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# Association of FTO Gene Variants with Some Biochemical Markers of Type 2 Diabetes Mellitus Patients in Iraqi Population

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# Abstract

**Background:** The Fat-mass and obesity associated (*FTO*) gene modulates the gene expression through methylation–demethylation modifications since it is part of Fe (II) - and 2-oxoglutarate-dependent dioxygenases superfamily. This study was carried out in the Department of Clinical Laboratories / College of Applied Medical Sciences / University of Kerbala during the period from November 2022 to April 2024. The study aimed to investigate the association between the variation in the *FTO* gene and serum level of some biochemical markers in Type 2 Diabetes Mellitus Patients within the Iraqi Population.

**Patients and Methods:** One hundred volunteers participated in this study, 50 individuals with Type 2 DM as a patient's group (25 females and 25 males), and 50 apparently healthy individuals as a control group (25 females and 25 males). The ages of all participants were ranged between 25 to 75 years at the time of the investigation. We investigate three sites in the *FTO* gene (*FTO* 1, *FTO* 2, and *FTO* 3). The variation of the *FTO* gene was investigated by the Sanger sequencing method. The levels of biochemical markers were measured in blood serum.

**Results:** The results of the present study identified the presence of four previously registered variants in *FTO* gene. These variants might be of interest to *FTO* gene studies due to their presence in the coding regions that included in the gene expression.

**Conclusion:** The two variants, 53769662 T/A and 53782363 C/A, may be the most important variables because there are statistical associations with some biochemical markers.



# ارتباط متغيرات جين FTO مع بعض المعلمات الكيموحيوية عند مرضى السكري من الذوع الثاني في المجتمع العراقي زيد عبد الحسين كاظم، جودت نوري غائب

#### الخلاصة

المقدمة: يُعد جين FTO (مرتبط بالكتلة الدهنية والسمنة) أحد الأعضاء في عائلة الإنزيمات ثنائية الأكسجين التي تعتمد على الحديد (Fe II) والـ 2-أوكسو جلوتارات، حيث يُعدّل تعبير الجين من خلال تعديلات الميثيل والدي-ميثيل. تم إجراء هذه الدراسة في قسم المختبرات السريرية / كلية العلوم الطبية التطبيقية / جامعة كربلاء خلال الفترة من نوفمبر 2022 إلى أبريل 2024. هدفت الدراسة إلى التحقيق في العلاقة بين التباين في جين FTO ومستوى بعض العلامات البيوكيميائية في مصل الدم لدى مرضى السكري من النوع الثاني داخل المجتمع العراقي.

**المرضى وطرق العمل:** شارك في هذه الدراسة مئة متطوع، 50 منهم يعانون من مرض السكري من النوع الثاني كمجموعة مرضى (25 أنثى و25 ذكر)، و50 فردًا يتمتعون بصحة جيدة كمجموعة ضابطة (25 أنثى و25 ذكر). تراوحت أعمار جميع المشاركين بين 25 إلى 75 عامًا في وقت إجراء الدراسة. تم التحقيق في ثلاثة مواقع في جين FTO (1 FTO، 2 FTO)، و3 FTO). تم تحليل التباين في جين FTO باستخدام طريقة تسلسل سانجر. كما تم قياس مستويات العلامات البيوكيميائية في مصل الدم.

ا**لنتائج:** حددت نتائج هذه الدراسة وجود أربع متغيرات مسجلة سابقًا في جين FTO. قد تكون هذه المتغيرات ذات أهمية في دراسات جين FTO نظرًا لوجودها في المناطق المرمزة التي تشارك في تعبير الجين.

الاستنتاج: قد يكون المتغيران T/A 53769662 وC/A 63782363 هما الأكثر أهمية، نظرًا لوجود ارتباطات إحصائية مع بعض العلامات البيوكيميائية.

#### 1. Introduction

The FTO also known as alpha-ketoglutarate-dependent dioxygenase FTO is an enzyme that in humans is encoded by the FTO gene that is located on chromosome 16. As one homolog in the Alkylatin B family proteins, it is the first mRNA demethylase that has been identified(Jawiarczyk-Przybyłowska et al., 2023; Jia et al., 2012). Human obesity appears to be associated with specific FTO gene variations (Popović et al., 2023; R.J.F. and G.S.H., 2014). The transcribed FTO protein's amino acid sequence bears a strong resemblance to that of the oxidatively demethylating enzyme AlkB. FTO belongs to the superfamily of non-heme ironcontaining proteins called alpha-ketoglutarate-dependent hydroxylases. It was initially found that recombinant FTO protein could, albeit inefficiently, catalyze the demethylation of 3-methylthymine in single-stranded DNA and 3-methyluridine in single-stranded RNA(Gerken et al., 2007; Xu et al., 2023). N6methyladenosine (m6A), a nucleoside that is often modified in RNA, was later discovered to be a significant substrate of FTO. Obesity raises the risk of several common diseases, making it an important global health concern. It's unclear whether hereditary factors contribute to obesity. A common mutation in the FTO gene, which predisposes to diabetes through an influence on body mass index, was found during a genome-wide search for genes linked to type 2 diabetes susceptibility (Frayling et al., 2007; Tian et al., 2023). A typically elevated triglyceride deposition and the generation of hepatic glucose can result from enhanced FTO expression, which can also promote de novo lipogenesis, decrease lipolysis and fatty acid oxidation, and boost gluconeogenesis(Witka et al., 2019).

Diabetes Mellitus term describes a metabolic disorder of multiple an etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both(Ahmed, 2024; AL-Sahi et al., 2024). DM is characterized by immune-mediated (Type 1 diabetes), insulin resistance (Type 2 diabetes), gestational hyperglycemia, or other chronic hyperglycemia; genetic, environmental, infectious, or medication-induced problems; or affects the beta cells of the islets of Langerhans(Abdulhakeem et al., 2023; Azeez et al., 2024). Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia, insulin resistance and relative insulin deficiency. Over 23 million Americans live with diabetes mellitus, out of the 366 million individuals who have the condition worldwide. By 2030, this figure will increase to 552 million.(Damanik and Yunir, 2021; Qalaf et al., 2024) The causes of T2DM are not completely understood but there is a strong association between overweight, obesity, family history, and ethnicity(Aschner, 2017; Basu et al., 2013). The aim of the study: Investigate the Association of FTO gene variants with some biochemical markers in Type 2 Diabetes Mellitus patients of Iraqi Population.

### 2. Materials and Methods

#### 2.1. Blood Sample Collection

One hundred volunteers participated in this study, 50 individuals with Type 2 Diabetes Mellitus as a patient's group (25 females and 25 males) and 50 apparently healthy individuals as a control group (25 females and 25 males). The ages of all participants were ranged between 25 to 75 years at the time of the investigation. The blood samples were collected from the individuals in Al-Imam Al-Hassan Center for Endocrinology and Diabetes in Karbala city / Iraq. An ethical consent form was signed by each volunteer. Six milliliters of the venous blood sample were obtained from each participant using gel tubes, and the blood was drawn using disposable syringes under sterile condition. The collected blood was centrifuged to separate serum to be used later. The levels of biochemical markers HbA1c, FBS, Cholesterol, TG, LDL, HDL, VLDL, FIB and CRP were measured in blood serum using the ARCHITECT c4000 clinical chemistry instrument from Abbott Diagnostics

#### **2.2.** Molecular Detection

A total volume of 25 µl was used in the PCR reaction (5 µl DNA, 2 µl from each primer Table 1, 8 µl master mix, and 8 µl nuclease free water). The PCR program that was used to amplify the target sequence of *FTO* 1, *FTO* 2, and *FTO* 3 region consisted of 35 cycles, each cycle included denaturation for 30 seconds at 94°C, annealing for 45 seconds at 57°C and extension for 45 seconds at 72°C. Agarose gel electrophoresis was used to separate PCR product bands on 1% agarose gel stained by fluorescent Redsafe dye. The gel electrophoresis system was set at 70 volts for 60 minutes, and then the gel was displayed under UV transilluminator to check the PCR products (see Fig.1, Fig.2, and Fig.3).



**Figure 1:** PCR Products (225 Bp) Found in Study Samples That Demonstrates the FTO Gene's FTO 1 Target Region's Presence. Lanes 1-14, PCR Products. Lane 15, DNA Ladder.



**Figure 2:** PCR Products (183 Bp) Found in Study Samples That Demonstrates the *FTO* Gene's *FTO* 2 Target Region's Presence. Lanes 1-14, PCR Products. Lane 15, DNA Ladder.



**Figure 3:** PCR Products (297 Bp) Found in Study Samples That Demonstrates the *FTO* Gene's *FTO* 3 Target Region's Presence. Lanes 1-14, PCR Products. Lane 15, DNA Ladder.

Primer name		Primer sequence	PCR product size	
FTO 1		5'- TCTAAATTATTAATCAGGGCCATTT-3'	225 haas main	
FIUT	FTO -Reverse	5'- TGTCCTACCACCCTGTTTACC-3'	225 base pan	
	FTO -Forward	5'- ACAGTGCCAGCTTCATAGCC -3'	192 hass main	
F10 2	FTO -Reverse	5'- TTGAGGTGCCATTCCTCAAT -3'	183 base pair	
	FTO -Forward	5'- TTGAATGAAATAGGATTCAGAAGAGA -3'	207 haas main	
F103	FTO -Reverse	5'- TGTCCAAACAGTAGGTCAGGAA -3'	297 base pair	

Table	1:	Primers	Designed	for	Am	plification	of	FTO	Gene.
I unic		1 milero	Designed	101	1 1111	philoution	O1	110	oune.

#### 2.3. Nucleotides Sequencing and Analysis

In the present study, three regions of the *FTO* gene were selected, and we named them *FTO* 1, *FTO* 2, and *FTO* 3. (see Fig.4, Fig.5, and Fig.6). PCR products from 24 patients, along with 12 PCR products from control group (total= 36) for each target region of the *FTO* gene were sent to the Alpha DNA (S.E.N.C.) Corporation in (Montreal, Quebec, Canada) to perform nucleotide sequencing. Sanger sequencing method was applied using an automated DNA sequencer (see Fig.7). The results of sequencing were manually examined using bioinformatics tools, and they were compared to human reference gene sequences that already uploaded to the National Center for Biotechnology Information (NCBI). The NCBI's Basic Local Alignment Search Tool (BLAST) was used to complete the alignments. The target gene's sequenced area was examined by using Molecular Evolutionary Genetics Analysis X (MEGAX), where the CLUSTALW program carried out several sequence alignments to validate the existence of variants found by the BLAST tool. The locations of every variant found in the current study were reported and examined using Ensembl Genome Browser's tools to determine the type of variant and forecast its functional implications (see Fig.8, Fig.9, Fig.10 and Fig.11).

Primer3I	Plus			Primer3Manager	Help				
pick primers from a I	ONA sequence	e			About	Source Code			
< Back									
Pair 1:									
☑ Left Primer 1: ZAID FTO 1-F									
Sequence:	TCTAAATT	ATTAATCAGGGCC	ATTT						
Start: 96	Length: 2	5 bp Tm: :	58.5 °C G	C: 28.0 %	ANY: 7.0	SELF: 0.0			
Right Primer 1: ZAID FTO 1-R									
Sequence:	TGTCCTAC	CACCCTGTTTAC	c						
Start: 320	Length: 2	1 bp Tm: :	58.8 °C G	C: 52.4 %	ANY: 2.0	SELF: 1.0			
Product Size: 225 b	p	Pair A	ny: 7.0 Pa	air End: 1.0					
Send to Primer3Manag	er Reset F	orm							
1 TT:	PAGAGCAG	AACTTAGTAT	ATAGCAACTG	CGATACAA	ST GTTAGATATC				
51 AT:	PTTTATTA	GGGTTTAGTA	ATTGCATAAA	TAAAAGAGA	AT GAAAG <mark>TCTAA</mark>				
101 AT	PATTAATC	AGGGCCATTT	ATCTATGAGA	CACTACAG	GC ATTGTGTCTA				
151 GCC	CCTGTGGG	TTTACATTAG	TTAGGGTAGG	TTATTGCT	GC AACGTACCCT				
201 AAG	CTTGATAT	GATTTTTGCT	GCAAAAATCA	TATCAAAA	FA GTCTATAATG				
251 GC	TAAACAT	AATAAAATGC	ATTTCTTGTT	TATGTAACA	AG TAATGAGTA <mark>G</mark>				
301 GT	AAACAGGG	TGGTAGGACA	TTTTCCTCTC	TGTATTCA	IT TAGGGATCTA				
351 AG	CTGAAGGA								

Figure 4: Forward and Reverse Primer Design for FTO 1 Gene in Primer 3 Plus Program.

Primer3P	lus				<u>Primer3Manager</u>	Help		
pick primers from a D	NA sequend	:e		About	Source Code			
< Back								
Pair 1:								
☑ Left Primer 1: ZAID FTO 3-F								
Sequence:	TTGAATGA	AATAGGATTCAGA	AGAGA					
Start: 2	Length: 2	6 bp Tm: f	59.7 °C G	FC: 30.8 %	ANY: 6.0	SELF: 0.0		
Right Primer 1: ZAID FTO 3-R								
Sequence:	TGTCCAA	ACAGTAGGTCAGG	AA					
Start: 298	Length: 2	2 bp Tm: f	59.6 °C G	FC: 45.5 %	ANY: 3.0	SELF: 0.0		
Product Size: 297 bp		Pair A:	ny: 3.0 P	air End: 0.0				
Send to Primer3Manage	Reset F	orm						
1 CTT	GAATGAA	ATAGGATTCA	GAAGAGATGA	TCTCAAAT	CT ACTTTATGAG			
51 ATA	ATGTCCT	TTTTAAAAAT	AAACACTAAC	ATCAGTTA	TG CATTTAGAAT			
LO1 GTC	TGAATTA	TTATTCTAGG	TTCCTTGCGA	CTGCTGTG.	AA TTTTGTGATG			
L51 CAC	TTGGATA	GTCTCTGTTA	CTCTAAAGTT	TTAATAGG	TA ACAGTCAGAA			
201 ATG	GAGTGGG	AGAGCATAAA	AGCAAACTGA	AATGCAAA	TA GCTGGTACCC			
251 TGA	AGCCATT	AACTTTAAGC	TGGTTATTCC	TGACCTAC	TG TTTGGACATA			
301 AGA	TGGTAGA	GAGGCTGAGT	GTGACTTGAA	CATTTGTT	CC TTAGAAACAC			
351 CAT	CCTTGGG							

Figure 5: Forward and Reverse Primer Design for FTO 2 Gene in Primer 3 Plus Program.

Primer3F	Plus			Primer3Manager	Help		
pick primers from a I	NA sequend	e			About	Source Code	
< Back							
Pair 1:							
☑ Left Primer 1: ZAID FTO 2-F							
Sequence:	ACAGTGC	CAGCTTCATAGCO	;				
Start: 98	Length: 2	0 bp Tm:	60.4 °C G	C: 55.0 %	ANY: 4.0	SELF: 1.0	
Right Primer 1:	ZAID FTO 2	?-R					
Sequence: TTGAGGTGCCATTCCTCAAT							
Start: 280	Length: 2	0 bp Tm:	60.5 °C G	C: 45.0 %	ANY: 6.0	SELF: 2.0	
Product Size: 183 b	p	Pair A	.ny: 4.0 Pa	air End: 0.0			
Send to Primer3Manag	er Reset F	orm					
1 CT1	AATAATG	TTTATTGAAT	GAGAGAATTT	AACTAATT	TC CGGTTTCCAT		
51 AA1	CACTTTA	AACTCGGTAT	TTGATTTCCT	TTTCCCTG	GG ACCTGTG <mark>ACA</mark>		
101 GTC	SCCAGCTT	CATAGCCTAG	TCTAGGCATG	CCAGTTGC	CC ACTGTGGCAA		
151 TC2	ATATCTG	AGCCTGTGGT	TTTTGCCTTA	GGTAAACT	GT AGAGATGGAC		
201 TC2	TGGAATG	CTTGGAAAAT	TTTTCAGTTT	ATGATAAT	GT GTAAATGTCG		
251 AG2	AGCCAATT	ATTGAGGAAT	GGCACCTCAA	AGTATTTG	GG TACTCTAGAT		
301 CAG	GACATGAC	CATCTTGGTG	TGTGAAATTT	TGCTAATG	CA TCTTTCCTAA		
351 TAC	AATATAC						

Figure 6: Forward and Reverse Primer Design for FTO 3 Gene in Primer 3 Plus Program.



**Figure 7:** An Automated Sanger DNA Sequencing Method Shows the Electropherogram with Peaks of The Forward Strand of the Sample Sequence



Figure 8: Detect (53769662 T/A) Variant in Study Sample



Figure 9: Detect (53782363 C/A) Variant in Study Sample



Figure 10: Detect (53786591 G/A) Variant in Study Sample

	Exons	FTO exon	s All exon	s in this I	region								916; r
	Variants	3 prime II	TR 5 prim		Coding se	auence	Frameshi	t Inframe	deletion	Inframe i	nsertion	Intergenic	975: r
		o prime o	TR Opini	COIN	county set	quence	rumeann	minarite	deletion	innumen	naertion	intergenie	035: r
		Intronic	Missense	Non-co	ding exon	Splice a	cceptor	Splice dono	Splice	region	Start lost	Stop gaine	d 159: r
			_	_									217: r
		Stop lost	Stop retai	ned Sy	nonymous								286: r
		-											5336:
	Markup	loaded											70: rs
											-		526: r
53785572	METTRAC	GAANGGTR	AGAGARAG		a contraction of the second seco		2 feat	ures			× rs	2151670120	53785573: r
53785632	CYCKRY	RBDRKGSCI	HABGCCTR	Montestano			2 reut				r s	1413561092	<u>53785635:</u> r
53785692	ATGWGG	CAAGAGA	YRAGACCA	Variation:	CND			Variation: <u>CSU7</u>	10023	uence altern	tion rs	2077714939	53785698; r
53785752	AYRCMAA	AAATTWGC	GKRYRTER	Class	dhenip			Causa	HCMD DUB	uence altera	uon rs	989414573	53785754: rs
53785812	ASKHAG	ACAANKG	KWRAMCMY	Location	16:527	86615		ocation	16-5278661	5	rs.	1356813876	<u>53785814:</u> r
53785872	TGLACE	CAGCH IGU	TGACADAR	Allolos	T/A (Ee	muard strand	0	Alleles	HOMD MUT	AT (Eorman	rs.	1014270430	<u>53785877;</u>
53785992	PRAMET	TTTAAAC	ARRORATO	Conserue	I/A (Fu	variant	<i>y</i>	Alleles	strand)	Al (Forwar	u re	130105988/	53785993 -
53786052	AYRGCT	TROAGGA	AGAHSETA	conseque	inces muon	variant		Consequences	intron varia	nt	-rs	533146975	53786054: rs
53786112	RARKOR	TKARRYOA	GATAHROT		INMUT	ranscript var	riant		NMD transc	ript variant	rs	1377388617	53786114: r
53786172	YYOYYS	CTACCSCA	GCAAACRC		non co	oding transcr	ipt variant		non codina	transcript v	ariant rs	949239628	53786173: rs
53786232	ATTTKTT	<b>FGGRR</b> TATO	RGATTWTA	Explore th	is variant				Then county	transeript re	IS.	1241673102	1 53786241: r
53786292	OGARTR	YARGAGAG	GAKRMAGT	Gene/Tran	nscript Location	ons		Explore this var	lant		IS	2077737523	<u>53786297:</u> r
53786352	RDTYTA	AGTINCAC	TYATTTT	Phenotype	e Data		-	Phenotype Data	9		15	2151672383	<u>53786353:</u> r
53786412	CHRONATO	TTTTTGGC/	RATYAKAA	CARTER	momora a state	TON A COMPA	AtoMont		5270652	1 52706	177.	1330784279	53780414: r
53786532	TTOAN	AABAABC	CTADODUC	DWWATC	CATTTAC	ATCHC	ANTTATT	ATTCTAVE	5378659	1 53786	532 · re	2077744630	33786471: E8 1 53786535+ P
53786592	TTCC	HRACTRCT	GTGARTTT	WTRANC	OMTTRO	ATAGTCTC	INRI IRVA	CTRARSTT	5378665	1 53786	596: rsi	2077746001	53786599: r
53786652	TTRRYR	OTAACAGT	CAGAART	ARKORO	ACWROMT	AAAARCRA	ANTGAAA	TOCDAATA	5378671	1 53786	654: rs	1029136397	53786655: r
53786712	CTODT	YCCYGAN	CATTAA	TTANG	TOOKTAT	TCHTGACC	TATOT	TRRACETA	5378677	1 53786	716: rs	546338783	53786718: rs
53786772	ADATKR	RGARAGD	TGACTO	CTYGA7	YATTTOT	TCCTTAS!	RACAECA	YCCTTRGG	5378683	1 53786	773: rs	1417127792	<u>53786775:</u> r
53786832	MTGGRYI	MAGTKGCI	YAYRCCYR	TGTTDCC	RGGRCTT	rgggagg	GASCYL	GRCRGATY	5378689	1 53786	832: rs/	2151673560	1 <u>53786836;</u> r
53786892	DISRRR	PCARYARA'	NRAAACTR	CTORC	CTAACAYR	JTGAAAT	CEATVIS	TACMAAAA	5378695	1 53786	892: rs.	1020718430	<u>53786894:</u> r

Figure 11: Detect (53786615 T/A) Variant in Study Sample

## 2.4. Statistical Analysis

Statistical analysis was carried out using SPSS version 22.0 (SPSS, IBM Company, Chicago, IL 60606, USA). Data were expressed as means  $\pm$  standard deviation if the data were normally distributed. Data were expressed as median $\pm$ IQR if the data were non-normal distributed. P  $\leq$  0.05 was statistically significant.

## 3. Results

The results of the statistical analysis showed the mean value, standard deviation, standard error, minimum and maximum value for the parameters included in the study (BMI, HbA1c, FBS, Cholesterol, TG, LDL, HDL, VLDL, FIB and CRP) for the patient's group and the control group. This information is presented in Table 2 and Table 3.

Variable Description								
Normal Value	Mean ±SD	Min.	Max.	SE				
18.5-24.9	31.36±4.67	25.7	43.0	0.66				
Below 5.7 %	8.42±1.72	6.3	11.4	0.24				
Below 100 mg/dl	194.38±49.14	134	280	6.95				
120-200 mg/dl	185.16±42.63	122	242	6.03				
35-160 mg/dl	148.82±56.16	68	271	7.94				
30-70 mg/dl	43.0±14.88	25	65	2.1				
30-130 mg/dl	112.36±33.81	54	154	4.78				
13-60 mg/dl	30.61±11.02	14	54	1.55				
200-400 mg/dl	307.91±52.27	182	392	7.39				
0-6 mg/l	4.16±3.09	0.7	11.1	0.43				
	Normal Value           18.5-24.9           Below 5.7 %           Below 100 mg/dl           120-200 mg/dl           35-160 mg/dl           30-70 mg/dl           30-130 mg/dl           13-60 mg/dl           200-400 mg/dl           0-6 mg/l	DescriptiNormal ValueMean ±SD18.5-24.931.36±4.67Below 5.7 %8.42±1.72Below 100 mg/dl194.38±49.14120-200 mg/dl185.16±42.6335-160 mg/dl148.82±56.1630-70 mg/dl43.0±14.8830-130 mg/dl112.36±33.8113-60 mg/dl307.91±52.270-6 mg/l4.16±3.09	DescriptionNormal ValueMean $\pm$ SDMin.18.5-24.9 $31.36\pm4.67$ $25.7$ Below 5.7 % $8.42\pm1.72$ $6.3$ Below 100 mg/dl $194.38\pm49.14$ $134$ 120-200 mg/dl $185.16\pm42.63$ $122$ $35-160$ mg/dl $148.82\pm56.16$ $68$ $30-70$ mg/dl $43.0\pm14.88$ $25$ $30-130$ mg/dl $112.36\pm33.81$ $54$ $13-60$ mg/dl $30.61\pm11.02$ $14$ $200-400$ mg/dl $307.91\pm52.27$ $182$ $0-6$ mg/l $4.16\pm3.09$ $0.7$	DescriptionNormal ValueMean $\pm$ SDMin.Max.18.5-24.9 $31.36\pm4.67$ $25.7$ $43.0$ Below 5.7 % $8.42\pm1.72$ $6.3$ $11.4$ Below 100 mg/dl $194.38\pm49.14$ $134$ $280$ 120-200 mg/dl $185.16\pm42.63$ $122$ $242$ $35-160$ mg/dl $148.82\pm56.16$ $68$ $271$ $30-70$ mg/dl $43.0\pm14.88$ $25$ $65$ $30-130$ mg/dl $112.36\pm33.81$ $54$ $154$ $13-60$ mg/dl $307.91\pm52.27$ $182$ $392$ $0-6$ mg/l $4.16\pm3.09$ $0.7$ $11.1$				

Table 2: Mean Values of the Biochemical Markers in The Patient Group.

The data presented in the table as means: ±SD standard deviation of mean, Min minimum, Max maximum, SE standard error. BMI refers to body mass index, HbA1c hemoglobin A1c, FBS fasting blood sugar, Cho cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density, lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen, CRP c-reactive protein

**Table 3:** Mean Values of The Biochemical Markers in The Control Group.

Variable	Description								
variable	Normal Value	Mean ±SD	Min.	Max.	SE				
BMI	18.5-24.9	32.16±4.58	26.4	46.5	0.64				
HbA1c	Below 5.7 %	5.59±0.41	5.0	6.0	0.55				
FBS	Below 100 mg/dl	113.73±11.96	97.0	126.0	1.69				
Cho	120-200 mg/dl	195.24±34.04	135.0	242.0	4.81				
TG	35-160 mg/dl	124.06±48.2	57.0	158.0	6.81				
HDL	30-70 mg/dl	44.44±10.85	21.0	69.0	1.53				
LDL	30-130 mg/dl	132.04±37.87	81.0	192.0	5.35				
VLDL	13-60 mg/dl	24.71±9.63	11.0	32.0	1.36				
FIB	200-400 mg/dl	274.62±25.83	203.0	297.0	3.65				
CRP	0-6 mg/l	3.03±1.92	1.2	4.6	0.27				

The data presented in the table as means: ±SD standard deviation of the mean, Min minimum, Max maximum, SE standard error. BMI refers to body mass index, HbA1c hemoglobin A1c, FBS fasting blood sugar, Cho cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen, CRP c-reactive protein.

The results of this work indicated that there was no significant difference when the mean height, weight, and BMI of the patients and controls were compared (p = 0.33, p = 0.09, p = 0.19, respectively). The comparisons of the mean FBS and HbA1C between the patients and control groups revealed a very highly statistically significant difference (p<0.001) with effect sizes of 2.23 and 2.26, respectively. The lipid profile analysis showed inconsistent findings, with statistically insignificant differences observed when comparing the mean serum cholesterol and HDL levels of the patients and controls (p=0.09, p=0.29). However, TG, LDL, and VLDL levels exhibited statistically significant differences, with highly significant disparities noted (p=0.01, 0.004, 0.003) when comparing the same two groups. The effect sizes of the comparisons mentioned later were as follows: 0.47, -0.55, and 0.57. Finally, the comparison of FIB revealed a highly statistically significant difference between the mean concentration levels of the patients and controls (p<0.001), with an effect size of 0.8. Additionally, CRP levels showed a statistically significant difference (p=0.016) between the two groups, with an effect size of 0.44 see Table 4.

Category	Mean	Standard Deviation	Standard Error	P-value	Cohen sd
Patients	85.344	11.5001	1.6264		
Controls	88.920	14.9933	2.1204	0.09	-0.27
Patients	165.320	9.4484	1.3362	0.22	-0.09
Controls	166.180	9.8077	1.3870	0.33	
Patients	31.362	4.6729	0.6608	0.10	0.17
Controls	32.166	4.5818	0.6480	0.19	-0.17
Patients	8.428	1.7272	0.2443	<0.001	2.26
Controls	5.590	0.4171	0.0590	<0.001	2.20
Patients	194.38	49.148	6.951	<0.001	2.23
Controls	113.73	11.967	1.692	<0.001	
Patients	185.16	42.638	6.030	0.00	-0.26
Controls	195.24	34.043	4.814	0.09	
Patients	148.82	56.165	7.943	0.01	0.47
Controls	124.06	48.206	6.817	0.01	
Patients	43.00	14.885	2.105	0.20	0.11
Controls	44.44	10.857	1.535	0.29	-0.11
Patients	112.36	33.819	4.783	0.04	0.55
Controls	132.04	37.871	5.356	0.04	-0.55
Patients	30.61	11.023	1.559	0.003	0.57
Controls	24.71	9.630	1.362	0.003	0.57
Patients	307.92	52.272	7.392	<0.001	0.8
Controls	274.62	25.839	3.654	<0.001	0.0
Patients	4.162	3.0936	0.4375	0.016	0.44
Controls	3.038	1.9232	0.2720	0.010	0.44
	Category Patients Controls Patients	Category         Mean           Patients         85.344           Controls         88.920           Patients         165.320           Controls         166.180           Patients         31.362           Controls         32.166           Patients         8.428           Controls         5.590           Patients         194.38           Controls         113.73           Patients         185.16           Controls         195.24           Patients         148.82           Controls         124.06           Patients         143.00           Controls         132.04           Patients         30.61           Controls         24.71           Patients         30.7.92           Controls         274.62           Patients         4.162           Controls         3.038	Category         Mean         Standard Deviation           Patients         85.344         11.5001           Controls         88.920         14.9933           Patients         165.320         9.4484           Controls         166.180         9.8077           Patients         31.362         4.6729           Controls         32.166         4.5818           Patients         8.428         1.7272           Controls         5.590         0.4171           Patients         194.38         49.148           Controls         113.73         11.967           Patients         195.24         34.043           Patients         148.82         56.165           Controls         124.06         48.206           Patients         143.00         14.885           Controls         124.06         48.206           Patients         112.36         33.819           Controls         132.04         37.871           Patients         30.61         11.023           Controls         24.71         9.630           Patients         307.92         52.272           Controls         274.62         25.839	Category         Mean         Standard Deviation         Standard Error           Patients         85.344         11.5001         1.6264           Controls         88.920         14.9933         2.1204           Patients         165.320         9.4484         1.3362           Controls         166.180         9.8077         1.3870           Patients         31.362         4.6729         0.6608           Controls         32.166         4.5818         0.6480           Patients         8.428         1.7272         0.2443           Controls         5.590         0.4171         0.0590           Patients         194.38         49.148         6.951           Controls         113.73         11.967         1.692           Patients         185.16         42.638         6.030           Controls         195.24         34.043         4.814           Patients         148.82         56.165         7.943           Controls         124.06         48.206         6.817           Patients         43.00         14.885         2.105           Controls         132.04         37.871         5.356           Patients         <	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

 Table 4: Description of Biochemical Marker P-Values (n=100)

The data presented in the table as means:  $p \le 0.05$  is considered statistically significant, BMI refers to body mass index, HbA1c hemoglobin A1c, FBS fasting blood sugar, Cho cholesterol, TG triglycerides, HDL high density lipoprotein, LDL low-density lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen, CRP c-reactive protein

Conventional PCR was employed to amplify the DNA target regions within the *FTO* gene. The PCR products (225 base pairs) of the *FTO* 1 region, (183 base pairs) of the *FTO* 2 region and (297 base pairs) of the *FTO* 3 region were detected in all of the study samples. This indicates the presence of the target regions in the *FTO* gene. Genetic analysis of the results detected four registered variants: [5376966 T/A; rs1558902] were detected in the *FTO* 1 region [53782363 C/A; rs8050136] were detected in the *FTO* 2 region and [53786591 G/A; rs996289, 53786615 T/A; rs9939609] were detected in the *FTO* 3 region see Table 5.

No.	Region	Variant Location	Allele	Consequence	Sample No.	Total samples
1	Intron	53769662	T/A	Intron Variant	1,3,4,5,6,7,9,11,12,13,14 15,16,17,19,21,22,23,24,25 27,28,29,31,33,34,35	28
2	Intron	53782363	C/A	Intron Variant	Intron Variant 3,6,7,11,15	
3	Intron	53786591	G/A	Intron Variant	1,3,4,5,6,9,10,11,12,14,15 16,17,19,22,23,24,25,27,28 29,32,33,34,36	25
4	Intron	53786615	T/A	Intron Variant 3,6,11,15,22		5

Table 5: Previously Registered Variants that are Detected in Study Samples.

The effects of *FTO* gene variations on the study parameters (BMI, HbA1c, FBS, Cho, TG, HDL, LDL, VLDL, FIB, and CRP) were investigated by comparing the level of each parameter in the samples sharing the same variation. It was found that the variant 53769662 T/A of the *FTO* 1 region is statistically significantly associations with cholesterol serum levels (p=0.03). The results revealed that there were no other significant associations with the rest of the parameters see Table 6 and Table 7.

 Table 6: Effects Of 53769662 T/A Variants on Study Parameters (Normally Distributed)

Parameters	53769662 T/A mutation	53769662 T/A mutation Mean±SD		P value	
Cho	Mutant	178.5±27.5	28	0.02*	
Ciio	Non-mutant	205.3±36.1	8	0.05*	
тс	Mutant	143.6±58.4	28	0.16	
16	Non-mutant	122.8±25.9	8	0.16	
пл	Mutant	41.3±10.7	7 28 0.02		
прг	Non-mutant	40.9±19.0	8	0.92	
IDI	Mutant	109.8±25.3	28	0.48	
	Non-mutant	118.1±42.5	8	0.40	
VI DI	Mutant	28.7±11.7	28	0.17	
VLDL	Non-mutant	Non-mutant 24.6±5.4 8		0.17	
EID	Mutant	288.9±54.2	28	0.58	
FID	Non-mutant	277.4±35.7	8	0.38	

The data presented in the table as means:  $\pm$ SD standard deviation of the mean p $\leq$ 0.05 is considered statistically significant Cho refers to cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen

Parameters	53769662 T/A mutation	Median±IQR	Frequency	P value				
DMI	Mutant	31.6±5.8	28	0.27				
BMI	Non-mutant	34.1±6.4	8	0.27				
HbA1c	Mutant	7.1±3.6	28	0.00				
	Non-mutant	7.1±5.5	8	0.99				
EDC	Mutant	155.6±103.0	28	0.00				
грэ	Non-mutant	155.6±158.0	±158.0 8					
CDD	Mutant	2.7±2.9	28	0.72				
CRP	Non-mutant	3.5±2.6	8	0.72				
The data presented in the table as means: $\pm IQR$ the interquartile, $p \le 0.05$ is considered statistically significant, BMI, refers to body mass index. HbA is hemoglobin A is ERS fasting blood sugar CRP creative protein								

Table 7: Effects of 53769662 T/A Variants on Study Parameters (Non-normally Distributed)

It was found that the variant 53782363 C/A of the *FTO* 2 region is statistically significantly associations with the FIB and CRP serum levels (p=0.04 respectively). The results revealed that there were no other significant associations with the rest of the parameters (see Table 8 and Table 9).

Parameters	53782363 C/A mutation	Mean±SD	Frequency	P value
CI	Mutant	181.0±35.4	5	0.70
CIIO	Non-mutant	185.0±31.0	31	0.79
TG	Mutant	156.0±48.1	5	0.45
	Non-mutant	136.3±54.3	31	0.43
HDL	Mutant	39.2±9.3	5	0.66
	Non-mutant	41.5±10.7	31	
LDL	Mutant	104.4±31.5	5	0.56
	Non-mutant	112.8±29.5	31	
VLDL	Mutant	31.3±9.6	5	0.44
	Non-mutant	27.3±10.9	31	0.44
FIB	Mutant	328.8±57.4	5	0.04*
	Non-mutant	279.5±46.7	31	0.04**
The data presented in the table as means: ±SD standard deviation of the mean, p≤0.05 is considered statistically				

Table 8: Effects Of 53782363 C/A Variants on the Study Parameters (Normally Distributed)

The data presented in the table as means:  $\pm$ SD standard deviation of the mean, p $\leq$ 0.05 is considered statistically significant, Cho refers to cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen

Parameters	53782363 C/A mutation	Median±IQR	Frequency	P value
BMI	Mutant	31.0±10.5	5	0.86
	Non-mutant	32.7±6.9	31	
TTL A 1 -	Mutant	$7.1 \pm 4.0$	5	0.80
пратс	Non-mutant	6.7±2.3	31	0.89
FBS	Mutant	157.1±115.0	5	0.89
	Non-mutant	145.6±66.0	31	
CRP	Mutant	3.6±2.9	5	0.04*
	Non-mutant	$1.4{\pm}1.9$	31	0.04*
The data presented in the table as means: ±IQR the interquartile, p≤0.05 is considered statistically				
significant, BMI refers to body mass index, HbA1c hemoglobin A1c, FBS fasting blood sugar, CRP c-				
reactive protein				

Table 9: Effects of 53782363 C/A Variants on the Study Parameters (Non-normally Distributed).

There were no statistically significantly associations between the 53786591 G/A of the FTO 3 region and all the parameters see Table 10 and Table 11.

Parameters	53786591 G/A mutation	Mean±SD	Frequency	P value
BMI	Mutant	32.9±5.7	25	0.40
	Non-mutant	31.6±2.8	11	0.49
Chol	Mutant	182.1±31.4	25	0.51
	Non-mutant	189.7±31.4	11	0.31
TG	Mutant	142.6±56.2	25	0.55
	Non-mutant	130.8±47.6	11	0.55
HDL	Mutant	42.9±11.4	25	0.14
	Non-mutant	37.3±7.4	11	0.14
LDL	Mutant	112.6±30.5	25	0.76
	Non-mutant	109.3±28.2	11	0.76
VLDL	Mutant	28.5±11.2	25	0.55
	Non-mutant	26.2±9.6	11	0.55
FIB	Mutant	286.7±51.5	25	0.05
	Non-mutant	285.5±50.4	11	0.95
The data presented in the table as means: $\pm$ SD standard deviation of the mean, p $\leq$ 0.05 is considered statistically significant BMI refers to body mass index. Cho cholesterol, TG triplycerides HDL high-				

Table 10: Effects Of 53786591 G/A Variants on Study Parameters (Normally Distributed).

iy mass in ex, Cho cholesterol, I density lipoprotein, LDL low-density lipoproteins, VLDL very-low-density lipoprotein, FIB fibrinogen

Parameters	53786591 G/A mutation	Median±IQR	Frequency	P value
HbA1c	Mutant	7.3±3.4	25	0.54
	Non-mutant	8.1±3.6	11	
FBS	Mutant	145.6±96.0	25	0.54
	Non-mutant	185.7±103	11	
CRP	Mutant	2.4±2.8	25	0.17
	Non-mutant	4.0±2.3	11	
The data present	ted in the table as means: ±IQ	R the interquartile range,	p≤0.05 is consider	red statistically
significant HbA1c refers to hemoglobin A1c, FBS fasting blood sugar, CRP c-reactive protein				

Table 11: Effects Of53786591 G/A Variants on Study Parameters (Non-Normally Distributed).

There were no statistically significantly associations between the 53786615 T/A of the *FTO* 3 region and all the parameters see Table 12 and Table 13.

Table 12: Effects Of 53786615 T/A Variants on Study Parameters (Normally Distributed).

Parameters	53786615 T/A mutation	Mean±SD	Frequency	P value
Cho	Mutant	189.6±35.2	5	0.70
	Non-mutant	183.6±31.0	31	
TG	Mutant	164.6±42.0	5	0.25
	Non-mutant	134.9±54.3	31	
HDL	Mutant	43.2±6.7	5	0.65
	Non-mutant	40.9±11.1	31	
LDL	Mutant	118.4±32.9	5	0.59
	Non-mutant	110.5±29.3	31	
VLDL	Mutant	33.0±8.4	5	0.25
	Non-mutant	27.0±10.9	31	
FIB	Mutant	323.2±50.7	5	0.08
	Non-mutant	280.4±48.6	31	
The data presented in the table as means: $\pm$ SD standard deviation of the mean, p $\leq$ 0.05 is considered statistically significant, Cho cholesterol, TG triglycerides, HDL high-density lipoprotein, LDL low-density lipoproteins, VLDL				

very-low-density lipoprotein, FIB fibrinogen

Table 13: Effects of 53786615 T/A Variants on Study Parameters (Non-Normally Distributed).

Parameters	53786615 T/A mutation	Median±IQR	Frequency	P value
BMI	Mutant	29.6±10.1	5	0.30
	Non-mutant	32.7±5.7	31	
HbA1c	Mutant	6.7±2.6	5	0.79
	Non-mutant	7.1±3.9	31	
FBS	Mutant	145.6±76.0	5	0.79
	Non-mutant	157.1±112.0	31	
CRP	Mutant	$1.4\pm4.5$	5	0.16
	Non-mutant	3.0±2.7	31	
The data presented in the table as means: $\pm IQR$ the interquartile range, p $\leq 0.05$ is considered statistically				
significant, BMI refers to body mass index, HbA1c hemoglobin A1c, FBS fasting blood sugar, CRP c-				
reactive protein				

#### Discussion

Obesity raises the risk of several common diseases, making it an important global health concern. It's unclear whether hereditary factors contribute to obesity. A common mutation in the *FTO* (fat mass and obesity associated) gene, which predisposes to diabetes through an influence on body mass index, was found during a genome-wide search for genes linked to type 2 diabetes susceptibility(Frayling et al., 2007). A typically elevated triglyceride deposition and the generation of hepatic glucose can result from enhanced *FTO* expression, which can also promote de novo lipogenesis, decrease lipolysis and fatty acid oxidation, and boost gluconeogenesis(Witka et al., 2019). These results imply that *FTO* is connected to the regulation of both body weight and glucose metabolism. While there is no doubt that variations in the *FTO* gene are linked to type 2 diabetes and obesity, the biological role of *FTO* remains unclear(Gerken et al., 2007; Han et al., 2010). Finally, we believe that the results of this study, particularly the four variants in the *FTO* gene's *FTO* 1 regions (53769662 T/A), *FTO* 2 regions (53782363 C/A) and *FTO* 3 regions (53786591 G/A and 53786615 T/A) could be significant in the field of *FTO* gene studies. The presence of these variants in important coding regions suggests their potential importance.

Furthermore, among four variants, two variants (53769662 T/A and 53782363 C/A) might be the most significant, as they exhibited a significant effect on certain study parameters. Where the variant 53769662 T/A showed a significant effect on the level of cholesterol in the blood, the variant 53782363 C/A showed a significant effect on the levels of FIB and CRP. To precisely identify their role in Type 2 Diabetes Mellitus patients, further studies are needed in future research. It must be noted that the study results were limited by the relatively small sample size of the patients and controls, suggesting the need for large-scale studies to corroborate the results and validate the findings.

#### Ethics approval and consent to participate

The Institutional Ethics Committee in the Department of Clinical Laboratories / College of Applied Medical Sciences/ University of Kerbala approved this study (IQ.UOK.CAMS.DCL.REC.2). Informed consent was taken from every patient in their language regarding willingness to participate in the study. Patient confidentiality was maintained during all research procedures.

#### Author contributions

Both authors have contributed to the writing and approved the manuscript before submission.

#### **Conflicts of interest**

There are no conflicts of interest.

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