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Impact of tumor necrosis factor-α and interleukin 6 polymorphisms on type 2 diabetes mellitus Sudanese patients

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Informed consent: the aim of the study was explained to all participants in a simple language. The samples were collected from the individuals who agreed to participate in this study.

Patient consent for publication: permission for publication has been obtained from the individuals who agreed to participate in this study.

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Abstract

Extensive studies in humans over the last decades have shown the significant functions of cytokines in diabetes development. The present study aimed to assess the impact of tumor necrosis factor (TNF)- α and interleukin (IL) 6 polymorphisms on type 2 diabetes mellitus (T2DM).

The study involved 450 participants; 200 individuals were included in the control group, and 250 individuals represented T2DM patients. The polymerase chain reaction-restriction fragment length polymorphism technique was used to identify the genotypes and alleles of the TNF- α 308G/A variants rs1800629 and IL-6 (-174 C \rightarrow G) variants rs1800629, while amplification refractory mutation system polymerase chain reaction is used to identify genetic variations of IL-6 (-174 C \rightarrow G).

The result revealed a statistically significant (p=0.0028) difference in the frequency of the AA genotype of the TNF- α rs1800629 variant between the study group and the control group. Interestingly, the findings also showed a significant difference (p=0.0001) in the frequency of the CC genotype of the IL-6-rs1800795 variant between the study and control groups.

The TNF- α gene (308G/A) and the IL-6 (-174 C \rightarrow G) polymorphism were found to be strongly related to an elevated risk of T2DM in the Sudanese population.

Introduction

Type 2 diabetes mellitus (T2DM) is a complex set of metabolic illnesses characterized by chronic hyperglycemia.^{1,2} The International Diabetes Federation estimates that 536.6 million adults people worldwide currently suffer from diabetes mellitus in 2024, and this is expected to rise to 783.2 million by 2045.^{2,3} T2DM is defined by decreased insulin production from pancreatic beta cells and insulin resistance.¹⁻⁴ Diabetes mellitus is a chronic condition that significantly lowers the quality of life. It is regarded as one of the most significant and prevalent conditions seen in medical clinics, and because of the numerous complications and comorbidities associated with this pathology, it currently poses a serious risk to the entire world. Over time, it may cause damage to the kidneys, heart, blood vessels, eyes, nerves, and heart.^{5,6}

The pathogenicity of insulin resistance and T2DM has been related to the immune system. The pathogenicity of insulin resistance and T2DM has been related to immune system activation and subclinical chronic inflammation; several authors suggested that inflammatory cytokines like interleukin (IL) 6 and tumor necrosis factor (TNF) may be important mediators in the pathophysiology of T2DM, linking the disease to several other frequently occurring disorders believed to have inflammatory causes.^{3,6-11} Several studies have demonstrated that TNF- α plays a crucial role in the development of insulin resistance and T2DM by inhibiting intracellular signaling from the insulin receptor.¹²⁻¹⁵ Trapali *et al.* stated that TNF- α is essential in the development of insulin resistance and T2DM, by inhibiting intracellular signaling the disease route and T2DM.¹¹ Furthermore, several polymorphisms in the IL-6 gene have been associated with an increased risk of T2DM, according to Jamil *et al.*¹⁶ Numerous other studies have shown that IL-6 is probably required to maintain glucose homeostasis.¹⁶⁻¹⁹

Nonetheless, Sudan was included as one of the nations with a diabetes prevalence of more than 12% in the 2019 International Diabetes Federation's diabetes atlas.¹¹ This is in line with a previous study conducted in Sudan that found that the prevalence rates of uncontrolled T2DM and T2DM were comparatively higher at 80.0% and 20.8%, respectively.⁵

Most of the published data about diabetes mellitus in Sudan was epidemiological studies, few research determined the genetic aspect. The present work aimed to determine the association between TNF- α , and IL-6 polymorphisms with T2DM among Sudanese patients.

Materials and Methods

Study population and sampling

The current work is a case-control study, carried out at Fedail Specialist Hospital in Khartoum, Sudan, over three years (2019-2022). The purpose of the research was explained to the study population, and the blood samples were collected from those who agreed and signed the consent. The ethical clearance (AAU-MLT-DCC-25489) was obtained from the ethical committee of Medical Laboratory Sciences, Alzaiem Alazhari University, Sudan.

The study population involved 450 individuals with fasting glucose levels <100 mg/dL without the use of glucose-lowering drugs; 200 of them do not have a history of diabetes nor a diagnosis as diabetic patients, and they were represented as a control group. The remaining 250 participants were T2DM patients, and they were represented in the study group. Both groups were matched, and they are free of bacterial or viral infections, cancer, cardiovascular disease, arthritis, renal, hepatic, or endocrine disorders, and other conditions at the time of the sample.

Assay of biochemical markers

The following biochemical markers were measured using the Cobas C311 clinical chemistry autoanalyzer (Roche Diagnostics, Mannheim, Germany): cholesterol, glycated hemoglobin (HbA1c), fasting plasma glucose, triglycerides, total low-density lipoprotein (LDL) cholesterol, and highdensity lipoprotein (HDL) cholesterol.

Genotyping analysis of tumor necrosis factor-a

The genomic DNA was isolated from the peripheral blood leukocytes for each participant using the Promega-USA DNA Purification Kit (Madison, USA). The polymerase chain reaction (PCR)-restriction fragment length polymorphism test was used to identify the genotypes and alleles of the TNF- α 308G/A variants rs1800629 and IL-6 (-174 C \rightarrow G) variants rs1800629.²⁰ The genomic region containing the TNF- α 308G>A variant was amplified using a specific set of primers (forward primer: AGGCAATAGGTTTTGAGGGCCAT, reverse primer: TCCTCCCTGCTCCGATTCCG). The PCR program was done according to the following conditions: denaturation for 10 minutes at 94°C, followed by 35 cycles, each consisting of 30 seconds of denaturation at 94°C, 30 seconds of annealing at 62°C, 35 seconds of extension at 72°C, and 10 minutes of final extension at 72°C. The products of the PCR for rs1800629 G>A (107 bp) were digested by Nico1 into 87 bp and 20 bp. The reaction mixture included 10 μ L (0.2 μ g) of PCR products, 1 μ L of restriction enzymes with 17 μ L of nuclease-free water, and 2.0 μ L of 10XNE buffer. This cocktail was incubated at 37°C for 5 hours. The digested PCR products were loaded into 3.0% agarose gel electrophoresis and visualized using an ultraviolet transilluminator.

Detection of interleukin 6 (-174 $C \rightarrow G$) gene polymorphisms:

The amplification-refractory mutation system (ARMS) PCR is applied in this study to identify genetic variations of IL-6 (-174 C \rightarrow G). The Primer 3 software was used to create ARMS primers (Fo-outer CGATGGAGTCAGAGGAAACTCA, Ro-outer primer: primer: I-G-inner TTTTCCC GGAGATAGAGCTTCTCTTTCGTTCCCG, primer: F I-C-inner GACCAA CCTAGTTGTGTGTCTTGCC, and R primer: TGTGACGTCCTTTAGCATC). The reaction was carried out using 20 µL of a reaction mixture (Microgen Inc., Korea) that contained 10 µL of Master, 2.0 µL of DNA, and 2.0 µL of each primer comprising 25 pmol. The thermocycling process involved denaturation at 94°C for 10 minutes, followed by 35 cycles of denaturation at 94°C, 35 s of annealing at 63°C, and a final extension at 72°C for 5 minutes. An ultraviolet transilluminator was used to observe the PCR results after they had been analyzed using 2.0% agarose gel electrophoresis.

Statistical analysis

The analyses have been managed using SPSS version 22 (IBM, Chicago, IL, USA), a statistical software for the social sciences. The continuous variables are categorized using the mean \pm standard deviation. An independent *t*-test was used in the study to compare continuous variables and evaluate group differences. A chi-square test was used to categorize variables that were grouped as frequency and percentage. The genes that were linked to one another were identified using odds ratios and 95% confidence intervals. Chi-square testing was utilized to look at the genotype frequency values' Hardy-Weinberg equilibrium. For statistical significance, a two-tailed p<0.05 threshold was established.

Results

Biochemical analyses presented in Table 1 indicated elevated levels of HbA1c and fasting blood glucose in the study group compared to the control group, with values of $9.6\pm2.3\%$ vs. $5.6\pm0.40\%$ and 200 ± 71 mg/dL vs. 88.1 ± 11 mg/dL, respectively, highlighting typical clinical features of T2DM in the study group. The study group's fasting plasma glucose, LDL, HDL, total cholesterol, triglycerides, and HbA1c values were found to be significantly correlated with the control group.

Fasting blood glucose (FBG), HbA1c, and genotype distribution in control individuals and T2DM patients were shown to be extremely significantly correlated with single-nucleotide polymorphism (SNP) rs1800629 GG/AA, with the exception of FBG and HbA1c (Table 2). FBG and HbA1c levels were greater in T2DM patients with GG genotypes than in those with GA and AA genotypes (p=0.002, 003).

SNP rs 180795 showed similar significant results. In both the control group and T2DM patients, a GG/CC connection was seen between genotype distribution, FBG, and HbA1c, except for FBG and

HbA1c (Table 3). FBG and HbA1c levels were greater in T2DM patients with GG genotypes than in those with GC and CC genotypes (p=0.040, 003) (Table 4).

According to Table 4, there was a statistically significant (p=0.0028) difference in the frequency of the AA genotype (rs1800629 variation) between the study group and the control group. Similar results were obtained for the frequency of the A allele, which was detected in 20.7% of the study group and 32.2% of the control group. There was a significant variation in frequency (p=0.0003). Additionally, Table 4 shows the association was found to be valid under the additive (p=0.0028), recessive (p=0.0099), and dominant (p=0.0003) genetic models.

Table 5 shows that there was a significant difference (p=0.0001) in the frequency of the CC genotype (rs1800795 variation) between the study group and control groups. The rates were 5% and 18%, respectively. The frequency of the C allele, which was found to be 21% in the control group and 34.4% in the study group, and the prevalence of the G allele, which was found in 79% of the control group and 65.4% of the study group, also showed notable variations and were both statistically significant (p=0.0001). Furthermore, it was observed that the link held under the additive (p=0.0001), recessive (p=0.0001), and dominant (p=0.0036) genetic models (Table 5).

Discussion

Diabetes mellitus is a metabolic disease that is characterized by elevated plasma glucose levels, which over time, leads to cell damage in the eyes, nerves, heart, blood vessels, and renal. Statistical data show that the amount of frequency of diabetes mellitus cases has been gradually growing over time. However, T2DM is supposed to be a polygenic disease that occurs due to complex interactions between numerous environmental factors and genes.²⁰⁻²³

The present study aimed to determine the impact of TNF- α and IL-6 polymorphisms on T2DM Sudanese patients. According to the best of our knowledge, this is the first molecular-based study carried out in Sudan that discussed the relationship between TNF- α and IL-6 polymorphisms in T2DM.

Our results showed significant increases (p=0.0001) in body mass index (BMI) among the study group (T2DM), with a mean of $28.5\pm1.2 vs. 23.2\pm1.1$. This finding suggested that BMI is a risk factor for T2DM among the Sudanese population. Similar findings were pointed out by several authors.^{10,13} Moreover, the study group showed high levels of HbA1C and fasting blood glucose compared to the control group (9.6±2.3 vs. 5.6±0.40 and 200±71.0 vs. 88±11); these findings indicate uncontrolled T2DM. Also, the study group showed abnormal lipid profiles, which included excessive triglycerides, cholesterol, and LDL with low HDL which may reflect the impact of diabetes mellitus. Moreover, the current study showed a strong correlation between the study group and BMI, HbA1c, triglycerides, total cholesterol, LDL, and HDL, since these are the common clinical signs of diabetes mellitus, the findings were consistent with many previous publications.^{7,10,24}

Our results revealed noteworthy correlations between the study group (T2DM) and both rs 1800795 and rs 1800629 variations; the A and C alleles were more prevalent among the study group. Numerous studies have indicated that polymorphisms in TNF- α (rs1800629) and IL-6 (rs180795) enhance the risk of developing T2DM, which is consistent with our findings.^{3,6,8,13-15}

Similarly, Martinez *et al.* examined the association between the polymorphisms for TNF- α (rs 180629), IL-6 (rs 1800795) and T2DM; they reported a substantial rise in the chance of developing T2DM.¹⁰ Other authors such as Rodrigues *et al.* disagreed with our findings, claiming that TNF- α (rs1800629) and T2DM are unrelated.⁷ Jamil *et al.* stated the same report concerning the relation between T2DM and polymorphisms in rs1800629.¹⁶ This inconsistency in the results may be owing to the different study populations.^{15,16}

Liju *et al.*,²⁴ Abdellatif *et al.*,²⁵ Khdair *et al.*,²⁶, Huang *et al.*,²⁷ Shi *et al.*²⁸, reported that the precise genetic risk factors linked to T2DM may vary depending on the ethnicity and genetic composition of the population in question, While Obirikorang *et al.* highlight that various groups and ethnicities generated diverse results.²⁹ Our findings demonstrated that T2DM patients (study group) had a significantly higher prevalence of the A/A genotype of the TNF-G308A gene, particularly rs1800629,

compared to the control group (7.2% vs. 1.5%, p<0.0028). Martinez *et al.* reported that T2DM patients had significantly higher frequencies of the A/A genotype (p=0.004) than the control groups, which is consistent with our finding.¹⁰

According to our findings, T2DM patients had significantly higher frequencies (p=0.0001) of the homozygous C alleles of the IL-6 (rs1800795) mutation than healthy controls. These results agreed with those of Obirikorang *et al.*, who found that the C allele was significantly more common in T2DM patients than in control groups (p=0.0010).²⁹ Our findings demonstrated that, across all genetic models, both the RS1800629 and RS1800795 polymorphisms were significantly associated with T2DM in Sudanese. These results are consistent with recent research that was carried out in different demographic areas.^{3,21,22,28,30}

Conclusions

The TNF- α gene (308G/A) and the IL-6 (-174 C \rightarrow G) polymorphism were found to be strongly related to an elevated risk of T2DM in the Sudanese population.

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Variables	Patient (n=250)	Control (n=250)	Р
Gender (male/female)	130/120	132/118	0.7900
Age (years)	58±15	56±14	0.7600
BMI (kg/m^2)	28.5±1.2	23.2±1.1	0.0001
Fasting plasma glucose (mg/dL)	200±71	88±11	< 0.0010
Total Cholesterol (mg/dL)	207±45	170±24	< 0.0010
Triglyceride (mg/dL)	155±36	124±31	< 0.0010
LDL-C (mg/dL)	111±31	77.8±26	0.0035
HDL-C (mg/dL)	39±8.10	46±17	0.0030
Heamoglobin A1c(%)	9.6±2.30	5.6 ± 0.40	< 0.0010

 Table 1. Comparative results of biochemical markers in obese type 2 diabetes mellitus patients and healthy subjects.

Comparisons were performed by independent samples *t*-test; data are mean \pm standard deviation; p<0.05 is statistically significant. n, number of individuals; body mass index (BMI); high-density lipoprotein-cholesterol (HDL-C); low-density lipoprotein-cholesterol (LDL-C).

Table 2. Statistical	analysis of clinica	al parameters in	association wit	h genotype dis	stribution of
rs1800629 GG/AA	in 450 subjects (25	50 type 2 diabete	es mellitus cases	and 200 contr	ol subjects).

Parameters	Subjects	GG	GA	AA	Р
BMI (kg/m ²)	T2DM	26.7±0.9	27.4±0.83	27.7±0.74	0.785
	Controls	24.6±1.80	24.7±0.80	25.4±0.80	0.150
FBG (mg/dL)	T2DM	144±33.50	202±61.5	273±49.0	0.002
	Controls	88.0±10.45	89.0±9.40	88.0±9.52	0.790
HbA1c%	T2DM	8.50±1.30	10.3±0.24	11.2 ± 0.30	0.003
	Controls	5.67±0.53	5.73±0.44	5.76±0.56	0.854
TG (mg/dL)	T2DM	154±40.0	161±35.0	148 ± 38.0	0.952
	Controls	126±31.5	124±26.0	131±35.40	0.536
HDL-C (mg/dL)	T2DM	41.4±8.65	42.2±9.40	31.0±7.10	0.743
	Controls	48.75±6.8	45±7.84	44.7±6.0	0.524
LDL-C (mg/dL)	T2DM	109±32.5	112±33.6	108±31.2	0.965
	Controls	80±26.0	78±24.7	82±26.8	0.832
Total chl (mg/dL)	T2DM	197±40.7	213±46.0	203±46.2	0.843
	Controls	171±27.4	176±23.2	183 ± 23.3	0.700

Data is shown as mean \pm standard deviation; p<0.05 is statistically significant. BMI, body mass index; FBG, fasting blood glucose; TG, triglyceide; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; chl, cholesterol; T2DM, type 2 diabetes mellitus.

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Parameters	Subjects	GG	GC	CC	р
BMI (kg/m^2)	T2DM	26.75±0.93	26.41±0.92	27.88±0.85	0.963
	Controls	24.50±1.65	24.60±0.87	24.70±1.20	0.404
FBG (mg/dL)	T2DM	156.7±36.8	262.0±61.5	270.6±51.4	0.040
	Controls	88.5±9.75	89.0±9.50	89.5±9.8	0.950
HbA1c%	T2DM	$8.70{\pm}1.68$	11.40 ± 2.5	11.62 ± 2.84	0.002
	Controls	5.80±0.50	5.78±0.45	5.67±0.44	0.740
TG (mg/dL)	T2DM	157±30.34	156±31.00	148±45.58	0.779
	Controls	125 ± 30.00	124±31.85	126±36.71	0.664
HDL-C (mg/dL)	T2DM	41.90±8.74	35.97±7.60	41.10±9.23	0.524
	Controls	45.64±6.75	45.34±7.85	45.81±5.92	0.830
LDL-C (mg/dL)	T2DM	109.5±33.3	113.3±31.5	108±32.1	0.623
	Controls	79.0±26.54	80.0±27.53	79.2±18.10	0.150
Total Chl (mg/dL)	T2DM	203±40.54	213±49.02	188±43.44	0.488
	Controls	173 ± 26.90	178 ± 23.82	183 ± 16.42	0.295

Table 3. Statistical analysis of clinical parameters in association with genotype distribution of rs1800795 GG/CC in 450 subjects (250 type 2 diabetes mellitus cases and 200 control subjects).

Data is shown as mean \pm standard deviation; p<0.05 is statistically significant. BMI, body mass index; FBG, fasting blood glucose; TG, triglyceide; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; chl, cholesterol; T2DM, type 2 diabetes mellitus.

Table 4. Genotypes distribution,	allele frequency, and	l genetic models c	of the tumor necrosis
factor G308A gene rs1800629 van	iant among the study	population.	

rs1800629 variant		Controls g (n=200	roup)	Patients group (n=250)		OD (050) CD		
		Frequency	%	Frequency	%	OR (95% CI)	р	
		GG	120	60	107	42.8		
Genotype	s ^a	GA	77	38.5	125	50	1.82(1.23-2.67)	0.0023
		AA	3	1.5	18	7.2	6.72(1.92-23.48)	0.0028
Alleles ^b		G	317	79.3	349	67.8	1.76(1.29-2.39)	0.0003
		А	83	20.7	161	32.2		
genetic	Additive	GG	120	60	107	42.8	6.72(1.92-23.48)	0.0028
model ^c		AA	3	1.5	18	7.2		
	Recessive	AA	3	1.5	18	7.2	0.20(0.10-0.67)	0.0099
		GG+GA	197	98.5	232	92.8		
	Dominant	GG	120	60	107	42.8	2.00(1.37-2.92)	0.0003
		GG	120	60	107	42.8		

Comparisons were performed by the chi-square test (X²). CI, confidence interval; OR, odds ratio and the data is represented as number and %. ^aGenotypes GA *vs*. AA, GG *vs*. AA; ^bG alleles *vs*. A alleles; ^cadditive model (AA *vs*. GG), recessive model AA *vs*. GG+GA), and dominant model (GG *vs*. +GA+AA).

Variant (rs1800795)		Controls gr (n=200)	oup	p Patients gro (n=250)				
		Frequency	%	Frequency	%	OR (95% CI)	р	
		GG	126	63	123	49.2		
Genotype	es ^a	CG	64	32	82	32.8	1.30 (0.80-2.00)	0.1943
		CC	10	5	45	18	4.6 (2.20-9.60)	0.0001
Alleles ^b		G	316	79	328	65.6	2.00(1.50-2.70)	0.0001
		С	84	21	172	34.4		
genetic	Additive	GG	126	63	123	49.2	4 60 (2 20 0 60)	0.0001
model ^c		CC	10	5	45	18	4.00 (2.20-9.00)	0.0001
Recessive		CC	10	5	45	18	0.20 (0.12.0.40)	0.0001
		GG+GC	190	95	205	82	0.30 (0.12-0.49)	0.0001
Dominant		GG	126	63	123	49.2	1 75 (1 20 2 60)	0.0026
		GC+CC	74	27	127	50.8	1.73 (1.20-2.00)	0.0036

 Table 5. Genotype distribution, allele frequency and genetic models of the interleukin 6 gene

 rs1800795 variant among the study population

Comparisons were performed by the chi-square test (X^2). CI, confidence interval; OR, odds ratio and the data is represented as number and %. ^aGenotypes GC vs. CC, GG vs. CC; ^bG alleles vs. C alleles; ^cadditive model (CC vs. GG), recessive modelCC vs. GG+GC), and dominant model (GG vs. +GC+CC).