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Interaction effects of *FTO* polymorphisms on post-surgery weight, and post-BMI after bariatric surgery

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Abstract

Background: Bariatric surgery (BS) is considered the intervention most effective for patients with severe obesity and to maintain weight loss and glycemic control for the long-term.

Objective: To analyze the effects of genotypes and haplotypes of the *FTO* and *MC4R* genes on total body weight loss (TBWL), post-surgery weight, and post- BMI after bariatric surgery.

Methods: We retrospectively selected 101 patients from Bajío High Specialty Regional Hospital, León Guanajuato, México who underwent Roux-en-Y gastric bypass (RYGB) to register their body mass index (BMI), blood pressure, biochemistry characteristics, and comorbidities. Post-surgery, patients were quoted for registered anthropometry and blood pressure. Glucose, lipid and hepatic profiles, insulin, leptin, and ghrelin were measured, and rs9939609, rs9930506, and rs1421085 *FTO* were genotyped.

Results: After 6 (4–8) years post-surgery, TBWL was 34.7 kg, and post-surgery BMI was 33.8 kg/m^2. BS induced a remission of T2D in 82% and a remission of hypertension in 78% of patients. Post-surgery weight was higher in carriers of the risk genotypes for the rs9939609 and rs1421085 polymorphisms. TBWL was lower in those with risk genotypes for the rs993056 and rs1421085 polymorphisms. Insulin and HOMA-IR were higher in the risk genotype of three *FTO* polymorphisms. There were significant interaction effects of rs9930506 and rs1421085 *FTO* risk genotypes on weight and BMI in response to BS.

Conclusions: Genotypes and haplotypes of *FTO* influence TBWL, insulin levels, and HOMA-IR. We found an interaction effect of rs9930506 and rs1421085 risk genotypes with response to BS on weight and BMI.

Keywords: Obesity, Bariatric surgery, Interaction of *FTO*, TBWL, Post-surgery weight

Introduction

Obesity is associated with increased morbidity and mortality and is a risk factor for cardiovascular disease. Therefore, preventing and treating obesity has become a major public health goal [1]. Bariatric surgery is considered the intervention most effective for patients with severe obesity (BMI ≥40 kg/m^2 or ≥35 kg/m^2) with comorbidities [2] and to maintain weight loss and glycemic control in the long-term [3]. In addition, improvement or long-term remission of comorbidities such as T2D, hypertension, and dyslipidemia after bariatric surgery has been reported [4].

One of the most effective surgical methods for obesity treatment is Roux-en-Y gastric bypass (RYGB), which has been well documented to achieve sustained long-term results [2]. Nevertheless, some studies have reported that 20-30% of patients do not achieve satisfactory weight loss post BC [3,5]. One of the factors involved in the unsuccessful results of BS may be genetic polymorphisms, which remains to be investigated. Given the known associations between the *FTO* gene and obesity, it is important to examine the role of variants in this gene in bariatric surgery outcomes. In a study performed in 146 patients undergoing Roux-en-Y gastric bypass and genotyped to rs9939609 *FTO* found that the carriers of one or two risk alleles TA and AA rs9939609 *FTO* had increased body weight and BMI at 3-, 4-, and 5-years following surgery compared with TT patients [6]. At 36, 48, and 60 months after bariatric surgery, body weight, fat mass, and BMI were higher, while EBWL was lower in carriers of rs9939609 *FTO* [7]. The study performed in 168 Mexican mestizos and 81 patients with other ancestral origins showed a statistical association of rs9939609 with smaller changes in postoperative %EBWL and BMI [8]. Role of polymorphisms rs1421085 and rs9930506 of *FTO* on the success of bariatric surgery has been studied little. Therefore, identifying genetic factors related to weight loss in bariatric surgery outcomes may help to guide weight management strategies pre- and post-surgery. The objective of the study was to analyze the effect of rs9939609, rs1421085 and rs9930506 of the *FTO* gene polymorphisms on changes in weight, BMI, TBWL, and metabolic variables after bariatric surgery.

Material and Methods

Subjects

We performed a retrospective analysis of the information contained in the medical files of patients from the surgery service of the Bajío High Specialty Regional Hospital, León Guanajuato, México, who underwent Roux-en-Y gastric bypass (RYGB) only from May 2010 to November 2021, resulting in 169 patients registered. Of them, 101 agreed to participate in the study. We collected personal and clinical data, and the conditions before bariatric surgery, such as weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), comorbidities, hypertension, dyslipidemia, and diabetes were registered. All participants were fully informed of the aims of the study and were asked to sign informed consent to participate in the study. The study was carried out according to the ethical standards of the Declaration of Helsinki (1983) and in agreement with the Good Clinical Practice guidelines. The study was approved by the Institutional Ethics Committee of the University of Guanajuato (CIBIUG-P70-2020) and by the Investigation Committee of Bajío High Specialty Regional Hospital (CEI-36-2020), León Guanajuato, México.

Post-surgery procedure

The patients were quoted at 8 AM to record their personal and clinical data, anthropometric measurements were taken, and systolic and diastolic blood pressures were measured in a sitting position after ten minutes of rest. Weight was measured with a Roman-type Tanita BC533 scale, and height was measured using a SECA 406 Stadiometer to calculate BMI (kg/m^2). Changes in BMI (ΔBMI), total body weight loss (TBWL), percent of total body weight loss (%TBWL), and percent excess body weight loss (%EBWL), in which ideal weight is defined by the weight corresponding to a BMI of 25 kg/m^2 were calculated according to Brethauer *et al.* [9]. Venous blood samples were taken after overnight fasting for the measurement of serum glucose and lipid profile, hepatic profile, serum insulin, leptin, and ghrelin levels and for DNA extraction. Serum glucose and lipid and hepatic profiles were measured using enzymatic methods, insulin, leptin, and ghrelin concentrations were measured using ELISA kits (ALPCO Immunodiagnostic AG, Stubenwald-Allee, Bensheim, USA). Insulin resistance was calculated using the homeostasis model assessment (HOMA-IR) with the formula fasting glucose X fasting insulin/22.5 (U/L) [10].

SNP genotyping

Genomic DNA was isolated from whole blood using a commercial kit. Genotyping of rs9939609, rs9930506, and rs1421085 *FTO* polymorphisms (SNPs) was carried out with quantitative polymerase chain reaction (qPCR) using validated TaqMan® probes and TaqMan™ Genotyping Master Mix enzyme (Thermo Fisher Scientific, Inc., Waltham, MA, USA) following the supplier specifications.

Statistical analysis

The normality of the distribution of data was assessed by the Kolmogorov-Smirnov test. Hardy-Weinberg equilibrium was evaluated. We used descriptive statistics to present the data as the mean ± standard deviation (SD) or median (25-72 quartiles). To compare groups, we used the T test or Mann-Whitney test or ANOVA according to the distribution of data. Chi-square or Fisher´s exact tests were used to compare categorical variables. To evaluate the interaction effects of *FTO* polymorphisms with weight and BMI, we designed a variance analysis of repeated measures of one factor. A p value of <0.05 was considered significant. Analyses were carried out using the statistical Statistica 7 package (Statsoft Inc., Tulsa, OK, USA).

Results

We included a total of 101 patients, 78 women and 23 men, with a median of 6 (4–8) years after bariatric surgery. **Table 1** shows the anthropometric, clinical, and metabolic characteristics of the patients' post-surgery. In this cohort, TBWL was 34.7 (22.9–48.9), %TBWL was 23 (16.6–33), %EBWL was 58.5 (40–79), and ideal weight was 64 (58.5–68.9). All polymorphisms were in Hardy Weinberg equilibrium.

Table 1. Anthropometric and clinical characteristics of patients at 6 years after bariatric surgery n=101.

Age (years)	47 (40–54)
Sex m/f	23/78
Weight (kg)	82 (73–103)
Height (m)	1.60 (1.53–1.66)
BMI (kg/m^2)	33.8 (29.1–38.8)
SBP (mmHg)	122 (112–132)
DBP (mmHg)	74 (60–80)
TBWL (kg)	34.7 (22.9–48.9)
%TBWL	23 (16.6–33)
%EBWL	58.5 (40–79)
Glucose (mmol/L)	4.88 (4.6–5.2)
Total cholesterol (mmol/L)	3.95 (3.43–4.49)
HDL-cholesterol (mmol/L))	1.39 (1.16–1.6)
LDL-cholesterol (mmol/L)	2.0 (1.87–2.22)
Triglycerides (mmol/L)	1.06 (0.88–1.48)
Total protein (g/L)	7.0 (6.7–7.3)
Serum Albumin (g/L)	3.9 (3.8–4.1)

AST U/L	27 (23–33)
ALT U/L	23 (18–31)
Alkaline Phosphatase UI/L	87 (73–102)
Total Bilirubin (μmm/L)	10.2 (8.5–11.9)
Indirect Bilirubin (μmm/L)	6.8 (5.1–8.5)
Direct Bilirubin (μmm/L)	3.4 (1.7–5.1)
Insulin μIU/L	12.6 (9.5–17.5)
HOMA-IR	2.73 (1.94–4.35)
Serum Leptin (ng/mL)	25 (14.5–37.9)
Serum Ghrelin (pg/mL)	322 (270–506)

The values are expressed as the median and interquartile range. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; HDL: High Density Proteins; HOMA-IR: Homeostasis Model Assessment Insulin Resistance; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

rs9939609, rs9930506, and 1421085 *FTO* polymorphisms dominant model, after surgery

Under the dominant model, the carriers of one or two risk alleles of the rs9939609 polymorphism showed 8.8 kg more and higher serum insulin, HOMA-IR, and serum leptin levels than the wild type. In the carriers of one or two risk (AG and GG) alleles of rs9930506 polymorphism, the TBWL were lower than in AA carriers. Instead, total cholesterol, insulin, and insulin resistance levels were higher than those of the wild type. Regarding polymorphism rs1421085, in the carriers of the risk genotypes TC and CC, the post-surgery weight, serum insulin, and insulin resistance were significantly higher than those in carriers of the TT genotype, but TBWL was low in the TC and CC groups **(Table 2)**.

Analysis of rs9939609 (T>A) and rs1421085 (T>C) haplotypes

In the carriers of the rs9939609A and rs1421085C risk haplotype of *FTO* polymorphisms, the TBWL and %EBWL were significantly lower than in the other haplotypes (F=3.42, p=0.020 and F=16.73.47, p=0.018, respectively).

Analysis of rs9939609 (T>A) and rs9930506 (A>G) haplotypes

The carriers of the rs9939609**A** and rs9930506**G** risk haplotype lost less total weight (TBWL) (p=0.008), and serum insulin and HOMA-IR (p=0.003, and p=0.009) were significantly higher than in the other haplotypes.

Interaction effects of *FTO* polymorphisms in bariatric surgery

Significant interaction effects of both rs9930506 and rs1421085 *FTO* risk genotypes on weight and BMI in response to bariatric surgery were found. No interaction effects of rs9939609 risk genotypes by bariatric surgery were observed **(Table 3)**.

Discussion

After a median of 6 (4–8) years from bariatric surgery, we analyzed the effects of *FTO* gene polymorphisms on pre-surgery weight, post-surgery weight, pre-BMI, post-BMI, TBWL, % EBWL, and metabolic condition. Successful bariatric surgery in terms of weight outcomes has been described as >50% excess weight loss (%EWL), 20-30% loss of initial weight or achieving a BMI <35 kg/m^2 [11]. Our cohort maintained a %TBWL of 58.5 (40-79) and a BMI of 33.8 (29-38.8) 6 years after bariatric surgery. In addition, metabolic parameters corresponded to individuals without

Table 2. *FTO* polymorphism Dominant Model.

rs9939609 T>A				
	TT n= 40	**TA and AA n = 61**	**T ó Z**	**p**
Post-surgery Weight (Kg)	84 ± 16.6	92.8 ± 24.2	t=- 1.98	0.049
Serum Insulin μIU/L	12.0 ± 4.8	16.2 ± 9.2	t=-2.66	0.008
Serum Leptin (ng/mL)	24.5 ±16	32.5 ± 21	t=-2.01	0.049
HOMA-IR	2.69 ± 1.2	3.8 ± 2.6	t=-2.49	0.014
rs9930506 A>G				
	AA n= 41	**AG and GG n= 59**	**Z**	**p**
Pre-surgery BMI (kg/m^2)	50.3 (45.7– 55.2)	45.3 (42.5–54.6)	Z=1.91	0.05
TBWL Kg	38.3 (25.2– 59)	33 (18.6–41.8)	Z=2.35	0.018
Total Cholesterol (mmol/L) (mg/dl)md/dL(mg/dl)	3.77 (3.2–4.34)	4.18 (3.6–4.7)	Z=-2.09	0.036
Serum Insulin (μIU/L)	10.5 (7.5–13.4)	13.7 (10.5–9.4)	Z=-3.53	0.0004
HOMA-IR	2.28 (1.7–2.92)	3 (2.18–4.9)	Z=-3.47	0.0005
rs1421085 T>C				
	TT n= 44	**TC and CC n=55 5559**	**T**	**p**
Post-surgery weight (Kg)	84 ± 16	93.9 ± 25	**-2.29**	0.023
TBWL (Kg)	42.5 ± 20	32.5 ± 20	2.49	0.014
Serum insulin (μIU/L)	12 ± 4.9	16.2 ± 9.3	-2.67	0.008
HOMA-IR	2.68 ± 1.3	3.82 ± 2.6	-2.58	0.011

BMI: Body Mass Index; TBWL: Total Body Weight Loss; *: Z, Mann and Whitney; T: t Student

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Table 3. The *FTO* genotypes and response to bariatric surgery (variance analysis of repeated measure of one factor).

rs9930506 A>G					
	AA (n=41)		**AG and GG (n=59)**		**p**
	Before surgery	**After surgery**	**Before surgery**	**After surgery**	**Genotype**
Weight (Kg)	128.5 ± 25.5 121 (117–140)	85 ± 16* 81.7 (76–93.9)	125.4 ± 26.3 121 (106–140)	92.8 ± 24.6* 89 (73–110)	**0.007**
BMI (kg/m²)	51.7 ± 10.8 50.3 (45.7–55.2)	34 ± 6.2* 33.8 (29–38.5)	47.9 ± 8 45.3 (42.5–54.6)	35.3 ± 7.8* 34 (29.3–39.4)	**0.002**
rs1421085 T>C					
	TT (n=44)		**TC and CC (n=55)**		**p**
	Before surgery	**After surgery**	**Before surgery**	**After surgery**	**Genotype**
Weight (Kg)	126.4 ± 23.7 12 1(116–138)	84 ± 16* 80.4 (73–94.5)	**126.4** ± 28 121 (106–142)	93.9 ± 25* 91.7(73.3–111)	**0.014**
BMI (kg/m²)	50.6 ± 10 50 (44.5–54.3)	33.3 ± 6* 33.2 (29–38.2)	48.4 ± 9 46 (41.3–54.8)	35.8 ± 8* 35.5 (29.6–40.7)	**0.005**

Data presented as median ± ED, and median 25–75 quartile. BMI: Body Mass Index. p value = genotype interaction, variance analysis of repeated measure of one factor. *p<0.00001 difference within-subject before and after surgery.

metabolic problems and had important remission of T2DM and hypertension. Nevertheless, the patients had moderately satisfactory results in weight loss, TBWL, and %EBWL. Our data still shows clinical variability in outcomes of patients after RYGB.

An association of the risk rs9939609 genotype with smaller changes in postoperative BMI and %EBWL in patients with obesity after RYGB has been reported [7,8]. In our work, post-surgery weight, insulin, leptin, and insulin resistance levels were significantly higher in carriers of one or two risk alleles. In a recent study, carriers of the AT genotype had less weight loss than carriers of the TT genotype and lower resting-state activity in posterior cingulate cortex at 12-60 months after laparoscopic sleeve gastrectomy [12], which suggests that the *FTO* gene may play an important role in the long-term outcomes of bariatric surgery. The effect of the rs9930506 *FTO* polymorphism on the outcomes after bariatric surgery has been briefly explored. In our previous work in patients with severe obesity, we found at baseline that carriers of one or two risk alleles rs9930506 *FTO* weighed 34 kg more than wild-type carriers. After sleeve gastrectomy (SG), we found a higher weight loss in carriers of one or two risk alleles (37 kg) in comparison with wild-type carriers (13.7 kg), similar results were observed in BMI 11.5 vs 5.2 kg/m^2, total cholesterol, insulin, and insulin resistance at 6 months of SG [13]. Several studies have confirmed the association of rs1421085 *FTO* with the risk of development obesity [14]. We found that carriers of the risk TC and CC genotypes had higher post-surgery weight and insulin and HOMA-IR levels and minor TBWL than carriers of the TT genotype. Interestingly, in the three polymorphisms of the *FTO* gene, higher insulin and HOMA-IR levels in risk genotypes. In a previous report, subjects with the rs9939609A risk allele were significantly associated with higher plasma insulin levels (P=0.05) and higher HOMA-IR (P=0.02) [15]. The variance analysis of repeated measures of one factor showed interaction effects between of rs9930506 and rs1421085 *FTO* polymorphisms with bariatric surgery on weight and BMI. This is the first report of interaction effects of these *FTO* polymorphisms with anthropometric changes for BS. In the literature, we found only one study by Harbron *et al.* that showed an association of the *FTO* rs1421085 and 17817449 haplotypes with dietary intake, eating behavior, and psychological health [16].

Limitations

The first limitation is that we carried out only two evaluations of the patients, pre-surgery and post-surgery 6 (4–8 years), and therefore, we do not have data on the changes in BS outcomes at a short-time (6 or 12 months, per example). Another limitation is the small sample size, which could not influence the lack of association of rs9939609 with bariatric surgery on weight and BMI.

Conclusions

In this cohort, we showed the effect of rs9939609 and rs1421085 risk genotypes on post-surgery weight, and also the effect of the rs9930506 and rs1421085 risk genotypes on TBWL. Insulin and insulin resistance levels were higher in risk genotypes of three *FTO* polymorphisms. In the carriers of the rs9939609 and rs1421085 risk haplotype, as well as, in the rs9939609 and rs9930506 risk haplotype, TBWL were lower than those of the other haplotypes. Analysis additionally confirmed the interaction effects of rs9930506 and rs1421085 risk genotypes with response to bariatric surgery on weight and BMI. These results may be considered as a screening tool prior to bariatric surgery to help clinicians predict weight loss for patients with severe obesity and could be used prior to surgery to prognosticate their success.

Conflict of Interest

All authors of this paper state that they do not have any direct or indirect financial or other relationship that might lead to conflicts of interest.

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Elva Perez-Luque and Claudia Martinez-Cordero developed the study design and wrote the manuscript. Edgar S. Daza-Hernández and Norberto Muñoz-Montes selected of the patients and data collection. Nicté Figueroa-Vega and Edgar S. Daza-Hernández developed and carried out the experiments. Elva Perez-Luque and

Mónica I. Cardona-Alvarado carried out data interpretation and statistical analysis. All authors reviewed and approved the manuscript and approved the submission of the article.

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