INPLASY

The Outcome of Metabolic and Bariatric Surgery in Morbidly Obese Patients with Different Genetic Variants Associated with Obesity: A Systematic Review

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ADMINISTRATIVE INFORMATION

Support - UKC Ljubljana.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 July 2024 and was last updated on 07 July 2024.

INTRODUCTION

Review question / Objective The aim of this systematic review is to examine how genetic variants influence MBS outcomes in morbidly obese patients.

Rationale Obesity is a significant risk factor for several of the leading causes of mortality worldwide, including cardiovascular disease, stroke, diabetes, and various forms of cancer. According to the latest data of the Institute of Health Metrics and Evaluation (IHME), which are from 2021, obesity is the sixth leading risk factor for death in the world. In 2021, obesity was accountable for 129 million (95% UI 56.0–202) disability- adjusted life years (DALYs) and 3.71 million (1.85–5.66) deaths worldwide. Studies have proven that obesity leads to the development of obesity-related diseases, such as: diabetes mellitus type 2 (T2D), metabolic syndrome, hypertension, hyperlipidemia, chronic kidney disease, cardiovascular disease, obstructive sleep apnea, osteoarthritis, malignancies as well as metabolic dysfunction-associated steatotic liver disease (MASLD). Weight loss interventions such as diet, exercise and metabolic and bariatric surgery (MBS) reduce all-cause mortality in obese adults. MBS is linked to a decreased risk of premature death and the development of obesity-related diseases at the population level. The most frequently performed MBSs are laparoscopic sleeve gastrectomy (LSG), Roux-en-Y gastric bypass (RYGB), one-anastomosis gastric bypass (OAGB), adjustable gastric banding or laparoscopic gastric banding (AGB or LAGB), and biliopancreatic diversion (BPD) with or without duodenal switch. BPD with or without duodenal switch is a surgical method primarily used to treat metabolic syndrome with severe metabolic complications and some genetic forms of obesity. MBS is recommended for patients with a BMI >35 kg/m2 regardless of comorbidities, patients with T2D and a BMI >30 kg/m2 and patients with a BMI 30-34.9 kg/m^2 who haven't achieved significant or sustained weight loss or improvement in comorbidities through non-surgical methods. It treats obesity effectively through several biological

mechanisms, many of which are still not completely understood. Although MBS is highly effective for long-term weight loss in morbid obesity, about 20% of patients fail to maintain over 50% excess weight loss. Twin and close relative studies suggested a genetic component to weight loss, indicating that genetic factors may influence the outcomes of MBS. Modern technology and genome-wide association studies (GWAS) have opened a whole new world of theories that allowed us to tap into the genetic background of obesity and obesity-related diseases. The genetics of obesity has two distinct forms – syndromic and non-syndromic. The non-syndromic form consists of monogenic obesity (POMC, NPY, LEP, LEPR, MC3R, MC4R, FTO, PC1, GHSR etc.) and polygenic obesity (UCP1, UCP2, UCP3, ADRB1, ADRB2, ADRB3, SLC6A14 etc.). Researches in the past decade have been focusing on genes as well as single nucleotide polymorphisms (SNPs) and their association with weight loss, eating behavior, biochemical markers, cardiovascular and metabolic parameters after MBS.

Condition being studied We studied the outcomes of MBS in morbidly obese adult patients and the associations with different genetic variants/polymorphisms across various studies.

METHODS

Search strategy An extensive literature search was performed in PubMed, Embase, Medline and Cochrane library to identify eligible studies. . Additional search of grey literature or hand searching wasn't performed. The used search terms were the following: (exp obesity/ OR exp morbid obesity/ OR exp diabetic obesity/) AND (exp bariatric surgery/) AND ((genetic variant.mp. OR exp genetic variability/) OR (exp gene/) OR (exp single nucleotide polymorphism/ OR exp genetic polymorphism/ OR polymorphism.mp.)) All the search results were summed up and duplicates were removed. For the first selection two reviewers screened potentially relevant articles based on the title and abstract and according to predefined eligibility criteria. For the second selection, full articles were read to determine further inclusion. Cross-references of relevant studies and reviews were screened. The used search terms were the following: (exp obesity/ OR exp morbid obesity/ OR exp diabetic obesity/) AND (exp bariatric surgery/) AND ((genetic variant.mp. OR exp genetic variability/) OR (exp gene/) OR (exp single nucleotide polymorphism/ OR exp genetic polymorphism/ OR polymorphism.mp.)).

Participant or population Adult patients aged 18 years or older diagnosed with morbid obesity undergoing MBS.

Intervention MBS.

Comparator NA.

Study designs to be included Randomized controlled studies, Cohort Studies on human population.

Eligibility criteria Inclusion criteria: - Adult patients aged 18 years or older diagnosed with morbid obesity undergoing MBS
- Presence of a defined genetic variant/ polymorphism of interest
- Availability of follow-up data after MBS

Exclusion criteria: - Studies including non-human subjects (animal studies)
- Observational studies without a pre-surgery and post-surgery comparison (cross-sectional studies)
- Reviews, letters to the editor and preprints (focusing on primary research articles)
- Not available in English language
- Not freely available.

Information sources PubMed, Embase, Medline, Cochrane library databases and Cross-referencing.

Main outcome(s) 1,572 studies were identified with 52 meeting the inclusion criteria. Two reviewers independently filtered and selected studies, including relevant cross- references. Research focused on polymorphisms in genes such as UCP2, UCP3, 5-HT2C, MC4R, FKBP5, FTO, CAT haplotypes, LYPAL-1, PTEN, FABP-2, CNR1, LEP656, LEP223, GLP-1R, APOA-1, APOE, ADIPOQ, IL-6, PGC1a, TM6SF2, MBOAT7, PNPLA3, TCF7L2, ESR1, GHSR, GHRL, CD40L, DIO2, ACSL5, CG, TAS2R38, CD36, OBPIIa, NPY, BDNF, CLOCK, and CAMKK2. Most studies explored associations with post-surgery weight loss, while some examined metabolic, cardiovascular, taste, and eating behavior effects as well. Understanding the role of genetic factors in weight loss and metabolic outcomes post-BS can help tailor personalized treatment plans for improved efficacy and long-term success. Further research with larger sample sizes and extended follow-up is needed to clarify the effects of many genetic variants on BS outcomes in morbidly obese patients.

Quality assessment / Risk of bias analysis While this review provides valuable insights, it is important to acknowledge several limitations. The

included studies varied in sample size, genetic variants studied, methodologies, and types of bariatric surgery procedures, which may introduce heterogeneity and affect the generalizability of the results. Additionally, many studies had short follow-up periods, limiting our understanding of the long-term impacts of genetic factors on bariatric surgery outcomes. Future research should prioritize larger, more diverse cohorts with extended follow- up periods to validate these findings and explore additional genetic variants or possible combined effects. Longitudinal studies could offer deeper insights into how genetic factors influence weight changes and the recurrence of obesity-related comorbidities.

Strategy of data synthesis The findings were summarized by integrating the results across studies by design, population, demographic data and outcomes without statistical pooling. Key findings were grouped according to the genetic variant/polymorphism and the type of bariatric surgery. Patterns and differences in outcomes were highlighted, and the potential influ-ence of factors such as patient demographics and follow-up duration were discussed. The quality and risk of bias of the included studies were also assessed and considered in the interpretation of the results.

Subgroup analysis Studies were grouped based on variables such as the type of bariatric surgery performed, patient demographics (e.g., age, sex, race/ethnicity), and specific genetic variants or polymorphisms examined to determine if outcomes varied across different patient populations and surgical procedures.

Sensitivity analysis Not reported.

Language restriction English.

Country(ies) involved Slovenia.

Keywords obesity; morbid obesity; metabolic and bariatric surgery; genetic variant;polymorphism; single nucleotide polymorphism.

Contributions of each author

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