ESR1 and FTO genetic variants: impact on body weight reduction following bariatric surgery

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Received: 20 June 2023
Revised: 10 July 2023
Accepted: 13 July 2023
Published: 6 October 2023

The Egyptian Journal of Surgery 2023, 42:676–684

Background
Variation in reduction of body weight after bariatric surgery has been observed. Genetics may have a role in the varying outcomes among obese patients. Aim of this research work was to examine the effect of genetic variants within the Fat Mass and Obesity-Related gene (FTO) (rs9939609) and Estrogen Receptor Alpha gene (ESR1) (rs712221) on body weight reduction and blood glucose control in obese individuals, six months following laparoscopic sleeve gastrectomy (LSG).

Patients and methods
Ninety obese individuals with BMI $\geq$35 kg/m^2 undergoing LSG were recruited and followed up after 6 months. Genotyping for FTO gene (rs9939609) and ESR1 gene (rs712221) variants was done using Real-Time PCR (TaqMan probes).

Results
FTO (rs9939609) genotype AA was found to be associated with more obesity before operation (*P* value 0.005) and lead to successful surgery and weight loss (*P* value 0.023, OR 0.080, 95%CI 0.009–0.702). Patients with risk allele A had more weight loss and BMI reduction after operation compared to patients with non-risk allele T (*P* value $<$0.001). ESR1 (rs712221) genotype TT was found to be associated with more reduction of body weight six months after surgery when compared to genotypes TA and AA (*P* value 0.001). Carriers of the allele T of the ESR1 (rs712221) had more reduction of HbA1c after operation compared to patients with allele A (*P* value $<$0.001).

Conclusion
The single nucleotide variants; rs9939609 of FTO and rs712221 of ESR1 may be considered potential predictors of body weight reduction and/or blood sugar control following bariatric surgery for obese individuals.

Keywords:
Fat Mass and Obesity-Related gene, Estrogen Receptor Alpha gene, laparoscopic sleeve gastrectomy

Egyptian J Surgery 42:676–684

1110-1121

Abbreviations: BMI: Body mass index **ESR1:** Estrogen Receptor Alpha gene, **EWL:** Estimated weight loss, **FTO:** Fat Mass and Obesity-Related gene, **LMGB:** Laparoscopic mini gastric bypass, **LSG:** Laparoscopic sleeve gastrectomy, **MAC:** Mid-arm circumference, **MAMC:** Mid-arm muscle circumference, **PCR:** Polymerase chain reaction, **SPSS:** Statistical Package for the Social Sciences, **SNVs:** Single nucleotide variants, **TSF:** Triceps skin fold.

Declarations: Ethical approval and consent to participate: The study protocol was approved by the Research Ethics Committee (Code: MS-207-2019) and all participants gave informed consents.

Availability of data and material: the data that support the findings of that study are available upon reasonable request from the corresponding author.

Funding: this study was funded by Cairo University research fund.

Authors Contribution: **Tarek Ramzy**: Study design conception, data analysis, supervision of practical work and critical revision of manuscript. **Susan El Zayat**: Sample collection, practical work, data analysis, literature search and manuscript revision. **Marwa Sheta**: Study design conception, data analysis, supervision of practical work and critical revision of manuscript. **Mohamed D Sarhan**: Surgical procedures, critical revision of manuscript. **Tamer Elgaabary**: Surgical Procedure, critical revision of manuscript. **Reham Zeyada (corresponding Author)**: Drafting manuscript, data review, literature search and revision of manuscript.

Introduction

Obesity is an important risk factor for a myriad of chronic ailments and represents a significant economic burden, not to mention health concerns. The basic underlying etiology of obesity is multifactorial and is an interplay between lifestyle, environmental, and genetic elements. It is therefore crucial to decipher the interaction between these elements when designing a targeted approaches for the management or prevention of obesity [1].

Lifestyle changes remain a critical factor in the management of morbid obesity, however, when targeting significant, long term outcome, bariatric surgery is considered by the World Health Organization to be the only approach. The earliest surgical procedures were performed as early as the 1950s but were associated with high mortality rates. Later on, following numerous studies and modifications, dramatic improvements were attained in obesity co-morbidities [2]

It was however observed that outcome of bariatric surgery was not consistent among people receiving it and hence it was suggested that genetic factors may have a role in that . It was suggested that the genetic variants of certain genes if indeed proven to be involved can serve as a screening tool for physicians to help select patients that would mostly benefit from the surgery through predicting degree of body weight reduction and possibly better glycemic control [3]. The genes in that study were the Fat Mass and Obesity-Related gene (FTO) and Estrogen Receptor Alpha gene (ESRα or ESR1),

Genome-Wide Association Study (GWAS) recognized FTO gene as one of the earliest obesity-related gene [4]. Recent research work supported the notion that the single nucleotide variant (SNV) (rs9939609) of the FTO, which is the interest of this study, especially when homozygous for the A allele, is strongly associated with obesity. Actions of the FTO gene product include demethylation of N6-methyladenosine of ghrelin mRNA, this affects the total ghrelin level, and consequently increases food intake. In addition, it influences lipid and glucose metabolism through hepatic signaling pathways [5].

ESR1 gene is located on chromosome 6q25.1, its relationship to pathogenesis of obesity is not as clear as that of the FTO gene but, the ESR1 gene is involved in several metabolic pathways affecting growth, and hence it was suggested that this may correlate possibly with body weight and body mass index (BMI) [6].

Therefore, the target of this work was to detect the effect of single nucleotide variants (SNVs) within the FTO gene (rs9939609) and ESR1 gene (rs712221) on weight reduction and blood glucose control in obese patients, 6 months after laparoscopic sleeve gastrectomy.

Patients and methods

Study population

This study was performed on 90 obese patients undergoing bariatric surgery in the form of laparoscopic sleeve gastrectomy (LSG) during the period starting July 1st, 2019 till the end of September, same year. They were then followed up after 6 months.

The study protocol was approved by the Research Ethics Committee (Code: MS-207-2019) and all participants gave informed consents.

Inclusion criteria:

(1) Patient's age ranged from 20–55 years.
(2) Patient's BMI of 40 kg/m^2 or more or patients with BMI of 35 kg/m^2 or more with obesity–related health conditions, such as hypertension or type 2 diabetes mellitus.

Exclusion criteria:

Patients who have previously undergone other bariatric surgery than gastric sleeve surgery.

All subjects enrolled in the study were subjected to:

(1) **History taking:** including history of diabetes mellitus, hypertension and previous operations, and current medications.
(2) **Clinical examination:** was done before and again six months after the sleeve gastrectomy . It included Anthropometric measurments in the form of weight, height, waist circumference, triceps skin fold (TSF) and mid-arm circumference (MAC).
(3) **Calculations:**
    (a) Body mass index (BMI) and mid-arm muscle circumference (MAMC) were calculated twice (before and 6 months after the sleeve gastrectomy).
    (b) Percentage of estimated weight loss (EWL) was calculated once after 6 months of the sleeve gastrectomy.

Laboratory investigations

(1) Routine investigations: were done before and repeated again six months after the sleeve gastrectomy)
   (a) Fasting blood glucose.
   (b) Hemoglobin A1c.
   (c) Lipid profile (Total cholesterol, Total triglycerides, HDL, LDL).
(2) Genetic analysis of rs9939609 of FTO gene and rs712221 of ESR1 gene single nucleotide variant by real-time PCR. The assay was carried out using TaqMan probes and primers. Assays were carried out on Applied biosystems *Step One Real-time PCR system.

Sampling

After a 12 hours fast, eight ml of blood were drawn by aseptic venipuncture and divided into the following:

(1) Two ml in EDTA tubes for genomic DNA assay. DNA samples were stored at −80°C till genetic analysis is done, where rs9939609 of FTO and rs712221 of ESR1 were assayed for allelic discrimination using TaqMan Real-Time PCR assay.
(2) Two ml on EDTA vacutainer tube for HbA1c assay.
(3) Two ml of blood were added plain vacutainer tubes for lipid profile assay.
(4) Two ml of blood were added to Fluoride tube for measuring fasting blood glucose.

Blood chemistry analytes were assayed on Dimension*clinical chemistry system using kits supplied by Siemens.

DNA extraction

Was done using the GF-1 Blood DNA Extraction kit (Vivantis** with Catalog no. GF-BD-050)

Amplification and Real-time PCR allelic discrimination assays

- Real-Time PCR with sequence-specific primers were used
- Assays were designed using TaqMan SNV Genotyping Assays (Applied Biosystems).
- **PCR** amplification was performed on **Applied Biosystem step one Real-Time PCR System.**
- Allelic Discrimination Plate Read and Analysis:

Following PCR amplification, endpoint plate read was done on Applied Biosystems Real-Time PCR System. The Sequence Detection System (SDS) Software used the fluorescence measurements made during the plate read. Fluorescence values were plotted based on the signals from each respective well. The fluorescence signals plotted indicated which allele was in each patient sample as shown in Figs. 1 and 2.

Statistical methods

Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA) was used for data coding and entry. Mean and standard deviation were used for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Group comparisons were done using unpaired t test or analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables. For non-normally distributed quantitative variables, non-parametric Kruskal–Wallis test and Mann-Whitney test were employed. Comparisons between pre and post values were done using paired t test [7]. χ^2 test was performed for comparing categorical data. Pearson correlation coefficient or Spearman correlation coefficient were used to examine correlations between quantitative variables [8]. Binary logistic regression to compare genotype and allele frequencies between groups. Odds ratio (OR) with 95% confidence intervals was calculated [9]. *P* values less than 0.05 were considered significant.

Results

FTO gene (rs9939609) and ESR1 gene (rs712221) genotype distribution is shown in Table 1

Regarding FTO gene rs9939609 variant analysis:

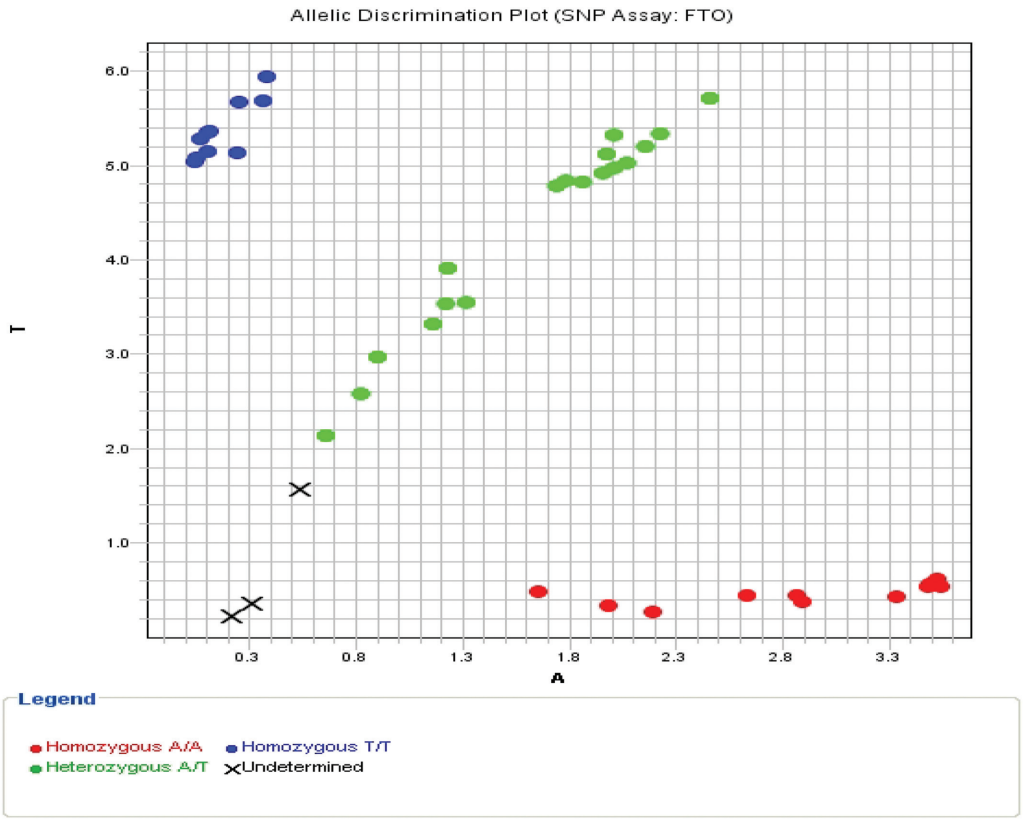
Patients were divided into three groups according to genotypes (AA, AT, and TT) of FTO gene rs9939609 and their laboratory and clinical data were compared. A highly statistically significant difference was detected in weight loss and BMI reduction percentages (*P* value < 0.001). There was however no statistically significance detected in changes of biochemical parameters as shown in Table 2.

According to results and follow up after surgery, the patients were divided into 2 groups based on % EWL:

Group 1: 16 patients with EWL more than 50% after 6 months of surgery

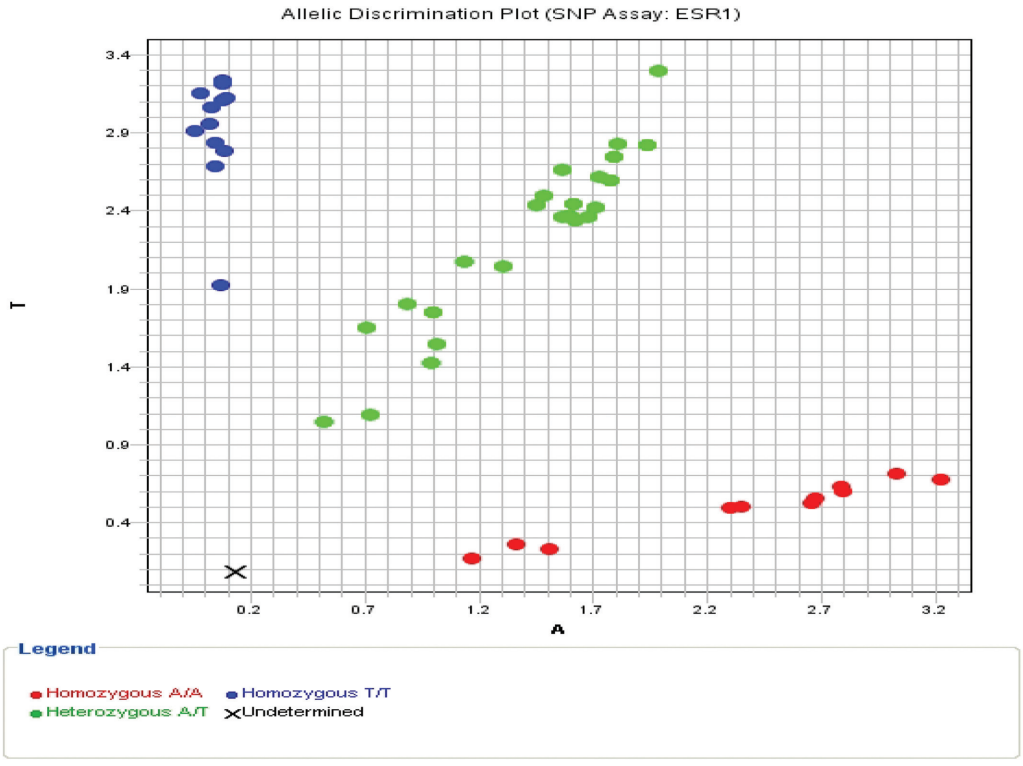
Group 2: 74 patients with EWL less than 50% after 6 months of surgery

Figure 1



Allelic discrimination plot of (rs9939609 of FTO gene).

Figure 2



Allelic discrimination plot of (rs712221 of ESR1 gene).

Table 3 shows genotype distribution, while Table 4 shows allele frequencies of FTO gene (rs9939609) in the two groups

Table 1 The genotype frequency of FTO gene (rs9939609) and ESR1 gene (rs712221) among the studied patients

	Genotype (*n*=90)	Number (%)
rs9939609 of FTO gene	AA	24 (26.7%)
	AT	40 (44.4%)
	TT	26 (28.9%)
rs712221 of ESR1 gene	TT	23 (25.6%)
	TA	44 (48.8%)
	AA	23 (25.6%)

Similarly regarding ESR1 gene variants

Patients were divided into three groups according to genotypes (TT, TA, and AA) of ESR1 gene and their laboratory and clinical parameters were compared (Table 5). A highly statistically significant difference was detected in weight loss and BMI reduction percentages (*P* value 0.001). It was found that there was no statistically significance detected in biochemical parameters as shown except for HbA1c reduction.

Comparison of weight loss, BMI and HbA1c reduction between the carriers of the ESR1 alleles is shown in Table 6

Table 2 Comparison between genotypes of rs9939609 of FTO gene regarding changes in anthropometric measurements and laboratory investigations before and 6 months after surgery

	rs9939609 of FTO gene			
	AA (*n*=24) Mean (SD	AT (*n*=40) Mean (SD	TT (*n*=26) Mean (SD	*P value
Pre Weight (kg)	138.08 (18.65)	123.28 (16.12)	131.54 (17.98)	0.005
Post Weight (kg)	102.83 (15.36)	97.10 (13.34)	108.62 (15.79)	0.009
weight loss %	25.67 (3.75)	21.05 (4.15)	17.19 (4.60)	<0.001
Pre BMI (kg/m^2)	53.03 (6.98)	48.00 (5.99)	50.32 (5.87)	0.009
Post BMI (kg/m^2)	39.45 (6.12)	37.78 (4.90)	41.61 (5.65)	0.024
BMI loss %	25.74 (3.80)	21.22 (4.43)	17.36 (4.69)	<0.001
Pre Waist circumference (cm)	137.08 (14.92)	131.67 (10.18)	134.88 (11.97)	0.211
Post Waist circumference (cm)	123.63 (18.12)	118.20 (12.09)	121.31 (14.76)	0.345
Waist circumference loss %	10.11 (5.29)	10.35 (3.94)	10.24 (4.67)	0.668
Pre TSF (mm)	29.17 (5.59)	27.75 (4.00)	27.69 (4.51)	0.428
Post TSF (mm)	24.25 (6.65)	24.45 (4.28)	23.77 (5.32)	0.877
TSF loss %	17.84 (10.37)	12.09 (6.97)	14.63 (10.46)	0.048
Pre MAC (cm)	44.40 (6.05)	41.20 (4.95)	42.08 (5.15)	0.070
Post MAC (cm)	36.75 (6.35)	34.87 (4.74)	36.04 (5.41)	0.382
MAC loss %	17.42 (5.82)	15.37 (4.76)	14.53 (4.99)	0.235
Pre MAMC (cm)	35.08 (5.23)	32.48 (4.52)	33.37 (4.73)	0.114
Post MAMC (cm)	29.13 (5.23)	27.19 (4.16)	28.57 (4.70)	0.226
MAMC loss %	17.11 (6.46)	16.31 (4.91)	14.51 (5.78)	0.378
Pre Cholesterol (mg/dl)	200.50 (42.50)	196.87 (28.94)	204.38 (34.87)	0.690
Post Cholesterol (mg/dl)	180.29 (32.09)	176.85 (24.20)	183.19 (31.57)	0.675
Cholesterol loss %	9.08 (8.15)	9.61 (8.74)	10.22 (6.27)	0.483
Pre Triglycerides (mg/dl)	160.04 (73.20)	143.75 (59.12)	146.27 (53.67)	0.577
Post Triglycerides (mg/dl)	133.79 (57.87)	121.45 (44.92)	124.77 (43.63)	0.611
Triglycerides loss %	15.03 (9.96)	13.35 (13.33)	13.93 (10.89)	0.492
Pre HDL (mg/dl)	42.17 (10.53)	43.63 (10.77)	41.27 (7.48)	0.624
Post HDL(mg/dl)	43.08 (8.05)	45.45 (10.13)	43.92 (8.28)	0.578
HDL loss %	−7.25 (30.00)	−7.04 (22.58)	−7.93 (18.85)	0.881
Pre LDL (mg/dl)	126.25 (42.65)	123.88 (34.01)	136.96 (34.01)	0.349
Post LDL (mg/dl)	110.54 (29.50)	108.93 (23.81)	115.50 (27.42)	0.609
LDL loss %	9.83 (12.48)	6.63 (32.66)	14.15 (15.09)	0.305
Pre FBG (mg/dl)	129.00 (50.23)	139.10 (52.97)	152.08 (59.68)	0.324
Post FBG (mg/dl)	111.50 (31.08)	111.22 (29.50)	126.35 (41.56)	0.167
FBG loss %	9.88 (16.15)	15.95 (16.55)	14.23 (11.81)	0.462
Pre HbA1c (%)	6.04 (1.91)	6.24 (1.77)	6.34 (1.58)	0.827
Post HbA1c (%)	5.33 (1.08)	5.45 (1.06)	5.63 (1.17)	0.621
HbA1c loss %	9.11 (11.75)	10.57 (10.89)	10.27 (6.34)	0.507

Table 3 Distribution of genotypes of FTO gene (rs9939609) in the two studied groups according to percentage of EWL

	Group 1 (n=16)		Group 2 (n=74)				95% CI	
	Count	%	Count	%	*P value	OR	lower	upper
rs9939609 of FTO gene								
AA	8	50.0%	16	21.6%	0.023	0.080	0.009	0.702
AT	7	43.8%	33	44.6%	0.130	0.189	0.022	1.633
TT	1	6.3%	25	33.8%		Reference		

Table 4 Allele frequencies of FTO gene (rs9939609) in the two studied groups according to percentage of weight loss

	Group 1 (n=16)		Group 2 (n=74)				95% CI	
	Count	%	Count	%	*P value	OR	lower	upper
rs9939609 of FTO alleles								
allele A	23	71.9%	65	43.9%	0.006	0.306	0.133	0.707
allele T	9	28.1%	83	56.1%		Reference		

Table 5 Comparison between genotypes of rs712221 of ESR1 gene regarding changes in anthropometric measurements and laboratory investigations before and 6 months after surgery

	rs712221 of ESR1 gene			
	TT (n=23) Mean (SD)	TA (n=44) Mean (SD)	AA (n=23) Mean (SD)	*P value
Pre Weight (kg)	129.52 (19.75)	130.64 (19.19)	127.74 (15.22)	0.830
Post Weight (kg)	98.26 (17.73)	102.95 (15.23)	103.74 (12.43)	0.401
Weight loss %	24.22 (4.81)	20.95 (4.11)	18.52 (6.06)	0.001
Pre BMI (kg/m^2)	50.56 (5.58)	50.21 (7.09)	49.07 (6.37)	0.714
Post BMI (kg/m^2)	38.24 (5.14)	39.57 (5.58)	39.96 (6.27)	0.546
BMI loss %	24.42 (4.94)	21.08 (4.31)	18.64 (6.04)	0.001
Pre Waist circumference (cm)	133.52 (11.37)	135.70 (12.81)	131.39 (11.72)	0.381
Post Waist circumference (cm)	120.78 (14.38)	122.02 (15.24)	117.48 (13.99)	0.488
Waist circumference loss %	9.76 (4.12)	10.26 (4.61)	10.73 (4.75)	0.827
Pre TSF (mm)	28.70 (4.12)	28.05 (5.06)	27.65 (4.29)	0.743
Post TSF (mm)	24.87 (4.86)	24.00 (5.99)	23.91 (4.11)	0.780
TSF loss %	13.91 (7.65)	15.06 (10.87)	13.45 (7.35)	0.970
Pre MAC (cm)	42.98 (5.10)	42.05 (5.87)	42.13 (5.00)	0.791
Post MAC (cm)	36.65 (5.97)	35.20 (5.61)	35.74 (4.40)	0.586
MAC loss %	15.03 (5.76)	16.30 (5.29)	15.14 (4.43)	0.656
Pre MAMC (cm)	33.97 (4.48)	33.15 (5.20)	33.44 (4.63)	0.807
Post MAMC (cm)	28.83 (5.12)	27.65 (4.82)	28.23 (3.84)	0.612
MAMC loss %	15.44 (6.42)	16.57 (5.64)	15.49 (4.88)	0.680
Pre Cholesterol (mg/dl)	197.35 (34.53)	202.02 (33.44)	198.83 (37.42)	0.857
Post Cholesterol (mg/dl)	172.83 (30.73)	185.09 (28.81)	175.87 (24.24)	0.190
Cholesterol loss %	11.90 (10.13)	7.97 (6.61)	10.60 (7.09)	0.038
Pre Triglycerides (mg/dl)	169.13 (58.94)	143.36 (62.59)	138.96 (59.50)	0.179
Post Triglycerides (mg/dl)	137.17 (45.85)	125.64 (50.90)	114.35 (43.67)	0.276
Triglycerides loss %	18.02 (11.65)	10.92 (10.63)	15.73 (12.64)	0.080
Pre HDL (mg/dl)	42.74 (9.56)	43.30 (10.63)	40.96 (8.56)	0.652
Post HDL (mg/dl)	43.22 (9.64)	45.64 (8.64)	43.13 (9.31)	0.440
HDL loss %	−4.75 (26.54)	−8.01 (17.45)	−8.71 (30.65)	0.927
Pre LDL (mg/dl)	122.22 (34.98)	129.84 (37.30)	131.39 (37.39)	0.649
Post LDL (mg/dl)	102.26 (26.89)	115.86 (27.54)	111.43 (21.63)	0.133
LDL loss %	13.94 (17.68)	6.01 (30.22)	12.33 (14.22)	0.225
Pre FBG (mg/dl)	134.91 (46.99)	142.82 (51.76)	140.30 (66.92)	0.855
Post FBG (mg/dl)	110.43 (27.12)	117.80 (35.93)	116.83 (37.53)	0.696
FBG loss %	14.91 (14.35)	14.68 (15.04)	11.15 (16.87)	0.344
Pre HbA1c (%)	6.32 (1.94)	6.22 (1.74)	6.11 (1.59)	0.922
Post HbA1c (%)	5.24 (0.93)	5.51 (1.16)	5.61 (1.13)	0.487
HbA1c loss %	14.14 (11.86)	9.65 (8.57)	6.90 (9.44)	0.070

Table 6 Comparison of weight, BMI and HbA1c before and 6 months after surgery between carriers of T & A alleles of ESR1 gene (rs712221)

	rs712221 of ESR1 alleles		
	allele T (*n*=90) Mean (Standard Deviation)	allele A (*n*=90) Mean (Standard Deviation)	*P value
Pre Weight (kg)	130.07 (19.27)	129.16 (17.16)	0.738
Post Weight (kg)	100.56 (16.52)	103.36 (13.73)	0.218
Weight loss %	22.62 (4.73)	19.71 (5.28)	<0.001
Pre BMI (kg/m^2)	50.39 (6.30)	49.63 (6.68)	0.433
Post BMI (kg/m^2)	38.89 (5.34)	39.77 (5.88)	0.295
BMI loss %	22.79 (4.88)	19.83 (5.34)	<0.001
Pre HbA1c (%)	6.27 (1.83)	6.16 (1.65)	0.681
Post HbA1c (%)	5.37 (1.05)	5.56 (1.13)	0.247
HbA1c reduction %	11.95 (10.49)	8.25 (9.03)	0.025

Discussion

The sex distribution of obesity in Egypt seems to be far from being balanced where 42.2% of males are overweight and 21.4% are obese while 33.3% of females are overweight and 48.5% are obese [10]

The basic etiology of obesity is long term energy imbalance due excess caloric intake relative to energy expenditure through metabolic and physical activity. Still, the etiology of obesity remains a highly complex process influenced by a myriad of factors among which are genetic, environmental, psychological, social and economic factors. These interact in varying degrees thus influencing the final outcome [11].

Genetic contribution associated with obesity is generally classified into 2 types: Syndromic and Nonsyndromic obesity [12]. Nonsyndromic polygenic obesity, the more frequently encountered form of obesity, arises when a person's genetic make-up is combined with an environmental or societal/lifestyle factors that encourage energy consumption over energy expenditure. Hence the final result tends to be a consequence of both a genetic susceptibility and unhealthy lifestyle [13].

Regarding the results of the current study, in respect to the studied variants; firstly, FTO gene variant (rs9939609) exhibited a frequency of homozygous allele genotype (AA) that represented 26.7%, which agrees with the frequencies described by [14,15] that were 25% & 22% respectively.

As for the Pre-surgery weight, results in this study showed significant difference in body weight (*P* value 0.005) and BMI (*P* value 0.009) when comparing carriers of AA genotype versus AT and TT genotype. That was in agreement with [16] who stated that individuals with FTO rs9939609 AA genotype exhibited higher values of body weight (*P* value 0.002) and BMI (*P* value 0.001) when compared to AT and TT genotypes Similar results were reported by [17,18].

Regarding percentage of weight loss 6 months after surgery, upon comparing different genotypes, carriers of the AA genotype exhibited the highest percentage of weight loss 25.67% whereas carriers of the AT genotype exhibited 21.05% weight loss finally carriers of the TT genotype had a 17.19% with a statistically significant difference between the three genotypes (*P* value <0.001)

Furthermore, the patients were divided into 2 groups depending on estimated weight loss percentage. Group 1 were patients with estimated weight loss more than 50% after 6 months, whereas group 2 were patients with estimated weight loss was less than 50%. Upon examining the genotype distribution between the two groups it was found that the AA genotype was more highly represented in Group 1 (50%) and much less in Group 2 (21.6%), (*P* value 0.023)

When examining the difference in frequency of the A allele between the two groups, again, the A allele was more heavily represented In Group 1 representing 71.9% there is in Group 2 where it only represented 43.9% which was again statistically significant (*P* value 0.006)

Going over the published literature regarding the weight loss after surgery with different FTO genotypes it was found that; in agreement with the results of the current study [3], have reported that obese people with genotype AA (rs9939609) exhibited greater BMI reduction when compared to patients

with TT/AT genotypes 6 month after undergoing laparoscopic mini gastric bypass. In **2016** a meta-analysis of weight loss trials was done by [19] it was found that individuals who were homozygous FTO rs9939609 variant allele (AA genotype) demonstrated greater weight loss than individuals with TT genotype after diet/lifestyle interventions. This was in agreement with this study so as with study done by [20].

It was stated by [21] that, although the SNV of rs9939609 in FTO was not associated with reduction of body weight by dietary restriction, it might however be associated with more pronounced weight reduction by surgery.

On the other hand, according to the work published in **2012 by** [22], it was found that the initial weight loss with the TT genotype was higher three months after biliopancreatic diversion surgery however there was no significant difference in weight loss 9 to 12 months later between different genotypes of the FTO gene. Another work done by [23,24] came to the same conclusion, finding no significant difference in weight loss six months after surgery when comparing different FTO genotypes.

The results in the present study showed no association between the different genotypes of FTO rs9939609 and fasting plasma glucose or the parameters of lipid profile. This was in agreement with [25] who stated in **2020** that blood lipids are not influenced by the FTO rs9939609 polymorphism. But a study published in **2016** by [26]. reported that the fasting plasma glucose values differed significantly across the genotypes (*P* value 0.002).

Regarding ESR1 gene (rs712221) genotype frequency, in this study the TT genotype represented (25.6%), TA genotype represented (48.8%) and AA genotype represented (25.6%) and this was in harmony with the research done in **2009** by [27] where the TT genotype represented (25.2%) while TA genotype represented (47.3%) and AA genotype represented (27.5%).

Regarding presurgery body weight, in the current study there was no statistically significant difference in the presurgery body weight or body mass index in carriers of different genotypes of the ESR1 gene. However, on comparing percentage of weight loss 6 months after surgery, among different genotypes, carriers of the TT genotype exhibited the highest percentage of weight loss 24.22% whereas carriers of the TA genotype exhibited 20.95% weight loss finally carriers of the AA genotype had a 18.52% with a statistically significant difference between the three genotypes (*P* value 0.001). Counting absolute allele frequency in the whole studied group, both alleles were equally represented. However, when comparing weight loss percentage between the two alleles, carriers of the T allele exhibited bigger weight loss and more marked HbA1c reduction which was statistically significant (*P* values 0.001 and 0.025, respectively)

Aligning with the current study [3], noted that both of the ESR1 (rs712221) and FTO (rs9939609) were remarkably associated with body weight reduction and improvement of blood glucose control in obese patients undergoing laparoscopic mini gastric bypass (LMGB). Morbidly obese individuals harboring genotypes TT on rs712221 and AA on rs9939609 had more weight loss than other participants carrying different genotypes six months after undergoing the surgery.

Furthermore, according to [3] there might be a synergistic effect between the two variants. The highest degree of weight loss post LMGB was observed when they simultaneously had both risk genotypes on rs712221 and rs9939609.

Regarding other laboratory parameters, in this study there was no significant difference in laboratory parameters in different genotypes except for total cholesterol reduction 6 months after surgery which was significantly higher (*P* value 0.038)in carriers of the TT genotype compared to other genotypes which was in agreement with a study done in **2008** by [28]

And partially in agreement with [29] who found significant associations between ESR1 rs712221 and LDL (*P* value 0.029) but non with triglyceride, and total cholesterol levels in African American population

Conclusion

Based upon the findings in this study, the single nucleotide variants; rs9939609 of FTO and rs712221 of ESR1 may be considered as markers or potential predictors of the degree of weight loss and/or glycemic control after laparoscopic sleeve gastrectomy for obese patients. Despite the above obvious controversy, according to [30] it's important to realize that success of bariatric surgery can be defined as weight loss of more than 20% of initial weight or BMI $<35\,kg/m^2$ at 3–5 years after surgery. Therefore, long term follow up might tell a different story.

Acknowledgement
Not Applicable.

Financial support and sponsorship
Nil.

Conflicts of interest
The authors declare no competing interests.

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