Obesity Surgery (2019) 29:1169–1173
https://doi.org/10.1007/s11695-018-03623-4

ORIGINAL CONTRIBUTIONS

Monogenic Obesity Mutations Lead to Less Weight Loss After Bariatric Surgery: a 6-Year Follow-Up Study

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Published online: 5 February 2019

Abstract

Objectives Bariatric surgery is emerging as the most effective treatment option for patients with obesity. Hypothalamic arcuate nucleus plays an important role in metabolic homeostasis. However, the influence of mutations related to the feeding center on weight loss after bariatric surgery is still unclear. We aimed to diagnose monogenic obesity by whole exome sequencing (WES) and explore whether monogenic mutations influence the effectiveness of bariatric surgery.

Methods We collected obese patients aged 15 to 55 with a BMI > 28 kg/m^2 and who underwent laparoscopic sleeve gastrectomy from March 2011 to June 2017 in Shanghai. Data related to weight loss and metabolic characteristics preoperatively and postoperatively were collected, including fasting blood glucose (FBG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. WES was performed in obese patients using genomic DNA from whole blood samples.

Results We investigated the proportion of 131 obese adults with one mutation as high as to 8.4% and then evaluated the association between these mutations and weight loss. Mutation carriers had less weight loss over both short-term and long-term periods. Survival analyses indicated it was harder to attain the goal of 20% weight loss for mutation carriers ($P_{\text{log-rank}} = 0.001$; $P_{\text{breslow}} < 0.001$), and the difference remained significant with a Cox regression model. Improvement in FBG, HDL cholesterol, and triglyceride levels postoperatively was observed in both groups, while there were significant differences between the two groups.

Conclusions Our data indicated that 8.4% of obesity cases were caused by change in genetics, and mutations had negative effects on the efficacy of bariatric surgery.

Keywords Monogenic obesity · Bariatric surgery · Weight loss · Mutations · Whole exome sequencing

Yangyang Li and Hong Zhang contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11695-018-03623-4) contains supplementary material, which is available to authorized users.

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Introduction

A recent investigation showed that the proportion of adults with a BMI of 25 or more was 36.9% for men and 38.0% for women in 2013 [1]. Over the past 30 years, the prevalence of overweight and obesity combined has risen constantly by 27.5% for adults and 47.1% for children. It is currently believed that genetics plays a pivotal role in the development of obesity, with a heritability from 0.58 to 0.83 [2]. Therefore, it is important to recognize how genetic variations influence human obesity. Monogenic obesity is described as rare and severe early-onset obesity that involves a mutation in a single gene critical for metabolic homeostasis; some of these genes include *MC4R*, *MC3R*, *LEP*, *LEPR*, *PC1*, *POMC*, and *SIM1*. Nearly, all these genes are located in the central

melanocortinergic pathway, which controls the hypothalamic feeding center.

The Utah Mortality and Swedish Obese Subjects studies both demonstrated the safety and efficacy of bariatric surgery in treating severely obese patients, with a maximum weight loss of up to 20–32% [3, 4]. However, only sporadic monogenic obese patients with *LEPR* or *MC4R* mutations who underwent bariatric surgery have been reported to date, and weight loss of these patients varied greatly from 7 to 76% [5]. Thus, more convincing evidence is needed to evaluate the efficacy and safety of bariatric surgery in monogenic obesity. In this study, we sought to determine whether monogenic mutations influence the effectiveness of bariatric surgery.

Methods

Subjects

Obese patients aged 15 to 55 with a BMI > 28 kg/m^2 and who underwent laparoscopic sleeve gastrectomy at Shanghai Ninth People's Hospital or Shanghai Sixth People's Hospital from March 2011 to June 2017 were recruited for this study. Gastric sleeve patients were maintained on liquids for 2 weeks postoperatively. All patients were followed up at 3, 6, 12, 18, and 24 months and then yearly for the next 5 years.

Sequencing

Whole exome sequencing (WES) was performed for the molecular diagnosis of monogenic obese patients, with further confirmation by Sanger sequencing. We screened known genes, including *LEP*, *LEPR*, *MC3R*, *MC4R*, *PCSK1*, *SIM1*, and *POMC*. Detailed information on Sanger sequencing has been described previously [6]. WES was performed in 131 obese patients using genomic DNA from whole blood samples. DNA was processed with the NimbleGen SeqCap EZ Exome v3.0 capture reagent (capture target = 64 Mb, Roche) and TruSeq DNA Sample Prep Kits (Illumina). Samples were sequenced with paired-end 150-bp reads on an Illumina HiSeq 3000 platform according to the manufacturer's instructions (Illumina, San Diego, CA, USA). For variant calling, we used the Burrows-Wheeler Aligner (bwa-mem, version 0.7) to align the sequences, Picard (version 2.5.0) to identify and flag duplicated reads, and GATK HaplotypeCaller (version 3) to perform quality score recalibration and jointly call variants in all the WES samples.

Data Analysis

Subjects were divided into two groups based on the presence of monogenic mutations. Data are shown as the means ± standard deviations. For comparisons of demographic information such as age and sex between the two groups, independent *t* tests and chi-square tests were performed. Multiple linear regression was used to analyze the relationship between explanatory variables and weight loss. Time to weight loss attainment was compared between the two groups with the use of a Wald test for the estimated hazard ratio (HR) and 95% confidence intervals (CIs) based on a Cox model, with adjustments for the confounding factors age, gender, and BMI at baseline. A decrease in weight by more than 20% compared with the preoperative weight was defined as attainment. The Kaplan–Meier method was used to estimate the attainment rates of the different groups. A two-tailed *P* value of 0.05 was considered statistically significant. Statistical analyses were carried out with the use of SAS software (version 8.0; SAS Institute) and IBM SPSS Statistics software (version 20).

Table 1 Basic information of 11 mutation carriers

Case	Gene	Mutation	CADDscore	MetaSVM	Polyphen2	Sex	Age	BMI	Initial wt (kg)
1	MC4R	G231S	25.1	T	P	F	32	54	141.61
2	LEP	H118L	14.9	T	B	M	39	46	136
3	MC3R	L314F	17.36	T	P	F	49	51.7	124.35
4	MC4R	C277X	37	–	–	M	–	–	–
5	MC4R	V166I	27.3	T	P	M	18	38	122
6	MC4R	c.1350delA	–	–	–	M	49	35.4	99
7	LEPR	A1033T	0.002	T	B	M	28	42.4	139
8	LEPR	Q463X	37	–	–	F	27	35.6	103
9	MC4R	V166I	27.3	T	P	F	33	40.4	110
10	SIM1	T758R	23.3	T	P	F	28	43.9	127
11	PCSK1	A201T	27.3	D	D	F	28	41.5	–

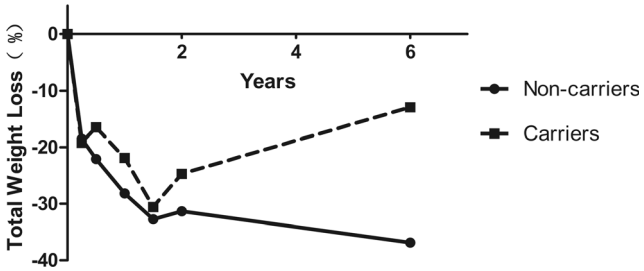

Fig. 1 Six-year postoperative weight loss curves in obese patients with/without mutations

Results

Molecular Diagnosis of Monogenic Obesity

Heterozygous functional mutations were detected in 11 of the 131 patients (8.40%) and all confirmed by Sanger sequencing. These mutations were located on *LEP*, *LEPR*, *MC4R*, *MC3R*, *SIM1*, or *PCSK1* (Table 1). The baseline characteristics of all the patients, including age and BMI prior to surgery, are shown in Supplemental Table 1. Moreover, we used three mutation predictor software programs to predict the impact of each mutation. Except for A1033T on *LEPR*, all the observed mutations would have negative effects on protein function. We found a total of one frameshift mutation on *MC4R*, two nonsense mutations on *MC4R* and *LEPR*, respectively, and eight missense mutations in the remaining genes.

Monogenic Obesity Carriers Had Less Weight Loss After Bariatric Surgery

All patients were invited to complete follow-up visits starting at 3 months after surgery. We concluded that patients would lose weight after bariatric surgery, as shown in Fig. 1. Most patients attained maximum weight loss at the 1.5-year follow-up time point, and then either the weight or the weight loss was maintained. From the 6-month follow-up after surgery, carriers steadily showed less weight loss than non-carriers did. The difference in weight loss at the 6-year follow-up

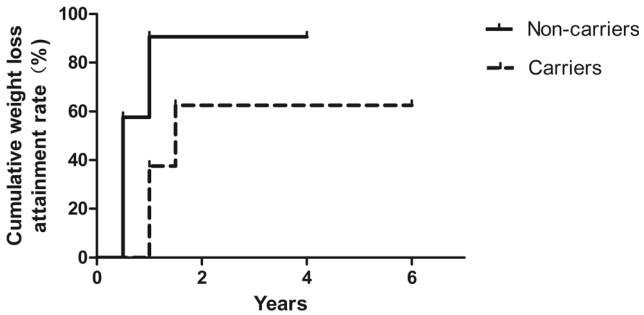

Fig. 2 The association between cumulative weight loss attainment rates and mutation status. A decrease in weight by more than 20% compared with the preoperative weight was defined as attainment. $P_{\text{log-rank}} = 0.001$; $P_{\text{breslow}} < 0.001$; $P_{\text{cox-regression}} = 0.021$; HR (95% CI) = 3.187 (1.189, 8.545), after adjusting for age, sex, and BMI

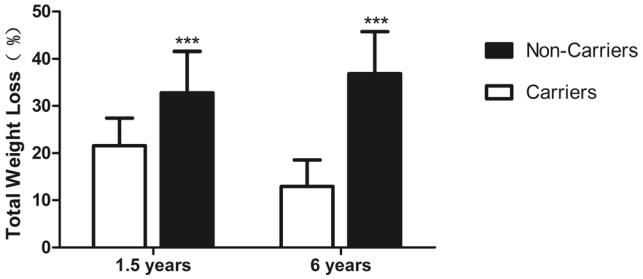

Fig. 3 Short-term and long-term weight loss after sleeve gastrectomy surgery. β and 95% CI were calculated by multiple linear regression after adjusting for sex, age, and BMI. For 1.5 years: $P = 0.001$, β (95% CI) = − 0.121 (− 0.189, 0.053); for 6 years: $P < 0.001$, β (95% CI) = − 0.297 (− 0.383, 0.210). Data represent mean ± sd. ***$P < 0.001$

between the two groups reached statistical significance ($P < 0.001$), with mutation carriers experiencing a more obvious rebound in weight.

Then, we explored the association between mutations and the rates of attaining target weight loss (Fig. 2). Survival analyses indicated that non-carriers were markedly more likely to achieve their weight loss goal ($P_{\text{log-rank}} = 0.001$; $P_{\text{breslow}} < 0.001$). A Cox regression analysis adjusting for age, gender, and BMI at baseline also revealed that patients without mutations were more likely to attain their weight loss goal ($P_{\text{cox-regression}} = 0.021$; HR [95% CI] = 3.187 [1.189, 8.545]).

To evaluate the effect of mutations on weight loss after surgery, we used a multiple linear regression model to analyze the weight loss at 1.5 years and 6 years after surgery. The maximum weight loss that could be achieved in the two groups was different (Fig. 3). At 1.5 years, mutation carriers had a lower maximum weight loss value. The β and 95% CI were calculated (β [95% CI] = − 0.121 [− 0.189, 0.053], P = 0.001) after adjusting for sex, age, and BMI. For the long-term observation, compared to non-carriers, mutation carriers had more difficulties in maintaining their weight loss (Fig. 1). The β and 95% CI were calculated (β [95% CI] = − 0.297 [− 0.383, − 0.210], $P < 0.001$) after adjusting for sex, age, and BMI.

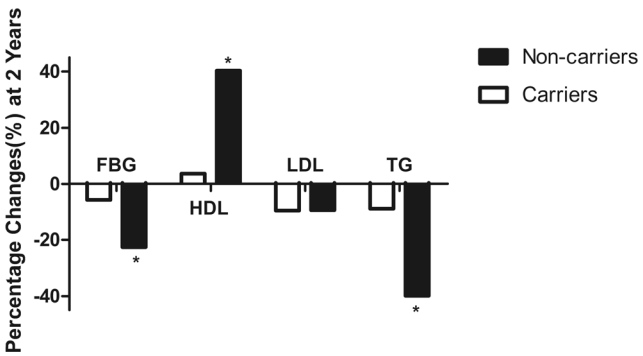

Fig. 4 Percent changes from baselines of fasting blood glucose, HDL cholesterol, LDL cholesterol, and triglycerides. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$

In our study, both two groups had achieved diabetes remission at 2 years (Fig. 4). Fasting blood glucose decreased 5.72% from baseline in mutation carriers vs. 22.59% in non-carriers ($P = 0.04$). An increase in mean HDL cholesterol was observed in both groups, and there was a significant difference between the two groups (mutation carriers 3.61%; non-carriers 45.67%; $P = 0.05$). At 2 years, mutation non-carriers had greater percent reductions in triglycerides from baseline than carriers (mutation carriers 8.89%; non-carriers 39.88%; $P = 0.01$). However, no significant difference in LDL cholesterol was observed between the two groups (mutation carriers 9.59%; non-carriers 9.44%; $P = 0.98$).

Conclusion

Our study showed that the prevalence of monogenic obesity mutations in our Chinese obese bariatric surgery recipients is approximately 8.4%. We identified 11 obese patients with 10 different mutations that impair the function of the feeding center. To the best of our knowledge, our results are the first to demonstrate that various monogenic obesity mutations may affect postoperative weight loss, especially mutations in *SIM1*, *PCSK1*, or *MC3R*. Patients with mutations lost significantly less weight than non-carriers, as was hypothesized, which is in concordance with a previous sporadic case with complete MC4R deficiency [7].

The current recommendations for the treatment of obese adults include three steps [8]: first, therapy to improve diet and physical activity as well as implement behavioral changes; second, available pharmacotherapy as an adjunct to lifestyle modification; and third, bariatric surgery, which is the most effective and long-term treatment for individuals with severe obesity or type 2 diabetes [9, 10]. Bariatric surgery was initially designed for anatomical changes, including the restriction of food intake and nutrient malabsorption, whereas recently an increasing amount of data demonstrated that postoperative weight loss and improvement in metabolic comorbidities had largely been attributed to the effects of the surgery: reduced hunger, increased satiation, mediated gut hormones, improved gut microbiome, and increased diet-induced energy expenditure [11, 12]. These metabolic responses resulting from bariatric surgery might rely on the function of hypothalamic neurons to be responsive to nutrients and circulating gut hormones [13], which explained why patients with mutations in the hypothalamic energy homeostasis center experienced less weight loss to some extent.

Although we concluded that long-term weight maintenance was required for the function of the arcuate nucleus, most patients had some degree of weight loss during the short term. Obesity has important effects on the risk of coronary heart disease. It was reported that the HR for cardiovascular disease was 1.23 with BMI [14]. Bariatric surgery resulted in a significant improvement in parameters affected by metabolic syndrome, including glucose tolerance, insulin sensitivity, blood triglyceride, and high-density lipoprotein (HDL) cholesterol levels. The cumulative overall mortality during up to a 16-year follow-up showed a hazard ratio of 0.76 in the surgery group compared with the control group [15]. It is still unclear whether obese patients, especially mutation carriers, could benefit from short-term postoperative weight loss to improve their metabolism and reduce the long-term cardiovascular disease risk. More prospective and extensive studies are required in the future to confirm the efficacy and effectiveness of bariatric surgery on weight loss and metabolic improvement for mutation carriers.

Funding Information This work is supported by the National Key Research and Development Program of China (2016YFA0502003), the National Natural Science Foundation of China (81570713), the National Key Research and Development Program (2016YFC0903303), the Shanghai Municipal Education Commission-Gaofeng Clinical Medicine Grant Support (20152527), the Outstanding Academic Leaders of Shanghai Health System (2017BR008), and the Yangtze River Scholar.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all participants.

Human and Animal Rights The study was performed in accord with the ethical standards of the Declaration of Helsinki.

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