Association between inflammatory obesity phenotypes, FTO-rs9939609, and cardiovascular risk factors in patients with type 2 diabetes

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is ninth major cause of death and accounts for approximately 451 million (age 18–99 years) cases worldwide.[1,2] Obesity, sedentary lifestyle, dyslipidemia, unhealthy dietary pattern, and nutrients deficiency are important risk factors for the T2DM development and its complications.[3,4] The cardiometabolic risk factors, including hypertension, insulin resistance, dyslipidemia, and cardiovascular disease (CVD), are greater in patients with T2DM compared to healthy people. However, T2DM-related complications are not same for all patients with T2DM.[5] Previous studies showed that the vascular atherosclerotic risks were higher in abdominally obese diabetic patients than in the diabetics without abdominal obesity.[6] It is recognized that obesity-related inflammatory cytokines (adipocytokines) are risk factors for the development of T2DM and its complications.[7] Excess adipose tissue in obese patients by activation of the immune system leads to an increase in interferon-γ-producing Th1 cells and a decrease in anti-inflammatory regulatory T cells, which induces insulin resistance.[8] However, various forms of obesity do not have the same adverse effects on health status. Not all obese people display inflammatory

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unhealthy state and not all normal-weight people have inflammatory healthy state.\textsuperscript{[9]} In addition, studies have shown that C-reactive protein (CRP) is an inflammatory marker independent of obesity associated with glycemic status.\textsuperscript{[10]}

Therefore, it is possible that inflammatory or noninflammatory obesity could be helpful in explaining the variation in the cardiometabolic risk factors in T2DM. It seems that noninflammatory obesity phenotype is a low-risk subgroup and inflammatory nonobesity phenotype is a high-risk subgroup for CVD. Therefore, the assessment of cardiometabolic risk factors in inflammatory subgroup among obese people needs more research.\textsuperscript{[11]}

Finding out the etiology of inflammatory obesity in T2DM is important. FTO (fat mass and obesity associated) gene is one of genetic factors for predisposing to T2DM, obesity, and probably inflammatory obesity.\textsuperscript{[12]} The previous studies have shown that the FTO-rs9939609 risk variant (A allele) was associated with increased risk of T2DM and indices of obesity such as body mass index (BMI), hip circumference (HC), waist circumference (WC), and waist–hip ratio (WHR) compared to wild type (TT).\textsuperscript{[13,14]} In addition, evidence suggests that there is a significant relationship between FTO rs9939609 polymorphism A allele and more high-sensitivity CRP (hs-CRP) levels.\textsuperscript{[15]}

Currently, there is no consistent evidence regarding differences in terms of cardiovascular risk factors between inflammatory and noninflammatory obese diabetic patients. In addition, no study has been evaluated the role of FTO rs9939609 polymorphism in inflammatory obese patients. Thus, the aim of our study was to compare cardiometabolic risk factors in inflammatory obesity phenotypes with regard to the role of the FTO rs9939609 gene polymorphism.

\textbf{MATERIALS AND METHODS}

\textbf{Participants}

A cross-sectional study was performed in Ahvaz, Southwest of Iran, during 2018–2019. In the present study, 165 patients with T2DM using simple random sampling were screened from an endocrine clinic. Patients with T2DM were screened based on fasting blood sugar (FBS) >126 mg/dl and recruited based on the inclusion and exclusion criteria. Inclusion criteria were as follows: 20–65 years of age and BMI between 18.5 and 35 kg/m\textsuperscript{2}. Exclusion criteria were as follows: pregnancy, lactation and estrogen therapy in women, insulin therapy, inflammatory disease and use of anti-inflammatory agents, liver dysfunction, adrenal or thyroid dysfunction, and cancer. Obesity was defined based on BMI >30 kg/m\textsuperscript{2}. The inflammation condition was defined as a serum hs-CRP level >3.9 mg/L based on the optimal cutoff point of hs-CRP for inflammatory state in diabetic patients. Participants were grouped into four groups: (1) low inflammatory normal weight (LINW), (2) high inflammatory normal weight (HINW), (3) low inflammatory obese (LIO), and (4) high inflammatory obese (HIO).

\textbf{Ethical approval}

The study protocol conforms to the ethical guidelines of the Declaration of Helsinki, and all procedures involving patients were approved by the Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran. Furthermore, informed consent form was obtained from the participants.

\textbf{Anthropometric and blood pressure measurement}

Weight and height of individuals were determined in an overnight fasting status using a standard scale (Seca). BMI was calculated using the formula: (weight [kg]/[height\textsuperscript{2} [m]). WC and HC were measured. WHR was calculated. The systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were measured. To evaluate the patient’s blood pressure, the participants sit on a chair and have no physical activity 1 h. The mean arterial pressure (MAP) was calculated: \((2\times DBP + SBP)/3\).\textsuperscript{[16]}

\textbf{Dietary intake and physical activity measurement}

The usual dietary intake of participants in the previous year was collected by the interviewer using the valid and reliable food frequency questionnaire. Physical activity level was questioned. Physical activity defined as: ≥3 times/week and each time >30 min.

\textbf{Biochemical measurements}

The blood samples were collected in the fasting status. The blood samples were centrifuged. Part of the serum was used to evaluate the lipid profiles. The concentrations of total cholesterol (TC), triglyceride (TG), high-density lipoprotein-cholesterol (HDL-C), and low-density lipoprotein-cholesterol (LDL-C) were measured by an autoanalyzer. The atherogenic index of plasma (AIP) was calculated as the logarithm of molar ratio of TG/HDL-C.\textsuperscript{[17]} FBS was immediately measured using enzymatic method by Pars–Zamoon kits (Tehran, Iran). The serum hs-CRP, insulin, interleukin-6 (IL-6), and total antioxidant capacity (TAC) concentrations were assessed by ELISA kits. The insulin resistance in the homeostasis model (homeostatic model assessment-insulin resistance [HOMA-IR]) was calculated as follows: FBS (mg/dL) × fasting serum insulin (mU/mL)/405.

\textbf{Genotyping of the FTO rs9939609}

The genomic DNA extraction from whole blood was done by the DNA purification Kit according to the instructions of the manufacturer (Sinaclon, Iran). We used PCR-RFLP
(polymerase chain reaction-restriction fragment length polymorphism) of FTO rs9939609 gene for genotyping the single-nucleotide polymorphisms (SNPs).

The primers F: 5’-AACTGGCTCTTGAATGAAATAGGA TTCAGA-3’) and (R: 5’-AGAGTAACAGAGACTAT CCAAGTGCGATAC-3’) were used for amplifying a DNA fragment (containing rs9939609 polymorphism).

The PCR product of the FTO rs9939609 was digested by restriction enzyme (SacI), which recognized the SNP T to A in the first intron of FTO gene. The RFLP products were resolved by performing electrophoresis on a 2.5% agarose gel. The T allele produced a 182 bp band and the A allele produced 154 bp and 28 bp bands. Hence, homozygous wild-type TT genotype has the 182 bp band only; homozygous mutated AA genotype has the 154 and 28 bp bands; and heterozygous TA genotype has the 182, 154, and 28 bp bands.

Statistical analysis
The software SPSS 20.0 (SPSS Inc., Chicago, IL, USA) was used to analyze data. The data normality was checked by Kolmogorov–Smirnov test. The Chi-squared test, Student’s t-test, and ANOVA were used to evaluate differences within groups, followed by the Tukey’s post hoc test. P < 0.05 was considered statistically significant. Odds ratios for AIP-based obesity and FTO phenotypes were measured using logistic regression using low-risk groups as the reference.

RESULTS
Out of the 165 patients with T2DM recruited, ten had incomplete data (genotyping, blood results, dietary, and medical information). Consequently, the data were analyzed for 155 patients consisting of 77 (49.7%) males and 78 (50.3%) females, with a mean age of 53.03 ± 9.98 years (range: 20–65 years). Table 1 displays anthropometric and biochemical characteristics between males and females. The optimal cutoff point for hs-CRP to detect obese T2DM was 3.9 mg/L. The inflammation health was defined as a serum hs-CRP level <3.9 mg/L (sensitivity of 52% and specificity of 78.0%). Based on obesity and inflammatory state, the patients were grouped into four groups: 47 LINW (30.3%), 44 HINW (28.4%), 29 LIO (18.7%), and 35 HIO (22.6%).

Table 2 shows that there were no significant differences in dietary intake and demographic characteristics (age, gender, physical activity, dietary intake, education levels, and taking medication) between groups.

Table 3 indicates comparison of anthropometric measures and biochemical variables between four groups according to the inflammatory condition. Based on within-group analysis, there were no significant differences in age between groups.

As expected, the BMI and WC were more in obese groups (LIO and HIO) than normal-weight groups (LINW and HINW). The patients in the inflammatory unhealthy groups (HINW and HIO) have significantly higher levels in AIP [Figure 1] and hs-CRP when compared to the inflammatory healthy groups (LINW and LIO). There were no significant differences between any of the four group in WHR, SBP, DBP, MAP, HR, glycemic status (FBS, insulin, and HOMA-IR), profile lipid (TG, VLDL, HDL, LDL and cholesterol), IL-6, and TAC.

The genotype frequencies for FTO rs9939609 were 28.4%, 54.8%, and 16.8% for AA, AT, and TT genotype, respectively. Pearson’s Chi-square test showed that there was a significant different between groups in the frequency of FTO rs9939609 genotype (AA, AT, and TT, P = 0.003). The most frequent of high-risk genotype (AA) was in HIO, LIO, HINW, and LINW, respectively [Table 4].

The odds ratios of AIP according to inflammatory obesity and FTO phenotypes were summarized in Table 5. The inflammatory unhealthy groups (HIO and HINW) had

### Table 1: General characteristics of the participants

| Variables                          | Total (n=155) | Male (n=77) | Female (n=78) | P    |
|------------------------------------|--------------|------------|--------------|------|
| Age (years)                        | 53.03±9.98   | 52.39±10.42 | 53.64±9.55  | 0.44 |
| Weight (kg)                        | 80.46±12.47  | 85.93±11.86 | 75.21±10.71 | <0.001|
| BMI (kg/m²)                        | 29.64±3.80   | 28.67±3.37  | 30.57±3.97  | 0.002|
| WC (cm)                            | 101.08±7.48  | 99.23±6.02  | 102.70±8.26 | 0.006|
| WHR                                | 0.97±0.05    | 0.98±0.04   | 0.96±0.05   | 0.07 |
| SBP (mmHg)                         | 13.42±2.23   | 13.78±1.97  | 13.06±2.41  | 0.04 |
| DBP (mmHg)                         | 8.52±1.36    | 8.86±1.34   | 8.19±1.31   | 0.002|
| HR (b/min)                         | 84.66±11.98  | 82.83±12.40 | 86.44±11.36 | 0.07 |
| MAP                                | 10.15±1.55   | 10.50±1.49  | 9.81±1.55   | 0.006|
| TG (mg/dl)                         | 190.11±104.89| 199.10±120.20| 181.23±87.08| 0.29 |
| HDL (mg/dl)                        | 48.77±9.49   | 45.87±6.54  | 51.63±11.02 | <0.001|
| LDL (mg/dl)                        | 76.49±28.54  | 75.24±28.66 | 77.68±28.56 | 0.60 |
| Cholesterol (mg/dl)                | 161.63±38.70 | 157.19±38.28| 166.01±38.87| 0.15 |
| VLDL (mg/dl)                       | 38.35±21.96  | 40.48±25.59 | 36.25±17.59 | 0.23 |
| AIP                                | 0.54±0.25    | 0.57±0.25   | 0.51±0.25   | 0.08 |
| FBS (mg/l)                         | 176.79±65.97 | 169.52±57.91| 183.97±72.73| 0.17 |
| Insulin (ng/dl)                    | 13.09±6.04   | 13.20±5.55  | 12.99±6.50  | 0.83 |
| HOMA-IR                            | 5.62±3.31    | 5.56±3.18   | 5.67±3.43   | 0.85 |
| hs-CRP (mg/l)                      | 3.88±0.84    | 3.81±0.63   | 3.95±0.99   | 0.32 |
| IL-6 (ng/ml)                       | 2.02±1.53    | 1.99±1.65   | 2.04±1.42   | 0.85 |
| TAC                                | 0.39±0.12    | 0.42±0.10   | 0.38±0.14   | 0.03 |

BMI=Body mass index; WC=Waist circumference; WHR=Waist-to-hip ratio; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; HR=Heart rate; MAP=Mean arterial pressure; TG=Triglyceride; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; VLDL=Very-LDL; AIP=Atherogenic index of plasma; FBS=Fasting blood sugar; HOMA-IR=Homeostatic model assessment of insulin resistance; hs-CRP=High-sensitivity C-reactive protein; IL-6=Interleukin-6; TAC: Total antioxidant capacity.
higher odds ratios than LINW as reference group. Patients with genotype AA (odds ratio = 1.34 [0.16–11.19]) and AA-AT
(odds ratio = 1.22 [0.21–6.96]) have shown nonsignificantly higher AIP levels compared to TT individuals.

**DISCUSSION**

In this study, we found that irrespective of obesity, T2DM patients with inflammatory unhealthy condition have similar degree of increased atherogenic risk compared to patients with inflammatory healthy phenotypes. In fact, our findings suggest that the role of inflammatory status in developing atherogenic problems is stronger than obesity. To our knowledge, this is the first study that has evaluated the association between inflammatory obesity phenotypes with cardiometabolic risk factors in T2DM patients.

In accordance with our findings, Lin et al. reported that HINW men have higher carotid intima–media thickness as a risk factor for subclinical atherosclerosis compared to
Table 3: Anthropometric and biochemical characteristics according to the inflammatory condition

| Variables                         | LINW (n=47)          | HINW (n=44)          | LIO (n=29)          | HIO (n=35)          | P      |
|-----------------------------------|----------------------|----------------------|---------------------|---------------------|--------|
| BMI (kg/m²)                       | 26.82±1.84<sup>c</sup> | 27.50±1.79<sup>e</sup> | 33.80±3.59          | 32.37±2.53          | <0.001 |
| WC (cm)                           | 97.40±6.31<sup>c</sup> | 97.92±5.41<sup>e</sup> | 107.20±6.71         | 105.61±6.62         | <0.001 |
| WHR                               | 0.96±0.04            | 0.98±0.04            | 0.95±0.06           | 0.97±0.05           | 0.12   |
| SBP (mmHg)                        | 13.90±2.23           | 13.27±2.14           | 13.29±2.08          | 13.04±2.43          | 0.33   |
| DBP (mmHg)                        | 8.86±1.43            | 8.43±1.33            | 8.60±1.23           | 8.10±1.33           | 0.08   |
| HR (±)                            | 81.27±12.20          | 87.81±12.50          | 87.04±9.47          | 83.88±12.40         | 0.06   |
| MAP                               | 10.54±1.55           | 10.04±1.54           | 10.16±1.41          | 9.74±1.61           | 0.13   |
| TG (mg/dl)                        | 174.17±113.25        | 207.32±112.15        | 164.03±76.44        | 211.49±99.89        | 0.14   |
| HDL (mg/dl)                       | 49.36±9.06           | 47.84±10.58          | 50.01±9.08          | 48.11±9.19          | 0.74   |
| LDL (mg/dl)                       | 78.34±30.01          | 74.34±30.18          | 78.41±26.79         | 75.01±26.51         | 0.88   |
| Cholesterol (mg/dl)               | 161.87±61.60         | 162.09±38.71         | 161.55±33.08        | 160.77±40.57        | 0.99   |
| VLDL (mg/dl)                      | 35.27±24.35          | 42.46±23.94          | 33.34±15.10         | 41.51±20.25         | 0.19   |
| AIP                               | 0.48±0.27<sup>c</sup> | 0.59±0.26<sup>c</sup> | 0.48±0.18<sup>d</sup> | 0.60±0.24<sup>d</sup> | 0.04   |
| FBS (mg/l)                        | 189.49±55.94         | 176.89±60.45         | 173.48±78.39        | 162.37±73.15        | 0.32   |
| Insulin (ng/dl)                   | 13.62±5.66           | 11.52±5.46           | 14.53±5.58          | 13.09±7.32          | 0.19   |
| HOMA-IR                           | 6.42±3.47            | 4.72±2.07            | 5.90±2.58           | 5.36±4.49           | 0.10   |
| hs-CRP (mg/l)                     | 3.40±0.74<sup>c</sup> | 4.45±0.47<sup>e</sup> | 3.26±0.83<sup>f</sup> | 4.37±0.49<sup>f</sup> | <0.001 |
| IL-6 (ng/dl)                      | 1.78±1.29            | 2.05±2.05            | 1.97±1.03           | 2.36±1.44           | 0.44   |
| TAG                               | 0.40±0.11            | 0.37±0.13            | 0.41±0.10           | 0.40±0.14           | 0.70   |

Table 4: Fat mass and obesity associated (rs9939609) genotypes frequency in groups

| Genotype | Total (%) | LINW (%) | HINW (%) | LIO (%) | HIO (%) | P* |
|----------|-----------|----------|----------|---------|---------|----|
| AA       | 44 (28.4) | 7 (14.9) | 12 (27.3) | 9 (31.0) | 16 (45.7) | 0.003 |
| AT       | 85 (54.8) | 36 (76.6) | 23 (52.3) | 11 (38.0) | 15 (42.9) |    |
| TT       | 26 (16.8) | 4 (8.5)  | 9 (20.4)  | 9 (31.0)  | 4 (11.4)  |    |

*Difference between TT, AT and AA between four groups. LINW=Low-inflammatory normal-weight; HINW=High-inflammatory normal-weight; LIO=Low-inflammatory obese; HIO=High-inflammatory obese

Table 5: Odds ratios for atherogenic index of plasma based inflammatory obesity and FTO-rs9939609 Phenotypes

| Groups | Inflammatory obesity phenotypes | LINW | HINW | LIO | HIO | P     |
|--------|---------------------------------|------|------|-----|-----|-------|
| OR     | Reference                        | 6.97 | 4.19 | 16.44 |       | 0.02  |
|        |                                  | (1.23-39.33) | (0.43-55.43) | (2.17-124.68) |     | 0.007 |

| Groups | FTO-rs9939609 phenotypes | TT | AT | AA | AA-AT | P     |
|--------|------------------------|----|----|----|-------|-------|
| OR     | Reference              | 0.87 | 1.34 | 1.22 |       | 0.89  |
|        |                       | (0.13-5.72) | (0.16-11.19) | (0.21-6.96) |     | 0.81  |

*Significant difference between LINW compared to HINW; *Significant difference between LINW compared to LIO; *Significant difference between HINW compared to LINW; *Significant difference between HINW compared to LIO; *Significant difference between LIO compared to HIO.

The possible mechanisms of CRP role in plaque deposition and atherosclerosis are complex. CRP may facilitate monocyte adhesion and macrophage infiltration in atherosclerotic lesions. Moreover, CRP inhibited endothelial nitric oxide synthase and impaired vasoreactivity. Evidences reported CRP found in lipid microdomains of endothelial cells and plaques. We did not find any different in glycemic profile between inflammatory obesity phenotypes. Previous studies indicated that elevated serum hs-CRP level was associated with an increased degree of glycemic variables. On the other hand, some theories suggested that inflammation during obesity is not all bad for T2DM.
that each additional copy of the obesity-risk allele (AA) of FTO gene was associated with an increase in CRP level (1.14-fold in men and 1.12-fold in women).\textsuperscript{[30]}

Saucedo \textit{et al.} suggested that lower concentrations of adiponectin and higher concentrations of pro-inflammatory tumor necrosis factor-alpha were associated with the \textit{FTO} rs9939609 risk allele A in women with gestational diabetes mellitus after adjusting for maternal prepregnational body weight.\textsuperscript{[31]} Furthermore, recently, a study observed that the carriers of risk allele A of \textit{FTO} Polymorphism rs9939609 had increased CRP and insulin values.\textsuperscript{[32]} However, some studies did not report an association between the \textit{FTO} rs9939609 variant and inflammatory state.\textsuperscript{[28,29]} Animal studies demonstrated that independent of body weight, \textit{FTO} gene influences the metabolic outcomes by alteration of nuclear factor kappa B signaling in hypothalamus.\textsuperscript{[33]}

\textbf{CONCLUSION}

T2DM patients with inflammatory condition are at high risk for atherogenic risks than patients with inflammatory healthy status. The results of our research show the more importance of inflammatory status in the development of atherosclerosis compared to obesity. The nonobese patients with inflammatory condition indicated atherogenic risks similar to patients with inflammatory obesity, therefore, they should be considered as a high risk group. The obesity-risk genotype AA of \textit{FTO} gene was associated with an increased risk for inflammatory obesity in T2DM patients.

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\textbf{Conflicts of interest}

There are no conflicts of interest.

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