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Obesity Risk Prediction among Women of Upper Egypt: The impact of FTO rs17817449 gene polymorphism, serum ghrelin and high sensitivity C- reactive protein

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ABSTRACT

Obesity is one of the main threats to the human health. It is a major risk factor for hyperinsulinemia, hypertension, hyperlipidemia, type II diabetes mellitus, and atherosclerotic cardiovascular disease. FTO gene variants have been associated with obesity and diabetes mellitus in different populations, but its role in the susceptibility of these diseases remains unknown. The present study is undertaken to assess the contribution of the FTO rs17817449 gene variants towards obesity and diabetes development and to evaluate the role of ghrelin and hs-CRP on the outcome of obesity in the Upper Egyptian women. A total of 229 subjects, 115 obese (65 non diabetics, 50 diabetics) and 114 non obese non diabetic controls were included in this case control study. Genotyping of FTO gene rs17817449 (T>G) polymorphism was performed by mutagenically separated PCR (MS-PCR) method. Estimation of serum gherlin, hs-CRP levels, related anthropometric and metabolic parameters were performed. The results revealed higher frequency of FTO rs17817449 G allele among obese subjects (46.5%) and obese diabetics (45%) compared to the controls (33.3%) which comprise about 1.75 times increase in the risk for obesity ($p<0.01$). The distribution of the GG and TG genotypes of FTO were 25.2%, and 42.6% among obese non diabetic, 24% and 42% among obese diabetic and 14.9% and 36.8% among controls respectively. FTO-GG genotype variant was significantly associated with weight, BMI and

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waist and hip circumference ($p<0.05$ for each). FTO GG carriers had 2.54 times the possibility to have obesity more than TT carriers. Ghrelin levels were significantly decreased and hs-CRP levels were significantly increased in obese subjects compared to the controls ($P<0.001$ for each). There was a significant negative correlation between serum ghrelin and hs-CRP ($p<0.05$). No significant association was detected between FTO genotypes and each of ghrelin, hs-CRP, lipid profile, fasting glucose or insulin levels. In conclusion, the G allele of FTO rs17817449 genotyping is associated with increased obesity risk but there is a lack of association with diabetes. It is also associated with some obesity indices as BMI, hip and waist circumference in the Upper Egyptian women. Both Ghrelin and hs-CRP could play a role in developing obesity. To the best of our knowledge, this is the first study of FTO SNP in Upper Egyptian women. Switching off this FTO faulty gene variant by the recent therapies (as certain foods or gene therapy) will prevent the percentage of women who is affected by this risk allele to get obese via burning rather than storing energy.

Key words: FTO gene polymorphism, ghrelin, hs-CRP, Obesity

INTRODUCTION

Obesity is one of the most common medical disorders that have an impact on morbidity and mortality. Excess body fat may accumulate to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems (**Haslam and James, 2005 and Prakask et al., 2016**). Also, obesity could play a central role in the metabolic syndrome, which include hyperinsulinemia, hypertension, hyperlipidemia, type 2 diabetes mellitus (T2DM), several cancers, and an increased risk of atherosclerotic cardiovascular disease **(Kelishadi, 2007).** T2DM is a complex disease caused by β- cell dysfunction and/or insulin resistance, which is promoted by multifactorial genetic or environmental factors. It is frequent in the setting of obesity that the genetic variations influencing obesity may also affect diabetes **(Xiao et al., 2015).**

Obesity and T2DM have reached epidemic proportion world-wide and the prevalence is increasing especially in developing countries. It

is estimated that >50% of global population will be overweight or obese by 2030 **(Kelly et al., 2008 and Saldana-Alvarez et al., 2016).** And about 592 millions will be diabetic by 2035. This could highlight the importance for novel methods to prevent and treat these pandemic diseases **(Guariguata et al., 2014 and xiao et al., 2016).**

An individual predisposition to obesity and T2DM is determined by the interaction between genetic and environmental factors. The fat mass and obesity-associated gene (FTO) was the first obesity susceptibility gene identified and continues to be the locus with the largest effect on body mass index (BMI) and obesity risk **(Loos and Yeo, 2014 and Prakask et al., 2016**). The single nucleotide polymorphisms (SNPs) that are clustered in the first intron of FTO gene, located on chromosome 16q12.2, display the strongest association with obesity. FTO primarily functions as a demethylase and is involved in control of energy homeostasis, adipogenesis and DNA methylation **(Saldana-Alvarez et al., 2016).**

FTO mRNA is expressed in the hypothalamic nuclei and is regulated by fasting, feeding, eating behavior, revealing an important link between FTO gene and hunger sensation **(Ursu et al., 2015).** A strong association of FTO variant (rs17817449) with obesity was observed in European and Indian population. However, no association was found among African- Americans **(Prakash et al., 2011).** Due to such controversies, more studies are needed to explore the association of FTO rs17817449 variant gene polymorphism with obesity and obesity-related parameters in different ethnic individuals.

Ghrelin is a 28-amino-acid peptide with an octanoylated Ser-3 residue and expressed in stomach entero-endocrine cells. A key regulator of plasma ghrelin level is food intake where its plasma level is elevated under starvation and decreased after food intake in response to an increase of glycemia **(Ghigo et al., 2005).** Plasma ghrelin level is negatively correlated with body mass index. It exerts an inhibitory effect on insulin secretion resulting in increased glucose levels **(Verhulst and Depoortere, 2012).**

Chronic inflammation is a common factor in obesity and DM and the pro-inflammatory markers like high sensitivity C-reactive protein (CRP) play an important role in their existence **(Alemzadeh and Kichler, 2014).** High sensitivity C reactive protein is a member of the pentraxin protein that is attached to the plasma membrane of damaged cells causing cell death through activation of a complement cascade. It

is an independent predictor of myocardial infarction, peripheral arterial disease and stroke **(Kaptoge et al., 2010).** Adipose tissue is an important source of circulating hs-CRP which is increased among obese subjects according to the degree of adiposity and distribution of body fat **(Lai et al., 2010).** Elevated levels were reported in T2DM and metabolic syndrome, suggesting that, the inflammatory processes may play a strong role in the pathogenesis of these diseases **(Alemzadeh and Kichler, 2014).**

The aim of the present study was to:

1-Clarify the association of the FTO rs17817449 gene polymorphism with obesity and diabetes mellitus in a sample of Upper Egyptian women. 2- Evaluate the role of gherlin hormone and hs-CRP on obesity outcome and their relation with FTO gene polymorphism as risk factors for obesity.

MATERIAL AND METHODS

Subjects:

The present study is a case control study in which 365 participants were recruited between 2013 and 2014. All were Egyptians, who were randomly attended Assiut University Hospital outpatient clinics for obesity and weight reduction programs along with volunteers.

Medical history including age, occupation, family history of obesity, history of drug intake and onset of obesity were taken. All participants were subjected to routine physical examinations. Measurements of blood pressure (mm Hg), body weight (kg), height (cm), calculation of BMI (kg/m²), waist circumference (cm), hip circumference (cm), waist/hip ratio, measurement of fat, water and muscle percent by bioelectrical impedance scale (Korona KFW 5505 scale, Germany) were carried out by a trained nurse.

Exclusion criteria included individuals with cardiac, hepatic or renal affections, those with endocrine disorders, pregnancy, lactation, chronic drug intake and malignancies. Of the 365 interviewed, 229 aged 18- 50 years were fully enrolled in the study. Obese individuals (115 cases) were those with a BMI of ≥ 30 kg/m² and non-obese subjects (114 controls) had a BMI between 18.5 to 24.99 kg/m2 according to the definition of obesity by World Health Organization, **(Sturm, 2007).** The obese subjects were subdivided into 65 women without and 50 women with diabetes. The diagnosis of diabetes was according to WHO criteria for fasting plasma glucose (≥7.0 mmol/L),

or HbA1C (≥6.5%) or previously diagnosed as T2DM **(Puavilai et al., 1999).**

All participants signed a written informed consent for participation in the study. The study was approved by the Faculty of Medicine, Assiut University ethical committee in accordance with Helsinki declaration (1975).

Biochemical analysis:

Ten ml venous blood samples were obtained after an overnight fast, and divided into 2 parts. Five ml were collected on EDTA for DNA extraction, and the other 5 ml were left in room temperature for serum separation which was preserved at -70°C till the assay of biochemical markers.

The levels of serum cholesterol, LDL-C, HDL-C, triglycerides, ALT and fasting glucose were determined using enzymatic colorimetric kits supplied by Biodiagnostics, Egypt. Fasting insulin was determined by an ELISA kit supplied by DRG international instruments inc, Germany. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated (Fasting insulin (µIu/ml) X fasting glucose (mmol/L)/22.5 **(Matthews et al., 1985).** Serum gerhlin was measured using Bio® Human, Enzyme Immunoassay Kit according to manufacturer's instruction (Ray Biotech, USA). Serum hs-CRP was measured by an enzyme immunoassay kit supplied by Diagnostics Biochem, Canada.

Genotyping:

Genomic DNA was isolated from peripheral whole blood collected on EDTA using QIAamp DNA mini kit (Qiagen) according to the manufacturer's instructions. FTO SNP rs17817449 was detected using mutagenically separated polymerase chain reaction (MS-PCR) **(Rust et al., 1993).** The following four primers (MS-PCR) were used to amplify 420 bp fragment of DNA containing the SNP, where, 180 and 280 bp fragments represent T and G alleles respectively:

FTO449F 5'- TACATTTACTCAAGAGTTTGTCTTTTCT-3,
FTO449R 5'- TATTCAGATGAGTTACACTAAAAGCTG-3,
FTO449TR 5'-GAGCTGGACTGTTAAATTAAATCA -3', and
FTO449GF 5'- AGCTTGGCACACAGAAATG-3'

PCR was carried out using 12.5 µl PCR master mix (Qiagen), 100 ng of genomic DNA, 250 nmol for each primer, 2.5 mM $MgCl_2$ and up to 25 µl of nuclease free water. The amplification was conducted on VERTI 96 Thermal Cycler (Applied Biosystems) as follows:

initial l0-min denaturation at 95°C, followed by 35 cycles denaturation at 94°C for 30s , annealing at 55°C for 30s and extension at 72°C for 60s, then a final extension step of 10 min at 72°C. PCR products were electrophoresed on ethidium bromide stained (0.5 µg/ml) 1% agarose gel containing 1X TEA buffer and visualized by BioDoc gel documentation system (USA).

These genotyping patterns were: 2 fragments for GG of 420 and 280 bp, 3 fragments of 420, 280 and 180 bp for GT, and 2 fragments of 420 and 180 bp for TT (Figure 1). Genotyping validation of this method was performed by re-genotyping of 10% of samples by 2 independent personels and a recall of 95%, 100% concordance was obtained.

Statistical analysis

SPSS version 15 was used for data analysis. The results were expressed as mean ± SD for continuous data or frequencies and percent for qualitative data. Chi- square and independent student-t test were used for comparison between the two studied groups. Genotypes and allele distributions were compared between obese and non obese subjects using Chi-square (X^2) test, odds ratio and confidence intervals were also estimated. ANOVA test and Post-hoc test was used for comparison between different carriers. Hardy-Weinberg calculation was used to determine whether the observed genotype frequencies for the studied SNP are consistent or not with Hardy-Weinberg equilibrium. Person correlation was used to evaluate the association between different parameters. $p<0.05$ is considered significant.

RESULTS

The demographic, anthropometric and biochemical variables:

Demographic, anthropometric and biochemical characteristics of obese subjects and controls are presented in Table (1). Family history is exhibited by about 75.47% of obese women compared to 17.39% of controls. Non working subjects represented about 70% of obese subjects and 16% of controls ($p<0.001$ each). Among obese subjects about 64% of them were obese since childhood. Systolic and diastolic blood pressure were higher in obese compared to controls ($p<0.05$ each).

Concerning anthropometric parameters, weight, height, BMI, waist and hip circumference, fat% and W/H ratio were significantly

higher in obese subjects than controls ($p<0.001$ each).On the other hand, water and muscle% were significantly lower in obese than controls ($p<0.001$ each). Obese subjects showed significantly higher values of serum hs-CRP, total cholesterol, LDL-C, triglycerides, ALT and fasting glucose than controls ($p<0.001$ each). Also, the HOMA-IR levels were significantly increased in obese as compared to controls ($p<0.05$). On the other hand, serum HDL-C and ghrelin levels were decreased in obese than controls ($p<0.01$ and $p<0.001$ respectively).

The anthropometric and biochemical characteristics of obese diabetic and non diabetic subjects and controls are presented in Table (2). Obese diabetics showed significantly higher values of total cholesterol, fasting glucose and HOMA-IR values than obese non diabetic subjects ($p<0.01$, $p<0.001$ and $p<0.001$ respectively). On the other hand obese diabetic subjects showed significantly lower BMI than obese non diabetics ($p<0.05$).

Genotypes and allele frequencies:

The genotype and allele frequencies among obese subjects and controls are shown in Table (3). All genotype distributions of obese women and controls were compatible with Hardy-Weinberg equilibrium. The minor G allele of FTO rs17817449 polymorphism was significantly higher in obese (46.5%) than controls (33.3%) (OR=1.74, CI= 1.19-2.50, $p<0.05$). The distribution of the TG and GG genotype variants of FTO were 42.6%, and 25.2% respectively among obese women and 36.8% and 14.9% respectively among controls. The FTO polymorphism was significantly associated with obesity risk in both the dominant (TG+GG vs. TT) and recessive (GG vs. TT+TG) tested inheritance models (OR=1.97, CI=1.15-3.36, $p<0.05$ and OR=1.92, CI= 0.98-3.74, $p<0.05$ respectively). After adjusting genotypes for diabetes, the GG carriers have 2.75 times more obesity risk than TT carriers.

The genotype and allele frequencies among obese diabetics and controls are shown in Table (4). The minor G allele was higher in diabetics (45%) compared to controls (33.3%), (OR=1.82, CI= 1.14-2.64, $p<0.05$). The distribution of the TG and GG genotype variants of FTO were 42%, and 24% respectively among diabetic subjects. Both the dominant (TG+GG vs. TT) and recessive (GG vs. TT+TG) tested inheritance models showed non significant association with diabetic risk.

Influence of FTO gene polymorphism on metabolic and anthropometric parameters:

The relation between the different genotype variants of FTO, anthropometric and biochemical parameters among obese subjects are shown in Table (5). Carriers of G allele in homozygous form (GG) showed significant associations with weight, BMI, waist and hip circumference compared to subjects with TT ($p<0.05$ each). Whereas carriers in heterozygous form (TG) genotype showed significant association with height compared to subjects with TT ($p<0.05$). On the other hand, comparing the GG with GT carriers, they showed difference as regards all the studied parameters but not reach the statistical significance except for BMI, waist and hip circumference ($p<0.05$ each).

The relation between the different genotype variants of FTO, anthropometric and biochemical parameters in obese diabetic subjects are shown in Table (6). Carriers of G allele in homozygous and heterozygous form showed significant associations with BMI compared to TT form ($p<0.05$ each). Whereas G allele in homozygous form (GG) showed significant association with waist circumference compared to subjects with TG ($p<0.05$). On the other hand, there was no significant associations between serum levels of each of ghrelin, hs-CRP, lipid profile, fasting glucose, insulin and FTO gene polymorphisms in obese and diabetic womem (Table 5 and 6).

A significant negative correlation between serum ghrelin and hs-CRP ($p<0.05$) and a significant positive correlation between ghrelin and HDL-C levels ($p<0.01$) were found in obese subjects (data are not shown).

Table(1): Demographic, anthropometric and biochemical characteristics of controls and obese subjects.

Variables	Controls (n= 114)	Obese patients (n= 115)
Age (years)	**40.89±9.54**	**39.71±9.88**
Family history of obesity n(%)		
Yes	**20 (17.39%)**	**86 (75.47%)***
No	**94 (82.61%)**	**29 (24.53%)**
Occupation n (%)		
Working	**96 (84%)**	**35 (30.19%)***
Non working	**18 (16%)**	**80 (69.81%)**
Onset of obesity n (%)		
Since childhood	**----------**	**73 (64%)**
Within adulthood	**----------**	**42 (36%)**
Blood pressure (mm Hg)		
Systolic	**118.86±11.58**	**123.09±17.63***
Diastolic	**75.13±8.61**	**78.73±11.67***
Anthropometric parameters		
Weight (Kg)	**62.11±11.46**	**90.84±14.18***
Height (cm)	**166.63±9.44**	**158.66±7.55***
BMI (Kg/m²)	**22.26±2.55**	**36.45±5.67***
Waist circumference(cm)	**65.83±7.18**	**101.66±12.69***
Hip circumference (cm)	**82.16±6.52**	**117.30±13.24***
W/H ratio	**0.80±0.11**	**0.87±0.08***
Differential body weight		
Fat %	**24.51±4.56**	**42.59±7.49***
Water %	**49.62±10.01**	**37.24±3.55***
Muscle %	**31.18±6.49**	**23.43±2.24***
Serum ghrelin (ng/ml)	**24.71±7.90**	**18.55±6.31***
Serum hs-CRP (ng/ml)	**1.92±1.62**	**4.09±1.45***
Lipid profile		
Total cholesterol (mg/dl)	**153.19±37.50**	**182.49±52.76***
LDL-C (mg/dl)	**92.31±40.77**	**138.88±53.34***
HDL/C (mg/dl)	**46.87±25.64**	**32.72±8.41***
TG (mg/dl)	**111.09±55.54**	**150.97±43.33***
Insulin sensitivity		
Fasting glucose (mg/dl)	**96.74±17.57**	**141.44±68.9***
Serum insulin (µl U/ml)	**9.46±5.51**	**12.25±7.23**
HOMA-IR n/(%)		
<2.6	**114 (100%)**	**93 (80.77%)***
>2.6	**0 (0%)**	**22 (19.23%)**
HOMA-IR values	**1.94±1.01**	**4.27±3.01***
ALT (U/ml)	**44.60±9.36**	**51.85±12.31***

Datais presented as mean ± SD or number and %

*p value < 0.05 is considered statistically significant.

Table (2): Anthropometric and biochemical characteristics of controls and obese subgroups.

Variables	Controls (n=114)	Obese non diabetics (n=65)	Obese diabetics (n=50)
Anthropometric parameters			
Weight (Kg)	**62.11±11.46**	**92.68±13.84***	**88.45±14.39***
Height (cm)	**166.63±9.44**	**158.32±5.75***	**158.44±9.45***
BMI (Kg/m²)	**22.26±2.55**	**37.21±5.67***	**35.47±5.57*#**
Waist circumference(cm)	**65.83±7.18**	**102.10±12.69***	**101.08±12.81***
Hip circumference (cm)	**82.16±6.52**	**116.32±11.97***	**118.56 ±14.67***
W/H ratio	**0.80±0.11**	**0.88±0.07***	**0.86±0.08***
Differential body weight			
Fat %	**24.51±4.56**	**43.36±7.39***	**42.42±8.65***
Water %	**49.62±10.01**	**36.94±3.14***	**37.63±4.03***
Muscle %	**31.18±6.49**	**23.28±2.06***	**23.62±2.47***
Serum ghrelin (ng/ml)	**24.71±7.90**	**19.36 ±6.19***	**16.97±6.40**
Serum hs-CRP (ng/ml)	**1.92±1.62**	**3.96±1.68***	**4.36±0.79***
Lipid profile			
Total cholesterol (mg/dl)	**153.19±37.50**	**170.79±53.98***	**197.69±47.47*#**
LDL-C (mg/dl)	**92.31±40.77**	**137.85±52.80***	**140.21±54.55***
HDL/C (mg/dl)	**46.87±25.64**	**32.83±8.75***	**33.56±8.03***
TG (mg/dl)	**111.09±55.54**	**149.04±37.45***	**153.49±50.25***
Insulin sensitivity			
Fasting glucose (mg/dl)	**96.74±17.57**	**99.93±19.65**	**195.41±72.78*#**
Serum insulin (µl U/ml)	**9.46±5.51**	**11.36±7.76**	**12.25±7.43***
HOMA-IR values	**1.94±1.01**	**2.80±1.87**	**7.17±2.78*#**
ALT (U/ml)	**44.60±9.36**	**50.67±12.40***	**53.27±12.16***

Data is represented as mean ± SD
p value < 0.05 is considered statistically significant.
* Significant difference of obese with and without DM versus controls at p<0.05.
# Significant difference of obese with DM versus obese without DM at p<0.05.

Table (3): Genotyping and alleles frequencies distribution of FTO rs17817449 T>G gene polymorphism in controls and obese subjects

	Controls (n=114)	Obese (n=115)	OR (95% CI)	OR (95% CI)[a]
Genotype				
TT	**55(48.2%)**	**37(32.2%)**		
TG	**42(36.8%)**	**49(42.6%)**	**1.73 (0.97-3.11)**	**1.83 (0.91-3.89)***
GG	**17(14.9%)**	**29(25.2%)**	**2.54 (1.22-5.25)***	**2.75 (1.18-6.40)***
Recessive				
TT+TG	**97(85.0%)**	**86(74.8%)**		
GG	**17(14.9%)**	**29(25.2%)**	**1.92 (0.99-3.74)***	**2.02 (0.95-4.30)**
Dominant				
TT	**55(48.2%)**	**37(32.2%)**		
TG+GG	**59(51.7%)**	**78(67.8%)**	**1.97 (1.15-3.36)***	**2.09 (1.10-3.99)***
Allele				
T	**152(66.7%)**	**123(53.5%)**		
G	**76(33.3%)**	**107(46.5%)**	**1.75 (1.19-2.54)***	

Data is represented as number and %
*p< 0.05 is considered statistically significant.
OR: odds ratio, CI: confidence interval
[a] Adjusted for diabetes

Table (4): Genotyping and alleles frequencies distribution of FTO rs17817449 T>G gene polymorphism in controls and obese diabetic subjects

	Controls (n=114)	Obese diabetics (n=50)	OR (95%CI)
Genotype			
TT	**55(48.2%)**	**17(34%)**	
TG	**42(36.8%)**	**21(42%)**	**1.61 (0.76-3.44)**
GG	**17(14.9%)**	**12(24%)**	**2.03 (0.91-5.72)**
Recessive			
TT+TG	**97(85.0%)**	**38(76%)**	
GG	**17(14.9%)**	**12(24%)**	**1.80 (0.79-4.13)**
Dominant			
TT	**55(48.2%)**	**17(34%)**	
TG+GG	**59(51.7%)**	**33(66%)**	**1.80 (0.91-3.61)**
Allele			
T	**152(66.7%)**	**55(55%)**	
G	**76(33.3%)**	**45(45%)**	**1.82 (1.14-2.64)***

Data is represented as number and %
*p< 0.05 is considered statistically significant.
OR: odds ratio, CI: confidence interval

Table (5): The relationship between different genotype variants of FTO rs17817449 gene and the anthropometric and biochemical data in obese subjects

Variables	Carriers of TT (n=37)	Carriers of TG (n=49)	Carriers of GG (n=29)
Anthropometric parameters			
Weight (Kg)	**88.75±10.76**	**88.90±15.08**	**96.78±15.20***
Height (cm)	**161.35±7.26**	**157.0±7.69***	**158.03±6.93**
BMI (Kg/m²)	**34.69±4.98**	**36.28±5.80**	**38.98±5.52*#**
Waist circumference(cm)	**99.46±13.34**	**100.43±12.24**	**106.52±11.71*#**
Hip circumference (cm)	**113.59±12.24**	**116.47±13.71**	**123.41±11.878*#**
W/H ratio	**0.88±0.07**	**0.87±0.08**	**0.86±0.08**
Differential body weight			
Fat %	**41.37±6.52**	**42.88±8.46**	**45.08±8.45**
Water %	**37.74±3.13**	**37.39±3.92**	**36.34±3.35**
Muscle %	**23.76±1.93**	**23.61±2.50**	**22.70±2.07**
Serum ghrelin (ng/ml)	**17.95±7.83**	**18.20±5.59**	**19.65±6.30**
Serum hs-CRP (ng/ml)	**4.17±1.46**	**3.98±1.70**	**4.21±0.97**
Lipid profile			
Total cholesterol (mg/dl)	**174.09±56.85**	**183.88±55.55**	**190.84±41.48**
LDL-C (mg/dl)	**134.75±55.16**	**138.15±59.27**	**145.38±39.80**
HDL/C (mg/dl)	**33.01±9.27**	**32.96±8.42**	**32.76±6.67**
TG (mg/dl)	**147.89±50.22**	**157.19±39.01**	**144.39±40.86**
Insulin sensitivity			
Fasting glucose (mg/dl)	**139.59±72.14**	**150.39±74.47**	**128.68±53.29**
Serum insulin (µl U/ml)	**9.56±4.67**	**12.12±8.14**	**14.64±7.59**
HOMA-IR values	**3.67±2.42**	**4.40±3.41**	**4.60±2.83**
ALT (U/ml)	**53.35±13.98**	**52.78±12.86**	**48.21±8.43**

Data is represented as mean ± SD
$p < 0.05$ is considered statistically significant.
* Indicates significant difference vs. carriers of TT at $p<0.05$
# Indicates significant difference vs. carriers of TG at $p<0.05$

Table (6): The relationship between different genotype variants of FTO rs17817449 gene and the anthropometric and biochemical data in diabetic subjects

Variables	Carriers of TT (n=17)	Carriers of TG (n=21)	Carriers of GG (n=12)
Anthropometric parameters			
Weight (Kg)	**85.54±9.14**	**88.70±17.64**	**92.12±14.38**
Height (cm)	**162.12±8.31**	**156.86±10.02**	**156.00±9.09**
BMI (Kg/m²)	**32.77±3.42**	**36.32±6.60***	**37.80±4.84***
Waist circumference(cm)	**99.06±12.46**	**98.77±10.79**	**108.01±14.97#**
Hip circumference (cm)	**117.00±11.85**	**115.62±15.94**	**125.92±15.00**
W/H ratio	**0.85±0.05**	**0.86±0.09**	**0.86±0.10**
Differential body weight			
Fat %	**42.19±6.24**	**41.71±9.91**	**43.98±9.73**
Water %	**37.26±2.95**	**38.27±4.78**	**37.03±4.07**
Muscle %	**23.44±1.81**	**24.01±2.90**	**23.18±2.56**
Serum ghrelin (ng/ml)	**16.61±10.34**	**17.00±4.71**	**17.20±7.03**
Serum hs-CRP (ng/ml)	**4.63±0.39**	**4.33±0.94**	**4.18±0.81**
Lipid profile			
Total cholesterol (mg/dl)	**187.38±53.61**	**206.35±46.09**	**197.16±41.07**
LDL-C (mg/dl)	**128.31±65.76**	**148.67±54.64**	**142.27±34.31**
HDL/C (mg/dl)	**32.30±10.22**	**32.70±6.67**	**33.13±7.71**
TG (mg/dl)	**136.98±62.97**	**171.84±43.67**	**144.79±29.48**
Insulin sensitivity			
Fasting glucose (mg/dl)	**188.87±81.6**	**216.4±67.33**	**167.9±66.7**
Serum insulin (µl U/ml)	**8.93±0.31**	**13.53±6.25**	**16.20±6.02**
HOMA-IR values	**7.11±0.60**	**7.40±3.14**	**6.65±3.22**
ALT (u/ml)	**55.88±14.37**	**52.64±12.33**	**50.67±7.97**

Data is represented as mean ± SD.
$p < 0.05$ is considered statistically significant.
* Indicates significant difference vs. carriers of TT at $p<0.05$
# Indicates significant difference vs. carriers of TG at $p<0.05$

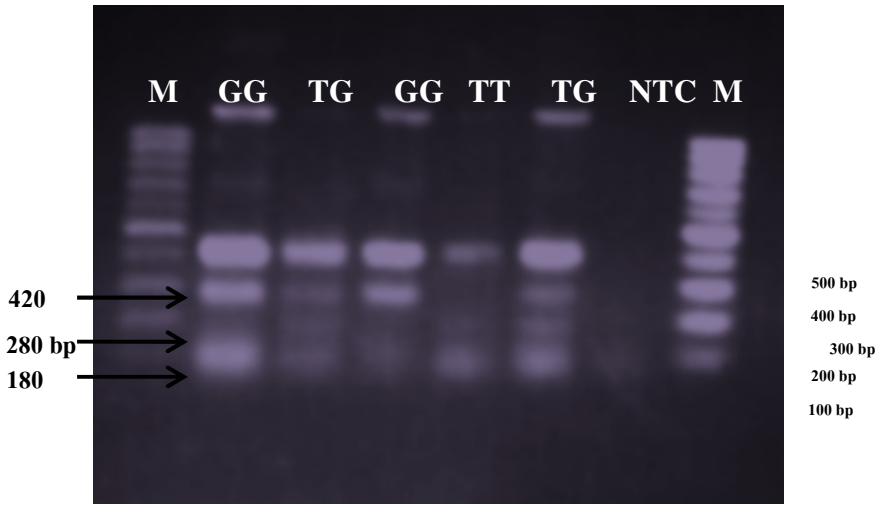

Fig (1): Tetra-MS PCR for the detection of FTO rs17817449 T>G genotypes. M: 100 bp DNA marker, the product sizes were 180 bp for T allele, 280 bp for G allele, and 420 bp for control. NTC is the no template control.
The GG genotype is identified by the presence of 2 fragments of 420 and 280 bp, the TG genotype is identified by 3 fragments of 420, 280, and 180 pb, whereas the TT genotype is identified by the presence of 2 fragments of 420 and 180 bp.

DISCUSSION

Obesity is one of the major public health problems and a leading preventable cause of death worldwide. Obesity is closely related to a number of pathological disorders such as hypertension, non-insulin dependent diabetes, some types of cancer and metabolic syndrome. It is a multi-factorial disorder and is affected by an interplay of genetic, molecular and environmental factors **(Cha et al., 2008 and Duicu et al., 2016).**
FTO gene has been found to contribute to obesity risk and has the largest effect on BMI.. There are groups of common SNPs of FTO as rs9939609, rs17817449 and rs3751812 that are associated with obesity. However, the molecular mechanisms by which FTO variants increase the personal susceptibility to overweight and obesity remain

unclear (**Loos and Yeo, 2014, Duicu et al., 2016 and Saldana-Alvarez et al., 2016).**

In the present study, assessment of the association of the FTO rs17817449 gene polymorphism with obesity and some obesity related indices or metabolic parameters were done. The data of the present study revealed that the minor allele (G) frequency for FTO rs17817449 was higher in obese and obese diabetic women than controls. G carriers were at higher risk for obesity that had 1.75 times more than T carriers. Also, GG genotype had 2.54 times and GT genotype had 1.73 times the possibility for having obesity. G allele was significantly associated with weight, BMI, waist and hip circumference. On the other hand, no significant association of FTO minor allele was detected with either serum ghrelin, hs-CRP, lipid profile, fasting glucose or insulin.

These results are in accordance with those obtained from the study of **Dina et al. (2007)** who showed that FTO gene may play a significant role in the body weight regulation as it is highly expressed in hypothalamus, so it can be influenced by appetite and hunger and is regulated by eating behavior. In addition, they reported that the minor allele (G) of FTO rs17817449 were strongly associated with obesity. **Do et al. (2008)** found significant associations between FTO rs17817449 and BMI, weight, and waist circumference ($p<0.001$ each). In addition, they reported its influence on fasting insulin, metabolic rate and plasma leptin which confirm that this genetic variant contributes to the etiology of obesity.

The data of the present study confirmed the results of **Scuteri et al. (2007)**, **Cha et al. (2008), Huback et al. (2008), Villalobos-Comparan et al. (2008), Price et al (2008) and Church et al. (2009)** who reported associations of FTO gene polymorphism with obesity, BMI and hip circumference. **Prakash et al. (2011)** found the same results in north Indian population with about 47.2 % minor allele frequency in obese subjects. **Zermeno-Rivera et al. (2014)** suggested that, the FTO rs17817449 is associated with obesity and predisposes individual to fat deposition in the thoracic and breast region causing the gynoid phenotype in Mexican women. In addition, **Saldana-Alvarez et al. (2016)** reported the significant association of FTO SNP rs17817449 with class II/III obesity and that the GG carriers were on average 2.18 kg/m² heavier than the TT carriers.

The association between FTO rs17817449 and obesity risk have not been found in other groups such as Japanese **(Horikoshi et al., 2007),** Oceanic **(Ohashi et al., 2007**), Chinese **(Li et al., 2008),** and African Americans (**Wing et al., 2009)** populations.

Chauhan et al. (2011) and **Raza et al. (2014)** investigated the association of FTO gene polymorphism with T2DM in Northern India. They observed no significant association between them and need further studies on a large sample size**.** In addition, **Friedman et al. (2016)** reported that, no association of FTO and DM was found in Brazillan morbidly obese subjects,

On the other hand, **Rees et al. (2011)** observed a significant association of FTO rs9939609 with T2DM in South Asia but this relationship was only partly accounted by BMI or waist circumference. Also, **Xiao et al. (2015)** and **Xiao et al. (2016)** found association between FTO SNP of rs805136 and rs9939609 and T2DM and obesity through the function of BMI in Uyghur population from northwest China. **Khodaeian et al. (2015)** found controversial results due to the heterogeneity in ethnicity and genetic background and they thought that studies on a large sample size will be helpful in identifying diabetes susceptible genes in Iranian population.

The biochemical role of FTO in obesity susceptibility remains unknown but several recent studies have begun to shed light on its function. It may be responsible for controlling the eating behavior and body metabolism as it is highly expressed in hypothalamic nuclei which govern the energy balance**.** It catalyzes Fe(II)- and 2OG-dependent DNA demethylation with concomitant production of succinate, formaldehyde and carbon dioxide **(Gerken et al., 2007, Price et al., 2008 and Prakash et al., 2011).** It has been recently shown that**,** FTO could activate two other genes (IRX3 and IRX5) which may direct the cell to store energy in persons with the risk allele. In contrast, in cells with the normal wild variant the same two genes are switched off and this causes cells to burn energy **(Claussnitzer et al., 2015).** This normal allele will predispose their carriers to a lower body weight, BMI and waist circumference**.** The trials to switch off this FTO risk variant by any recent therapy as certain foods or gene therapy will prevent the percentage of women who is affected by this allele to get obese via burning instead of storing energy **(Coghan, 2015).**

Almen et al. (2012) reported that FTO could influence the methylation of genes that encode transcriptional regulators as KARS and TERF2IP. Also, it can affect the methylathion of transcriptional co-activators that are induced by estrogen as BCAS3. This interaction between the genetic and epigenetic factors may in part explain the genetic susceptibility to obesity through FTO gene variants (**Almen et al., 2012 and Saldana-Alvarez et al., 2016).**

The levels of FTO mRNA in arcuate nucleus are regulated by feeding and fasting states **(Prakash et al., 2011).** In murine models, the FTO mRNA transcript is correlated with food intake, suggesting that this gene may participate in energy homeostasis. Also, the mouse brain has been shown recently to express FTO protein which serves as the main regulator of energy balance and BMI regulation. Furthermore, subjects with at least one copy of the FTO risk allele had higher food intake than those with two copies of the wild type allele **(Saldana-Alvarez et al., 2016).**

Ghrelin, a gut hormone, is released from the gastrointestinal tract in response to nutrients ingestion and could regulate the body weight. Its circulating levels may alter the appetite, food intake and modulate brain activity. It is implicated in blood glucose homeostasis and regulation of insulin secretion **(Verhulst and Depoortere, 2012)**.

The results of present study showed a significant decrease in the serum levels of ghrelin in obese subjects compared to the controls. These results are in a line with **Tschop et al. (2000)** who found decreased ghrelin levels in obese Caucasians than lean and Pima Indians. Moreover, **Cumming, (2006)** suggested that the ingestion of nutrients (mainly carbohydrates) were associated with decreased plasma ghrelin which can be resulted from neurally transmitted intestinal signals augmented by insulin secretion. In addition, **Charipour et al. (2013) and Saad et al. (2013)** found decreased ghrelin levels in overweight subjects with no correlations with glucose, total cholesterol, HDL-C, HDL-C and triglycerides. **Buss et al. (2014)** demonstrated its negative correlation with insulin resistance. **Perez-Tilve et al. (2011)** suggested that ghrelin could stimulate the gene expression of lipogenic enzymes like acetyl COA carboxylase, fatty acid synthase and in turn, it modulates adipose tissue metabolism.

The hs-CRP is a product of adipose tissue and considered as a pro-inflammatory cytokine that is released in response to inflammation to

reduce the resolution of these conditions and found to be associated with metabolic syndrome **(Alezadeh and Kichler , 2014).** The results of the present study showed a significant increase in the serum levels of hs-CRP in obese subjects compared to the controls. Moreover, a significant negative correlation was found between ghrelin and hs-CRP in obese subjects. This correlation may indicate their associated role in modulating the energy balance and sub-clinical inflammatory status in those obese subjects.

These results were in agreement with **Faucher et al. (2012), Fronczyk et al. (2014), Bhavita et al. (2015) and Honorio-Franco et al. (2015)** who found that, obese subjects were presented with higher hs-CRP levels than overweight and normal subjects. Obesity is found to be associated with chronic inflammation with production of cytokines and activation of pro-thrombotic and pro-inflammatory signaling pathways that may lead to T2DM, myocardial infarction and stroke **(Alemzadeh and Kichler, 2014**).

Karra et al. (2013) studied the link between FTO gene and ghrelin and showed that FTO could regulate ghrelin hormone, a key mediator of ingestive behavior resulting in the reduced satiety, increased energy intake and increased food cue responsivity**. Zou et al. (2008)** suggested that the lower ghrelin levels in obesity are part of a negative feedback to inhibit appetite and body weight. This could clearly explain the results of the present study.

Recently, it has shown that, in cell culture, FTO over-expression can reduce ghrelin-mRNA-N6-methyladenosine methylation, concomitantly, increasing ghrelin mRNA and peptide levels. FTO gene could regulate the circulating level of ghrelin and attenuate the post prandial appetite by modulating the neural responses to food images in brain reward regions**.** It has been found that FTO polymorphism can regulate the expression of genes at large kilobases of distance as well as the expression of FTO gene itself and the regions for transcription factors binding **(Hernandez- Caballero and Sierra-Ramirez, 2015**). These findings may throw some light about how FTO obesity risk alleles predispose to increased energy intake and obesity in human **(Karra et al., 2013)**.

Conclusion:

This study revealed an association between FTO rs17817449 (T>G) gene polymorphism and obesity in Upper Egyptian women sample. It showed the minor allele (G) association with obesity risk

and suggested that the GG variant is associated with the measures of adiposity like BMI, weight, hip and waist circumference. Ghrelin and hs-CRP also may play essential roles in developing obesity. To the best of our knowledge this is the first study that showed the role of FTO rs17817449 genetic variant with regard to obesity risk in Upper Egypt (Assiut) sample of study. Additional studies that clarify the association between FTO polymorphism, ghrelin and other biochemical markers are needed with a large sample size to verify our findings. The trials to switch off this FTO faulty gene variant by the recent therapies as certain foods or gene therapy will prevent the percentage of women who is affected by this risk allele to get obese via burning rather than storing energy.

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الملخص العربى

التنبؤ بحدوث السمنة بين السيدات فى صعيد مصر: دور كلا من التحور الجينى لجين FTOوهرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية

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كلية الطب ، جامعة أسيوط ، أسيوط

ان مرض السمنة من الامراض الاساسية التى تهدد صحة الانسان و هو من اهم عوامل الخطورة لزيادة الحساسية لهرمون الانسولين ، ارتفاع ضغط الدم، زيادة نسبة الدهون فى الدم ، البوال السكرى النوع الثانى ، تصلب الشرايين و امراض القلب و الاوعية الدموية . و قد وجدت علاقة بين التحور الجينى لجين ال FTO و حدوث مرض السمنة و مرض البوال السكرى فى الكثير من الشعوب المختلفة ولكن دوره كعامل من عوامل الخطورة لزيادة نسبة الاصابة بهذه الامراض ما زال تحت الدراسة. و تهدف هذه الدراسة الى

دراسة الارتباط بين التحور الجينى لجين ال FTO و مرض السمنة و البوال السكرى و ايضا معرفة دور كلا من هرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية كعوامل خطورة لحدوث هذه الامراض بين السيدات فى صعيد مصر.و تشتمل هذه الدراسة على ٢٩٩ شخص. ١١٥ يعانون من السمنة (تم تقسيمهم الى مجموعتين : المجموعة الاولى تشمل ٦٥ سيدة لا تعانى من مرض البوال السكرى و المجموعة الثانية تشمل ٥٠ سيدة تعانى من مرض البوال السكرى)، هذا بالاضافة الى ١١٤ من الاصحاء كمجموعة ضابطة. و تم تعيين كل من التحورات الطارئة لجين FTO بطريقة MS-PCR كما تم قياس مستويات هرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية فى السيرم و علاقتهم بالقياسات الانثروبومترية و الدلالات البيوكيميائية و الحالة الاكلينيكية للمرضى.

و قد اوضحت نتائج هذه الدراسة الى ارتفاع معدل الاليل G لجين ال FTO فى مرضى السمنة (٤٦.٥ %) و مرضى السمنةاللاتى تعانى البوال السكرى (٤٥%) عن الاصحاء (٣٣.٣%) و التى تمثل حوالى ١.٧٥ مرة زيادة لخطورة حدوث السمنة. كما وجد ان النمط الجينى GG (البديل المتماثل) و النمط الجينى GT (البديل المتخالف) موجود فى السيدات اللاتى تعانى السمنة بنسبة ٢٥.٢% و ٤٢.٦ % و فى السيدات اللاتى تعانى من مرض السكر بنسبة ٢٤% و ٤٢% مقارنة ب ١٤.٩% و ٣٦.٨% فى الاصحاء على الترتيب. كما ان النمط الجينى GG يرتبط ارتباطا ذو دلالة احصائية بالوزن و محيط الخصر و محيط الحوض وBMI. كما وجد ان المرضى الحاملين للنمط الجينى GG لديهم قابلية لحدوث مرض السمنة بزيادة قدرها ٢.٥٤ مرة عنها فى حاملى النمط الجينى TT.

و من ناحية اخرى وجد نقص ذو دلاله احصائية فى مستوى هرمون الجريلين فى المرضى عن الاصحاء و زيادة ذو دلالة احصائية فى مستوى البروتين المتفاعل سى ذو الحساسية العالية فى المرضى عنه فى الاصحاء. ووجدت علاقة عكسية ذات دلالة احصائية بين هرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية و لم توجد اى علاقة بين التحورات الجينية لل FTO و كلا من هرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية و نسبه الدهون و الجلكوز و الانسولين.

و نستخلص من هذه الدراسة: ان الاليل G يرتبط بزيادة معدل حدوث مرض السمنة بين سيدات صعيد مصر كما يرتبط بزيادة BMI و محيط الخصر و محيط الحوض. كما ان كلا من هرمون الجريلين و البروتين المتفاعل سى ذو الحساسية العالية يمكن ان يلعب دورا هاما فى حدوث مرض السمنه و تعتبر هذه الدراسة اول دراسة اجريت بين السيدات فى صعيد مصر و هناك محاولات كثيرة لغلق التحور الجينى لل FTO عن طريق علاجات حديثة مثل انواع معينة من الاطعمه او العلاج الجينى الذى يقلل من نسبة حدوث مرض السمنة ويجعل الجسم قادرا على الحرق اكثر من اختزان الطاقة.