banding [13]. To our knowledge, Chen *et al.* performed the first study of genetic susceptibility testing in weight-loss prediction in the Chinese population, while most other studies were performed in Caucasian populations [14]; they found that the rs660339 (Ala55Val), on exon-4 of the uncoupling-proteins-2 (UCP2), was associated with morbid obesity and played an important role in obesity development and weight-loss after LGB. These results suggest that genetic markers may be useful new clinical tools to guide obesity therapies. Another study of 300 severely obese subjects who underwent LGB found that women who carried eight melanocortin 4 receptor gene (MC4R) variants lost less weight three years after surgery than non-carriers [15]. Similarly, polymorphisms from the guanine-nucleotide binding protein alpha stimulating activity polypeptide 1 (GNAS1) and beta polypeptide 3 (GNB3) genes were not associated with three year weight-loss in these subjects [16]. Finally, a study of 77 patients receiving LGB and 227 receiving OAGB found that UCP2 rs660339 (Ala55Val) was associated with LGB induced weight-loss in T allele carriers. They lost more weight at 12 and 24 months compared with patients with the CC genotype [12]. No association was found in OAGB patients despite experiencing a greater weight-loss than LGB patients.

RYGB is an effective therapy for patients with extreme obesity [17]. In a study of 1011 white individuals who underwent RYGB surgery, the variants in or near obesity genes, such as FTO (fat-mass and obesity-associated), INSIG2 (insulin induced gene 2), MC4R (melanocortin-4-receptor), and PCSK1 (proprotein-convertase-subtilisin/kexin-type-1), were associated with poorer weight-loss outcomes after RYGB [18]. Mutations in MC4R represent the most common monogenic cause of human obesity. BMS in monogenic and syndromic forms of obesity [19,21]. BMS has also been performed in few of MC4R mutation carriers. After RYGB, lower body weight reduction and worse improvement of metabolic complications was found in MC4R mutation carriers versus non-carriers [20,21]. Another study of 1433 RYGB patients who were studied for two years before and after surgery showed that patients with the MC4R (I251L) common allele could achieve better weight-loss over a longer period after surgical interventions [22].

LSG has become increasingly popular around the world since 2000 [23]. LSG has become an effective, stand-alone therapy for morbidly obesity, with stable weight-loss and resolution of obesity associated comorbidities [24,25], but there have been few studies of the association between genetic factors and the outcomes of LSG. In 2016, Shanti *et al.* found that, after LSG, patients in the family group, in which patients had a family member who had undergone LSG, experienced significantly greater weight loss than the control group, while family members living together showed no advantage over those who lived separately [26]. This suggests that genetic factors may have a great influence on the outcomes of LSG. Another study aimed to explore the effects of the rs9939609 FTO gene polymorphism after LSG [27]. Although the rs9939609 FTO gene polymorphism was thought to have a positive effect on weight-loss after lifestyle intervention, LGB and OAGB, the studies did not find any differences between mutant and wild-type groups after LSG [28-30]. More studies are needed to evaluate the association between genetic factors and the outcomes of LSG.

OAGB is an effective bariatric technique for treating overweight and morbid obesity, controlling and improving excess-weight-related comorbidities [31].Chen *et al.* found that the rs660339 (Ala55Val), on exon-4 of the UCP2, was associated with morbid obesity [15]. Studies to evaluate the association between genetic factors and the outcomes of OAGB are needed.

Moreover, Sarzynski *et al.* performed a study estimating the effect of genetic factors on the outcomes of BMS in 1443 patients (vertical banded gastroplasty: $n = 966$; banding: $n = 293$; gastric bypass: $n = 184$) [14]. From the 11-variant SNPs, only FTO rs16945088 was associated with maximum weight-loss only after gastric banding. These results suggest that the physiological and genetic factors influencing weight-loss after BMS may differ by surgery type. It remains to be seen whether the genetic factors influencing weight change are similar between various weight-loss methods such as exercise, diet and BMS.

GWASs CLINICAL OUTCOMES OF BMS

Obesity is known to be a complex disease influenced by multiple genetic and environmental factors. With advances in genetic technology and the huge number of BMS, it is feasible to perform GWASs of the variable clinical outcomes of BMS. These GWASs suggest that genetic variation can affect weight-loss after surgery. To date, 17 common obesity loci have been identified through GWASs [32] and associations have been confirmed for several candidate genes [33]. However, it is unclear whether DNA sequence variation in these same genes affects the outcome of weight-loss interventions. Hatoum *et al.* have done several studies on this subject and provided persuasive evidence suggesting that there are strong genetic determinants of weight-loss after RYGB [34, 35]. In a cohort study of 848 patients, by comparing weight-loss after

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RYGB within pairs of genetically related and genetically unrelated individuals, they found similar weight-loss within pairs of related individuals, whereas unrelated individuals exhibited far less similarity in weight-loss outcomes after the same procedure [34]. Since part of this effect may be mediated through environmental factors, they also identified pairs of genetically unrelated individuals who were living together and found that their weight-loss after RYGB was no more similar than completely unrelated pairs of individuals and much greater than between first-degree relatives [34]. To identify genetic factors contributing to weight-loss, the team performed GWASs of 693 genetically unrelated individuals undergoing RYGB and then replicated this analysis in an independent population of 327 individuals [35]. They found that a 15q26.1 locus near ST8SIA2 and SLCO3A1 was significantly associated with weight-loss. An animal study performed later supported the above conclusion [35]. These findings provide strong evidence for specific genetic influences on weight-loss after RYGB and underscore the biological nature of the response to this type of BMS.

In a cohort of 1143 patients, by comparing 86 obese patients who had the least percentage excess body weight loss (%EBWL) and 89 patients who had the greatest %EBWL at two years after RYGB surgery, Rinella *et al.* tried to identify genetic factors contributing to this weight-loss [36]. The first-stage cohort was genotyped for 730, 767 SNPs, and 111 SNPs were identified. In the endorsement stage, between these SNPs, 17 SNPs are the most significant, covering 6 genes/regions IGF1R, PKHD1, CITED2/NMBR, IPO11/HTR1A, CENPF/KCNK2 and GUCY1A2. In another examination of 34 obesity and waist-to-hip ratio associated SNPs, rs4771122 in an intron of MTIF3 was the most significantly associated SNP with long-term weight loss after surgery [37]. All these studies suggested that genetic variation can affect weight-loss after BMS.

GENETIC RISK SCORE AND CLINICAL OUTCOME OF BMS

Genetic risk score (GRS) explained the combined impact of various potentially risk contributing SNPs by creating one continuous variable that indicates the likelihood of developing a disease or a trait, such as weight-loss [38]. GRS is calculated in a weighted or unweight manner; however, the effect of the FTO allele variance explained was only 0.34% [39], meaning that the remaining individual variance in BMI may be attributed to other genetic and non-genetic factors, so GRS might be a more efficient and sensitive way of evaluating individual variance, including individual response after BMS.

Bandstein *et al.* identified two weighted GRSs, composed of BMI and waist-to-hip ratio associated SNPs, which were based on a selection of genetic variants with significant impact on weight-loss after RYGB surgery [40]. They found that patients with the lowest GRS had a significantly higher excess BMI loss than higher scoring patients. This observation supports the hypothesis that patients carrying none or only a small number of the risk alleles of obesity show more efficient weight-loss after RYGB surgery than carriers of multiple risk variants. The GRS may be useful in pre-surgical evaluation of the risks of patients undergoing RYGB surgery.

GENETICS AND EPIGENETICS OF OBESITY

Recent understanding of the genetics and epigenetics of obesity and how these findings influence responses to treatments, numerous studies on the genetics of obesity have been reported. Epigenetics study of changes in DNA that regulate gene expression patterns without alterations in the nucleotide sequence, which are potentially transmitted to an individual's descendants [41]. As to obesity influenced responses to BMS, the epiobesigenic genes play vital roles, including controlling processes such as glucose tolerance, appetite, adipogenesis and inflammation [42].

Researchers have found that the obesity can be influenced by genetic variations in the melanocortin-4-receptor (MC4R), neuropeptide-Y-receptor-Y2 (Npy2R), fat mass and FTO and neuropeptide-FF-receptor-2 (NPFFR2) in adult populations [43]. For paediatric obesity, a current finding recommended that the leptin-receptor (LEPR) and protein-kinase-C (PRKCH) might influence the obesity of infants [44]. A study of nearly 250000 individuals and 2.8 million polymorphisms confirmed 14-loci that were already known to be associated with obesity and revealed 18 new loci [39].

Another meta-analysis of associations between BMI and approximately 2.4 million SNPs was conducted among 27715 East Asians, and identified 10 obesity-associated loci at the GWAS significance level [45]. Findings from these studies might shed light on new pathways involved in obesity. Still many pathways warrant further clarification. The proposed molecular mechanism that could mediate this control is epigenetics. Dick *et al.* conducted an analysis of 450 million CpG (50-C-phosphate-G-30) sites, and made an association between BMI with raised DNA-methylation at hypoxia-inducible transcription factor 3A (HIF3A) [46]. Another study of 4 million CpG sites in 74 individuals showed that variable methylated regions may be used in the prediction of disease [47]. Furthermore, a twin-based study has shown an association between the serotonin transporter SLC6A4 promoter hyper-methylation in blood leucocytes, and increased BMI and waist circumference levels [48].

DNA-methylation presents a mechanism through which environmental factors could control insulin sensitivity in obesity. Barres R. *et al* assessed DNA-methylation in skeletal muscle from obese people before and after RYGB [49]. Obesity was associated with altered expression of a subset of genes enriched in metabolic process and mitochondrial function. After weight-loss, the expression of the majority of the identified genes were normalized to levels observed in normal-weight, healthy controls. Among the 14 metabolic genes investigated, promoter methylation of 11 genes were normalized to levels observed in the normal-weight, healthy subjects. Barres R. et al showed that promoter methylation of *PGC-1α* and PDK4 are altered with obesity and restored to non-obese levels after RYGB-induced weight-loss [49]. A genome wide DNA methylation investigation of skeletal muscle revealed that obesity is associated with hypermethylation at CpG shores and exonic regions close to transcription start sites [49]. This finding provides evidence that obesity and RYGB induced weight-loss have a dynamic effect on the epigenome.

CONCLUSION AND OUTLOOK

Genetics have a considerable contribution to the development of different forms of obesity. In all forms of obesity, dieting and physical activities do not result in significant weight-loss and is associated with a high rate of weight regain [20, 21]. BMS techniques used for weight-loss have demonstrated to be effective but variable in their results. Genetics identification might suggest new approaches that could be used to develop novel therapies for obesity, diabetes, and related metabolic comorbidities. Furthermore, progress in understanding of genetic obesity mechanisms, particularly by applying whole-exome sequencing, may probably help physicians to identify new molecular anomalies in patients with severe early-onset obesity in the near future in order to better understand the pathophysiology of more common forms of obesity and to improve their care management [19-21]. For this reason,

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we strongly recommend surgeons to be aware of the potential applications of this field for better selection and treatment of obese patients. This review attempts to provide an overview of the genetics and epigenetics associated with responses to different BMS process. From the studies described above, we can see that genetic factors affect the outcomes of obesity treatment and, at the same time, that the current results are far from conclusive. Despite having a long way to go, the prospects are promising. With more and more studies being conducted, the introduction of precision obesity treatment is brought nearer. As BMS is the most effective long-term treatment for morbid obesity, we pay special attention to the association between genetic factors and clinical outcomes of BMS. We can predict that, in the future, when receiving a new patient in our obesity department; we will be able to determine the patient's personal responses to the different treatments through genetic testing, so that we can choose the most appropriate method, from noninvasive to invasive. Also, in the future, genetic factors might provide a reliable pre-operative method of profiling patients who will successfully sustain weight-loss. Such a prediction would be used for choosing the optimal treatment for patients, avoiding unnecessary adverse effects and costs.

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