ABS ANNALS OF BARIATRIC SURGERY Annals of Bariatric Surgery

Original Article

Title: The Potential Role of Personalized Medicine in Bariatric Surgery

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Received: Feb 04, 2021/ Published Online: Feb 18, 2021

Abstract

Background: Bariatric surgery recognized as the best therapy for severe obesity. Weight loss after surgery is, however, extremely variable and genetically influenced. Genome-wide association studies (GWAS) have identified many single nucleotide polymorphisms (SNP) related to weight, body fat proportion and additionally feeding behaviors. Thus, the aim of this study was to research the effects of sequence variants and determined SNP on patient's responses to bariatric surgery.

Methods: This review article summarizes studies that were investigating the influence of genetic polymorphisms in different effectiveness of bariatric surgery and weight loss pathways. Scopus and PubMed database were consistently searched up to January 2021, for GWAS studies providing knowledge relating to the genetic factors that have an effect on the bariatric surgery outcomes.

Results: The evidences from GWAS studies showed that many genes and SNPs affected the individual responses to bariatric surgery. the most of these SNPs is associated to genes that regulate the lipolysis/lipogenesis pathways, adipose cell metabolism, metabolic process chain, insulin resistance, insulin/glucagon metabolism, feeding behavior and appetite-sensing state. At this regard, rs16945088 SNP of FTO (fat mass and obesity-associated) sequence, MC4R (melanocortin 4 receptor), rs660339 (Ala55Val) SNP of uncoupling proteins 2 (UCP2), leptin receptor gene (Lys656Asn and Asn656Asn), gucagon-like peptide 1 receptor gene (rs6923761) and INSIG2 (insulin induced gene 2) are the most studied and affecting polymorphisms that have influence on bariatric surgery outcomes.

Conclusion: Genetic background encompasses an important impact on weight loss after bariatric surgery. within the future, genetic testing could probably be employed in the pre-surgical assessment of patients with severe obesity for selecting the best surgery procedure for patients, avoiding supernumerary adverse effects and prices.

Key Words: obesity Surgery, gastric Bypass, Single nucleotide Polymorphisms, Genome-Wide Association Studies, GWAS, SNP

Introduction

From the genomic perspective, polygenic morbid obesity is that the most frequent in humans. it has been outlined as the results of a complex interaction between genetic, behavioral, nutritional and different environmental factors (1). intensive evidence has documented a consistent impact of genomic factors on body composition and obesity. These and

ancestral origin have additionally been connected to the surgical outcome such as surgical weight loss (2). Bariatric surgery recognized as the most efficient therapy for severe obesity. Weight loss after surgery is, however, extremely variable and genetically influenced. Genome-wide association studies (GWAS) have known several single nucleotide polymorphisms (SNP) related to weight, body fat percentage and additionally feeding behaviors.

moreover, the degree of weight loss and treatment success is very variable and potential surgery-associated complications shouldn't be underestimated (3). Thus, the detection of reliable pre-surgical indicators for a risk-benefit assessment before the intervention would be of high value. Weight loss following bariatric surgery is influenced by genetic variants (4). Thus, the aim of this study was to research the results of the effects variants and determined SNP on patient's responses to bariatric surgery.

Methods

This review summarizes studies that were investigation the influence of genetic polymorphisms in different effectiveness of bariatric surgery and weight loss pathways. Scopus and PubMed database were systematically searched up to January 2021, using the Mesh term of "Obesity Surgery", "Gastric Bypass", "Single nucleotide Polymorphisms", "Genome-Wide Association Studies", "GWAS", "SNP" for GWAS studies providing knowledge relating to the genetic factors that have an effect on the bariatric surgery outcomes.

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Results

Several publications have illustrated that some polymorphisms on several genes were statistically associated to weight loss after bariatric surgery (5). On study sequenced the MC4R (melanocortin 4 receptor) gene in 972 patients undergoing bariatric surgery and located that Patients with MC4R genetic mutation experienced lesser changes in weight loss. based on their studies, the authors ended that MC4R is important for sustained and sturdy weight loss after bariatric surgery (6).

Other study results demonstrated a statistical association between POMC (Proopiomelanocortin) (rs1042571) and weight loss at 6 and 12 months after bariatric surgery. Although ST8SIA2 and ADIPOQ (Adiponectin, C1Q And Collagen Domain Containing) polymorphisms were associated to this weight loss at 18 and 24 months, their impact was less significant than POMC. It was interesting to see that despite the fact that MM and nM displayed similar genotypes, nM had greater % excess weight loss. A similar trend for a greater net weight loss in surgical patients was observed for the two FTO (fat mass and obesity-associated) SNPs (rs16945088(10) and rs9939609(27)) (7). The fat mass and obesity associated gene (FTO) has the strongest association to BMI as shown in a study including more than 340,000 people (8). However, the explained variance of the FTO effect allele was earlier published to be only 0.34 % (9), meaning that the remaining individual variance in BMI may be attributed to other genetic and non-genetic factors. This machine learning tool has been used previously to screen or reduce dimensions in large GWAS datasets (10). Similarly, other investigation observed a trend towards greater weight loss for uncoupling proteins 2 (UCP2) rs660339 (11). Poitou et al. in 2005 (12) reported that some SNPs associated to LEP (Leptin) and ADIPOQ are involved in endocrine signals produced by the adipose tissue. In a French study, the same SNPs were associated to weight loss after adjustable gastric band (13). These authors speculated that these polymorphisms might have an influence in the modulation of adiposity signals on the surgically induced weight loss. Some SNPs in APOA2 (Apolipoprotein A2) have also been related to body weight across different populations. These authors demonstrated that some LEPR (Leptin Receptor) polymorphisms were associated to three to four times a higher risk for obesity and hyper-cholesterolemia (14). Moreover, they also demonstrated the impact of high saturated fatty acid consumption with a significantly increased risk for obesity among carriers with

APOA5/LEPR polymorphisms (15). The APOA family, specifically the APOA4 isoform, has also been linked to significantly higher lipoprotein plasma levels in obese patients who underwent bariatric surgery. This molecule has also been inputted as a satiety factor due to its property for gastric-emptying inhibition in a proteomic study (16). A group of genes related to the melanocortin system including POMC and MC4R that were statistically associated to the postoperative weight loss deserve special attention. From a physiological point of view, this system has been involved in an extraordinary and diverse number of physiological functions including energy homeostasis and appetite regulation (17).

Several studies suggested that morbid obese individuals have the A-C haplotype for the ADIPOQ -11391 and -11377 SNPs are prone to show a higher reduction in circulating lipid levels after bariatric surgery than other subjects, therefore having more benefits from this intervention (13).

others publications showed that three other important genes which are associated with weight loss, named MC4R, TFAP2B (Transcription factor AP-2 beta), and LYPLAL1 (Lysophospholipase Like 1) (18). MC4R has been implicated in eating regulation and metabolism. The protein responds to the agonist alpha- and beta-MSH, which is antagonized by agouti gene-related peptide in the hypothalamus regulating energy intake (19). Studies investigating the impact of common MC4R SNPs on bariatric surgery outcome led to contradictory results (20). Activating enhancer binding protein 2 beta (TFAP2B) and lysophospholipase-like 1 (LYPLAL1) have not been linked yet to post-surgery weight loss. However, in a meal intervention study, the TFAP2B-associated SNP rs987237 was linked to weight loss in the high-fat diet group (21). LYPLAL1 is expressed in regions known to regulate energy metabolism such as the hypothalamus and brain stem (22). LYPLAL1 was associated with weight loss effects in obese patients undergoing lifestyle changes (23). some studies suggested an index named Genetic risk scores which describes the collective impact of several potentially risk contributing SNPs by creating one continuous variable that indicates the likelihood to develop a disease or a trait, such as weight loss (24) Based on a selection of genetic variants, it developed a weighted GRS and estimated the post-surgery weight loss in dependency of the considered risk variants (23).

Conclusion

These results revealed that genetic background has a significant impact on weight loss after bariatric surgery. 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 non-invasive to invasive. Also, in the future, genetic factors may 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. genetics and epigenetics associated with responses to obesity treatment, since the study of this field of medicine is rapidly growing and evolving., 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, so future GWAS studies would clarify this pathway.

Conflicts of Interest: *The authors declared no conflict of interest*
Funding: *None*
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Cite this article as: Hatami M, Mohammadi-Farsani GH. The Potential Role of Personalized Medicine in Bariatric Surgery. *Ann Bariatr Surg. 2020 (Dec);9(2).5.*

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