Serum FTO Protein Levels in Newly Diagnosed Type 2 Diabetes Patients in Syria: A Case–Control Study

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ABSTRACT:

Introduction:

Type 2 diabetes is often accompanied by obesity, particularly visceral obesity. On the other hand, The FTO protein is associated with body mass index (BMI). It acts as an enzyme that induces epigenetic modifications in multiple genes. suggesting that the FTO protein is associated with several metabolic disorders, such as type 2 diabetes. Our study aimed to evaluate the protein levels of FTO in Syrian patients newly diagnosed with type 2 diabetes.

Methods:

This case–control study involved 80 participants selected from the National University Hospital in Damascus.it divided into two primary groups: 44 newly diagnosed type 2 diabetic patients and 36 nondiabetic participants, including 22 obese participants and 14 normal weight participants.

Serum levels of FTO protein were measured by Sandwich Enzyme-Linked ImmunoSorbent Assay (ELISA), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), fasting insulin (FINS) and insulin resistance were assessed for each participant. The statistical analysis was performed using IBM SPSS statistics (version 27) software. The Mann–Whitney test, the independent t test, ANOVA and the Kruskal–Wallis test were used. Correlations were assessed via Pearson's test and via Spearman's test for the subgroups. A p value < 0.05 was considered statistically significant.

Results:

The serum levels of FTO protein did not differ between type 2 diabetes and nondiabetic participants($p>0.05$), but they differ between the obese-nondiabetic group and the normal weight- nondiabetic group($p<0.05$). Serum FTO levels were correlated with insulin($p=0.001$) and insulin resistance($p=0.001$) in the nondiabetic group, but were not correlated with newly diagnosed type 2 diabetes($p>0.05$).

Discussion:

Serum levels of FTO appear to be more strongly associated with obesity than with diabetes.

Keywords: Type 2 diabetes, obesity, FTO protein, insulin, insulin resistance, Syrians.

1.Introduction:

Type 2 Diabetes (T2D) is a multifactorial metabolic disorder. T2D accounts for 90–95% of diabetes cases, and it is one of the most significant noncommunicable chronic diseases that seriously threatens human health. This type of diabetes is characterized by two main insulin-related abnormalities: insulin resistance and β-cell dysfunction [1]. According to International Diabetes Federation (IDF) statistics for 2024, 19% of Syrians suffer from type 2 diabetes, and the number is expected to increase if the risk factors for the disease are not controlled [2]. Type 2 diabetes is often associated with obesity, especially visceral obesity, which leads to chronic inflammation in the body[3] , contributing to the development of heart diseases, hypertension and cancer in addition to diabetes [4].

The *fto* gene is located on chromosome 16q12.2 and was named the "FATSO gene" because of its large size (approximately 410.50 kb) [5]. The *fto* gene was originally thought to be associated with programmed cell death, several neurological diseases, growth failure, early death in children, and the phenomenon of fused fingers in embryos [6]. However, in 2007, Genome-Wide Association Studies (GWAS) identified it as the first gene related to body mass index (BMI), so it was renamed fat mass and obesity-associated protein (FTO)[7].

The *fto* gene contains 8 introns and 9 exons and encodes the 2-oxoglutarate Fe+2-dependent AlkB family dioxygenase. Although this enzyme is involved in DNA repair and demethylation, this process is reversible [8]. Methyl-6-adenosine (m_6A) is considered the main substrate for the FTO protein.

The FTO protein is expressed in various tissues with high expression levels in the hypothalamus. FTO plays a role in posttranscriptional regulatory processes such as RNA splicing, nuclear production, degradation, and translation [9]. Different studies have shown the relationship between gluconeogenesis and lipogenesis [10], indicating its role in regulating appetite and metabolic processes [11] [12].

The number of studies on serum FTO protein levels is limited, especially in diabetic patients, and there are no studies on FTO protein within the Syrian population. Therefore, our study aimed to assess the serum levels of FTO protein in newly diagnosed Syrian patients with type 2 diabetes. Our study is the first to assess the serum levels of FTO protein in newly diagnosed type 2 diabetic patients.

2.Materials and Methods

2.1. Study design:

This case–control study was conducted with 80 participants divided into two primary groups: 44 newly diagnosed diabetes patients and 36 nondiabetic individuals from the Endocrinology Department at the National University Hospital in Damascus, Syria.

The primary study groups were further divided into subgroups "(four groups)".

The case group was divided into two subgroups: obese diabetic patients and nonobese diabetic patients, *the control group* was divided into two subgroups: nondiabetic obese individuals and nondiabetic normal weight individuals.

2.2. Ethical considerations:

This study was approved by the Biomedical Research Ethics Committee at Damascus University under the number PH-210224-210 on February 2024[13]. A blood sample was drawn after the participants signed the consent form (one form per participant). The samples were collected between February 2024 and March 2025 at the National University Hospital in Damascus.

2.3. The inclusion criteria for the study groups were as follows:

-Inclusion criteria for the case group: the obese diabetic patients were newly diagnosed with T2D according to the American Diabetes Association (ADA) criteria [14], with obesity defined by the World Health Organization (WHO) (BMI ≥30 kg/m²) [15]. The participants were between 38 and 65 years of age.

Nonobese Diabetes patients newly diagnosed with T2D according to the ADA criteria [14], with a BMI ≤30 kg/m² on the basis of the WHO criteria [15]. The participants were aged between 38 and 65 years.

-Inclusion criteria for the control group:

nondiabetic obese individuals: No diabetes diagnosis, obesity defined by the WHO criteria (BMI ≥30 kg/m²) [15], aged between 38 and 65 years.

Nondiabetic normal weight individuals: No diabetes diagnosis, normal weight based on WHO criteria (BMI between 18.5 and 24.9 kg/m²) [15], aged between 38 and 65 years.

2.4. The Exclusion criteria for the study groups:

Individuals treated with insulin or antihyperglycemic agents, lipid-lowering agents, loop or thiazide diuretics, those with cardiovascular diseases, thyroid diseases, liver or kidney disorders, autoimmune diseases, infectious diseases and cancers .Women with polycystic ovary syndrome, pregnant women and breastfeeding mothers.

2.5. Anthropometric measurements and indices Body:

The participants were examined by endocrinologists, and the required research data were gathered, including a review of each participant's medical history and anthropometric measurements.

Weight and height were measured via a standardized scale, with participants wearing light clothing and no shoes. Waist, hip, and neck circumferences were measured via a no stretchable measuring tape. Waist circumference (WC) was measured between the lower rib and the hip bone, passing over the navel, with the tape measure held flat against the skin without applying pressure. Hip circumference (HC) was measured at the widest point of the buttocks, also without applying pressure, with the torso upright and feet together. Neck circumference (NC) was measured with the head in a neutral position, with the tape passing across the thyroid cartilage without applying pressure.

2.6. Sample collection, preparation and analysis:

After a 12-hour overnight fast, 6 mL of venous blood was collected from each participant via sterile venipuncture and distributed into two tubes. A 2 mL blood sample was collected in an EDTA tube, which was used for the estimation of glycated hemoglobin as a percentage of total hemoglobin, using a kit for turbidimetric inhibition immunoassay (TINIA) provided by Roche Diagnostics, Switzerland [16]. The remaining 4 mL of blood was placed in a clot activator tube. After blood clotting, the sample was centrifuged at 3000 × g for 15 minutes, and a portion of the serum was collected for immediate determination of fasting blood glucose via an enzymatic colorimetric test via a Roche kit, Switzerland [17]. The remaining serum was stored at −80°C until further analysis of fasting serum insulin and serum FTO protein levels. Serum insulin levels were measured via an electrochemiluminescence immunoassay (ECLIA) via a kit provided by Roche Diagnostics, Switzerland [18].

Serum FTO protein levels were measured via an ELISA kit provided by My BioSource, USA [19].

The laboratory work was conducted at the National University Hospital Laboratory in Damascus.

2.7. Calculations:

Body mass index (BMI) was calculated by dividing weight (kg) by the square of height (m^2). The waist/hip ratio (WHR) and waist/height ratio (WHtR) were subsequently calculated. Insulin resistance was determined via the HOMA-IR formula = fasting glucose (mg/dl) x fasting insulin (μU/mL)/405**.**

2.8. Statistical analysis:

The data were manually collected in an Excel spreadsheet. Statistical analyses and study correlations were performed via IBM SPSS Statistics version 27. Numerical data are expressed as the mean ± standard deviation for normally distributed samples and as the median ± interquartile range for nonnormally distributed samples. Numerical variables were compared between primary groups via the Mann–Whitney test and the independent t test. For comparisons between subgroups, ANOVA and the Kruskal–Wallis test were used, depending on the sample distribution pattern. The chi-square test was used for categorical variables. Correlations were assessed via Pearson's test for the primary groups and via Spearman's test for the subgroups. A p value < 0.05 was considered statistically significant.

3. Results:

3.1 Demographic and anthropometric parameters:

- This study was a case–control study that included 44 newly diagnosed individuals with T2D and 36 control participants without diabetes (22 obese and 14 normal weight individuals). There were no significant differences between the groups in terms of age or sex ($p > 0.05$).
- Differences between groups: Significant differences were observed between the subgroups (normal weight without diabetes, obese without diabetes, nonobese diabetes and obese diabetes) in terms of weight, BMI, WC, HP, NC, Waist/hip ratio (WHR), and Waist/height ratio (WHtR)

($p < 0.001$). However, no differences in any of the demographic parameters were found between the obese without diabetes group and the obese with diabetes group ($p > 0.05$). See Table 1

Table1: Demographic and anthropometric parameters of the studied group.

Variable	Normal weight without diabetic (n=14)	Obese without diabetic (n=22)	Non obese diabetes (n=22)	Obese diabetes (n=22)	P	P1	P2	P3	P4	P5	P6
Age	47.38±6.9	47.45±6.4	52.5±6.5	49.1±6.9	0.057*	1	0.085	0.539	1	1.88	1
sex	-	-	-	-	0.173***						
male	7(50%)	10(45.45%)	17(77.27%)	12(54.54%)	-						
female	7(50%)	12(54.54%)	5(22.72%)	10(45.45%)	-						
Weight(kg)	58±6.1	100±15.9	77.35±11	102.1±16.3	0.001*	0.001	0.001	0.001	1	0.001	0.001
Height(m)	164.3±9.3	166.36±11.9	169.18±10.6	166.68 ± 9.9	0.637*	1	1	1	1	1	1
(BMI) kg/m^2	21.38±1.67	34.7±4.4	26.9±2.25	34.8±7.6	0.001**	0.001	0.001	0.001	0.778	0.043	0.001
WC	79.3±4.9	112.14±1.94	100.9±6.4	116.77±10.8	0.001*	0.001	0.001	0.001	0.432	0.001	0.001
HC	93.46±4.8	120.64±6.9	104.55±5.4	118.1±11.7	0.001*	0.001	0.001	0.001	1	0.001	0.001
WHR	0.85 ±0.05	0.93±0.09	0.96±0.05	0.99±0.09	0.001*	0.15	0.895	1	0.058	0.001	0.001

WHtR	0.48±0.04	0.67±0.05	0.59±0.04	0.7±0.06	0.001*	0.001	0.001	0.001	0.603	0.001	0.001
NC	34.15±1.86	40.1±4.6	39.71±3.5	42.8±3.9	0.001*	0.001	1	0.051	0.110	0.001	0.001

BMI: Body Mass Index, WC: Waist Circumference, HC: Hip Circumference, WHR: Waist/Hip Ratio, WHtR: Waist/Height Ratio, NC: Neck Circumference

P1 between normal weight and obese groups.

P2 between obese without diabetic and nonobese diabetes groups

P3 between non obese diabetes and obese diabetes groups

P4 between obese and obese diabetes groups

P5 between non obese diabetes and normal weight groups.

P6 between obese diabetes and normal weight groups.

*Anova test, **Kruskal–Wallis, ***chi-square test

3.2. Differences of laboratory results between primary groups:

- Significant differences in fasting blood glucose, fasting insulin, insulin resistance and glycated hemoglobin levels were detected between the primary groups ($p < 0.05$). However, the serum levels of the FTO protein did not differ between the primary groups ($p > 0.05$). See Table 2.

Table 2: Comparison of the laboratory results among the primary groups.

groups / variable	Control without Diabetes(n=36)	Diabetes(n=44)	P
FBG (mg/dl)	92.9±8	174±100	0.001[a]
FINS (uU/ml)	7.8±8.79	10.9±10.85	0.014 [a]
HOMO IR	1.82±1.96	6.15±4.4	0.001 [a]
HBA1c	5.56±0.38	9.3±2.2	0.001 [b]
FTO (Pg/ml)	17.74±7.6	16.26±10.42	0.618 [a]
a: Mann–Whitney, b: independent-T- test, P value FBG: fasting blood glucose, FINS: fasting insulin			

3.3. Differences of laboratory results between subgroups:

- When the primary groups were subdivided into subgroups, significant differences in fasting glucose, fasting insulin, insulin resistance, glycated hemoglobin, and serum levels of FTO protein were observed among the subgroups ($p < 0.05$). See Table 3.

- The variation in FTO levels across the subgroups was attributed to the difference in FTO protein levels between normal weight individuals and obese individuals without diabetes ($p < 0.05$). See Table 3.
- No significant differences in fasting insulin or serum FTO protein levels were detected between specific groups (obese individuals without diabetes or obese individuals with diabetes) and individuals (normal weight individuals without diabetes or nonobese individuals with diabetes). See Table 3
- **Table3** Comparison of laboratory results between subgroups

Variable	Normal weight without diabetic (n=14)	Obese without diabetic (n=22)	Nonobese diabetes (n=22)	Obese diabetes (n=22)	P	P_1	P_2	P_3	P_4	P_5	P_6
FBG (mg/dl)	88.74±7.42	92.54±4.3	213.64±69.24	164.63±44	0.001[c]	1	0.001	0.002	0.001	0.001	0.001
FINS (uU/ml)	5.8±1.7	13.17±5.6	10.31±5.2	17.65±7.14	0.001[c]	0.002	0.557	0.001	0.057	0.135	0.001
HBA1c (%)	5.4±0.2	5.7±0.3	9.83±2.4	8.8±1.9	0.001[d]	1	0.001	1	0.001	0.001	0.001
HOMO IR	1.27±0.4	3±1.27	5.4±3.1	6.47 ±3.5	0.001[d]	0.008	0.008	1.38	0.001	0.001	0.001
FTO (Pg/ml)	14.36±4.5	20.83±5.97	18.46±7.5	17.74±8	0.049[d]	0.042	1	1	0.410	0.633	1
c: One -WAY ANOVA, d: Kruskal wails											

P1 between normal weight and obese groups.
P2 between obese without diabetic and nonobese diabetes groups
P3 between non obese diabetes and obese diabetes groups
P4 between obese and obese diabetes groups
P5 between non obese diabetes and normal weight groups.
P6 between obese diabetes and normal weight group

3.4 Correlations between the serum FTO protein levels and various parameters in the primary groups:

- In the control group (obese and normal weight), there was a positive correlation between serum FTO protein levels and weight, BMI, WC, HP, WHtR, NC, FINS, and HOMA-IR. However, in the diabetes group, a positive correlation was observed only between age and serum levels of the FTO protein. See Table 4.

Table4: correlations between serum levels of FTO protein and various parameters in the primary study groups.

Variable	Control without Diabetes (n=36)		Diabetes (n=44)	
	r	p	r	p
Age	-0.135	0.440	0.585	0.001
Weight	0.602	0.001	-0.008	0.958
BMI	0.594	0.001	0.039	0.803
WC	0.449	0.002	0.125	0.418
HP	0.555	0.001	0.017	0.915
WHR	0.180	0.302	0.158	0.307
WHtR	0.575	0.001	-0.095	0.542
NC	0.433	0.009	0.170	0.270
FBG	1	0.287	0.12	0.437
FINS	0.560	0.001	-0.079	0.611

HBA1c	-0.003	0.987	0.08	0.606
HOMO IR	0.556	0.001	0.036	0.816

3.5 Correlations between FTO protein levels and laboratory parameters in subgroups:

- However, when the primary groups were divided into subgroups, the correlation became insignificant for most parameters in the control groups (normal weight without diabetes – obese without diabetes) ($p > 0.05$). The positive correlation in the diabetes subgroups (obese/nonobese) remained significant with age Table 5.

Table5: Correlations between serum levels of FTO protein and laboratory parameters in subgroups**.**

Variable	Normal weight without diabetic		Obese without diabetic		Nonobese diabetes		Obese diabetes	
	r	p	r	p	r	p	r	P
Age	0.355	0.234	-0.287	0.196	0.645	0.001	0.564	0.006
Weight	0.687	0.01	0.303	0.171	-0.131	0.561	0.046	0.84
BMI	0.006	0.986	0.315	0.154	-0.042	0.852	0.287	0.196
WC	-0.028	0.929	0.231	0.302	-0.059	0.794	0.269	0.226
HP	-0.299	0.321	0.360	1	-0.014	0.952	0.007	0.977
WHR	0.113	0.713	-0.108	0.633	-0.167	0.458	0.213	0.341
WHtR	-0.437	0.135	0.064	0.778	-0.017	0.940	0.534	0.010
NC	0.738	0.004	0.26	0.256	-0.476	0.029	-0.048	0.832
FBG	0.575	0.04	-0.247	0.268	-0.90	0.691	0.157	0.487
FINS	-0.115	0.707	0.336	0.126	0.018	0.93	-0.258	0.247
HBA1c	-0.036	0.907	-0.067	0.767	-0.215	0.337	0.210	0.348
HOMO IR	0.044	0.887	0.305	0.167	-0.023	0.921	-0.147	0.514

4- Discussion:

Type 2 diabetes is considered a multifactorial metabolic disorder in which environmental, genetic, and epigenetic factors contribute to its pathogenesis. By controlling for environmental factors (such as lifestyle and diet), the influence of genetic and epigenetic factors may be mitigated. Regardless of the underlying causes of T2D, all of these causes lead to a unified pathogenic process characterized by pancreatic insufficiency in insulin secretion, along with the presence of insulin resistance [20].

The FTO protein is a nonspecific protein that is expressed abundantly in the brain and metabolic tissues [21]. FTO acts as a regulator of metabolic processes by modulating the gene expression of various genes at different stages [9]. Consequently, numerous studies have explored the relationships between FTO protein expression and metabolic disorders, including obesity, diabetes, polycystic ovarian syndrome [22], hepatic steatosis [23], and cancer [24].

In this context, Wang et al [25] investigated the relationship between fto gene expression and T2D severity using RT-PCR and Western blotting which included 110 individuals newly diagnosed with T2DM and 60 healthy individuals, they reported that the FTO protein was associated with type 2 diabetes severity and that the FTO protein level was correlated with obesity indices and blood glucose indices. additionally, Yang et al [26] studied 102 patients with T2D and 107 controls and reported that FTO altered the expression of genes related to glucose metabolism, resulting in the development of hyperlipidemia in T2DM patients. Another study conducted by El Gayed et al [27] which included 100 T2DM patients and 50 healthy revealed that increased FTO gene expression and its serum protein levels are associated with increased T2DM severity. In addition,

previous histological and serum study conducted by Taneera et al [28] suggested that FTO plays a crucial role in β-cell survival, metabolism, and function, whereas serum FTO levels did not significantly differ between individuals with diabetes or obesity and their healthy counterparts.

The aim of our study was to evaluate the serum levels of FTO protein in diabetic patients and compare them with those in a control group of nondiabetic individuals, including both obese and normal weight individuals. The samples were divided into two primary groups (diabetic/nondiabetic) to understand the association between FTO and diabetes, and since the FTO protein is related to body mass index (BMI), we further divided the primary groups based on BMI to clarify the independent associations of FTO with obesity and diabetes.

Our results revealed no significant difference in serum FTO levels between the case and control groups ($P = 0.618$) (Table 2). Although FTO is known to be associated with metabolic disorders, assessment of serum levels could not fully explain these results. However, in previous serum level studies in other countries, such as the United Arab Emirates in 2024[28], FTO protein levels did not differ between the serum of diabetic patients and that of controls. Moreover, a tissue-based study within the same research area revealed a concurrent decrease in FTO gene expression in the pancreatic tissues of diabetic patients, along with a reduction in the gene expression of beta-cell proliferation genes, survival genes and insulin secretion genes.

In contrast, the serum levels of FTO protein varied significantly when the primary groups were divided into subgroups ($P<0.05$) (Table 3). This result can be attributed to the differences observed between the obese nondiabetic group and the normal weight group ($P_1=0.042$).in our study the difference may be explained by the effect of obesity, which is an inflammatory state that disrupts metabolic tissues such as the pancreas, liver,

skeletal muscles and adipose tissue[29]; thus, increased serum levels of the FTO protein could reflect its overexpression in these tissues in obese individuals.

Our findings did not reveal a significant difference in FTO protein levels among diabetic patients, regardless of obesity status ($P > 0.05$) (Tables 2, 3). No previous study was divided in the same way, although metabolic dysfunction peaks, which could be attributed to pancreatic damage during the progression of the disease. According to gene view islet (data not show, see Additional file 1) and other tissues studies, FTO expression is more abundant in pancreatic cells—particularly in beta cells—than in other metabolic tissues [21]. However, during type 2 diabetes pathogenesis, some previous studies reported that FTO expression decreases, and the FTO protein might be turned over rapidly [30] or undergo methylation of the FTO gene [31] in remaining cells. This effect might be reflected in the serum levels measured.

A correlation analysis between the levels of FTO protein and fasting blood glucose and HbA1c levels, as shown in Table (4), revealed that the correlation between FTO and these parameters was not significant in either the diabetic patients or the control groups ($P > 0.05$). According to a previous article, FTO acts as a regulator that regulates glucose metabolism via its epigenetic effects [32]. In addition, in previous serum studies investigating the relationship between FTO and blood glucose levels, a study in Egypt in 2021[27] reported a positive correlation in the studied sample. However, the inclusion/exclusion criteria under which the samples were selected differed from the criteria used in our study.

However, in our study, elevated serum levels of FTO protein did not necessarily correlate with fasting blood glucose levels. The increase in serum levels of FTO may precede the increase in blood glucose levels at the time of T2D diagnosis, and disease progression may be associated with

changes in FTO levels before diagnosis. The absence of a correlation in the control group may be due to the sample inclusion criteria. A middle-stage (prediabetic) comparison between diabetes and obesity would be helpful to clarify the relationship between FTO and fasting glucose levels.

Since HbA1c reflects average blood glucose levels over the last 120 days and FTO is not associated with blood glucose levels, it is predictable that FTO is correlated indirectly with glucose levels or that our features of the samples were not significantly correlated.

The serum levels of FTO protein were correlated with insulin levels and insulin resistance in the control group ($P < 0.05$) (Table4), but the correlation was not significant in the diabetic patient group ($P > 0.05$). The correlation between the FTO protein and insulin remains a subject of ongoing research. Previous histological studies have shown that elevated FTO levels cause the overexpression of several pancreatic genes, such as INS genes, thereby stimulating insulin production [28][30]. Which corresponds with insulin hypersecretion and the development of insulin resistance in the control group. Additionally, FTO influences other genes involved in insulin secretion, such as VAMP2, which is associated with the fusion and docking of insulin vesicles within the pancreas [28]. These findings may help explain the relationships among FTO protein levels, insulin levels, and insulin resistance in the control group.

However, Hong-Qi et al. in MIN6 pancreatic β-cells[33] reported that the overexpression of FTO influenced the production of free radicals, activation of the NF-κB pathway, and subsequent endoplasmic reticulum stress in the pancreas, accompanied by mitochondrial dysfunction affecting ATP production. This excess FTO contributes to pancreatic stress, and the onset of diabetes contributes to other factors. The cells may attempt to mitigate this pathway by altering the methylation of the *fto* gene in the pancreas. However, our findings that serum levels of FTO vary among diabetic patients

and that protein levels do not decrease uniformly. This discrepancy may be attributed to the enzymatic efficiency of the protein [32] or single nucleotide polymorphisms [24][29].

Several previous studies have investigated the relationships among FTO, insulin levels, and insulin resistance. For example, a study conducted in Egypt in 2021[27] revealed a correlation between serum FTO protein and insulin levels and insulin resistance in obese diabetic patients, despite differences in sample criteria and FTO protein expression was correlated with complications in obese diabetic patients; however, our study revealed that FTO protein levels were correlated with insulin resistance without disease in the control group.

FTO protein was correlated with obesity indices (waist circumference, hip circumference, neck circumference, waist/height ratio, weight, and body mass index) in the control group (Table 4), but the correlation disappeared in the diabetic group, possibly because of changes in FTO protein levels during the pathogenesis of diabetes. In previous studies, obesity indices were related to metabolic syndrome[34][35], and a previous review[36] reported that FTO protein levels may be an indicator of metabolic syndrome [37] [38]. El-Gayad et al. in Egypt [27] reported a positive correlation between FTO levels in diabetes patients and obesity indices, but the study sample criteria were different. We suggest that the FTO protein is a marker for obesity a stronger than diabetes.

When correlations were analyzed within subgroups, the results varied (Table5). It is possible that the sample size reduced the statistical significance of these correlations or that the association between FTO and control samples appeared to be due to changes in body mass index (BMI) and the development of a general metabolic disorder, which did not affect the variables equally in the same potency.

Our results also revealed a correlation between serum levels of FTO protein and age in the patient group ($P < 0.05$), whereas no such correlation was observed in the control group ($P > 0.05$) (Tables (4,5). Our findings contrast with those of some studies on the relationship between FTO and age, both in animal models and in human serum, which reported no significant effect of age on FTO protein levels. The association between FTO and age in the patient group may be attributed to the specific characteristics of the patient samples, and the exact cause remains unclear. [21].

The mean ± standard deviation of HbA_1c for the obese-non diabetic group was 5.7±0.3%, although the ADA recommended for nondiabetic individuals for HbA1c is ≤5.6%, but obesity [39], insulin resistance [40] and other parameters [41], which were not measured in our study, increase HbA1c; this effect is revisable when the BMI is controlled.

Our study evaluated serum levels of FTO protein in type 2 diabetic patients. In light of the limitations of previous studies, we selected newly diagnosed, untreated patients receiving anti-diabetes drugs who did not suffer from any other diseases or who received treatments that might influence metabolic changes [27][28]. However, the limitations of our study include the limited sample size, the difficulty in identifying type 2 diabetic patients with normal weight and without secondary diseases, the optimal group for comparison with the nondiabetic normal weight group, the fact that almost all nonobese diabetic patients were overweight, and the lack of associations between FTO protein levels and other laboratory parameters.

5. Conclusion:

Serum FTO protein levels seem to be more strongly associated with obesity than with diabetes. Moreover, our findings indicate a significant correlation between FTO protein levels and insulin and insulin resistance, independent of diabetes diagnosis.

List of abbreviations:

Fat mass and obesity-associated protein: FTO

Type 2 Diabetes: T2D

American Diabetes Association: ADA

International Diabetes Federation: IDF

Turbidimetric inhibition immunoassay: TINIA

Methyl-6-adenosine: m_6A

Electrochemiluminescence immunoassay: ECLIA

Body mass index: BMI

The waist/hip ratio: WHR

Waist/height ratio: WHtR

Genome-Wide Association Studies: GWAS

Waist circumference: WC

Hip circumference: HP

Fasting insulin: FINS

Fasting blood glucose: FBG

Declarations:

Ethics approval and consent to participate: Serum samples were obtained after getting the ethical approval from the Biomedical Research Ethics Committee (BMREC) at Damascus University (February -2024) (ID number: PH-210224-210) [13]. A written informed consent was taken from each participant.

Consent for publication: Not applicable.

Availability of data and materials: All materials and all data generated during this study are included in this article.

Competing interests: The authors declare no competing interest

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Authors' contributions: SIH: designed the work and revised it. HSAA collected the data and samples, performed the ELISA assay and the statistical analysis. SIH and HSAA both interpreted the results, wrote and drafted the manuscript. All authors read and approved the final manuscript.

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