ABSTRACT:

Background: Emerging evidence suggests that the FK506 binding protein 51 (FKBP5/FKBP51), encoded by the *FKBP5* gene, influences weight and metabolic regulation. The T-allele of a functional polymorphism in *FKBP5* (rs1360780), has been associated with the expression of FKBP51 and weight loss after bariatric surgery.

Objective: To examine the role of the *FKBP5* rs1360780 polymorphism in relation to age, sex and type of surgery in weight loss after bariatric surgery in patients with severe obesity.

Setting: University Hospital in Spain

Methods: A cohort of 151 obese patients submitted to Roux-en-Y Gastric Bypass (RYGB) (62.3%) and Sleeve Gastrectomy (SG) (37.7%) were followed-up during 24-months (t_{24m}; loss to follow-up: 0%). During the post-operative period body mass index (BMI), percentage of excess and total weight loss (%EWL and %TWL) were evaluated.

Results: The BMI analysis showed an effect of the interaction *FKBP5* genotype by sex (p = 0.0004) and a tendency to the interaction genotype by surgery (p-value = 0.048), so that men carrying the T-allele had higher BMI at t_{24m} than those without the T-allele, and T-allele carriers that underwent SG had higher BMI at t_{24m} than the non-carriers. Additionally, we found an interaction between *FKBP5* and age for the %EWL and BMI (p-value = 0.0005 and p-value = 1.5 e-7, respectively), whereby individuals older than 48 years with the T-allele displayed significant differences for the analyzed variables at t_{24m} compared with the homozygotes for the alternate C-allele showing lower weight loss.

Conclusion: *FKBP5* rs1360780 genotype has specific effects on weight loss outcomes after bariatric surgery depending on sex, age and type of surgery, suggesting worse results in older males carrying the T allele who have undergone SG.

Keywords: obesity, bariatric surgery, weight loss outcomes, BMI, follow-up, gender, age, *FKBP5* gene, rs1360780.

INTRODUCTION

Bariatric surgery is currently the most effective long-term treatment for severely obese patients. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) are the most common bariatric procedures. However, there is considerable inter-individual variation in surgery outcome and particularly in relation to weight loss, clinical benefits, and in reductions in morbidity and mortality [1]. Given the costs and dangers surrounding bariatric surgery, there is an urgent need to identify predictors of response, i.e. which individuals are most likely to respond well to the intervention, and those who may respond better to alternative treatments.

Studies to date have suggested a variety of complex factors as moderating weight loss outcomes, including clinical, psychological, demographic, and biological factors. Specifically, previous studies have revealed age, sex, pre-operative weight and body mass index (BMI), physical activity, T2D or other obesity associated disorders (e.g.: anxiety or depression) as moderators of bariatric surgery outcomes [1,2].

Regarding age, some studies have revealed that RYGB is less effective at inducing weight loss in those over the age of 45 [3,4], whilst others have revealed no differences [5]. In relation to sex, it is well known that men and women differ in terms of fat storage and metabolism [6] and studies indicate that bariatric surgery may be more effective in men than women [7,8].

About 3-4% of the cases of obesity are monogenic with early onset, abnormal feeding behavior and neuroendocrine disorders, mainly caused by mutations in genes implicated in the Leptin/melanocortin pathway [9]. However, most of the cases arise from the interplay of many genes of minor effect and environmental factors.

Biological factors should be also taken into account when studying weight loss outcomes after surgery [10]. Hatoum and colleagues (2011) described a high concordance after RYGB within pairs of first-degree relatives, compared to cohabitating or unrelated individuals, suggesting weight loss response to surgery is also heritable [11]. In this regard, the study of candidate genes on the outcomes of bariatric surgery suggests that specific variants in genes such as the *fat mass and obesity-associated* gene (*FTO*), *insulin induced gene 2* (*INSIG2*), *melanocortin 4 receptor* gene (*MC4R*) and *proprotein convertase subtilisin/kexin type 1* gene (*PCSK1*), play a role in the poorer weight loss outcomes after surgery [12].

A recent study investigated the association of the *FK506 binding protein-5* gene (*FKBP5*), which encodes for the protein FKBP51 in the hypothalamic-pituitary-adrenal (HPA) axis, and the outcome after bariatric surgery in obese patients [13]. FKBP5 is well recognized for its ability to be induced by exposure to psychological stress, inhibiting the glucocorticoid receptor (GR) activity and ultimately leading to the reduction of the HPA axis activation [14,15]. Animal models demonstrated that *FKBP51* knockout mouse embryonic fibroblasts showed reduced lipid accumulation and expression of adipogenic genes compared to wild-type animals [16]. Additionally, higher levels of hypothalamic FKBP5 expression were related to increased body weight gain [17].

Interestingly, the T allele of a functional polymorphism (rs1360780) in the *FKBP5* gene is associated with a greater induction of the *FKBP5* gene [18]. Hartmann and colleagues (2016) found in a sample of 42 obese patients that carriers of the T allele (i.e.: individuals with TT and CT genotype) had nearly 20% less excess weight loss and 10% less total weight loss compared with homozygotes of the alternate C allele over the 26-week follow-up period after surgery [13]. Consequently, these findings

provide evidence that a functional variant of the *FKBP5* gene moderates the clinical response of severe obesity to bariatric surgery. The aim of our study was to examine the role of *FKBP5* polymorphism (rs1360780) in a cohort of 151 obese patients submitted to bariatric surgery (RYGB or SG) and followed-up during 24-months. In addition to the genetic effect, we also aimed to explore the effect of other variables such as type of surgery, sex and age that could have an impact on the outcome of surgery on weight loss.

MATERIAL AND METHODS

Participants

The study recruited 151 morbidly obese patients awaiting for bariatric surgery in the Hospital Universitari Parc Taulí, Sabadell, Spain. All the patients were 18 years or older, with BMI ≥ 35 kg/m^2, and underwent either Roux-en-Y- gastric bypass (RYGB) or Sleeve gastrectomy (SG) bariatric surgery between 2008 and 2015. All subjects fulfilled the eligibility criteria for bariatric surgery and the type of technique was chosen according to European guidelines [19].

This cohort was evaluated pre-, peri and postoperatively by a multidisciplinary team (endocrinologists, clinical nurses, surgeons, dietitians and psychiatrists) in consecutive visits over a 2-year timespan according to the local protocol. This period was divided as follows: t_0: before surgery; t_{1m}: 1 month after surgery; t_{3m}: 3 months after surgery; t_{6m}: 6 months after surgery; t_{12m}: 12 months after surgery and t_{24m}: 24 months after surgery.

Anthropometric assessment

Measurements of weight, height and waist circumference were obtained from physical examination along the evaluated period.

To report weight loss we calculated for all the assessments (from t_0 to t_{24m}): i) Body Mass Index (BMI), ii) percentage of excess weight loss (%EWL), and iii) percentage of total weight loss (% TWL). The 151 patients completed all the assessments.

BMI was calculated in Kg/m^2 according to the formula *:* weight (Kg) / height (m^2). The %EWL was calculated as [(weight loss / excess weight) x 100], where excess weight was taken as the weight in kilograms above the weight corresponding to the BMI for 24.9 kg/m^2. The %TWL was calculated as [(weight loss / weight at t_0) x 100].

Ethics

All subjects were informed about our study and invited to participate in this prospective cohort. Informed consent was obtained from all participants included in the study. The Institutional Ethics Committee of Hospital Universitari Parc Taulí approved the protocol, and all investigations complied with the Helsinki Declaration.

Laboratory analysis:

Blood samples were collected from all patients and genomic DNA from blood was extracted using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotyping of the *FKBP5* polymorphism (rs1360780) was performed using TaqMan allelic discrimination assay from Life Technologies (Thermo Fisher Scientific, California, USA). The assay was run in a 384-well plate on the ABI PRISM 7900HT Fast Real-Time PCR System (Applied Biosystems, California, USA) using standard conditions. The final volume of each well was 5 µl, which contained 5 ng of genomic DNA, 2.5 µl of TaqMan Master Mix and 0.125 of 40x genotyping assay. SDS v.2.4 software was used for the data analysis of the genotypes. Testing for validity and accuracy of genotyping, we retested a 20% random sample. In all cases, genotypes were reproducible.

Statistical analysis

Variables are reported as mean ± SDs or percentages. The baseline characteristics of the sample were analyzed using the Pearson Chi-Square test for contingency tables or the non-parametric Mann-Whitney U test for continuous variables. Hardy-Weinberg equilibrium (HWE) for genotype frequencies in patients was calculated using chi-square tests (OEGE; Rodriguez, Gaunt, & Day, 2009). As the present study consisted in a prospective analysis of the variation of excess weight loss (%EWL), total weight loss (%TWL) and body mass index (BMI) changes in a follow-up of 24 months after bariatric surgery, generalized estimating equation models (GEE) were considered. The factors used in the models were time, *FKBP5* genotype, surgical technique, age, sex, T2D and the interactions *time x surgery, FKBP5 genotype x sex, FKBP5 genotype x surgery, FKBP5 genotype x age,* and *sex x surgery x FKBP5 genotype.* Furthermore, the effect of the age was also studied considering EGG models with age as dichotomous variable using the value of the median to determine the two groups of age. The comparison between the four groups of patients determined by their genotype and the age groups, was performed using the Kruskal-Wallis test followed by Benjamini & Hochberg *post hoc* test. All analyses were performed using RStudio 1.1.463 and p-values less than 0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics of the sample

The sample consisted of 151 Caucasian individuals, mainly women (78.1%). The participants were aged between 21-61 years (mean age = 46.33, SD = 10.01). Males and females differed slightly in terms of age (mean = 43.1, SD = 11.2 and, mean = 47.2, SD = 9.5, respectively, p-value = 0.04). All of them underwent either RYGB (n

= 94, 62.3%) or SG (n = 57, 37.7%), no differences on BMI were found between surgeries at baseline (Mean = 44.19, SD = 6.01 and Mean = 46.02, SD = 9.05, respectively, p-value = 0.607).

The *FKBP5* genotype frequencies were: 67 CC (44.4 %); 69 CT (45.7%) and 15 TT (9.9%). No deviations from HWE in the examined SNP was detected (χ^2 = 0.21, p-value = 0.65).These frequencies were similar to those found in European populations in 1000 Genomes (CC = 45%, CT = 44%, TT = 10%). Based on previous reports, we assumed a dominant model and due to the low frequency of T-allele, *FKBP5* genotype was converted into a binary variable for the analyses: CC genotype and T carriers (i.e.: genotypes CT and TT). No differences were observed between genotypic frequencies (CC or T carriers), sex, surgery, age, weight, BMI, excess weight and excess of BMI at baseline (Table 1).

In Table 2 we report information about waist circumference, metabolic variables and co-morbidities in ~~the~~ patients in ~~the~~ pre (t0) and postoperative (t24) period according to the genotype.

Longitudinal assessment

Main Effects: The study included the three variables of interest: %EWL, %TWL and BMI assessed longitudinally. The effect of time, age, sex, surgery, T2D and *FKBP5* genotype on the variables (%EWL, %TWL and BMI) was explored using a generalized equation model including the above mentioned variables and the interactions time x surgery, *FKBP5* genotype x sex, *FKBP5* genotype x surgery, *FKBP5* genotype x age, and sex x surgery x *FKBP5* genotype.

The test of model effects reported an effect of *time* on the variation of all the variables with a p-value < 2e-16 for %EWL, % TWL and BMI). The effect of surgery

and T2D was only significant on BMI (p-value = 0.01 and 0.003, respectively). Additionally, a strong effect of *age* was found for the %EWL (p-value = 6.2e-09) and %TWL (p-value = 4.5e-14) but not for BMI.

Interaction Effects: For %EWL and %TWL we found a statistically significant interaction between *time and surgery* (p-value = 0.00089 and 0.00083, respectively). Thus, patients submitted to a Sleeve Gastrectomy lost 8.58% and 4.01% less %EWL and %TWL respectively at t_{24m} than patients that underwent RYGB (p-value = 0.020 and 0.006, respectively) (Figure 1A and 1B). Furthermore, men with SG lost 4.52% less TWL than those with RYGB at t_{12m} but not at t_{24m} (p-value = 0.034) (Figure 1E).

Regarding the interaction between *FKBP5* and sex, it was only significant for BMI (p-value = 0.0004). These results pointed out that men carrying the T allele had higher BMI at t_{24m} than those non-carriers (Figure 2F). Additionally, a marginally significant effect of the interaction FKBP5 and surgery was found on BMI (p-value = 0.048)

The interaction between *age* and FKBP5 genotype was significant for BMI and %EWL (p-value = 6.8e-07 and p-value = 0.0007, respectively), and the interaction between sex, *FKBP5* and surgery for the three variables %EWL, %TWL and BMI was significant (p-values = 9.2e-05, 8.4e-05 and 0.0001, respectively). These results show significant differences in the outcome after surgery depending on *FKBP5* genotype, sex of the individuals and surgery, pointing out worst results in males carrying the T allele submitted to SG.

Given the strong effect of age reported before, we tried to study the influence of this factor in more depth. To this aim as the median of age was 48 years, we generated two groups: i) individuals under 48 years (n = 74) and ii) individuals with age equal or higher than 48 years (n = 77). Using the generalized estimating equation model, we

explored the effect of age using this new binary variable (i.e.: AgeD) on the %EWL, %TWL and BMI. The model included: time, surgery, *FKBP5* genotype, sex, AgeD and the interaction *FKBP5* x AgeD. According with the results previously reported, the analysis showed a strong effect of AgeD on the variables %EWL and %TWL for the total sample (p-value = 3.54e-08 and 3.61e-11 respectively). Similar results were found in men (p-value = 7.97e-05 for %EWL, and p-value = 4.24e-05 for %TWL) and women (p-value = 0.0002 for %EWL, and p-value = 4.03e-08 for %TWL).

Furthermore, we found a significant interaction *FKBP5* x AgeD on the %EWL and BMI for the total sample (p-value = 0.0005 and p-value = 1.48e-07, respectively) and by sex, in men (p-value = 0.0002 and p-value = 8.39e-07, respectively) and women (p-value = 0.018 and p-value = 0.0004, respectively).

In order to better understand the interaction between FKBP5 genotype and AgeD after two years of the surgery (t_{24m}), we divided patients in four groups according to their genotype and age group: Group 1 with individuals with age under 48 and CC genotype (n = 30), Group 2 with individuals with age under 48 and CT or TT genotype (i.e.: T carriers, n = 44), Group 3 with individuals older than 48 years and CC genotype (n = 37) and Group 4 with individuals older than 48 years and T carriers (n = 40). In Table 3 we report mean and SD for the analyzed variables (%EWL, %TWL and BMI) for each group at 24 months (t_{24m}). For the three outcomes patients of Group 4 (≥ 48 and T carriers) displayed the worse scores. These differences were statistically significant for the three variables analyzed (Table 3).

Post-hoc analysis showed for %EWL significant differences between groups 1 and 3 (p-value = 0.010) and groups 1 and 4 (p-value = 0.021). For the %TWL the differences were found between groups 1 and 3, groups 1 and 4, and groups 2 and 4

(p-value = 0.039, 0.016 and 0.016, respectively). Finally, for BMI differences were found between groups 1 and 3 (p-value = 0.027) (Figure 3).

DISCUSSION

Our study aimed to explore the role of different factors including type of surgery, age, sex, and *FKBP5* genotype on weight loss outcomes following bariatric surgery over 24 months in a sample of 151 patients with severe obesity.

The main finding was that males over 48 years old, who were T-allele carriers of *FKBP5* polymorphism (rs1360780) and had undergone sleeve gastrectomy (SG), displayed the worst weight loss outcome at 24 months after surgery.

As expected, our results seem to indicate an effect of the type of surgery on weight loss during the post-operative period. In this regard, individuals submitted to Roux-en-Y Gastric Bypass (RYGB) seem to have better outcomes at t_{24} compared with those individuals submitted to SG. These two bariatric procedures are the most commonly used in severe obese patients and are effective at promoting weight loss. Several studies have compared whether the results of these two techniques are equivalent. A recent meta-analysis pointed out that both procedures result in similar % of excess weight loss (%EWL) and body mass index (BMI) reduction levels at 6 and 12 months. However, % EWL and BMI reduction were significantly greater in the RYGB group 24 months after surgery [21]. These findings seem to support the trend observed in our cohort.

We studied the effect of age both as a continuous and dichotomous variable. In both cases we found a strong effect of age on the analyzed variables, whereby individuals older than 48 years showed less weight loss after surgery. The implications of age on weight loss after surgery are still controversial, with some studies showing no

significant difference [22,23] and others demonstrating less excess weight loss among patients older than 60 years in comparison with younger subjects [24,25]. A later publication where the authors applied a lower age limit, as we did in our study, reported differences in the percentage of excess BMI loss 12 months after surgery, whereby younger patients responded better [4]. One plausible explanation for this effect could be the impaired metabolic capacity and decrease in energy requirements in the elderly compared to young individuals as well as hormonal factors, especially in women. Only one previous study has reported a sex-specific effect of age on weight loss after bariatric surgery. In this study, Ochner and colleagues found that weight loss in the post-operative period was significantly reduced in women aged 55-65 years compared to women aged 20-45, but not in men [26]. In addition to metabolic rate and physical activity, the authors suggested that the menopausal status of these women could explain these findings. However, surprisingly, the effect of menopausal age on weight loss appeared to depend on surgery type since significant effects were detected in women undergoing gastric banding, but not RYGB. Unfortunately, we did not report menopausal status in our cohort.

Thus, pooling all these studies together, available data so far suggest that different types of bariatric surgery may have different effects on weight loss depending on sex and age, shedding some light on the etiological complexity of obesity.

Our data on the variability of the *FKBP5* gene and its association with weight loss after bariatric surgery did not show a direct association between genotype and the analyzed outcomes. Only one previous study by Hartman and colleagues (2006) have explored this hypothesis. They reported that T allele carriers at rs1360780 had nearly 20% less EWL and 10% less TWL compared to the CC individuals after a 26-

week follow-up in a cohort of forty-two obese patients [13]. The study by Hartman and colleagues is similar to ours regarding the analyzed polymorphism, age range and mean, design, follow-up of weight loss and analyzed variables (i.e. BMI, %EWL and %TWL). However, our study has several strengths. It includes a considerably bigger sample (n=151 patients, loss of follow-up was 0%), with a higher proportion of males. On the other hand, in Hartman´s study all patients were submitted to RYGB whereas in our study 37.7% underwent SG, allowing us to compare the effectiveness of both surgical methods. With an expanded sample size and considering age and type of surgery followed by the patients, we pointed out how these variables were not independent to explain the complexity of weight loss after bariatric surgery. In this regard, males carrying the T allele of *FKBP5* rs1360780 and submitted to SG, displayed worse scores for %EWL, % TWL and BMI. Also, bariatric surgery was less effective on older individuals (≥ 48 years). To the best of our knowledge, this is the first study exploring this polymorphism and its interaction with determinant factors associated with weight loss.

FKBP5 is well known for its important role as a molecular co-chaperone that inhibits glucocorticoid receptors activity, and consequently suppresses stress response [14,15]. Glucocorticoids have also systemic metabolic effects beyond the central nervous system, in organs such as skeletal muscle and adipose tissue [27]. *FKBP5* is expressed in peripheral and central tissues with its highest expression in adipose and skeletal muscle [28]. Specifically, the functional variant of the gene analyzed in the present study (rs1360780) has been associated with a higher levels of the FKBP5 protein and a prolonged cortisol response to stress measured by reduced cortisol suppression after different tests [29–31]. Unfortunately, we could not measure cortisol levels in our cohort, which is a limitation of the present study.

Given the polygenic nature of obesity, cumulative minor effects of different genes expressed in metabolic active tissues, either regulating *FKBP5* or other related pathways, could be implicated in the observed weight loss [32]. In our study, we have only analyzed a genetic variant in the *FKBP5* gene. However, weight loss after surgery can be attributed not only to the variability of this gene but also to other factors that could contribute to the outcome.. One interesting strategy in future genetic studies should be to estimate polygenic risk scores based on biologically meaningful gene sets, which can represent functional pathways associated to weight loss, including FKBP5 gene.

Additionally, other biological factors such as age, sex and hormones play an important role in both phenotype and response after the surgery procedure. On the other hand, environmental factors such as perceived stress, which tends to increase in obese patients, should be considered a key variable in the phenotype of obesity and the study of the weight loss after bariatric surgery [33].

The findings of this study have to be taken in light of some limitations. We did not measure cortisol levels that would be interesting to correlate with genotypes. As we only evaluate a single polymorphism we can not discard the effect of other genetic markers given the polygenic nature of obesity. Finally, the present study performed an exhaustive clinical assessment to discard cases of monogenic obesity. However, a genetic screening for the mutations in genes of the Leptin/Melanocortin pathway associated with these early and severe forms of obesity was not performed.

Future longitudinal studies with larger sample sizes, as well as a longer follow-up period, might shed some light on the role of *FKBP5* variability and its interaction with variables such as surgery, sex and stress. It might be worth using two well-

differentiated samples in terms of age (i.e.: young and old sample) like in previous studies [26]. The identification of potential predictors of success after bariatric surgery will be relevant in the near future for improving patients' quality of life.

Conclusions

In summary, in our longitudinal study comparing two different bariatric surgery procedures (RYGB and SG) and considering the effect of *FKBP5* variability, age and sex on the surgical outcome, we report better results for RYGB in men with the CC genotype. Our results show how age, sex and genotype have a different impact on weight loss depending on the surgical technique used. These findings provide a basis for further studies, which could include as procedure selection criteria not only BMI but also sex, age or different specific genetic variants that could have a significant impact on the surgery outcome.

Disclosures

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

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References

[1] Sun X, Li P, Yang X, Li W, Qiu X, Zhu S. From genetics and epigenetics to the future of precision treatment for obesity. Gastroenterol Rep 2017;5:266–70. doi:10.1093/gastro/gox033.

[2] Shen N, Caixàs A, Ahlers M, Patel K, Gao Z, Dutia R, et al. Longitudinal changes of microbiome composition and microbial metabolomics after surgical weight loss in individuals with obesity. Surg Obes Relat Dis 2019;15:1367–73. doi:10.1016/j.soard.2019.05.038.

[3] Scozzari G, Passera R, Benvenga R, Toppino M, Morino M. Age as a Long-Term Prognostic Factor in Bariatric Surgery. Ann Surg 2012;256:724–9. doi:10.1097/SLA.0b013e3182734113.

[4] Contreras JE, Santander C, Court I, Bravo J. Correlation Between Age and Weight Loss after Bariatric Surgery. Obes Surg 2013;23:1286–9. doi:10.1007/s11695-013-0905-3.

[5] Singhal R, Kitchen M, Bridgwater S, Super P. Age ≥ 50 does not influence outcome in laparoscopic gastric banding. Obes Surg 2009;19:418–21. doi:10.1007/s11695-008-9617-5.

[6] Fitzgerald SJ, Janorkar AV, Barnes A, Maranon RO. A new approach to study the sex differences in adipose tissue. J Biomed Sci 2018;25:89. doi:10.1186/s12929-018-0488-3.

[7] Andersen JR, Aadland E, Nilsen RM, Våge V. Predictors of weight loss are

different in men and women after sleeve gastrectomy. Obes Surg 2014;24:594–8. doi:10.1007/s11695-013-1124-7.

[8] Perrone F, Bianciardi E, Benavoli D, Tognoni V, Niolu C, Siracusano A, et al. Gender Influence on Long-Term Weight Loss and Comorbidities After Laparoscopic Sleeve Gastrectomy and Roux-en-Y Gastric Bypass: a Prospective Study With a 5-Year Follow-up. Obes Surg 2016;26:276–81. doi:10.1007/s11695-015-1746-z.

[9] Baxter J, Armijo PR, Flores L, Krause C, Samreen S, Tanner T, et al. Updates on Monogenic Obesity in a Multifactorial Disease 2019.

[10] Hunt SC, Hasstedt SJ, Xin Y, Dalley BK, Milash BA, Yakobson E, et al. Polymorphisms in the NPY2R Gene Show Significant Associations With BMI That Are Additive to FTO, MC4R, and NPFFR2 Gene Effects. Obesity 2011;19:2241–7. doi:10.1038/oby.2011.239.

[11] Hatoum IJ, Greenawalt DM, Cotsapas C, Reitman ML, Daly MJ, Kaplan LM. Heritability of the Weight Loss Response to Gastric Bypass Surgery. J Clin Endocrinol Metab 2011;96:E1630–3. doi:10.1210/jc.2011-1130.

[12] Still CD, Wood GC, Chu X, Erdman R, Manney CH, Benotti PN, et al. High allelic burden of four obesity SNPs is associated with poorer weight loss outcomes following gastric bypass surgery. Obesity (Silver Spring) 2011;19:1676–83. doi:10.1038/oby.2011.3.

[13] Hartmann IB, Fries GR, Bücker J, Scotton E, von Diemen L, Kauer-Sant'Anna M. The FKBP5 polymorphism rs1360780 is associated with lower weight loss after bariatric surgery: 26 months of follow-up. Surg Obes Relat Dis 2016;12:1554–60. doi:10.1016/j.soard.2016.04.016.

[14] Binder EB. The role of FKBP5, a co-chaperone of the glucocorticoid receptor in the pathogenesis and therapy of affective and anxiety disorders. Psychoneuroendocrinology 2009;34 Suppl 1:S186-95. doi:10.1016/j.psyneuen.2009.05.021.

[15] Zannas AS, Balsevich G, Gassen NC. The emerging role of FKBP5 in the regulation of metabolism and body weight. Surg Obes Relat Dis 2016;12:1560–1. doi:10.1016/j.soard.2016.05.016.

[16] Stechschulte LA, Hinds TD, Khuder SS, Shou W, Najjar SM, Sanchez ER. FKBP51 Controls Cellular Adipogenesis through p38 Kinase-Mediated Phosphorylation of GRα and PPARγ. Mol Endocrinol 2014;28:1265–75. doi:10.1210/me.2014-1022.

[17] Balsevich G, Uribe A, Wagner K V., Hartmann J, Santarelli S, Labermaier C, et al. Interplay between diet-induced obesity and chronic stress in mice: Potential role of FKBP51. J Endocrinol 2014;222:15–26. doi:10.1530/JOE-14-0129.

[18] Zannas AS, Wiechmann T, Gassen NC, Binder EB. Gene–Stress–Epigenetic Regulation of FKBP5: Clinical and Translational Implications. Neuropsychopharmacology 2016;41:261–74. doi:10.1038/npp.2015.235.

[19] Fried M, Yumuk V, Oppert JM, Scopinaro N, Torres A, Weiner R, et al. [Interdisciplinary European guidelines on metabolic and bariatric surgery]. Rozhl Chir 2014;93:366–78.

[20] Rodriguez S, Gaunt TR, Day IN. Hardy-Weinberg Equilibrium Testing of Biological Ascertainment for Mendelian Randomization Studies. Am J Epidemiol 2009;169:505–14. doi:10.1093/aje/kwn359.

[21] Magouliotis DE, Tasiopoulou VS, Svokos AA, Svokos KA, Sioka E, Zacharoulis D. Roux-En-Y Gastric Bypass versus Sleeve Gastrectomy as Revisional Procedure after Adjustable Gastric Band: a Systematic Review and Meta-Analysis. Obes Surg 2017;27:1365–73. doi:10.1007/s11695-017-2644-3.

[22] Wool D, Bellatorre N, Wren S, Eisenberg D. Male Patients Above Age 60 have as Good Outcomes as Male Patients 50–59 Years Old at 1-Year Follow-up After Bariatric Surgery. Obes Surg 2009;19:18–21. doi:10.1007/s11695-008-9734-1.

[23] Sosa JL, Pombo H, Pallavicini H, Ruiz-Rodriguez M. Laparoscopic gastric bypass beyond age 60. Obes Surg 2004;14:1398–401. doi:10.1381/0960892042583833.

[24] Sugerman HJ, DeMaria EJ, Kellum JM, Sugerman EL, Meador JG, Wolfe LG. Effects of Bariatric Surgery in Older Patients. Ann Surg 2004;240:243–7. doi:10.1097/01.sla.0000133361.68436.da.

[25] St Peter SD, Craft RO, Tiede JL, Swain JM. Impact of Advanced Age on Weight Loss and Health Benefits After Laparoscopic Gastric Bypass. Arch Surg 2005;140:165. doi:10.1001/archsurg.140.2.165.

[26] Ochner CN, Teixeira J, Geary N, Asarian L. Greater Short-Term Weight Loss in Women 20–45 versus 55–65 Years of Age Following Bariatric Surgery. Obes Surg 2013;23:1650–4. doi:10.1007/s11695-013-0984-1.

[27] Henneicke H, Gasparini SJ, Brennan-Speranza TC, Zhou H, Seibel MJ. Glucocorticoids and bone: local effects and systemic implications. Trends Endocrinol Metab 2014;25:197–211. doi:10.1016/j.tem.2013.12.006.

[28] Sidibeh CO, Pereira MJ, Abalo XM, J. Boersma G, Skrtic S, Lundkvist P, et al. FKBP5 expression in human adipose tissue: potential role in glucose and lipid metabolism, adipogenesis and type 2 diabetes. Endocrine 2018;62:116–28. doi:10.1007/s12020-018-1674-5.

[29] Ising M, Depping A-M, Siebertz A, Lucae S, Unschuld PG, Kloiber S, et al. Polymorphisms in the FKBP5 gene region modulate recovery from psychosocial stress in healthy controls. Eur J Neurosci 2008;28:389–98. doi:10.1111/j.1460-9568.2008.06332.x.

[30] Ising M, Maccarrone G, Brückl T, Scheuer S, Hennings J, Holsboer F, et al. FKBP5 gene expression predicts antidepressant treatment outcome in depression. Int J Mol Sci 2019;20:1–12. doi:10.3390/ijms20030485.

[31] Ferrer A, Costas J, Labad J, Salvat-Pujol N, Segalàs C, Urretavizcaya M, et al. FKBP5 polymorphisms and hypothalamic-pituitary-adrenal axis negative feedback in major depression and obsessive-compulsive disorder. J Psychiatr Res 2018;104:227–34. doi:10.1016/j.jpsychires.2018.08.003.

[32] Locke AE, Kahali B, Berndt SI, Justice AE, Pers TH, Day FR, et al. Genetic studies of body mass index yield new insights for obesity biology. Nature 2015;518:197–206. doi:10.1038/nature14177.

[33] Abraham SB, Rubino D, Sinaii N, Ramsey S, Nieman LK. Cortisol, obesity, and the metabolic syndrome: A cross-sectional study of obese subjects and review of the literature. Obesity 2013;21:E105–17. doi:10.1002/oby.20083.

Figure 1. Evolution of the three analyzed variables (%EWL, %TWL and BMI) over time and according to surgery (RYGB *vs* SG) in the total sample and by sex.

Figure 2. Evolution of the three analyzed variables (%EWL, %TWL and BMI) over time and according to genotype (CC or T carriers) in the total sample and by sex.

Figure 3. Evolution of the three analyzed variables (%EWL, %TWL and BMI) over time and according to age group (< 48 and ≥ 48) and genotype (CC and T carriers). The groups correspond to Group 1: < 48 + CC; Group 2: < 48 + T carriers; Group 3: ≥ 48 + CC and Group 4: ≥ 48 + T carriers.

Table 2. Anthropometric and metabolic variables and comorbidities of the sample according to *FKBP5* genotype in the Pre (t0) and post-operative (t24) period.

	Pre-operative (t0)		Post-operative (t24)	
Variables	CC (n = 67)	CT/TT (n = 84)	CC (n = 67)	CT/TT (n = 84)
WC (cm)	132.5 (14.53)	132.71 (13.48)	102.59 (13.14)	102.31 (10.98)
FPG (mg/dL)	104.66 (31.82)	113.30 (39.15)	88.44 (27.19)	88.76 (25.23)
Insulin (µUI/mL)	21.41 (18.46)	22.87 (16.03)	6.63 (3.46)	7.45 (3.13)
HbA1c (%)	6.16 (1.05)	6.29 (1.27)	7.11 (12.76)	5.53 (0.76)
Comorbidities, n (%)				
HTA				
No- HTA	26 (39.4%)	28 (33.7%)	45 (71.4%)	58 (71.6%)
Yes- HTA	40 (60.4%)	55 (66.3%)	18 (28.6%)	23 (28.4%)
DLP				
No-DLP	39 (59.1%)	41 (49.4%)	53 (84.1%)	68 (84%)
Yes-DLP	27 (40.9%)	42 (50.6%)	10 (15.9%)	13 (16%)
T2D				
No-T2D	49 (73.1%)	52 (61.9%)	63 (94%)	77 (91.7%)
Yes-T2D	18 (26.9%)	32 (38.1%)	4 (6%)	7 (8.3%)

WC: Waist Circumference; FPG : Fasting Plasma Glucose; Insulin; HbA1c: Hemoglobin A1c; HTA: Hypertension; DLP: dyslipoproteinemia; T2D: type 2 diabetes.