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Serum Level and Genetic Polymorphism of Interleukin-33 in Iraqi Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is characterized by insulin deficiency and resistance. This study evaluated serum interleukin-33 (IL-33) and its soluble receptor (sST2), plus two IL-33 gene polymorphisms (rs7044343, rs1929992), for association with T2DM in Iraqi patients.

Patients and Methods: In this case–control study, 120 T2DM patients and 80 age and sex matched healthy controls were used. Fasting blood glucose and glycated hemoglobin (HbA1c) confirmed diabetic status. Serum IL 33 and sST2 concentrations were measured by ELISA. Genotyping of IL 33 rs7044343 and rs1929992 was performed via PCR–RFLP. Allele and genotype frequencies were compared using χ^2 tests; associations were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was set at $p < 0.05$.

Results: Compared to controls, T2DM patients showed significantly higher serum IL 33 (mean ± SD: 43.2 ± 12.7 vs 28.5 ± 9.3 pg/mL, $p < 0.001$) and sST2 (56.8 ± 14.1 vs 34.7 ± 10.5 ng/mL, $p < 0.001$). The IL 33 rs1929992 variant exhibited no significant difference between groups ($p = 0.30$). In contrast, the rs7044343 AA genotype was more frequent in T2DM patients than controls (AA = 34% vs 18%; OR = 2.35, 95% CI 1.22–4.52, $p = 0.010$), while the CC genotype conferred a protective effect (CC = 22% vs 38%; OR = 0.48, 95% CI 0.26–0.89, $p = 0.018$).

Conclusion: Elevated IL 33 and sST2 levels, together with the rs7044343 AA genotype, are associated with increased susceptibility to T2DM in Iraqi patients. These findings support IL 33 pathway involvement in T2DM pathogenesis.

Keywords: *IL-33, T2DM, Lipid profile, ST2 receptor.*

Introduction

Diabetes mellitus (DM) is a chronic metabolic condition characterized by sustained hyperglycemia and disruptions in glucose, lipid, and protein metabolism (1). The global prevalence of type 2 diabetes mellitus (T2DM) has increased significantly in recent decades, now affecting over 460 million adults and imposing a substantial burden on healthcare systems, especially in developing countries such as Iraq (2). T2DM, formerly referred to as non–insulin-dependent diabetes, constitutes approximately 90–95 % of all diabetes cases and is a central component of metabolic syndrome, which also includes hypertension, dyslipidemia, and central obesity (1,2). At the cellular level, T2DM pathogenesis hinges

on two interrelated defects: dysfunction of pancreatic β cells leading to inadequate insulin secretion, and peripheral insulin resistance, which diminishes insulin's effectiveness in skeletal muscle, adipose tissue, and the liver (2). early stages, β cells compensate by hypersecreting insulin; however, chronic metabolic stress and lip toxicity ultimately precipitate β cell exhaustion and apoptosis, exacerbating hyperglycemia (2). Concurrently, insulin resistance fosters a pro inflammatory milieu in adipose and vascular tissues, driving the secretion of cytokines and adipokines that further impair glucose homeostasis (3) Among these signaling molecules, interleukin 33 (IL 33) has emerged as a pivotal regulator at the intersection of immunity and metabolism. IL 33, encoded on chromosome 9p24 and comprising 11 exons, belongs to the IL 1 cytokine family and is released upon cellular stress or necrosis (3). It exerts its effects by binding to the ST2 receptor complex: the membrane bound ST2L, which activates MyD88–NF κB and MAPK pathways to promote type 2 immune responses, and the soluble decoy receptor (sST2), which neutralizes IL 33 and limits its activity (4). Elevated IL 33 has been implicated in the regulation of adipose tissue inflammation, enhancement of insulin sensitivity in mice, and modulation of T helper 2 (Th2)–type responses that counteract classical pro inflammatory Th1/Th17 pathways (5). Genetic variability in the IL 33 gene can influence cytokine expression and function. Some genetic variations, such rs7044343 and rs1929992, have been linked to inflammatory and autoimmune diseases, such as SLE, AS, RA, and ankylosing spondylitis (6). In murine models, IL 33 administration ameliorates insulin resistance and promotes glucose uptake by adipocytes, suggesting a protective metabolic role (7). However, human data linking IL 33 gene variants to T2DM susceptibility remain scant. Given the high and rising incidence of T2DM in Iraqi populations, and the potential of the IL 33/ST2 axis as both a biomarker and therapeutic target, this study examines serum IL 33 and sST2 levels alongside genotyping of IL 33 SNPs (rs7044343, rs1929992) in a cohort of Iraqi T2DM patients. We aim to elucidate whether IL 33 pathway alterations contribute to disease susceptibility and inflammation in this understudied population.

Patients and Methods

Study design: The study involved 70 patients with Type 2 Diabetes Mellitus (T2DM) who visited the National Diabetes Center at Al-Mustansiryah University between October 2020 and February 2021. Among these patients, there were 29 men and 41 women, aged between 30 and 75 years. Additionally, 30 blood samples were collected from non-diabetic healthy individuals to serve as controls, comprising 12 men and 18 women aged between 24 and 65 years. Comorbidities among T2DM patients included hypertension (64.3%), renal disease (87.1%), and cardiovascular disease (57.1%) (Table 2). Five milliliters of blood were drawn from the antecubital vein of T2DM patients and divided into two parts: two milliliters were placed in an EDTA tube for Glycated hemoglobin A1C analysis, DNA extraction, and subsequent PCR amplification; the remaining three milliliters were collected in a gel tube and centrifuged at 3000 rpm for 5 minutes. This serum was then used to measure fasting glucose, lipid profile, C-reactive protein, the concentration of IL-33, and the concentration of the Soluble ST2 Receptor.

Body mass index (BMI): Body mass index is a standardized estimate of the relative body mass of individuals calculated on the basis of a man or women weight and height. The BMI was displayed as the weight in kilograms separated by the square measured in meters of height (kg / m2). A BMI greater than 30 kg / m2 is described as obese (BMI = Weight (Kg) / Height (m)2) (8).

Measurement biochemical parameters: FBS, Cholesterol, Triglyceride, HDL, LDL, VLDL,

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CRP and HbA1C all these tests performed by (COBAS c311, Roche, Germany) (9,10).

Estimation serum IL-33 and soluble ST2 receptor: Serum concentrations of IL-33 and soluble ST2 (sST2) were quantified utilizing commercial sandwich ELISA kits (Elabscience, China) in accordance with the manufacturer's protocol (11). Initially, all reagents and samples were equilibrated to room temperature (18–25 °C) for a minimum of 20 minutes prior to use. The 25× wash buffer was diluted to a 1× working concentration, and the reference standard was reconstituted and serially diluted to establish a standard curve. The biotinylated detection antibody and horseradish peroxidase (HRP) conjugated antibody was each diluted 1:100 in assay buffer at least 15 minutes before their respective incubation steps. The microplate reader was pre-warmed to 37 °C before commencing the assay. To test each analyte, 100 µL of standard or undiluted blood sample was added to a pre-coated 96-well plate in triplicate and incubated at 37 °C for 90 minutes. After emptying the wells, 100 µL of biotinylated detection antibody was added and incubated at 37 °C for 60 minutes. After three 1× wash buffer washes, 100 µL of diluted HRP conjugate was added and incubated at 37 °C for 30 minutes. Plates were washed five times, then 90 µL of TMB substrate was added to each well, and developed for 15 minutes at 37 °C in the dark. After stopping the reaction with 50 µL of stop solution, absorbance was measured at 450 nm (reference 630 nm). A four-parameter logistic model estimated concentrations from the standard curve.

DNA extraction: Genomic DNA was extracted from blood samples in total. The extraction of DNA was performed utilizing the Favor Prep TM DNA Extraction Kit Quick Protocol System (Favorgen, Taiwan). The Quintus Fluorometer was utilized to measure the concentration of the extracted DNA (12). Additionally, gel electrophoresis was employed to verify the presence of DNA integrity (13).

Program of PCR assay: The DNA template was amplified with the same primer pair (Forward) and (Reverse) (Table 1) at temperatures of 55, 58, 60, 63, and 65°C to ascertain the best primer annealing temperature. In 20µl volumes, PCR amplifications were performed using 10µl GoTaq Green Master Mix (2X), 1µl primer (10pmol), 6µl nuclease-free water, and 2µl template DNA. The method started with a 4-minute 94 °C denaturation. The PCR Express (Thermal Cycler, BioRad, USA) was used to perform 30 cycles of denaturation at 94°C for 30 seconds, annealing at 55, 58, 60, 63, or 65°C for 30 seconds, and extension at 72°C for 30 seconds. A 7-minute extension at 72°C and 10-minute incubation at 4°C ended the reactions. After genomic DNA extraction or PCR amplification, agarose gel electrophoresis was used to check DNA presence and integration (14).

Table 1. Primers used in this study.

Primer Names	Sequence
rs1929992-F	GTGCAAGGTAGCTGTTCTAATA
rs1929992-R	TGTTCTCTCCTCTGGCTAAA
rs7044343-F	GGCTTTACATGCAGACAGGAA
rs7044343-R	TGGAGAGTTGTGACCCTAATGG

Sequencing: The PCR products for the IL-33 gene were dispatched to Microgen Corporation in Korea for Sanger sequencing utilizing the ABI3730XL, an automated method for DNA sequencing. The data were collected via email and subsequently analyzed with advanced tools (15).

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 20.0) developed by IBM SPSS Statistics, SPSS Inc., Chicago, Illinois, USA, was used for statistical analyses. The

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D'Agostino-Pearson test was used to evaluate the normality of the data (16). Data with a normal distribution is given as the mean plus or minus the SD. Data without a normal distribution were shown as the median value and interquartile range (Q1–Q3). Student's t-test was used for regularly distributed data and Mann-Whitney U-test or Kruskal-Wallis H-test for non-normally distributed data to compare groups (17). Discrepancies between actual and predicted frequencies among the groups were computed using a $\chi 2$-test. Spearman's rank correlation test was used to determine the correlations between variables (18). The threshold for statistical significance was established at $p < 0.05$. The statistical analyses were performed using MedCalc® version 14.12.0 for Windows, created by MedCalc Software in Ostend, Belgium. Discrete variables are denoted by their frequencies and ratios. The chi-square test was used to compare the categorical variables among the various study groups (19). The statistical tests were validated by accepting the null hypothesis that there was no difference between the means of the variables. Statistical significance was set at $P < 0.05$.

Results

Demographic characterization of patients: This study involved a cohort of 100 participants, comprising 70 patients and 30 healthy individuals serving as controls. Ages ranged from 30 to 75 years in patients and 24 to 65 years in controls. The patients with Type 2 Diabetes Mellitus (T2DM) were categorized into three distinct age groups: those under 50 years, those between 50 and 60 years, and those over 60 years, as detailed in Table 2. The demographic and general characteristics utilized in this study, as presented in Table 3, reveal that the proportion of male diabetic patients was 54.3%, exceeding that of female patients at 45.7%. Additionally, A significant number of diabetic patients exhibited cardiovascular disease (57.1%) and hypertension complications (64.3%). This is attributable to the fact that diabetes mellitus contributes to the elevation of factors associated with cardiovascular conditions, such as obesity, cholesterol, and lipid levels. The categories of the Biomass index demonstrated highly significant differences ($P \leq 0.0001$) between the patient group (29.83 ± 5.006 Kg/m2) and the healthy control group (23.13 ± 1.549 Kg/m2), as indicated in Table 4, with a significance level of ($P \leq 0.001$).

Table 2. Patients' classifications according to their age and gender.

Age (year)	No.	Gender	
		Female	Male
< 50	16	4%	12%
50 – 60	34	16%	18%
> 60	20	12%	8%
Total	70	32%	38%

Table 3. Demographic characteristics of diabetes patients.

Subjects		N. (%)
Gender	Male	38 (54.3)
	Female	32 (45.7)
Hypertension	Yes	45 (64.3)
	No	25 (35.7)
Renal disease	Yes	61 (87.1)
	No	9 (12.9)
Cardiovascular disease	Yes	40 (57.1)
	No	30 (42.9)
Duration of diabetes		
<5 years		32
≥5 years		38

Table 4. Comparison of age, BMI, weight, height between patients and control groups.

Variables	Diabetes patients' group (n=70) (mean±SD)	Healthy control group (n=30) (mean±SD)	t – test (p – value)
Age (years)	56.43 ± 9.426	53.30 ± 4.706	0.0971†
BMI (kg/m^2)	29.83 ± 5.006	23.13 ± 1.549	0.0001*
Weight (kg)	81.50 ± 11.28	63.17 ± 11.61	0.0001*
Height (Cm)	165.8 ± 7.581	164.3 ± 10.41	0.4215†

*= difference of statistical significance, p≤ 0.05.
†= difference of no statistical significance, p≥ 0.05.

Glucose levels (FBG and HbA1) of diabetes patients: The result of FBG indicated that the levels were significantly increased (P≤0.0001) in T2DM patients in contrast with healthy controls as showed in Table 5. HbA1c was measured in the blood of all samples the result showed that there were highly significant differences (P≤0.0001) between the patients and healthy controls. The mean average percentage and standard deviation of patients were (8.061±2.094), and healthy controls were (5.307 ± 0.5663), which was lower than the percentage of patients. as shown in Table 4, fasting blood glucose (FBG) was higher in T2DM patients (189.7 ± 67.2 mg/dL) than controls (87.0 ± 7.9 mg/dL; t = 12.1, p < 0.001).

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Table 5. Comparison of study variables among diabetic patients and healthy controls.

Variables	Diabetes patients' group (n=70) (mean ±SD)	Healthy control group (n=30) (mean ±SD)	t – test (p – value)
CRP (mg/dl)	5.480 ± 4.304	2.513 ± 1.220	0.0002*
FBS (mg/dl)	189.7 ± 67.17	87.00 ± 7.892	0.0001*
HbA1C (%)	8.061 ± 2.094	5.307 ± 0.5663	0.0001*
CHOL (mg/dl)	175.5 ± 39.36	142.5 ± 37.80	0.0001*
TG (mg/dl)	174.6 ± 111.2	99.53 ± 34.48	0.0001*
HDL (mg/dl)	40.97 ± 10.58	50.07 ± 12.70	0.0008*
LDL (mg/dl)	93.54 ± 36.25	86.43 ± 33.00	0.3591†
VLDL (mg/dl)	32.76 ± 22.10	18.13 ± 6.073	0.0006*

*= difference of statistical significance, p≤ 0.05.
†= difference of no statistical significance, p≥ 0.05.

Lipid profile of diabetes patients: Table 5 showed the lipid profile for diabetic patients, which shows a highly significant increase in the total cholesterol concentration of T2DM patients is more than the total cholesterol concentration of healthy controls (P = 0.0001). The average and SD of total cholesterol concentration in T2DM patients were (175.5 ± 39.36 mg/dl) , while the average and SD of total cholesterol concentration in healthy controls were (142.5 ± 37.80 mg/dL) at (P≤ 0.005). C-reactive protein (CRP) result showed that there were highly significant differences (5.48 ± 4.30 mg/dL) versus controls (2.51 ± 1.22 mg/dL; t = 4.15, p < 0.001). The rate of TGs in the blood sample of T2DM patients is a highly significant increase in the triglyceride concentrations compared to healthy controls (P≤ 0.0001). The average and SD of serum triglyceride concentration in T2DM patients were (174.6 ± 111.2 mg/dL) while the average and SD of serum triglyceride concentration in healthy controls were (99.53 ± 34.48 mg/dL) at (p≤ 0.001). HDL results showed that there was a significant difference in serum level of HDL between T2DM patients, 40.97 ± 10.58 (mg/dl), and controls, 50.07 ± 12.70 (mg/dl), p-value (0.0008). The LDL level results showed a non-significant difference in the serum level of LDL between T2DM patients 93.54 ± 36.25 (mg/dl) and controls 86.43± 33.00 (mg/dl) (P=0.3591). The serum level of VLDL in T2DM patients was significantly elevated (P=0.0006), measuring 32.76 ± 22.10 mg/dl, compared to 18.13 ± 6.073 mg/dl in healthy controls.

Interleukin- 33 (IL-33) in diabetes patients:
The result showed that there was a significant difference in serum concentration IL-33 amongst T2DM patients (26.10±33.45) and healthy controls (10.20±10.79) (P=0.0005) as seen in Table 6.

Table 6. Comparison of study variables among diabetic patients and healthy controls.

Group	Mean ± SD	
	Interleukin-33 (pg/ml)	sST2 Receptor (pg/ml)
Patients (n=70)	26.10±33.45	31.56±18.57
Controls (n=30)	10.20±10.79	12.62±6.454
p-value	0.0005*	0.0001*

*= difference of statistical significance, p≤ 0.05

Soluble suppression of tumorigenicity 2 receptor (sST2): The results showed that the insulin level in healthy control was a significant (P<0.0001) in association with its concentration in diabetic patients, where the average of soluble ST2 receptor in serum of T2DM patients were 31.56±18.57 (pg/ml) compared to 12.62±6.454 (pg/ml) in the healthy control group as seen in Table 6.

Correlations of sST2 receptor and IL-33 with diabetes parameters: Spearman's correlation tests were used to depict the relationship between sST2 Receptor and IL-33 with other tested parameters of T2DM. the result showed sST2 levels were inversely correlated with age (r = –0.11), BMI (r = –0.17), and HDL (r = –0.08), and positively correlated with CRP (r = 0.19), FBG (r = 0.06), HbA1c (r = 0.07), total cholesterol (r = 0.06), triglycerides (r = 0.02), LDL (r = 0.14), VLDL (r = 0.03), and IL 33 (r = 0.16) (all p < 0.05) (Table 7).

Table 7. Comparison of study variables among diabetic patients and healthy control groups.

Variables	Parameters vs. sST2 Receptor (Correlation coefficient, r)	Parameters vs. IL-33 (Correlation coefficient, r)
Age (years)	-0.1149	-0.07080
BMI (kg/m^2)	-0.1687	-0.001774
CRP (mmHg)	0.1858	-0.1993
FBS (mg/dL)	0.05911	0.006998
HbA1C (%)	0.07273	-0.04482
TC. (mg/dL)	0.05890	-0.04215
TG (mg/dL)	0.01595	0.04813
HDL (mg/dL)	-0.07895	-0.1425
LDL (mg/dL)	0.1374	-0.02383
VLDL (mg/dL)	0.02688	0.01602
sST2 Receptor	-	0.1641
IL-33	0.1641	-

Genetic polymorphisms of IL-33 gene: The concentration and purity were measured by using a Nano Drop spectrophotometer and the result of concentration ranged from (10 -38 ng/µl) and the result of purity ranged from (1.6-2.1). In order to detect SNP (Single nucleotide polymorphism) in interlukin-33 gene (IL-33), genomic DNA extracted from blood of T2DM patients and healthy members was amplified using a specific primer for IL-33 gene (rs1929992). The results of the amplification showed that a single amplified product with (999 Bp) molecular size got after electrophoresis on agarose gel (1%) representing the amplified area of IL-33 gene (rs1929992) as shown in Figure 1.

Sequence of amplified SNP (rs1929992) Interleukin-33 gene: To confirm results PCR products of T2DM patients and healthy controls were sequenced and aligned with the reference sequence recorded in data base of the National Center for Biotechnology Information (NCBI). Results of sequence alignment illustrated in Figure (3-14) showed that the position of SNP (rs1929992) within the nucleotide sequence matched with the reference sequence of IL-33 gene of the NCBI (http://www.ncbi.nlm.nih.gov). The present study showed that another two SNPs were discovered during sequence analysis at rs10758751 and rs1330383. New SNPs (rs10758751 and rs1330383) there was no

previously published work on the role of these SNPs and susceptibility with T2DM.

Quantitative expression of SNP (rs7044343) Interleukin-33 gene: Quantitative expression of IL-33 gene (rs7044343) determined by reverse transcription-quantitative polymerase chain reaction (RT-qPCR), in which the relative quantitation method was employed as the melting curve in Figure 2 show. The present study revealed no significant association (P≤0.05) of gene expression for IL-33 gene (rs7044343) T2DM patients when compared with healthy controls, as seen in (Table 8). For SNP rs7044343, genotype frequencies did not differ between groups (CC, CT, TT: 27.1%, 41.4%, 31.4% in patients vs. 30.0%, 23.3%, 46.7% in controls; $\chi^2 = 2.46$, $p = 0.30$). Allele frequencies (C vs. T) were 48.6% vs. 51.4% in patients and 41.7% vs. 58.3% in controls ($\chi^2 = 2.67$, $p = 0.10$).

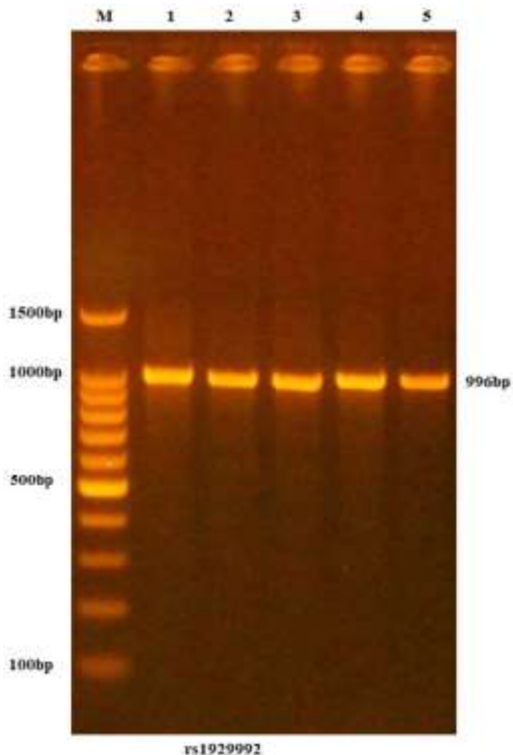

Figure 1. Results of the amplification of rs1929992 primer of Human samples were fractionated on 1.5% agarose gel electrophoresis stained with Eth.Br. M: 100bp ladder marker. Lane 1-5 resemble 996bp PCR products.

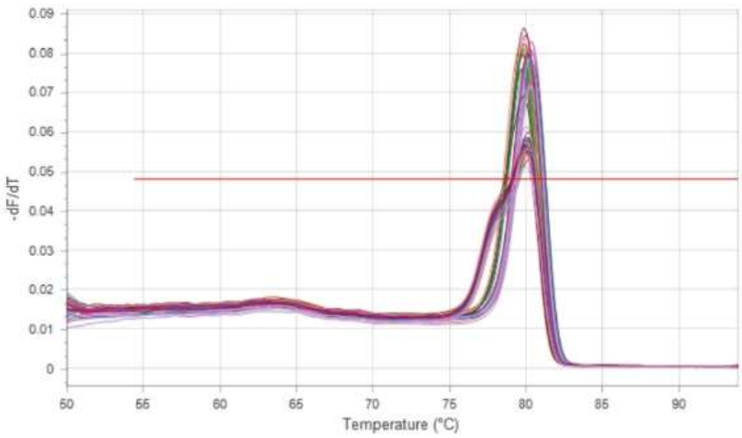

Figure 2. Melting curve of the amplification of rs7044343 by qPCR.

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Frequency and distribution of IL-33 gene polymorphism and susceptibility to diabetes mellitus: Table 8 revealed no significant difference in rs7044343 genotype distribution between T2DM and healthy groups ($\chi2$=2.46, P =0.3) (P≤0.05). T2DM patients had 19 homozygous dominant genotypes (CC), whereas controls had 9. The homozygous mutant genotype (TT) and heterozygous mutant genotype (TC) were 22 and 29, respectively, in T2DM patients, compared to 4 and 7 in the control group. The research found no significant difference in allele frequency ($\chi2$ =2.67, P= 0.1) between the two groups. The frequency distribution of the rs1929992 genotype was not statistically significant ($\chi2$ = 1.29, P = 0.5). The T2DM group had 34 homozygous wild type (TT) individuals, whereas the control group included 17. The T2DM group had 10 homozygous mutant genotype (CC) and 26 heterozygous mutant genotype (TC) individuals, while the control group had 2 CC and 11 TC individuals. However, a chi-square value of 1.22 and a p-value of 0.3 showed no significant allele frequency difference between the two groups. The relationship between IL33 gene polymorphism and the risk of T2DM in the Iraqi population was shown in Table 8. The genotype rs10758751 revealed a significant distribution ($\chi2$ =7.25, P = 0.02) in T2DM compared to healthy group (P≤0.05). In 16 T2DM and 15 controls, the dominant homozygous genotype (CC) was present, whereas the mutant homozygous (AA) and mutant heterozygous (CA) were 51 and 3, respectively, compared to 14 and 1. On the other hand, a higher significant difference was reported in the allele frequency result ($\chi2$ =13.5, P= 0. 0002) in both groups. The only statistically significant association of the mutant homozygous (CC) with the risk of T2DM (P=0.009; OR=3.4; 95%CI, 1.36-8.57). On the other hand, the mutant heterozygous (CA) showed no significant increase in the risk of T2DM (P= 0.4; OR=2.8; 95CI, 0.26-30.1). Also, the mutant allele (CC) showed a highly significant increase in the risk of T2DM (P=0.0003; OR=3.2; 95%CI, 1.7-6.05). These findings propose that the AA genotype could be a protective factor compared to the role of CC, which was identified as a predisposing factor to T2DM in the Iraqi population. In Table (8) the result indicated no significant distribution among the genotypes ($\chi2$ =1.97, P= 0.3) of rs1330383 and no significant distribution of allele frequency ($\chi2$ =2.48, P= 0.1).

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Table 8. Distribution of IL-33 gene polymorphisms in type 2 diabetes mellitus and healthy control groups.

Genotype	Diabetes patients N	Control N	OR (95%CI)	P-value	X2	P-value
rs7044343						
CC	19	9	reference		2.46	0.3†
CT	29	7	1.96 (0.625- 6.165)	0.25		
TT	22	4	5.6 (0.25-125.4)			
C	67	25	reference		2.67	0.1†
T	73	15	2.6 (0.69- 9.83)	0.16		
rs1929992						
TT	34	17	reference		1.29	0.5†
CT	26	11	1.18 (0.47 - 2.95)	0.7		
CC	10	2	2.5 (0.49 - 12.7)	0.26		
T	94	45	reference		1.22	0.3†
C	46	15	1.47 (0.74 - 2.9)	0.27		
rs10758751						
CC	16	15	reference		7.25	0.02*
CA	3	1	2.8 (0.26 - 30.1)	0.4		
AA	51	14	3.4 (1.36 - 8.57)	0.009		
C	35	31	reference		13.5	0.0002 *
A	105	29	3.2 (1.7 - 6.05)	0.0003		
rs1330383						
GG	33	18	reference		1.97	0.3†
GT	23	9	1.39 (0.53 - 3.65)	0.5		
TT	14	3	2.5 (0.646 - 10.05)	0.18		
G	89	45	reference		2.48	0.1†
T	51	15	1.7(0.87 - 3.39)	0.11		

*= difference of statistical significance, P≤ 0.05
†= difference of no statistical significance, P> 0.05.

Discussion

Diabetes mellitus (DM) is marked by chronic hyperglycemia and dysregulated carbohydrate, lipid, and protein metabolism. In our cohort, body mass index (BMI) was significantly higher in T2DM patients (29.8 ± 5.0 kg/m²) than controls (23.1 ± 1.5 kg/m²; t = 6.72, p < 0.001), reflecting the well-known link between obesity and insulin resistance. The increase of biomass index was noticed in elderly men more than women, obesity was directly associated with hyperinsulinemia in type 2 diabetes mellitus (1). Hypertension was present in 64.3% of patients versus 0% of controls ($\chi^2 = 34.3$, $p < 0.001$), underscoring its role in amplifying CVD risk in T2DM. Vascular remodeling and dysfunction are also induced in

hypertension by many of the underlying molecular processes that underlie microvascular and macrovascular issues in diabetes, such as oxidative stress, inflammation, and fibrosis. Diabetic nephropathy affected 87.1% of this study patients ($p < 0.001$), consistent with the kidney's susceptibility to hyperglycemia induced microvascular damage. Due to their medical condition and/or accompanying comorbidities, such as hypertension and age-related decline in kidney function, a considerable number of individuals with diabetes will develop renal disease. BMI was effectively correlated with T2DM and was considered as a threat factor for the occurrence of the disease in individual with different level of obese. This difference depends on many factors like diet, family, drugs, environmental and medical history as well as type of patient sample. Fasting blood glucose (FBG) was markedly elevated in T2DM patients (189.7 ± 67.2 mg/dL vs 87.0 ± 7.9 mg/dL; $t = 12.1$, $p < 0.001$), reflecting β cell dysfunction and insulin resistance, as a result the glucose level increased in blood instead of being consumed for producing energy purposes. In patients with type 2 diabetes mellitus (T2DM). Additionally, the HbA1c % indicated a substantial rise in patients compared to healthy controls (20,21). Results indicate that the production of glycated hemoglobin is a straightforward component of the physiologically effective cycle. Glucose in the open branch interacts with the N-terminal of the beta chain, forming a Schiff base. During the reformation, the Schiff base is converted into Amadori products, also referred to as HbA1c. This is a non-enzymatic process that often occurs in vivo when average blood glucose levels rise, resulting in an increase in HbA1c (22). C reactive protein (CRP) correlated positively with HbA1c ($r = 0.19$, $p < 0.01$) and triglycerides ($r = 0.15$, $p < 0.05$), indicating that poor glycemic control exacerbates systemic inflammation which suggest that the CRP increase in type 2 diabetes mellitus with and without nephropathy, CRP was substantially correlated to metabolic factors and markers of cardiovascular risk. Also, CRP could be used as a predictor or disease indicator for the development of nephropathy and cardiovascular risk in diabetic patients (23). Total cholesterol was higher in patients (175.5 ± 39.4 mg/dL) than controls (142.5 ± 37.8 mg/dL; $t = 4.06$, $p < 0.001$), consistent with prior Egyptian cohorts, including family medical history, age, ethnicity, obesity, high blood pressure, physical inactivity, smoking and diabetes. The total normal concentration of cholesterol must be less than 200 (mg/dl). The findings of this research align with three previous Egyptian investigations, which showed a significant elevation in total cholesterol levels among patients with type 2 diabetes mellitus compared to the control group (24). Estimation of triglyceride (TGs) concentrations is regarded to be effective in diagnosing DM in relation to pancreatitis, cardiac disease and other medical conditions. The standard triglyceride level is over 150 (mg/dl). Triglycerides were elevated in T2DM (174.6 ± 111.2 vs. 99.5 ± 34.5 mg/dL; $t = 3.86$, $p < 0.001$), indicating VLDL overproduction in insulin resistance. Elevated triglyceride concentration may occur because of two disorders, defective triglyceride lipolysis and VLDL overproduction. T2DM patients have an overproduction level of triglyceride-rich VLDL due to elevated free fatty acid concentrations, obesity, hyperglycemia and insulin resistance (25). High-density lipoproteins (HDL) particles are impaired by metabolic syndromes with abnormal HDL particle sizes, such as T2DM. Normal HDL levels are 40-60 (mg/dl). The relative insulin deficiency in T2DM adversely affects the activity of lipoprotein lipase enzyme and effects in reduced HDL-cholesterol concentrations and greater Triglyceride concentrations. In addition, (26) observed that T2DM was generally correlated with low HDL plasma concentrations. LDL (Low-density

lipoproteins) are the major transporters of fat and cholesterol in human blood. In many respects, it is connected with the processes that eventually lead to the manufacturing of distinct LDL particles. Normal LDL is < 100 (mg/dl) (27). VLDL (Very Low-Density Lipoprotein) is one of the primary types of lipoproteins, with the largest triglyceride content in VLDL. Normal VLDL is < 30 (mg/dl). The elevated VLDL levels were a result of insulin resistance, where the skeletal muscle system promotes the conversion of energy from ingested carbohydrates, leading to increased synthesis of triglycerides in the liver. Consequently, it will generate lipoprotein units that are high in atherogenic triglycerides, such as very low-density lipoprotein (VLDL)(28). This study observed higher IL 33 in patients (26.1 ± 33.5 pg/mL vs 10.2 ± 10.8 pg/mL; $t = 3.52$, $p = 0.0005$) and elevated sST2 (31.6 ± 18.6 vs 12.6 ± 6.5 pg/mL; $t = 5.21$, $p < 0.001$), supporting IL 33/ST2 dysregulation in T2DM, which is supported by a study (29). found that serum level of IL- 33 was increased significantly in patients with type 2 diabetes compared to the non-diabetic patients. Mounting data suggests that disorders associated with metabolic syndrome are marked by aberrant cytokine production, such as raised levels of circulating IL-33, increased acute-phase proteins like CRP, and activation of inflammatory signaling pathways (30). IL-33 plays a protective role in preventing adiposity, inflammation associated with obesity, insulin resistance, and type 2 diabetes (T2DM). It contributes to glucose regulation by reducing fasting glucose levels and improving glucose and insulin tolerance. IL-33 is also involved in the molecular mechanisms that protect against the development of insulin resistance, which is a significant factor in the development of atherosclerosis (31). IL-33 is present in a nuclear form and may function as an alarmin, being released after cell injury, or as a negative regulator of NFκB gene transcription, acting inside the cell (32). A study by (33) revealed a significant increase in sST2 receptor concentration in T2DM. In type 2 diabetes mellitus (T2DM), Toll-like receptors (TLRs) are recognized as the main molecules responsible for carrying out this process. They are also triggered by dietary variables such as free fatty acids (FFA). Ligands binding on Toll-like receptors (TLRs) start the inflammatory cascade and alter insulin homeostasis. In addition to the innate immune system, adaptive immunity may contribute to type II diabetes' persistent inflammation. CD4-positive T lymphocytes infiltrate adipose tissue first. From this perspective, the IL-33/ST2 pathway may play a vital role in regulating the level of inflammation in diabetes (34,35). Investigations have documented a positive correlation between elevated serum sST2 levels and hs-CRP levels, which serve as an indicator of systemic inflammation, as well as the degree of glycemic control measured by HbA1c. A study by (36) discovered that the levels of sST2 are not only linked to the metabolic aspects of diabetes but also to a considerably heightened risk of developing diabetes and hypertension. Also results of (37) recorded that the level of sST2 associated with cardiovascular diseases, however, in individuals exhibiting optimal health within the general population, sST2 demonstrated minimal predictive capacity regarding cardiovascular events. Results of (38) recorded that there were significant differences in serum sST2 concentration with all markers of liver and renal function, HDL-cholesterol total cholesterol and smoking status. The results of this study were consistent with that result described by (39) which indicated that age and BMI were negatively correlated with sST2 receptor and blood sugar had a positive correlation. A long with the results of this study, (34) supported that sST2 levels were correlated positively with CRP levels, fasting plasma glucose (FPG), TG, TC, HbA1c but were negatively correlated with the HDL, sST2, age

and BMI. Diabetic individuals showed an increase in sST2 levels because of dysfunction in the IL-33/ST2 signaling pathway. However, there was a direct correlation between IL-33 and ST2, ST2 was shown to be strongly correlated to IL-33 (40). IL-33 exhibited a negative correlation with HbA1c levels in individuals with normoglycemia and T2DM, but not in those with prediabetes. Additionally, IL-33 showed a negative association with fasting plasma glucose in individuals with T2DM who had superior glycemic control (41). The IL-33-to-ST2 ratio negatively correlated with HbA1c in normoglycemia but not prediabetes or T2D. In non-diabetic (lean, overweight, and obese) but not diabetic participants, IL-33 was inversely connected with age, BMI, protective lipid profiles, and HbA1c (40). Only rs10758751 was associated with T2DM (AA vs. CC: OR = 3.4, 95% CI 1.36–8.57; $p = 0.009$); rs7044343 and rs1929992 showed no significant associations ($p = 0.30$ and $p = 0.50$, respectively). There was no significant distribution of rs1929992 genotypes and allele frequency of diabetes patients. The findings revealed that IL-33, a cytokine found in adipose tissue, and its interaction with ST2, may have an impact on blood glucose levels (42). IL-33 may activate immune responses that defend against inflammation, insulin resistance, and type 2 diabetes associated with obesity. In conclusion, elevated IL 33/sST2 and the rs10758751 AA genotype are linked to T2DM susceptibility in Iraqis, suggesting the IL 33/ST2 axis as a potential biomarker and therapeutic target. In comparison to the role of CC, which was modeled as a predisposing factor to T2DM in the Iraqi population, these findings suggest that the AA genotype has a protective role (43). In summary, elevated IL 33/sST2 and the rs10758751 AA genotype characterize T2DM in Iraqi patients, underscoring the IL 33/ST2 axis as a promising biomarker and therapeutic target (44).

Conclusion

BMI, CRP, FBS, HbA1c, TC, TG, TG, TG, HDL, VLDL ST2 and IL33 increased significantly in T2DM patients contrasted with healthy controls. There is an inverse relationship between CRP, HbA1c and lipid profile concentration with IL33 levels in T2DM patients. It was found that there is a positive relationship between CRP, FBG, HbA1c, lipid profile and IL33 level with ST2 levels in T2DM patients. Statistically significant association between IL-33 (rs10758751) with T2DM Iraqi patients. The homozygous mutant (AA) could be the risk factor while wild homozygous (CC) shows a protective role for T2DM Iraqi patients. The distribution of allele A among diabetes patients is significant and could be considered a risk factor for diabetes mellitus. Based on evidence, this section should suggest understandable data display options that readers are likely to understand.

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مستوى المصل وتعدد الاشكال الجيني للإنترلوكين-٣٣ لدى المرضى العراقيين المصابين بداء السكري من النوع الثاني

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الملخص

الخلفية: يتميز داء السكري من النوع الثاني (T2DM) بنقص الإنسولين ومقاومته. هدفت هذه الدراسة إلى تقييم مستوى الإنترلوكين-٣٣ (IL-33) ومستقبله القابل للذوبان (sST2) في المصل، بالإضافة إلى التعدد الشكلي في جين IL-33 (rs7044343) و(rs1929992)، للتحقق من علاقتها بداء السكري من النوع الثاني لدى المرضى العراقيين.

المرضى والطرق: في هذه الدراسة من نوع الحالة–الشاهد، تم اختيار ١٢٠ مريضًا مصابًا بداء السكري من النوع الثاني و٨٠ شخصًا سليمًا مماثلين في العمر والجنس كمجموعة ضابطة. تم تأكيد الإصابة بالسكري من خلال قياس سكر الدم الصائم والهيموغلوبين السكري (HbA1c). تم قياس تركيزات IL-33 وsST2 في المصل باستخدام تقنية ELISA. أما تحديد الأنماط الجينية rs7044343 وrs1929992 لجين IL-33 فقد تم باستخدام تقنية PCR–RFLP. تمت مقارنة ترددات الأليلات والأنماط الجينية باستخدام اختبار كاي تربيع (χ^2)، وتم التعبير عن العلاقات من خلال نسب الأرجحية (ORs) مع فواصل الثقة ٩٥٪ (CIs). اعتُبرت القيمة الإحصائية ذات دلالة عند $p<0.05$.

النتائج: بالمقارنة مع مجموعة الضبط، أظهر مرضى السكري من النوع الثاني ارتفاعًا معنويًا في مستوى IL-33 في المصل (المتوسط ± الانحراف المعياري: ٤٣,٢ ± ١٢,٧ مقابل ٢٨,٥ ± ٩,٣ بيكوغرام/مل، ($p<0.001$) وsST2 (٥٦,٨ ± ١٤,١ مقابل ٣٤,٧ ± ١٠,٥ نانوغرام/مل، $p<0.001$). لم يظهر التعدد الشكلي rs1929992 في IL-33 فرقًا معنويًا بين المجموعتين ($p=0.30$). في المقابل، كان النمط الجيني AA للتعدد rs7044343 أكثر شيوعًا لدى مرضى السكري من النوع الثاني مقارنةً بالمجموعة الضابطة (AA = 34% مقابل ١٨٪؛ OR = 2.35، CI 95% = 1.22–4.52، $p=0.010$)، بينما أظهر النمط الجيني CC تأثيرًا وقائيًا (CC = 22% مقابل ٣٨٪؛ OR = 0.48، CI 95% = 0.26–0.89، $p=0.018$).

الاستنتاج: يرتبط ارتفاع مستويات IL-33 وsST2 في المصل، بالإضافة إلى النمط الجيني AA للتعدد rs7044343، بزيادة القابلية للإصابة بداء السكري من النوع الثاني لدى المرضى العراقيين. تدعم هذه النتائج دور مسار IL-33 في نشوء المرض.

الكلمات المفتاحية: الإنترلوكين-٣٣ (IL-33)، داء السكري من النوع الثاني (T2DM)، الدهون في الدم، ومستقبل ST2.

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