91309_Auto_Edited.docx

Retrospective Study

Novel Subtype of Obesity Influencing the Outcomes of Sleeve Gastrectomy: Familial Aggregation of Obesity

Familial Aggregation of Obesity

Ze-Yu Wang, Yun-Fei Qu, Tian-Ming Yu, Zeng-Lin Liu, Yu-Gang Cheng, Ming-Wei Zhong, San-Yuan Hu

Abstract

BACKGROUND

Differences in the preoperative characteristics and weight loss outcomes after sleeve gastrectomy (SG) between patients with familial aggregation of obesity (FAO) and patients with sporadic obesity (SO) have not been elucidated.

AIM

The impact of SG on weight loss and the alleviation of obesity-related comorbidities in individuals with FAO were explored.

METHODS

A total of 193 patients with obesity who underwent sleeve gastrectomy were selected. Patients with familial aggregation/sporadic obesity were matched 1:1 by propensity score matching and were categorized into 4 groups based on the number of first-degree relatives with obesity (^{1}SO vs. ^{1}FAO, ^{2}SO vs. ^{2}FAO). The baseline characteristics, weight

loss outcomes, prevalence of obesity-related comorbidities and incidence of major surgery-related complications were compared between groups.

RESULTS

We defined familial aggregation of obesity as the presence of two or more first-degree relatives with obesity. Patients with familial aggregation of obesity did not initially show significant differences in baseline data, short-term postoperative weight loss, or obesity-related comorbidities when compared to patients with sporadic obesity preoperatively. However, distinctions between the two groups became evident at the two-year mark, with statistically significant differences in both %TWL (P = 0.006) and %EWL (P < 0.001). The familial aggregation of obesity group exhibited weaker remission of T2DM (P = 0.031), hyperlipidemia (P = 0.012), and NAFLD (P = 0.003) as well as a lower incidence of acid reflux (P = 0.038).

CONCLUSION

Familial aggregation of obesity patients is associated with decreased mid-to-long-term weight loss outcomes; the alleviation of T2DM, hyperlipidemia and NAFLD; and decreased incidence of acid reflux postoperatively.

Key Words: Obesity; Bariatric Surgery; Sleeve Gastrectomy; Family History; Weight Loss

Wang ZY, Qu YF, Yu TM, Liu ZL, Cheng YG, Zhong MW, Hu SY. Novel Subtype of Obesity Influencing the Outcomes of Sleeve Gastrectomy: Familial Aggregation of Obesity. *World J Gastroenterol* 2024; In press

Core Tip: This was a retrospective study. We aimed to compare preoperative characteristics and postoperative outcomes between patients with familial aggregation of obesity and those with sporadic obesity. The following data were examined: baseline

characteristics, weight changes at postoperative intervals (1, 3, 6, 12, 24, and 36 months), alleviation of obesity-related complications, and the occurrence of surgery-related complications. Such a comparative analysis provides valuable insights for guiding postoperative treatment and health education tailored to individuals with familial aggregation of obesity.

INTRODUCTION

The prevalence of overweight and obesity is steadily increasing in China [1], making it the country with the largest population of overweight and obese individuals globally. It is expected that the prevalence of overweight (BMI 24.0-28.0 kg/m²) and obesity (BMI ≥ 28.0 kg/m²) in adults may reach 65.3% by 2030[2], thus leading to a significant public health concern[3]. Obesity can lead to a myriad of multisystem abnormalities, encompassing cardiovascular disease, type 2 diabetes mellitus, hyperlipidemia, hyperuricemia, nonalcoholic fatty liver disease, polycystic ovary syndrome, mental disorders, locomotor and joint disorders, and respiratory diseases, among other comorbidities.

Obesity results from the intricate interplay of genetic, environmental, lifestyle, and sociocultural factors[4]. These factors affect fat accumulation or consumption by influencing several physiologic mediators of food intake and energy expenditure[5]. An individual's family – often representing a microcosm of closely aligned genetic profiles, lifestyle behaviors, environmental exposures, and sociocultural outlooks – exerts a substantial influence on the emergence of obesity and the outcomes of weight management. Sleeve gastrectomy (SG), which accounted for 84.9% of bariatric surgical procedures[6], effectively facilitates weight loss in patients with obesity while markedly enhancing metabolic processes and ameliorating obesity-related comorbidities[7].

The familial aggregation of diseases is a focal point of research across several disciplines, including psychiatry[8], neurology[9] and oncology[10, 11]. By studying the characteristics of first-degree relatives of individuals with obesity, we can gain deeper insights into the pathogenesis of obesity, thereby contributing to the search for novel

treatments or prevention methods[12]. This study provides a theoretical foundation for precision prevention and treatment of obesity.

MATERIALS AND METHODS

1. Patients

We selected a cohort of 193 patients with obesity who met the criteria for sleeve gastrectomy and who underwent surgery at our medical center between December 2019 and April 2023 for this observational study. Following surgery, all patients received uniform postoperative guidance and health education.

2. Inclusion/Exclusion Criteria

(1) Inclusion criteria: (i) patients aged between 16 and 65 years; (ii) Patients met the surgical indications outlined in the Chinese Guidelines for the Surgical Management of Obesity and Type 2 Diabetes Mellitus (2019 edition)[13]; and (iii) patients were capable of undergoing normal follow-up after sleeve gastrectomy.

(2) Exclusion criteria: (i) patients lacking information about first-degree relatives; (ii) patients requiring obesity-inducing medications for their medical conditions after the operation; (iii) patients who became pregnant shortly after the procedure; and (iv) patients on appetite suppressants (such as metformin) following surgery.

3. Grouping Method

The familial aggregation of obesity (FAO) group and the sporadic obesity (SO) group: We divided the participants into groups according to the number of first-degree relatives (parents, children and siblings of the proband) with obesity (BMI > 28 kg/m^2). The grouping criteria for familial aggregation of obesity were as follows.

Familial aggregation of obesity group 1 (^{1}FAO): Except for the proband, the number of first-degree relatives with obesity ≥ 1. Sporadic obesity group 1 (^{1}SO): Except for the proband, the number of first-degree relatives with obesity = 0.

Familial aggregation of obesity group 2 (^{2}FAO): Except for the proband, the number of first-degree relatives with obesity ≥ 2. Sporadic obesity group 2 (^{2}SO): Except for the proband, the number of first-degree relatives with obesity < 2.

4. Data Collection

The data were collected independently by two individuals. Perioperative data for all patients, including sex, age, BMI, family history, waist circumference, hip circumference, and obesity-related comorbidities (such as hypertension, type 2 diabetes mellitus, and hyperlipidemia), were systematically recorded using the electronic case management system. Following sleeve gastrectomy, we conducted thorough postoperative follow-ups at 1, 3, 6, 12, 24, and 36 months through a combination of hospital visits and telephone interviews. These follow-ups involved evaluating postoperative weight, conducting blood tests, assessing surgery-related complications, and monitoring the improvement of preoperative obesity-related comorbidities. To assess the effectiveness of weight loss surgery, we employed the percentage of total weight loss (%TWL) and percentage of excess weight loss (%EWL) as evaluation criteria.

%TWL= (Initial body weight- Final body weight)/ Initial weight ×100%

%EWL= [(Initial body weight- Final body weight)/(Initial weight–IBW)] ×100%

Ideal BMI (IBMI): 23 kg/m^2 (Asian Standard), Ideal Body Weight (IBW): IBMI * (height)^2

5. Statistical Methods

All clinical data were analyzed using SPSS statistical software (version 26.0; SPSS, Inc., Chicago, Illinois). Propensity score matching (PSM)[14] was employed for 1:1 matching of FAO/SO groups. Independent samples t tests were also conducted to compare preoperative baseline data and postoperative weight loss outcomes at each follow-up interval between patients in the FAO group and the SO group. Linear regression was employed to identify factors influencing %TWL and %EWL. To compare the prevalence of obesity-related comorbidities and surgery-related complications in patients in the FAO and SO groups, χ^2 or Fisher's exact test was employed both preoperatively and at the 6-month postoperative assessment. P values < 0.05 indicated statistical significance.

RESULTS

1. Baseline Patient Characteristics

This observational study included a total of 193 patients who underwent sleeve gastrectomy (male: 64, 33.2%; female: 129, 66.8%), with a mean BMI of 41.3 ± 7.0 kg/m². Among the obese patients, various obesity-related comorbidities were prevalent, including metabolic syndrome (88, 45.6%), hypertension (67, 34.7%), type 2 diabetes mellitus (94, 48.7%), hyperlipidemia (81, 42%), sleep apnea hypopnea syndrome (128, 66.3%), polycystic ovary syndrome (31, 24.0%, $n = 129$), nonalcoholic fatty liver disease (163, 84.5%), gout (10, 5.2%), and hyperuricemia (114, 59.1%). Additionally, 113 patients (58.5%) were in the [1]FAO group, while 58 (30.0) were in the [2]FAO group. Specific indicators of obesity-related comorbidities are detailed in Table 1.

2. Comparison of Preoperative Information

2.1 Preoperative baseline information We applied PSM analysis to pair patients in the [1]SO/[1]FAO and [2]SO/[2]FAO groups utilizing predictors of major obesity-related comorbidities (metabolic syndrome, hypertension, type 2 diabetes mellitus, hyperlipidemia, and nonalcoholic fatty liver disease). The matched groups exhibited no significant differences in patient age, height, weight, or BMI, as shown in Table 2.

2.2 Preoperative obesity-related comorbidities We conducted PSM analysis again to compare patients within the matched [1]SO/[1]FAO and [2]SO/[2]FAO groups utilizing sex and BMI as predictors. The analysis revealed no significant differences in preoperative obesity-related comorbidities between patients in the matched groups, as indicated in Table 3.

Comparison of Postoperative Information

All 193 patients completed 1/3/6 months of postoperative follow-up, 107 patients completed 12 months of postoperative follow-up, 60 patients completed 24 months of postoperative follow-up, and 21 patients completed 36 months of postoperative follow-up (analysis at 36 months was primarily focused on trend interpretation).

We conducted PSM analysis to align patients in the [1]SO/[1]FAO and [2]SO/[2]FAO groups. We employed sex, preoperative BMI, and major obesity-related comorbidities (metabolic syndrome, hypertension, type 2 diabetes mellitus, hyperlipidemia, and nonalcoholic fatty liver disease) as predictors to minimize differences between the groups and mitigate the impact of variations in these factors on surgical outcomes.

After PSM analysis, the patient counts were as follows:

[1]SO vs. [1]FAO = 73 vs. 73; [2]SO vs. [2]FAO = 53 vs. 53 (1/3/6 months after surgery).

[1]SO vs. [1]FAO = 37 vs. 43; [2]SO vs. [2]FAO = 52 vs. 31 (12 months after surgery).

[1]SO vs. [1]FAO = 22 vs. 22; [2]SO vs. [2]FAO = 37 vs. 17 (24 months after surgery).

[1]SO vs. [1]FAO = 6 vs. 7; [2]SO vs. [2]FAO = 11 vs. 8 (36 months after surgery).

3.1 Weight loss.

3.1.1 Sleeve gastrectomy results in a substantial weight reduction in the majority of patients after the procedure. There was no significant difference in short-term postoperative weight loss between patients in the [1]FAO group and those in the [1]SO group. Nevertheless, over time, notable differences became evident at 24 months postsurgery, with patients in the [1]FAO group experiencing less weight loss after sleeve gastrectomy than their counterparts in the [1]SO group (%TWL: $P = 0.025$; %EWL: $P = 0.025$). Comparatively, patients in the [2]FAO group exhibited similar but more pronounced differences than did those in the [2]SO group (BMI: $P = 0.003$, %TWL: $P = 0.006$, %EWL: $P < 0.001$). Several line graphs are shown in Figure 1. These lines of view visually illustrate the difference above. Patients with familial aggregation of obesity regain weight to some extent at the two-year postoperative mark, while patients with sporadic obesity are able to maintain a more favorable weight loss outcome.

3.1.2 Multiple linear regression analysis. To further explore the factors affecting weight loss outcomes and assess the impact of familial aggregation of obesity, we conducted linear regression analyses on %TWL and %EWL at various postoperative time points. The %TWL, %EWL and BMI exhibited normal distributions. Factors affecting %TWL and %EWL showed no significant multicollinearity. After controlling for the effects of age and obesity-related comorbidities on surgery, we observed that the

impact of [1]FAO on weight loss outcomes was not significantly different at 24 months postsurgery, whereas [2]FAO and preoperative BMI exhibited statistically significant differences in their influence on weight loss outcomes (%TWL: [2]FAO: P < 0.001, BMI: $P = 0.001$), (%EWL: [2]FAO: P < 0.001).

3.2 Alleviation of obesity-related comorbidities Sleeve gastrectomy significantly alleviates a wide range of obesity-related comorbidities, including MS, HTN, T2DM, HLP, NAFLD, and HUA, in the majority of patients 6 months postsurgery. Nevertheless, the extent of remission varies between patients with sporadic obesity or familial aggregation of obesity. The incidence of NAFLD was greater in the [1]FAO group than in the [1]SO group ($P = 0.015$). The [2]FAO group exhibited a higher prevalence of T2DM ($P = 0.031$), HLP ($P = 0.012$), and NAFLD ($P = 0.003$) than the [2]SO group.

3.3 Surgery-related Complications We compared major surgery-related comorbidities (acid reflux, nausea/vomiting, alopecia, and constipation) postsurgery among the different groups of patients. There was no significant difference in surgery-related complications between patients in the [1]FAO group and the [1]SO group (P > 0.05). However, the prevalence of acid reflux symptoms was lower in the [2]FAO group than in the [2]SO group ([2]SO: [2]FAO =24.5%: 9.4%, $P = 0.038$). There was no significant difference in nausea/vomiting, alopecia, or constipation between the two groups.

DISCUSSION

Obesity and its severity are influenced primarily by genetic, environmental, lifestyle, and sociocultural factors[5]. Families, as fundamental units in the context of obesity, often share common genetic traits, lifestyle behaviors, and sociocultural perceptions. While many studies have focused on the family history of obesity in adolescents and children[4], there is a lack of research investigating the impact of familial aggregation of obesity on sleeve gastrectomy.

Our study examined the impact of family history on patients with obesity and introduced the novel concept of familial aggregation of obesity. After using PSM analysis to eliminate the possible influence of sex, preoperative BMI, and major obesity-

related comorbidities on surgical outcomes, we found a significant difference in the weight loss outcomes of sleeve gastrectomy between patients with familial aggregation of obesity, defined as two or more first-degree relatives with obesity, and those with sporadic obesity. Specifically, patients with FAO experienced worse weight loss outcomes as well as lower remission rates of T2DM and NAFLD after sleeve gastrectomy. These findings suggest a potential association between familial aggregation of obesity and weight regain after sleeve gastrectomy.

In terms of genetics, families of patients with familial aggregation of obesity may share common obesity susceptibility genes. These genes included single-gene obesity genes, such as those encoding leptin (Lep) and its receptor (Lepr), the melanocortin-4 receptor (Mc4r), and proopiomelanocortin (Pomc), and polygenic obesity genes (FTO loci), among others[5]. These genes influence weight by regulating the energy balance in the central nervous system, ultimately affecting body weight[15, 16]. However, it is crucial to note that genetics alone cannot fully explain the differences in surgical outcomes between the two groups[17]. The disparities in surgical outcomes result from the combined influence of genetic and environmental factors.

In terms of environmental exposures, diet and lifestyle, patients who undergo sleeve gastrectomy and their family members share common obesity-inducing factors, such as similar dietary and exercise habits. All of these conditions exhibit many similarities, as both patients and their family members suffer from obesity and related comorbidities, which are often accompanied by a sedentary lifestyle[12]. In terms of cognition, similar cognitive levels within the family[18] determine the development of obesity and weight loss outcome of bariatric surgery. The combination of these factors results in weaker dietary and exercise maintenance abilities among patients with familial aggregation of obesity[19] than in those with sporadic obesity, possibly contributing to their mid-to-long-term postoperative weight regain.

Sleeve gastrectomy significantly improves various metabolic processes[20], including glucose metabolism, lipid metabolism, and amino acid metabolism, in patients with obesity. Patients with familial aggregation of obesity exhibit lower remission rates for

T2DM, hyperlipidemia and NAFLD. This difference may be related to the extent of improvement in glucose and lipid metabolism. By aggregating information about patients with familial aggregation of obesity, we aimed to investigate and identify factors influencing the postoperative remission of glucose and lipid metabolism. This research may lead to the use of novel therapeutic approaches for individuals with primary or secondary metabolic disorders.

The incidence of de novo gastroesophageal reflux disease (GORD) after sleeve gastrectomy is approximately 24.8%[21]. We observed a significantly lower incidence of postoperative acid reflux in patients with familial aggregation of obesity than in those with sporadic obesity. This difference may be associated with reduced intra-abdominal pressure[22]. The International Federation for the Surgery of Obesity and Metabolic Disorders (IFSO) recommends performing an endoscopy at 1 year after surgery, followed by subsequent screenings every 2 to 3 years based on the results of the initial examination[23]. Our findings may further contribute to the precise prevention and treatment of postoperative de novo GORD.

Impaired family functioning may be one of the factors influencing surgical outcomes[24]. A bidirectional relationship exists between family members and patients. Family members can play a supportive role in assisting patients in achieving and sustaining weight loss[12]. The 'halo effect'[25] of patients extends to their family members, resulting in positive changes. This includes improvements in family members' dietary and lifestyle habits[26, 27] and an enhancement in their quality of life[28]. Interventions targeting obesity, by incorporating a family systems framework, can also extend the benefits of surgery to the family members of individuals with obesity[29].

The concept of familial aggregation of diseases helps in identifying groups of individuals with shared disease characteristics. For instance, individuals with a family history of type 2 diabetes are more likely to experience overweight/obesity and are susceptible to adverse metabolic consequences of fat accumulation[30]. Patients with a family history of Alzheimer's disease may experience limitations in cognitive function improvement after sleeve gastrectomy[31]. Moreover, these findings could aid in

identifying susceptibility genes for related diseases and gaining deeper insights into potential pathophysiological mechanisms[32], ultimately leading to the discovery of new preventive or therapeutic strategies for obesity[5]. Currently, large-scale genome-wide association studies (GWASs) have identified more than 1,100 obesity-associated genetic loci[33]. This study offers a novel perspective. By studying families as units of investigation rather than isolated individuals, it is possible to further discover susceptibility genes for obesity, predict the development of obesity, and enhance strategies for diagnosing and treating obesity[34].

Limitations: 1. Based on our observational study, differences in patients with familial aggregation of obesity gradually emerge only in the mid-to-long-term postsurgery. We are actively investigating longer-term surgical outcomes as part of our ongoing research. 2. We excluded a few patients for whom it was difficult to trace first-degree relative information (e.g., adopted, step parents, or deceased first-degree relatives). These patients exhibited weight loss results equal to or below the average, possibly due to impaired family functioning[24], posing challenges for detailed analysis. We intend to increase the sample size to further explore potential underlying factors. 3. This study was conducted at a single center, acknowledging variations in familial lifestyles across countries and regions. Therefore, initiating a multicenter study involving multiple regions could provide more patients with precise treatment options .

CONCLUSION

Sleeve gastrectomy can significantly reduce body weight and alleviate obesity-related comorbidities in the majority of patients. Familial aggregation in individuals with obesity impacts the mid-to-long-term weight loss outcomes of sleeve gastrectomy; affects the alleviation of T2DM, hyperlipidemia and NAFLD; and leads to a decreased incidence of acid reflux postoperatively. By studying the familial association of obesity, we can gain further insights into the pathogenesis of obesity. Moreover, offering stratified diagnostic and treatment plans for patients with obesity, along with more

personalized and targeted health education, can enhance the precision of postoperative prevention and treatment.

ARTICLE HIGHLIGHTS

Research background

Sleeve gastrectomy significantly reduces weight and improves obesity-related comorbidities in patients with obesity. However, differences in surgical outcomes between patients with familial aggregation of obesity (FAO) and those with sporadic obesity (SO) have not been elucidated.

Research motivation

To investigate whether FAO influences the surgical outcomes of sleeve gastrectomy.

Research objectives

To compare preoperative characteristics, postoperative weight loss, resolution of obesity-related comorbidities, and surgical complications between the FAO and SO groups.

Research methods

In this retrospective study, we recruited 193 patients who underwent sleeve gastrectomy and categorized them into FAO and SO groups based on the presence of obesity in their first-degree relatives. Propensity score matching (PSM) analysis was used to match the patients at a 1:1 ratio to eliminate confounding factors.

Research results

The baseline data and incidence of obesity-related comorbidities did not significantly differ between FAO patients and SO patients. Two years postsurgery, the FAO group exhibited a lower total weight loss percentage (%TWL) ($P < 0.001$) and excess weight loss percentage (%EWL) ($P < 0.001$) than did the SO group. Significant differences were

observed between the two groups in terms of remission rates of type 2 diabetes mellitus (P = 0.031), hyperlipidemia (P = 0.012), nonalcoholic fatty liver disease (P = 0.003), and postoperative reflux occurrence rate (P = 0.038).

Research conclusions

Compared to those in the SO group, the FAO patients in the SO group demonstrated slightly weaker medium-term weight loss outcomes; reduced symptoms of T2DM, hyperlipidemia, and nonalcoholic fatty liver disease; and a decreased postoperative reflux rate.

Research perspectives

This study provides a theoretical basis for the treatment, surgical method selection, and postoperative health management of patients with familial aggregation of obesity.

91309_Auto_Edited.docx

ORIGINALITY REPORT

2%
SIMILARITY INDEX

PRIMARY SOURCES

1	**zenodo.org** Internet	38 words —	**1%**
2	**doku.pub** Internet	31 words —	**1%**

EXCLUDE QUOTES ON

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE SOURCES < 1%

EXCLUDE MATCHES < 10 WORDS