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Original article

# A single FTO gene variant rs9939609 is associated with weight change and insulin resistance improvement in response to a robotic sleeve gastrectomy in individuals with severe obesity

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**Abstract**

**Background:** Genetic mechanisms have been involved in the weight response secondary to bariatric surgery.

**Objective:** The aim of our study was to evaluate the effects of the rs9939609 genetic variant on weight loss and metabolic parameters after sleeve gastrectomy.

**Setting:** Tertiary hospital.

**Methods:** A total of 95 participants were enrolled. Co-morbidities, biochemical evaluation, and anthropometric parameters were registered before and after 3-, 6-, and 12-month follow-up. Genotype of the rs9939609 fat mass and obesity-associated (FTO) gene was evaluated.

**Results:** We grouped the participants into 2 groups: carriers of A allele (TA+AA, 69.5%) and non-carriers of A allele (TT, 30.5%). We detected a statistically significant reduction of blood pressure, biochemical, and anthropometric parameters at 3 times during follow-up. After 6 months, changes of some parameters were greater in non-A allele carriers: weight (–39.6 + 4.0 kg versus –24.6 + 2.8 kg; $P = .02$), waist circumference (–21.1 + 2.1 cm versus –16.2 + 1.8 cm; $P = .04$), insulin (–12.3 + .9 mUI/L versus –8.9.1 + .2 mUI/L; $P = .02$), and homeostasis model assessment of insulin resistance (–3.1 + .1 units versus –2.3 + .1 units; $P = .02$ ). After 12 months, changes of the aforementioned parameters remained greater in non-A allele carriers. The percentage of participants with diabetes diminished earlier in the non-A allele carriers than A allele carriers at 6-month follow-up. The percentage of participants with diabetes at the end of the study was lower in non-A allele carriers (3.4% versus 12.1%; $P = .02$).

**Conclusions:** Our data suggest that non-A allele carriers of the genetic variant (rs9939609) of the FTO gene showed a better improvement of anthropometric and insulin levels in non-A allele carriers after a robotic sleeve gastrectomy. Both improvements are associated with a lower percentage of participants with diabetes at 12 months. (Surg Obes Relat Dis 2023;19:459–465.) 

*Key words:* FTO; Robotic sleeve gastrectomy; rs9939609; Insulin resistance; Weight loss

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The prevalence of obesity in the world is increasing [1,2]. Considerable evidence shows that obesity is related with numerous metabolic abnormalities and diseases such as hypertension, diabetes, hyperlipidemia, cardiovascular diseases, and cancer. People with obesity benefit from any amount of weight loss, whether resulting from lifestyle modification, drugs, or bariatric surgery, with the goal of achieving clinically meaningful weight loss of at least 5% [3], but bariatric surgery is the unique method that has been proven to result in significant weight loss for people with severe obesity. Sleeve gastrectomy is a commonly performed bariatric surgery worldwide [4]. Some evidence has demonstrated varied results in terms of weight improvement after bariatric surgery among individuals of different ethnicities [5,6]. This variation in weight loss and metabolic improvements could be explained by some parameters, including genetic background [7].

The fat mass and obesity-associated (FTO) gene located on chromosome 16q12 was the first identified obesity-associated gene by a genome-wide association study [8]. More than 250 single-nucleotide polymorphism (SNP) loci related to obesity have been reported; moreover, the FTO locus is the most frequently evaluated and the rs9939609 A-allele is one of the strongest risk factors for polygenetic obesity [9].

In recent research FTO pathway has been implied in the energy metabolism in adipose tissue [10]. Some intervention studies have explored the interaction between dietary intervention and FTO gene variant on anthropometric indices or metabolic parameters and contradictories results have been obtained [11–13]. Furthermore, some studies have investigated the effect of FTO variants on weight loss of participants with severe obesity undergoing bariatric surgery. Liou et al. [14] have demonstrated that individuals with obesity with risk genotype AA (rs9939609) had lower decrease in body mass index (BMI) and fasting glucose levels than individuals with TT/AT genotype in the 6 months after undergoing laparoscopic mini-gastric bypass. Another study [15] has evaluated the effect on weight loss of other variants of the FTO gene (rs1421085, rs1121980, rs8050136, rs7190492, rs16945088). This study found evidence that the rs16945088 FTO variant is associated with maximum weight loss secondary to banding surgery. Finally, de Luis et al. [16] reported that people with obesity with the A allele risk of rs9939609 variant showed slower weight loss than non-A allele carriers with the same amount of weight loss after 12 months secondary to a biliopancreatic diversion surgery. As far as we know, there is 1 investigation in the literature that has evaluated the role of this polymorphism on weight loss [17] after sleeve gastrectomy. The results showed no effect on weight, without evaluating biochemical parameters, and with a follow-up of only 6 months.

The aim of our study was to evaluate the effects of rs9939609 genetic variant of FTO gene on weight loss and metabolic parameters after a robotic sleeve gastrectomy in people with severe obesity.

## Methods

### *Study characteristics, inclusion and exclusion criteria*

A prospective study was carried out in our university hospital, with all participants recruited in our bariatric unit and submitted to sleeve gastrectomy by the same medical team. Ninety-five participants with severe obesity have been consecutively enrolled. All participants were informed about the research procedures and signed a written informed consent form before enrollment. The Ethics Committee of the HCUVa of Valladolid Spain (Committee 18/1080) approved the protocol and all were in accordance with the Declaration of Helsinki.

The inclusion criteria were (1) age between 25 and 65 years, (2) BMI $>40$ kg/m$^2$ or $>35$ kg/m$^2$ with associated co-morbidities, and (3) registration on a waiting list for bariatric surgery. The exclusion criteria were (1) active alcoholism; (2) uncontrolled hypothyroidism; (3) active Cushing syndrome; (4) genetic syndromes associated with obesity, coagulopathy, neoplasia, or renal or liver failure; (5) use of corticosteroids; and (6) diabetes treated with insulin. We excluded those under treatment with insulin to avoid participants with little pancreatic reserve and to avoid interference in blood determination systems of insulin levels.

### *Procedures*

This study was designed to evaluate the effect of rs9939609 variant on weight loss and metabolic changes in adult participants undergoing bariatric surgery; DNA was extracted from preoperative oral cell samples. Blood were collected for biochemical assessment. Medical records provided the history of dyslipidemia, hypertension, and diabetes. Anthropometric measurements and biochemical parameters were recorded at the baseline visit before surgery and at each visit after surgery at 3, 6, and 12 months. All bariatric participants have been undergoing robotic sleeve gastrectomy (SG) (Table 1). This robotic SG was realized using the DaVinci XTM (Intuitive Surgical LTD, Oxford, UK) platform with 5 trocars (four 8-mm robotic trocars and one 12-mm trocar for AirSeal iFS [CONMED Corp., Utica, NY]). The gastrocolic ligament was transected with the robotic Vessel Sealer ExtendTM (Intuitive Surgical LTD). Greater curvature was transected with the Signia Stapling System (Medtronic, Minneapolis, MN) and Endo GIA with Tri-Staple Technology (Medtronic). A 36F bougie was used for calibration. For the first 30 days, the participants ate a 1000-calorie diet supplemented with a protein module (Bificare) to reach 1.4 g per kilogram of ideal weight (BMI = 22 kg/m$^2$) and a distribution of macronutrients (20% protein, 30% fat, and 70% carbohydrates). After 1 month following SG, participants with obesity followed the

Table 1
Presurgical characteristics of the participants

| Parameter | Basal time |
|---|---|
| Participants with severe obesity* | 85 |
| Participants with BMI >50 kg/m$^2$ | 10 |
| Sex (female/male) | 71/24 |
| Age (yr) | 49.9 + 3.2 |
| BMI (kg/m$^2$) | 45.3 + 2.3 |

BMI = body mass index.
* Severe obesity: BMI >40 kg/m$^2$ and <50 kg/m$^2$.

same diet based on an intake of 1200 to 1400 calories with a distribution of macronutrient fats (35%, divided into 10% saturated, 20% monounsaturated, and 5% polyunsaturated) and carbohydrates (65%) and a contribution of proteins of 1.2 g per kilogram of ideal weight.

*Anthropometric measurements, blood pressure, and co-morbidities*

The participants' body weight was assessed using a manual balance, accurate within 50 g (Seca, Birmingham, UK). Height was assessed with a stadiometer accurate within .1 cm (Seca). BMI was calculated as body weight in kg/(height in m$^2$). Waist circumference (WC) was measured in the narrowest diameter between xiphoid process and iliac crest with a flexible tape measure (Omrom, Los Angeles, CA). Ideal weight was calculated with an ideal BMI of 22 kg/m$^2$. Systolic and diastolic blood pressure was measured 3 times and averaged with a random zero mercury sphygmomanometer (Omrom). All these parameters were determined in the morning before breakfast at baseline and subsequently at 3, 6, and 12 months.

Co-morbidities of obesity were defined as hypertriglyceridemia (triglycerides >150 mg/dL), hypertension (systolic and diastolic blood pressures greater than 140 and/or 90 mmHg, respectively), or elevated low-density lipoprotein (LDL) cholesterol (>100 mg/dL); participants who were taking medication for these pathologies were considered to have co-morbidities of obesity. To determine diabetes, any of the following criteria were necessary: (1) fasting blood glucose >126 mg/dL; (2) HbA1C >6.5%; (3) blood glucose after 2-hour oral glycose overload test >200 mg/dL; or (4) participants who were taking drugs for hyperglycemia. Diabetes remission was defined as 1 year off of diabetes medications with HbA1C <6.5% at 1 year.

*Biochemical assays, DNA extraction and genotyping*

Glucose levels were measured by an automated hexoquinase oxidase method (COBAS INTEGRA 400 analyzer [Roche Diagnostic, Montreal, Canada]). Insulin was realized by electrochemiluminescence assay (COBAS INTEGRA 400 analyzer [Roche Diagnostic]). The homeostasis model assessment for insulin resistance (HOMA-IR) was evaluated using these values with the following equation: (glucose × insulin / 22.5) [18]. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined using the COBAS INTEGRA 400 analyzer (Roche Diagnostic). LDL cholesterol was calculated using Friedewald formula (LDL cholesterol = [total cholesterol – HDL cholesterol – triglycerides] / 5) [19].

Genomic DNA was extracted from cells of the oral mucosa using the next kit extraction (Quantum prep, Biorad, Los Angeles, CA). The quality of DNA was assessed by the ratio of the 260- to 280 nm readings obtained by a spectrophotometer. Genotyping (rs9939609) was performed by using TaqMan OpenArray Genotyping platform (Thermo Fisher Scientific, Pittsburgh, PA). Samples were loaded using the AccuFill system, and amplification performed on the QuantStudio 12K Flex Real-Time qPCR instrument (Thermo Fisher Scientific). A total volume of 5 μL with 2.5 μL TaqMan OpenArray Master Mix (Applied Biosystems, Foster City, CA) and 2.5 μL human DNA sample were loaded and amplified on arrays. Genotype calling and sample clustering were performed in TaqMan Genotyper (LifeTechnologies, Carlsbad, CA). Hardy Weinberg equilibrium was determined with a statistical test ($\chi^2$). The variant of FTO gene was in Hardy Weinberg equilibrium ($P$ = .48).

*Statistical analysis*

SPSS Statistics version 23.0 (IBM, Armonk, NY) has been applied in this analysis. Power analysis reported at least 90 participants with the change in weight of 20 kg using A-allele frequency (45%) in participants with obesity, with a type I error of .05 and type II error of .10 (power = .9). The statistical analysis was realized with a dominant model with the combined AA and AT as a group and TT genotype as second group. The results were reported as average ± standard deviation. The normal distribution of variables was evaluated with the Kolmogorov-Smirnov test. Parameters with normal distribution were analyzed with a two-tailed Student's $t$ test. Categorical variables were analyzed with the $\chi^2$ test, with Yates correction as necessary. The statistical analysis to evaluate the gene–surgery interaction was univariate analysis of covariance with anthropometric and biochemical parameters at 3, 6, and 12 months, considering the genotype with a post hoc test Tukey. Bonferroni correction for multiple hypothesis testing was performed. $P < .05$ denotes significant difference.

## Results

A total of 95 participants with severe obesity received robotic SG. The parameters distribution before surgery is shown in Table 1. Of the 95 patients, 71 were women and 24 were men with an average age of 49.9 ± 3.2 years. The allelic frequency was .48 T and .52 A alleles.

Table 2
Changes in anthropometric variables for rs9939609 (mean + SD)

| Characteristic | TT (n = 29) | | | | TA or AA (n = 66) | | | |
|---|---|---|---|---|---|---|---|---|
| | 0 time | At 3 mo | At 6 mo | At 12 mo | 0 time | At 3 mo | At 6 mo | At 12 mo |
| BMI | 46.3 ± 3.1 | 40.5 ± 3.3* | 33.2 ± 2.9* | 32.1 ± 2.1* | 46.1 ± 2.9 | 40.4 ± 2.1* | 33.5 ± 2.1* | 32.9 ± 2.2* |
| Weight (kg) | 121.6 ± 11.2 | 104.1 ± 6.9* | 91.0 ± 5.1* | 85.1 ± 2.5* | 120.8 ± 7.2 | 103.5 ± 4.2* | 96.1 ± 3.1* | 92.1 ± 2.9* |
| WC (cm) | 124.8 ± 4.3 | 110.9 ± 3.1* | 103.9 ± 4.0* | 95.0 ± 3.1* | 124.7 ± 3.1 | 112.1 ± 3.0* | 108.1 ± 3.1* | 105.1 ± 4.1* |
| SBP (mmHg) | 142.0 ± 3.0 | 135.2 ± 2.9* | 128.1 ± 4.2* | 121.0 ± 3.0* | 144.2 ± 4.2 | 135.0 ± 2.1* | 130.1 ± 2.2* | 120.1 ± 2.1* |
| DBP (mmHg) | 88.1 ± 2.1 | 87.1 ± 3.2 | 84.0 ± 2.2* | 83.5 ± 3.1* | 91.0 ± 3.0 | 86.5 ± 3.0 | 84.1 ± 3.0* | 81.2 ± 2.2* |

SD = standard deviation; BMI = body mass index; WC = waist circumference; SBP = systolic blood pressure; DBP = diastolic blood pressure.
* $P < .05$ in each genotype group with baseline values. There are no statistical differences in demographic, anthropometric, and metabolic characteristics between the 2 genotype groups.

The genotypic frequency was 30.5% (29 participants) in TT genotype; 36.8% (35 participants) in TA genotype; and 32.6% (31 participants) in AA genotype. We grouped the participants in 2 groups: carriers of A allele (TA+AA, 69.5%) and non-A allele carriers (TT, 30.5%). The sex distribution was similar in both genotype groups (TT: 20.7% [n = 6] male and 79.3% [n = 23] female; TA+AA: 27.7% [n = 18] male and 72.3% [n = 48] female). Average age was similar in both genotype groups (TT: 50.2 ± 4.1 yr versus TA+AA: 49.8 ± 3.1 yr).

Table 2 shows changes in anthropometric parameters and blood pressure during each visit after SG. We did not detect statistical differences in anthropometric parameters and blood pressure at basal time in both genotypes. When the evolution of anthropometric parameters over time was revised, we detected a statistically significant improvement of systolic blood pressure, diastolic blood pressure, body weight, and waist circumference after surgery at 3, 6, and 12 months. Improvements in anthropometric parameters were greater at 6- and 12-month visits in non-A allele carriers than A allele carriers. After 6 months, deltas of these parameters were greater in non-A allele carriers; waist circumference (–21.1 ± 2.1 cm versus –16.2 ± 1.8 cm; $P = .04$). Finally, after 12 months, deltas of these parameters remained greater in non-A allele carriers; waist circumference (–29.0 ± 3.0 cm versus –19.2 ± 2.1 cm; $P = .02$). The remaining changes of the anthropometric parameters at 3 months were similar in both genotype groups. The improvement in blood pressure was similar in the 2 groups throughout the study.

Table 3 shows improvements in all biochemical parameters. Basal values of these parameters are similar in both genotype groups. As expected with the huge amount of weight loss, fasting glucose, insulin, HOMA-IR, total cholesterol, LDL cholesterol, and triglyceride levels decreased in both genotype groups in all the visits. Although the improvement of insulin levels and HOMA-IR was significant in both genotypes, these changes were greater in non-A allele carriers 6 and 12 months after surgery (Table 3). After 6 months, deltas of insulin levels and HOMA-IR were greater in non-A allele carriers than A allele carriers (insulin: –12.3 ± .9 mUI/L versus –8.1 ± .2 mUI/L, $P = .02$; HOMA-IR: –3.1 ± .1 units versus –2.3 ± .1 units, $P = .02$ ). Finally, after 12 months, deltas of insulin levels and HOMA-IR remained greater in non-A allele carriers than A allele carriers (insulin: –12.2 ± .8 mUI/L versus –9.0 ± .2 mUI/L, $P = .03$; HOMA-IR: –3.3 ± .1 units versus –2.2 ± .2 units; $P = .03$ ). The improvement in the remaining biochemical parameters was similar in the 2 groups throughout the study.

Table 4 reports the improvement in obesity co-morbidities throughout the study (percentage of hypertriglyceridemia, hypertension, and high-LDL cholesterol levels and type 2 diabetes). The basal percentages of these co-morbidities were similar in both genotype groups and all rates decreased. At 12 months after surgery, 6.8% of the participants who did not carry the A allele received statins and 9.9% of the carriers of the A allele. In the same period, 13.7% of the participants who did not carry the A allele received angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists and 13.6% of carriers of the A allele.

However, the percentage of participants with diabetes diminished earlier in the non-A allele carriers than A allele carriers at 6 months follow-up. At baseline, 20.6% of the participants who were not carriers of the allele a received metformin and 18.1% of the participants who were carriers of the allele A, with a nonsignificant mean time of diagnosis of diabetes between both groups (4.5 ± 2.1 yr versus 4.4 ± 1.8 yr, respectively). Baseline HbA1C levels were 7.5 ± .3% versus 7.4 ± .4%, with no statistically significant differences, and the percentage of participants with diabetes at the end of the study was lower in non-A allele carriers (3.4% versus 12.1%; $P = .02$). HbA1C levels at 12 months were lower in non-A allele carriers than A allele carriers (5.5 ± .1% versus 6.5 ± .2%; $P = .01$).

## Discussion

The current data showed a greater weight loss in non-A allele carriers of the rs9939609 variant in FTO gene after a robotic SG. This greater improvement in weight produces a greater response in insulin resistance and in the percentage of type 2 diabetes.

Table 3
Biochemical parameters for rs9939609 (mean + SD)

| Characteristic | rs9939609 | | | | rs9939609 | | | |
|---|---|---|---|---|---|---|---|---|
| | TT (n = 29 | | | | TA or AA (n = 66) | | | |
| | Baseline | At 3 mo | At 6 mo | At 12 mo | Baseline | At 3 mo | At 6 mo | At 12 mo |
| Glucose (mg/dl) | 114.1 ± 4.1 | 92.9 ± 3.9* | 90.3 ± 3.1* | 89.0 ± 3.2* | 111.5 ± 4.9 | 100.9 ± 5.0* | 93.1 ± 4.1* | 94.1 ± 5.0* |
| Total chol (mg/dl) | 198.3 ± 10.2 | 161.4 ± 9.1* | 160.1 ± 8.0* | 160.2 ± 4.1* | 200.3 ± 10.0 | 162.2 ± 8.3* | 160.9 ± 5.9* | 159.1 ± 4.0* |
| LDL chol (mg/dl) | 132.3 ± 8.1 | 104.2 ± 7.1* | 101.0 ± 3.1* | 98.1 ± 3.2* | 133.9 ± 7.0 | 105.1 ± 4.1* | 100.1 ± 3.1* | 99.8 ± 4.2* |
| HDL chol (mg/dl) | 46.1 ± 3.1 | 45.4 ± 2.4 | 44.9 ± 4.1 | 45.1 ± 3.3 | 46.2 ± 3.2 | 45.1 ± 2.2 | 44.7 ± 3.1 | 45.1 ± 630 |
| TG (mg/dl) | 145.5 ± 12.1 | 124.1 ± 11.2* | 112.2 ± 9.6 * | 105.5 ± 11.1* | 147.1 ± 9.9 | 125.2 ± 8.9* | 111.9 ± 8.8* | 105.7 ± 7.2* |
| Insulin (mUI/L) | 20.2 ± 2.4 | 12.1 ± 2.1* | 7.9 ± 2.8* | 8.0 ± 3.0* | 21.9 ± 2.1 | 14.1 ± 3.0* | 12.2 ± 3.1* | 12.9 ± 2.9* |
| HOMA-IR | 5.0 ± 1.2 | 2.5 ± 1.0* | 2.0 ± 0.9* | 1.7 ± 0.4* | 5.2 ± 0.8 | 3.1 ± 1.0* | 2.9 ± 0.9* | 3.0 ± 0.9* |

chol = cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglycerides; HOMA-IR = homeostasis model assessment of insulin resistance.

* $P < .05$ in each group with baseline values. There are no statistical differences between genotypes.

Many factors may potentially interact with bariatric surgery and produce highly variable outcomes in terms of weight loss and associated co-morbidities afterward. Evidence has shown that genes affect weight response and metabolic changes [20,21]. In our study, although no differences in basal weight and metabolic control were detected between A allele carriers and non-A allele carriers, the trend toward improvement of anthropometric parameters, insulin levels, and HOMA-IR was greater in non-A allele carriers than in A allele carriers after 6 months of the SG. Investigations demonstrated good glycemic control benefits from weight loss [22] and we hypothesized that the better insulin resistance improvement in non-A allele carriers might result from weight loss. A second hypothesis is that SG may impair insulin action via gut hormone modification, rather than by the way of weight loss. Moreover, the genetic effect may interact with gut hormone axis [23], but the possible mechanisms need to be explored in further studies. With regard to the interaction between genes and sleeve gastrectomy, our study has confirmed a deleterious association with A allele of rs9939609.

Previously, some studies have investigated the effect of FTO gene variants on weight loss in patients undergoing bariatric surgery [14–16]. One study [15] has investigated the role of 5 SNPs of the FTO gene (rs1421085, rs1121980, rs8050136, rs7190492, rs16945088) after a bariatric procedure. Only the variant rs16945088 remained statistically significantly associated with maximum weight loss, as the maximum weight loss for minor allele carriers was approximately 3 kg less compared with common allele homozygotes. This association was particularly evident in the participants who were operated with banding surgery, while no association was found in the gastric bypass group. Liou et al. [14] observed that participants with obesity and risk genotype AA (rs9939609) had lower decrease in BMI and fasting glucose levels than participants with TT/AT

Table 4
Preoperative and postoperative co-morbidities of the participants

| Parameters | Baseline | 3 mo | 6 mo | 12 mo |
|---|---|---|---|---|
| High levels of LDL cholesterol* | | | | |
| TT | 31.0% | 24.1% | 20.6% | 17.2%† |
| TA+AA | 36.3% | 30.3% | 28.7% | 16.6%† |
| High levels of TG‡ | | | | |
| TT | 24.2% | 20.6% | 17.2%† | 6.8%† |
| TA+AA | 27.3% | 21.1% | 18.1%† | 9.9%† |
| Blood hypertension§ | | | | |
| TT | 20.6% | 17.2% | 17.2% | 13.7%† |
| TA+AA | 24.2% | 19.6% | 16.6% | 13.6%† |
| Diabetes | | | | |
| TT | 20.6% | 13.7% | 10.3%† | 3.4%† |
| TA+AA | 18.1% | 15.1%† | 13.6%† | 12.1%† |

LDL = low-density lipoprotein; TG = triglycerides.

* High LDL cholesterol: >100 mg/dL.

† $P < .05$ in each group with basal values.

‡ High levels of TG = hypertriglyceridemia (triglycerides >150 mg/dL).

§ Hypertension = systolic and diastolic blood pressures >130 and 85 mmHg, respectively.

genotype 6 months after undergoing laparoscopic minigastric bypass. In the same study, these results have not been detected after undergoing laparoscopic adjustable gastric banding; perhaps gut hormone axis plays an unknown role. In another study [16], the rs9939609 variant was associated with a greater and earlier weight loss in participants with TT variant than participants with the A allele after a biliopancreatic diversion. Moreover, final weight loss after 9 and 12 months of a biliopancreatic diversion surgery was similar in both genotypes.

This greater weight loss after the aforementioned bariatric surgeries in participants with the T allele is associated with a visceral fat loss. In our present work we evaluated it indirectly in participants by determining the waist circumference, with the same results. This improvement in visceral fat may explain the improvement in glycemic status. It is well known that excess accumulation of visceral fat is related with impaired metabolic parameters [24]. This visceral obesity produce a high lipolysis activity within visceral adipocytes, with an increased delivery of free fatty acids into the portal system (liver tissue), resulting in a potential insulin resistance [25].

Moreover, lack of association between rs9939609 and weight loss secondary to Roux-Y gastric bypass (RYGB) was detected in women after 1 year [26]. The same lack of effect after RYGB was described after 24 months [27]. Perhaps the follow-up time after the intervention is also important in the results observed. For example, Kops et al. [28] did not detected an association of this SNP with weight loss during the first 24 months of RYGB surgery, but a direct effect was detected at 36, 48, and 60 months postsurgery, with TT genotype.

The reasons for the high variability in the aforementioned results are unknown, though some factors could be implied; ethnicity, ratio of sex distribution presurgical BMI of participants, dietary intake, duration of follow-up, socioeconomic status, frequency of physical activity, presence of metabolic co-morbidities, and type of bariatric surgery. Other new factors are currently being discovered, for example, Bandstein et al. [29] have demonstrated that presurgery vitamin D levels influence the size of genotype effects of rs9939609 on RYGB induced weight loss. The excessive BMI loss of vitamin D–deficient participants carrying AA exceeded that of vitamin D-deficient participants carrying TT genotype. This suggests that vitamin D may possess a biologic effect that can regulate the impact by which FTO gene impacts body weight regulation [30]. Finally, Wang et al. [31] reported that the magnitude of excess body weight reduction 2 years after bariatric surgery was correlated with the angiopoietin-like protein 4 (ANGPTL4) levels. It is critical that the relationship of this protein with FTO gene function is examined in future studies, especially in relation to the benefits of bariatric surgery.

Our work has some limitations. First, we did not measure tissue FTO levels in the study population. We did not determine tissue levels because their determination in the nervous system would be complex in these participants and probably does not clarify the mechanisms of molecular action of their action. Second, other unknown nongenetic factors could modulate the relationships in our design (exercise, hormone status, socioeconomical status, vitamin D levels, epigenetic factors, etc.). Third, the lack of a dietary assessment in the participants with obesity might be a bias. Fourth, we have not determined the levels of vitamin D or ANGPTL4, which are new factors involved in the response to weight loss after bariatric surgery and their relationship with SNPs of FTO gene. Fifth, the effect detected on visceral fat in our study, only with WC, may have important biases. Finally, the absence of a control group without bariatric surgery also might be a bias.

## Conclusion

In summary, our data suggest that non-A allele carriers of the genetic variant (rs9939609) of FTO gene showed a better improvement of anthropometric and insulin levels after robotic SG. Both improvements are associated with a lower percentage of participants with diabetes at 12 months. These results may serve to motivate future attempts to investigate predictive genes and optimal treatment protocols for weight reduction with bariatric surgery tailored to personalized medicine.

## Disclosures

*The authors have no commercial associations that might be a conflict of interest in relation to this article.*

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Editorial comment

# Comment on: A single FTO gene variant rs9939609 is associated with weight change and insulin resistance improvement in response to a robotic sleeve gastrectomy in subjects with severe obesity

Obesity is a multifactorial disease and its etiology encompasses environmental, molecular, genetic, and epigenetic components [1]. Therapeutic strategies to promote weight management include lifestyle modification (diet and physical exercise), pharmacotherapy, and surgical procedures. In this context, bariatric and metabolic surgery promotes substantial and long-term weight loss and improvement of related diseases such as hypertension, diabetes, and dyslipidemia [2]. However, despite the beneficial effect of surgical procedures, some studies reported interindividual variation and different patterns of response among individuals with obesity. Depending on the phenotypic response to treatment, patients may be classified as normo-responders, hypo-responders, or hyper-responders [3]. In line with this, single nucleotide polymorphisms (SNPs) have been associated with weight loss after different types of bariatric procedures [3]. The obesity-associated SNPs are also related to weight changes after obesity management and are mainly involved in metabolic pathways related to energy intake, thermogenesis, adipogenesis, and lipid metabolism [4]. To date, fat mass and obesity (FTO) locus is the gene most strongly related to obesity phenotype (body weight, body mass