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# Correlation between adiponectin level with common variant (rs9939609) of fat mass and obesity-associated gene in obese type 2 diabetic women

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**ABSTRACT**

**Introduction:** It is well-known that there is an association between rs9939609 polymorphism of fat mass and obesity-associated (*FTO*) gene with obesity in people from different ethnic background.

**Objectives:** This study aimed to assess the association of common polymorphism on adiposity indexes and type 2 diabetic mellitus (T2DM) and its association with adiponectin level in Iranian women.

**Patients and Methods:** A sample population of 83 obese patients was investigated in a study with case-control design. The patients' age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood sugar (FBS), insulin, insulin resistance, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), glycated hemoglobin, triglycerides (TG) and adiponectin level were measured. The genotype of *FTO* rs9939609 was considered using specific primers via PCR and sequencing.

**Results:** There was a significant difference between two groups (diabetic and non-diabetic) in terms of their age, FBS, HbA1c, LDL-C, SBP and DBP. The mean ± standard error (SE) of these parameters except for DBP and SBP were higher in diabetic group. The frequency of the TA genotype (48.27%) was higher in the diabetic group. The levels of FBS, HbA1c and insulin resistance index (HOMA-IR) were high in mutant group in comparison with wild group. There was no significant correlation between adiponectin level and anthropometric and metabolic parameters. However, in diabetic patients significant moderate positive correlation was found between HDL-C and adiponectin level ($r = 0.473$, $P = 0.01$).

**Conclusion:** The association of rs9939609 *FTO* polymorphism was significant with FBS, HbA1c, TG, insulin, HOMA and adiponectin level in obese diabetic women who harbored the mutant A allele.

Original

*Implication for health policy/practice/research/medical education:*
In a study on 83 obese women, significant association was found between *FTO* rs993609 polymorphism and FBS, HbA1c, TG, insulin, HOMA index and adiponectin level specially in diabetic women who had mutant genotype. In addition, adiponectin level showed positive significant correlation with HDL-C.

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## Introduction

The association between obesity, insulin resistance and hyperinsulinemia has been proved (1) and well-known as a key risk cause for the progress of type 2 diabetic mellitus (T2DM) and cardiovascular disease (2). Various hormones and cytokines are expressed in adipose tissues which affect the creating of insulin resistance, however, the molecular pathways about association of obesity, T2DM and cardiovascular disease have been understood poorly (3,4). The combination of different genes, life style

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and environment could result in obesity (5). Previous studies about genome-wide association revealed that rs9939609 as a common polymorphism of fat mass and obesity-associated (*FTO*) gene had significant association with obesity and body mass index (BMI) in the T2DM patients (6,7).

The association of different *FTO* variants with T2DM and BMI has been reported in white European people (8). The findings of these studies illustrated inconsistency with the results obtained from the studies conducted on Asian population. The reason for the observed inconsistency might be either different study designs, low sample sizes or racial differences (9-11).

The associations between *FTO* and obesity-linked different phenotypes were further studied in numerous populations (such as Caucasians and Asians peoples) (12,13). However, in African population this association was not confirmed (14). Moreover, the association of *FTO* gene with fasting glucose and insulin was reported, however, when the results were adjusted for body mass index (BMI), the association varied in some investigations (15,16), but confirmed in others (17,18). In addition to the association of *FTO* polymorphisms and T2DM, the key roles of secreted adipocytokines and adiponectin were determined in the inflammatory responses and insulin resistance (19-22). Moreover, the decrease of adiponectin level was reported in clinical and animal models studies. These findings could also be used for identifying insulin resistance prior to the progress of overt diabetes (23-27).

## Objectives

The main aim of our study was to investigate the association of previously recognized common variant of *FTO*; rs9939609 polymorphism, with adiposity and T2DM, and also its association with adiponectin level in a group of Iranian women with T2DM

## Patients and Methods

### *Patients*

In this case-control study, a total of 83 obese women (40 non-diabetes and 43 type 2 diabetes) were randomly selected from patients who referred to Tabriz University teaching hospital in Iran, after filling out informed consent form. The inclusion criteria for obese participants were: having body mass index (BMI) >30 kg/m$^2$, fasting blood sugar (FBS) more than 126 mg/dL, presence of T2DM, having no family relationship with the participants in non-diabetic group, and having no specific diseases or history of any chronic illness. Accordingly patients with other kidney disease and the users of corticosteroids and lipid-decreasing drugs were eliminated from the study.

### *Determination of the anthropometric indicators*

The measurement of anthropometric indicators was performed using the standard kit (Pars Azmun, Tehran, Iran). The age, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, and FBS of each participant was determined.

### *Blood sampling*

Blood samples were obtained from women after 8-12 hours of fasting and were transferred into tubes with EDTA in order to prevent them from clotting. The obtained samples were aliquoted and stored at –20ºC. The DNA was isolated and different biochemical parameters were determined from whole blood samples.

### *Calculating the biochemical parameters*

The total cholesterol (TC), high-density lipoprotein (HDL-C), and triglyceride (TG) concentration were measured using available enzymatic kit (Pars Azmun, Tehran, Iran). The Low-density lipoprotein cholesterol (LDL-C) was calculated by Friedewald equation:

LDL cholesterol = total cholesterol – HDL cholesterol–triglyceride/5 (mg/dL glycated). The hemoglobin ($HbA_{1c}$) level and the serum adiponectin were determined by NycoCard reader and enzyme-linked immunosorbent assay (ELISA: Crystal day Biotech Co., Ltd), respectively.

### *FTO genotyping; point mutation*

Genomic DNA was extracted from the peripheral blood according to the standard salting-out method. To amplify the *FTO* rs9939609 SNP, the forward primer (5'GTAGGAATACTAGGAGAGGAG 3') and the reverse primer (5' GCTTAAAGTTAATGGCTTCAGG 3') were designed using Oligo5 program. The PCR reactions were performed in 25 µL volumes containing 40 ng of template DNA and 0.4 µmol /L of each primer using 1X PCR Master kit (CinnaGen Co., Iran). The PCR amplification was performed in the following conditions: initial denaturation at 95°C for 2 minutes, 35 cycles of denaturation at 96°C for 20 seconds, annealing at 60°C for 40 seconds, extension at 72°C for 1 minute and a final extension of 72°C for 5 minutes. The size of the amplified PCR products was determined by comparing with the 50 bp DNA ladder (Fermantase Co., Canada) and the PCR products were electrophoresed (1% agarose gel). The subsequent analysis included multiple sequence alignment using the BLAST program (https://blast.ncbi.nlm.nih.gov/Blast.cgi) and Chromas software (version 2.6.2).

### *Ethical issues*

The research followed the tenets of the Declaration of Helsinki. Before the study, written informed consent was obtained from all patients who participated in the study. All information about individuals was coded and kept confidential. All trials were in compliance with Tabriz University of Medical Sciences statement and the study was approved by Ethics Committee (# 5/4/3475).

### *Statistical analysis*

The analysis of the data was done using *t* test/ANOVA (parametric data) and Mann–Whitney U test/Kruskal-Wallis (non-parametric data) and the results were reported as mean ± standard error (SE). The frequency of the allele and genotype was calculated. The Spearman's and Pearson's correlation coefficient was applied to evaluate

the correlation of adiponectin level with the parametric and non- parametric data. For statistical analysis, statistical package of SPSS 17.0 was used. A *P* value lower than 0.05 was considered statistically significant.

## Results

The genotyping of *FTO* SNP rs9939609 was performed on 83 obese women. The clinical parameters of these obese women in two groups are presented in Table 1. There was a statistically significant difference between two groups in terms of clinical parameters such as FBS, $HbA_{1c}$, SBP, DBP, insulin, HOMA and adiponectin level ($P < 0.05$). The mean ± SE of FBS and insulin resistance index (HOMA-IR) were higher in diabetic groups.

The amplification of *FTO* rs9939609 SNP by PCR produced a fragment size of ~450 bp in the patients (Figure 1) and the type of genotypes was determined with analyzing sequencing results. The allele and genotype frequncies in diabetic and non-diabetic obese women are shown in Table 2. The heterozygous and homogenous mutant genotype,(48%), and TA & TT (35%) had high frequencies in diabetic women. Table 3 shows the anthropometric, metabolic, and biochemical characteristics of participants in the three genotypes. There was a statistically significant difference of FBS, $HbA_{1c}$, TG, insulin level, and HOMA between two groups. There was also a significant difference of serum adiponectin levels among three groups. The findings also show that mean of serum adiponectin levels was higher in the wild type genotype (TT) in comparison with other mutant genotypes (TA > AA). Table 4 shows the

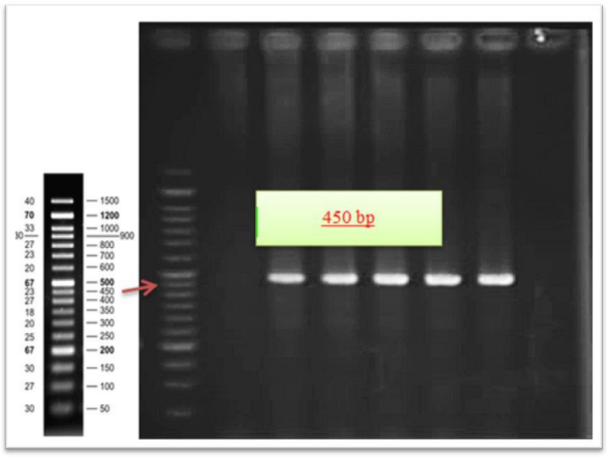


**Figure 1.** Fragment size of 450 bp of *FTO* gene which included rs9939609 SNP Line 1: 50 bp molecular weight ladder, and line 3 – 7: PCR product from participants

effect of rs9939609 SNP on various anthropometric and biochemical parameters in the diabetic and non-diabetic groups. The adiponectin level in diabetic group with AA genotype was higher than that with other genotypes in the same group, however, this difference was not statistically significant. In contrast to diabetic group, a significant difference between SBP and three genotypes in non-diabetic group was detected. Furthermore, no significant correlation between adiponectin, anthropometric and metabolic parameters except for HDL-C in diabetic patients was found ($r = 0.47$, $P = 0.01$; Table 5). According to the amount of *r* coefficient in Spearman's test, the strength of correlation was between 0.3 and 0.5 which was indicative of a low correlation.

## Discussion

The previous studies revealed important genetic effect of *FTO* gene polymorphisms (especially rs9939609) on BMI and obesity (28,29) and the development of related diseases, including diabetic nephropathy (30). In addition to these findings, the association of two polymorphisms *FTO* -rs9939609 and *MC4R*-rs17782313 with T2DM was investigated and the results suggested that this link depended on type of diet (Mediterranean diet) (31). The association of *FTO* gene variants with obesity and T2DM was reported in white Europeans. Yajnik et al in 2009 supported this strong association in Asians Indian Sikhs but they suggested that its probably was not mediated only through BMI rather through other related variants

**Table 1.** Clinical parameters of diabetic and non-diabetic groups

| Variable | ND ( n= 40) | D ( n= 43) | P value |
|---|---|---|---|
| Age (y) | 48.85±11.24 | 54.40±9.72 | 0.014[a] |
| FBS (mg/dL) | 88.10±9.34 | 172.33±48.89 | 0.001[a] |
| $HbA_{1c}$ (%) | 4.74±0.39 | 7.75±1.68 | 0.001[a] |
| TG (mg/dL) | 183.56±64.53 | 193.05±67.22 | 0.52 |
| TC (mg/dL) | 201.87±43.01 | 189.63±39.61 | 0.37 |
| BMI ($kg/m^2$) | 32.62±2.96 | 54.40±9.72 | 0.911 |
| SBP (mm Hg) | 120.75±6.55 | 116.79±24.44 | 0.005[a] |
| DBP (mm Hg) | 80.25±1.58 | 75.11±16.38 | 0.001[a] |
| LDL-C (mg/dL) | 145.08±51.03 | 148.47±59.97 | 0.783 |
| HDL-C (mg/dL) | 48.95±12.43 | 48.65±10.50 | 0.90 |
| Insulin (µIU/mL) | 23.1±11.58 | 21.89±4.14 | 0.001[a] |
| HOMA | 4.77±2.34 | 9.15±1.73 | 0.001[a] |
| Adiponectin (mg/L) | 38.58±5.3 | 31.4±5.96 | 0.001[a] |

[a]$P < 0.05$ considered as significant level, t-test for parametric data and Mann-whitney U test for non-parametric data.
Values are indicated as mean ± standard error. ND: non-diabetic, D: diabetic.

**Table 2.** Allele/genotype frequencies in diabetic and non-diabetic obese women

| SNP | Allele | D No. (%) | ND No. (%) | Genotype | D No. (%) | ND No. (%) |
|---|---|---|---|---|---|---|
| rs9939609 | T | 35 (40.7) | 72 (90) | TT | 3 (16.56) | 33(81) |
| | A | 51 (59.3) | 8 (10) | TA | 29 (48.27) | 6(18) |
| | | | | AA | 11(35.17%) | 1 (1%) |

Abbreviations: SNP, single nucleotide polymorphism; D, diabetic; ND, non-diabetic.

**Table 3.** Anthropometric characteristics and metabolic parameters based on rs9939609 SNP of *FTO* gene in patients

| Variable | Mean ± SE[a] | | | *P* value ( ANOVA) |
|---|---|---|---|---|
| | AA (n = 12) | TA (n = 35) | TT (n= 36) | |
| Age (years) | 52.17 ± 9.77 | 52.57± 9.68 | 50.47±12.24 | 0.707 |
| HDL-C (mg/dL) | 49.12±9.00 | 49.89±8.00 | 48.68±11.41 | 0.905 |
| BMI (kg/m$^2$) | 33.74±5.38 | 32.56±8.05 | 33.08±3.99 | 0.28 |
| SBP (mmHg) | 123.33±8.87 | 118.23±19.62 | 117.61±19.14 | 0.42 |
| DBP (mm Hg) | 78.33±10.30 | 76.57±13.04 | 78.33±11.83 | 0.39 |
| LDL-C (mg/dL) | 192.83±45.44 | 172.50±50.59 | 158.88±66.94 | 0.38 |
| FBS (mg/dL) | 173.33±52.38 | 160.00±55.29 | 90.86±2.54 | < 0.001[b] |
| $Hb_{A1c}$ (%) | 7.40±1.52 | 7.45±2.01 | 4.82±0.50 | < 0.001[b] |
| TG (mg/dL) | 168.50±35.92 | 211.80±77.14 | 172.72±53.62 | 0.02[b] |
| TC (mg/dL) | 179.75±43.20 | 203.03±40.68 | 189.42±46.57 | 0.44 |
| Insulin (µIU/mL)[c] | 31.65±12.96 | 16.84±2.54 | 24.88±12.85 | 0.007[b] |
| HOMA[d] | 13.37±5.48 | 6.88±1.05 | 5.15±2.6 | 0.00[b] |
| Adiponectin (mg/L)[e] | 22.94±5.94 | 31.29±6.23 | 42.31±6.61 | 0.004[b] |

[a] $P < 0.05$ is considered as significant level; [b] Values are indicated as mean ± standard error; [c] Chi-square = 10.01; [d] Chi-square = 17.77; [e] Chi-square=11.25

**Table 4.** The effect of rs9939609 SNP on various anthropometric and biochemical parameters in diabetic and non-diabetic groups

| Parameters | rs9939609 SNP | | | | | | *P* value | |
|---|---|---|---|---|---|---|---|---|
| | TT | | TA | | AA | | | |
| | ND | D | ND | D | ND | D | ND | D |
| Age ( y) | 49.28±11.41 | 67.00±9.53 | 46.83±11.17 | 53.76±10.11 | 47.00 | 52.64±3.049 | 0.88 | 0.04 |
| BMI (kg/m$^2$) | 32.81±3.55 | 32.77±8.73 | 32.06±1.87 | 34.08±5.51 | 33.03 | 34.08±1.66 | 0.58 | 0.75 |
| FBS (mg/dL) | 87.62±10.00 | 120.67±16.01 | 89.33±9.04 | 180.36±48.64 | 96.00 | 180.36±14.66 | 0.64 | 0.06 |
| SBP (mm Hg) | 81.33±33.79 | 121.03±1.43 | 117.78±4.15 | 120.00±0.00 | 123.63 | 123.63±2.78 | 0.02[a] | 0.94 |
| DBP (mm Hg) | 56.66±23.33 | 80.34±0.34 | 75.71±2.74 | 80.00±0.00 | 78.18 | 78.18±3.25 | 0.12 | 0.89 |
| $HbA_{1c}$ (%) | 5.76±0.40 | 4.70±0.41 | 8.01±0.33 | 4.75±0.13 | 7.61 | 7.61±0.42 | 0.80 | 0.71 |
| HDL-C (mg/dL) | 49.30±12.78 | 56.33±16.92 | 49.33±10.94 | 48.39±10.34 | 35.00 | 46.64±9.54 | 0.36 | 0.38 |
| LDL-C (mg/dL) | 138.91±49.03 | 164.67±5.34 | 231±9.21 | 150.36±48.95 | 134.36 | 134.36±58.90 | 0.83 | 0.43 |
| TG (mg/dL) | 173.00±55.54 | 163.00±28.61 | 237.33±88.04 | 165.73±36.31 | 165.73 | 165.72±10.94 | 0.90 | 0.90 |
| TC (mg/dL) | 197.62±45.76 | 146.67±18.38 | 220.83±62.89 | 175.73±42.89 | 224.00 | 175.72±12.93 | 0.43 | 0.31 |
| Insulin (µIU/mL) | 6.16±2.95 | 28.75±15.91 | 19.37±2.97 | 6.16±1.56 | 33.65 | 33.65±14.03 | 0.20 | 0.80 |
| HOMA | 1.72±0.82 | 5.90±3.22 | 8.06±1.20 | 1.38±0.37 | 14.38 | 14.38±5.90 | 0.15 | 0.80 |
| Adiponectin (mg/L) | 71.08±10.19 | 77.15±5.21 | 74.31±6.01 | 73.12±9.61 | 78.97 | 78.97±7.49 | 0.87 | 0.73 |

Values are indicated as mean ± standard error. ND: non-diabetic, D: diabetic.
[a] indicates significant association.

between these two populations such as body size and T2DM (32). The association of obesity and rs9939609 in the *FTO* gene was found in European Caucasian samples. A similar study examined this association with metabolic syndrome (MetS) in 2121 non-Caucasian participants form four different geographical origins. The findings illustrated that in comparison with non-carriers, carriers of one or more copies of A allele were expected to have more MetS (OR of 1.23) in a significant way and this association was much stronger among men. In conclusion, they reported the association between *FTO* rs9939609 with an increased risk for MetS in their studied population (33). The association of 52 *FTO* polymorphisms with obese children was assessed and the effect of these biomarkers on different parameters (anthropometric, clinical and metabolic) was determined. Also, the influence of the risk biomarkers was used to estimate the related inflammation and cardiovascular disease among Spanish children. The investigated parameters were high in the obese groups in comparison with the control group with normal BMI, whereas the adiponectin level and HDL-C were lower. The rs9939609 single-nucleotide polymorphism (SNP) along with three other polymorphisms (rs9935401, rs9939609 and rs9928094) had positive association with obesity (34). These results validated the previously-described association of *FTO* gene (in intron 1) with the obesity (35). In our study, a statistically significant difference between two groups regarding the parameters such as age, FBS, $HbA_{1c}$, LDL-C, DBP and SBP was detected. The mean ± SE of these parameters except for DBP and SBP were higher in diabetic group. Additionally, HOMA, insulin level and adiponectin concentration were more in diabetic group than in non-diabetic women. In addition, the observed differences between these levels were significant. Freathy et al in 2008 investigated whether the variation of *FTO* gene was associated with increased BMI, T2DM or not. They also investigated its related disorders in metabolic traits such as raising insulin, glucose level and TG in the 17 037 white European people. Each copy of A allele from

**Table 5.** Spearman's correlation coefficients of adiponectin with anthropometric and metabolic parameters in diabetic and non-diabetic groups

| Variable | Non-diabetic | | Diabetic | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| Age ( years) | 0.202 | 0.216 | -0.52 | 0.739 |
| HDL-C (mg/dL) | 0.212 | 0.270 | 0.473 | 0.010[a] |
| BMI (kg/m$^2$) | 0.017 | 0.918 | -0.104 | 0.505 |
| SBP (mm Hg) | 0.187 | 0.253 | 0.179 | 0.251 |
| DBP (mm Hg) | -0.173 | 0.292 | 0.248 | 0.109 |
| Insulin (µIU/mL) | 0.050 | 0.764 | 0.032 | 0.840 |
| HOMA-IR | 0.050 | 0.736 | 0.027 | 0.863 |
| LDL-C (mg/dL) | -0.238 | 0.213 | 0.097 | 0.669 |
| FBS (mg/dL) | 0.076 | 0.644 | 0.002 | 0.990 |
| $Hb_{A1c}$ (%) | 0.187 | 0.254 | 0.079 | 0.615 |
| TG (mg/dL) | 0.108 | 0.513 | 0.001 | 0.995 |
| TC (mg/dL) | 0.065 | 0.694 | 0.087 | 0.585 |

[a] indicates significant association.

*FTO* rs9939609 was linked with upper fasting insulin, glucose, TG and lower HDL-C. However, these associations were not observed after adjusting BMI. In addition, LDL-C, $HbA_{1c}$, and blood pressure (systolic and diastolic pressures) were in the estimated level and the association of *FTO* rs9939609 with a higher metabolic syndrome was found. The results suggested that the detection of association in the sample sizes more than 12 000 participants must be performed at *P* level less than 0.05 (36). It is well-known that in obese people, the plasma level of leptin is high because of increased body fat mass. The investigations revealed a functional link between insulin resistance and leptin levels in insulin-resistant T2DM men without depending of their body composition (37). However, some studies have reported differences between adiponectin level in both men and women (38). Beside this fact, findings on Japanese population suggested negative correlation between adiponectin concentration and homoeostasis model assessment and positive link with HDL-C regardless of age, gender and BMI (39). Weyer et al in 2001 determined plasma level of adiponectin and metabolic parameters of Caucasians (N = 23) and Pima Indians (N = 121), who had a high aptitude to be obese and have T2DM. The study illustrated a negative association between level of plasma adiponectin with body fat, waist-to-thigh ratio, fasting level of insulin level, and 2 hours glucose level, but positive correlation with insulin sensitivity (40). According to the results of this study, the frequency of TA genotype (48.27%) was higher in the diabetic group. However higher frequency of *FTO* genotype in non-diabetic group was related to TT (81%). The differences between FBS, $HbA_{1c}$, TG, insulin, HOMA and adiponectin level were significant in three genotype. The level of FBS, $HbA_{1c}$ and HOMA were higher in mutant group (AA, TA) in comparison with wild group (TT). In contrast, the order of the TG level was TA > TT > AA, the insulin level was AA> TT> TA, and adiponectin level was TT>TA>AA. No significant correlation was found between the parameters and adiponectin level except for HDL-C in diabetic group. There was a significant difference in adiponectin level between two investigated groups; Pima Indians and Caucasians; and Pima Indians with control group. This difference remained even after adjusting the analyses with obesity. These outcomes revealed that there was an association between obesity and T2DM with low level of adiponectin in different racial groups. The findings also indicated that in comparison with the range of obesity and glucose intolerance, the grade of hypo-adiponectinemia had much tighter association with insulin resistance and hyper-insulinemia (40). In line with these results, it was found out that the level of adiponectin in obese people was low (41-43). The examination of expression profile of adipocyte genes was determined via q-PCR through the differentiation process of pre-adipocytes to human adipocytes. Also, the impact of tumor necrosis factor alpha (TNF-α) on expressed profile of the correlated adipokines was investigated during the differentiation of adipocytes. The levels of adiponectin, leptin, monocyte chemoattractant protein-1, and nerve growth factor were measured in the medium by ELISA and the results demonstrated that the pattern of secreted protein dictated cellular mRNA level. The differentiated human adipocytes were treated with TNF-α and the findings revealed that the level of adiponectin had decreased significantly, other factors such as AGT and haptoglobin mRNA were increased and leptin and PAI-1 illustrated no change in level. According to the results, during the differentiation of adipocytes, the expression of adipocyte gene was changed and the pleiotropic effect of TNF-α was found on inflammation linked with production of adipokine (44). In addition, the adipocyte metabolism during the development and aging of 3T3-L1 adipocytes was studied. The results indicated that in older mature cells, insulin resistance was increased and glucose uptake and fuel consumption was reduced in comparison with young mature cells. Moreover, the gene expression of adiponectin and leptin was decreased in the aged adipocytes and adiponectin and leptin proteins had important role during energy metabolism (45). In addition, Degewa-Yamauch et al in 2005 stated that there was a significantly negative correlation between the expression of adiponectin gene and BMI. There was also a significant correlation between adiponectin mRNA and serum level of adiponectin. In subcutaneous adipocytes from thin people, TNF-α prevented the release of adiponectin but in the obese people it had no effect on subcutaneous or omental adipocytes. In addition to these results, dexamethasone could significantly inhibit the release of adiponectin during 24-hour treatment. Also, the synthesis of adiponectin in subcutaneous adipocytes was reduced due to lower level of adiponectin level in obese people and glucocorticoids controlled the expression of adiponectin gene in human adipocytes. Furthermore, TNF-α could not inhibit the synthesis of adiponectin directly in human adipocytes (46). Yamauchi et al showed that adiponectin gene is located in chromosome 3q27 and

is susceptible locus for T2DM and metabolic syndrome. In their study on obese mouse models, they confirmed the correlation between reduced expression of adiponectin level and insulin resistance due to reducing TGs amount in muscle and liver. This is the consequence of high expression of related molecules in usage of fatty-acid and loss of energy in muscle. Based on these data, they suggested that the replacement of adiponectin could offer a novel therapy for insulin resistance and T2DM (47). Duicu et al assessed any possible association of SNPs *FTO* gene (rs9939609 and rs17817449) with biomarkers (anthropometric and metabolic parameters) and both adiponectin and leptin level in 387 Romanian obese individuals. After genotyping of the *FTO* gene by PCR-RFLP, a significant link between rs9939609 SNP and obesity was found. The risk allele carriers for rs17817449 had higher level of anthropometric parameters (weight, BMI, TGs, fasting glucose and cholesterol) as well as high concentration of adiponectin. The results demonstrated strong association between both variants of *FTO* (rs9939609/rs17817449) and different measures of adiposity, TC, TG, and LDL-C levels (48). In the cohort study by Qi et al, rs9939609 of *FTO* was genotyped in men (N = 2287) and women (N = 3520). The plasma level of adiponectin and leptin was measured in diabetic people. They observed a decreasing association trend between rs9939609 of *FTO* and BMI in old men (more than 65 years) whereas this association in women was constant. Moreover, rs9939609 SNP was linked with lower level of adiponectin and leptin in women with diabetic disorder. In in vivo study, expression of *FTO* in mice adipocytes was nearly 50% less than in wild-type mice (49). In the total of 129 obese individuals, the metabolic parameters and the level of six adipocytokines were measured. In comparison with wild genotype, mutant genotype had higher amount of BMI, fat mass, weight, C reactive protein and leptin (50).

## Conclusion

The present study which was conducted with limited number of participants for three different genotypes, revealed significant association between *FTO* rs9939609 polymorphism with FBS, $HbA_{1c}$, TG, insulin, HOMA and adiponectin level in obese diabetic women harboring the mutant A allele. In addition, multiple comparisons of other SNPs will be completed in next studies.

## Limitations of the study

The results of this study were report of a small group of diabetic obese women. It is suggested that the study conducted on larger sample size patients.

## Authors' contribution

In this study, NZ as corresponding author and supervisor conducted the study; AO as an advisor contributed to the experimental design; HL analyzed the results and interpreted data; FS wrote the manuscript and with collaboration of MA, RM, MN, FG; and SP performed the experiments and collected the data.

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## Conflicts of interest

The authors declare no conflict of interest.

## Ethical considerations

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