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Role of IL-6 and IL-8 polymorphisms in Type I Diabetes mellitus

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ABSTRACT

Background: Type I Diabetes mellitus (DM type-I) is the second most frequent chronic disease. Inflammation has a critical role in DM and its complications. Genetic discrepancies of pro-inflammatory cytokines (as IL-6, IL-8) might converse susceptibility to DM and/or its complications by altering the function and/or expression of these cytokines. The current study aimed to evaluate the role of IL-6 rs0795(C/G) SNP and IL-8 rs7306 (C/T) SNP in T1DM among Egyptian patients. *Subjects & Methods:* The current study enrolled 100 persons; 50 DM-type1 patients and 50 age and gender matched healthy persons as a control group. Fasting blood sugar (FBS), postprandial blood glucose (PPBG), random blood sugar (RBS) and Hemoglobin A1C (HbA1C) were measured for all participants. Genotyping of IL-6rs1800795 and IL-8rs2227306 SNPs was done using real-time PCR. *Results:* IL-8rs2227306 T and IL-6rs1800795 G alleles showed higher frequency in DM-1 patients than controls (38% vs. 7%; OR = 8.25; 95% CI = 3.45-19.73; p <0.001* and 32% vs. 10%; OR = 4.18; 95% CI = 1.92-9.10; p <0.001*, respectively). Evaluation of the haplotype frequency of IL-6 and IL-8 SNPs declared that the risk of developing DM-1 increases 28 times if both alleles are present together in the same patient (P<0.001*). Correlation analysis did not show any significant relation between these SNP and sugar pictures among diabetic patients. *Conclusion:* IL-8rs2227306 T and IL-6 rs0795 G alleles frequency is very high among T1DM patients. They could be risk factors for DM-1, particularly if presented together but did not have any effect on the severity of DM.

Keywords: Type I Diabetes mellitus, IL-6 rs0795 SNP, IL-8 rs7306 SNP

1. INTRODUCTION

Type I Diabetes mellitus (DM type-I) is a chronic metabolic disease caused by defects in insulin secretion and/or function (Haghnazari and Sabzi, 2021). Its global prevalence is higher in developed countries than in developing countries and is expected to be 5.4% by 2025 (King et al., 1998).

This disorder is characterized by impaired metabolisms due to decreased insulin secretion or tissue sensitivity. There are two types of DM; in type-1 DM, insulin production is deficient from the pancreatic beta cells (Haghnazari and Sabzi, 2021). This decreased production is usually caused by injury or destruction of beta cells by infections or autoimmune disorders in genetically

predisposed persons. DM-1 accounts for 5-10% of diabetic patients and it usually starts at the age of 14 years. Approximately 5 to 10 percent of people with diabetes mellitus have the type 1 form of the disease (King et al., 1998; Haghnazari and Sabzi, 2021).

The decreased insulin results in impairment of the glucose utilization and amplifies glucose production. The increased plasma glucose then has multiple effects throughout the body. Recent reviews advocate inflammation as a critical component of DM and its complications. It was stated that many inflammatory molecules, including pro-inflammatory cytokines (as IL-6, IL-8) proposed to be critical factors in the development of micro vascular diabetic complications, including nephropathy (DN) (Ahluwalia et al., 2009).

Interleukin-6 (IL-6) has multiple effects. IL-6 receptor genetic variation resulted in a substantial change in IL-6 and IL6r serum levels. This in turn affects IL-6 signaling and inflammatory functions (Rafiq et al., 2007). It was reported that IL-6 precipitates insulin resistance via controlling differentiation, proliferation and cell apoptosis. In addition, irregular production of IL-6 causes inflammation that induces insulin resistance (Rehman et al., 2017).

IL-8 is the main regulator of macrophage activation. Its serum levels were reported to increase among diabetic patients and may be associated with worse inflammatory, glycometabolic profiles (Cimini et al., 2017). Exposure of phagocytes and mesenchyme cells to inflammatory stimuli results in IL-8 production (Baggiolini and Clark-Lewis, 1992).

Thus, genetic discrepancies in the genes encoding these inflammatory cytokines might converse susceptibility to DM and/or its complications by altering these cytokines' function and/or expression in Asian Indian patients (Ahluwalia et al., 2009). The current study aims to evaluate the role of IL-6 rs0795(C/G) SNP and IL-8 rs7306 (C/T) SNP in T1DM among Egyptian patients.

2. SUBJECTS AND METHODS

Study Design

The current study enrolled 100 persons attending Kafrelsheikh University hospital, Kafrelsheikh, Egypt. Participants were divided into 2 groups; DM group enrolled 50 cases with DM-type1 and the control group included 50 ages and gender matched healthy persons. Exclusion criteria include DM type 2, presence of hepatic, cardiac and/or renal decompensation. The study started from Sep. 2020 till July 2022.

Ethics approval

The proposal of the current study was revised and approved by the Ethics Review Committee of Faculty of Medicine, Kafrelsheikh University, Egypt (Sep. 2020; no.25/2020). The study follows the 1975 Declaration of Helsinki ethical guidelines without any risk to the participants. Informed consents were gathered from all participants. Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Samples

Six ml of blood was drawn from all participants. Three ml was used to separate serum for biochemical investigations and 3 ml was used for DNA extraction.

Biochemical investigations

Fasting blood sugar (FBS), postprandial blood glucose (PPBG), random blood sugar (RBS) and Hemoglobin A1C (HbA1C) were measured for all participants.

Genotyping of IL-6 rs0795 and IL-8 rs7306 SNP

Genomic DNA was extracted from the blood samples on EDTA using spin columns of QIAamp DNA Blood Mini Kit (Applied Bio Systems-Life Technologies); according to the manufacturer's instructions. The concentration and purity of DNA were assessed by nanodrop before real-time PCR (Ghazy and Alenzi, 2021).

Genotypic and allelic distribution of IL-6 rs0795 and IL-8 rs7306 SNPs was done using step one real-time PCR (Applied Bio System-Life Technologies Company, California, USA) using TaqMan SNP genotyping assay (IL-6 rs0795 SNP kit or IL-8 rs7306 SNP kit), as described by Ghazy and Alenzi, (2021) the analysis relied on the emitted fluorescence signals; FAM dye points to 1st allele and VIC dye specifies 2nd allele.

Statistical analysis of the data

Data were analyzed using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp). The Kolmogorov- Smirnov test was used to verify the normality of distribution of variables; comparisons between groups for categorical variables were assessed using Chi-square test; student t-test. F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups. Odds ratio (OR) and 95% confidence were used. Hardy-Weinberg equation was used to test the equilibrium. The significance of the obtained results was at the 5% level.

3. RESULTS

Subjects' demographic data

The current study enrolled 50 patients with DM-1 (23 males and 27 females) and 50 non-diabetic healthy controls (24 males and 26 females). Ages were ranging between 18 and 27 years in both groups (Table 1). No statistically significant difference was found between the studied groups regarding gender and age (P=0.841 and 0.363, respectively).

Biochemical investigations

There was a marked increase in FBS, PPBG, RBS and HBA1C among the diabetic group when compared to the control group (P<0.001*) (Table 1).

Table 1 Comparison between the two studied groups

Parameter	Negative control (n = 50)	DM Type 1 (n = 50)	p
Age (years)	22 ± 3.4	21.4 ± 3.2	0.363
RBS (mg/dl)	87 ± 6.3	363.3 ± 52.6	<0.001*
HBA1C (%)	4.5 ± 0.8	7.9 ± 0.5	<0.001*
FBS (mg/dl)	105.4 ± 7.7	220.9 ± 34.3	<0.001*
PPBG (mg/dl)	124.7 ± 11.4	362.7 ± 72.2	<0.001*

Data are presented by Mean ± SD, tests used were χ^2: Chi-square test, t: Student t-test
p: p-value, *: Statistically significant at p ≤ 0.05

Genotyping of IL-6 rs0795 and IL-8 rs7306 SNP

Hardy-Weinberg equation (HWE) was done to test for any possible deviations within all participants regarding the studied genotypes and no deviation was observed (P > 0.05) (Table 2). Comparing DM-1 patients with the controls revealed significant variations in the genotypic distribution of both IL-6 rs0795(C/G) and IL-8 rs2227306(C/T) SNPs. It was observed that the three genotypes are present in both DM-1 patients and controls (except for IL-8 TT genotype) with variable frequencies (Table 2).

IL-6 rs0795 CG and GG genotypes were more frequent among DM-1 patients in comparison with control groups (P=0.003* and <0.001*, respectively). Patients carrying GG genotype are at 14.7 times more susceptible to DM than CC genotype (OR=14.79, 95% CI=1.65-132.9, P=0.016*). IL-6 rs0795 G allele showed a corrected significant increased frequency in DM-1 patients (38% vs. 7%; OR=8.25; 95% CI=3.45-19.73; p <0.001*). Finally, allele and genotype frequencies of IL-6 rs0795 (C/G) SNPs showed statistically significant variations between DM-1 patients and controls (Table 2).

Genotyping of IL-8 rs7306 showed high CT and TT genotypes' frequency among DM-1 patients in comparison with controls (P <0.001*). Such difference was more obvious in allele frequencies as IL-8 rs7306 T allele frequency was higher in DM-1 patients when compared to controls (32% vs. 10%; OR = 4.18; 95% CI = 1.92-9.10; p <0.001*). Patients carrying IL-8 rs7306 T are 4.18 times more susceptible to DM-1 than C allele (Table 2).

Evaluation of the haplotypes frequency of IL-6 and IL-8 SNPs declared that the risk of developing DM-1 increases 3.526 times with IL-8 rs2227306T allele (P=0.005*), 7.156 times with IL-6 rs0795 G allele (P<0.001*) and 28 times if both alleles are present together in the same patient (P<0.001*) (Table 3).

Table 2 Comparisons of distributions of the genotypes of four SNP between control and patients which used the logistic regression analysis

	Control® (n = 50)	DM-1 (n = 50)	χ^2	P	OR (95% C.I)	*Adjust	
						p	OR (95% C.I)
IL-6 rs0795							
HWE	0.101	0.464					
CC®	44 (88%)	18 (36%)	–	–	1.0	–	1.0
CG	5 (10%)	26 (52%)	24.932*	<0.001*	12.7 (4.22 – 38.30)	<0.001*	13.74 (4.43 – 42.62)
GG	1 (2%)	6 (12%)	8.909*	0.003*	14.67 (1.65 – 130.7)	0.016*	14.79 (1.65 – 132.9)
Allele							
C®	93 (93%)	62 (62%)	–	–	1.0	–	1.0
G	7 (7%)	38 (38%)	27.556*	<0.001*	8.14 (3.42 – 19.40)	<0.001*	8.25 (3.45 – 19.73)
IL-8 rs7306							
HWE	0.432	0.467					
CC®	40 (80%)	22 (44%)	–	–	1.0	–	1.0
CT	10 (20%)	24 (48%)	10.843*	0.001*	4.36 (1.77 – 10.76)	<0.001*	4.80 (2.05 – 11.25)
TT	0 (0%)	4 (8%)	6.551*	0.010*	–	–	–
CT + TT	10 (20%)	28 (56%)	13.752*	<0.001*	5.09 (2.09 – 12.40)	<0.001*	5.03 (2.06 – 12.29)
Allele							
C®	90 (90%)	68 (68%)	–	–	1.0	–	1.0
T	10 (10%)	32 (32%)	14.587*	<0.001*	4.24 (1.95 – 9.21)	<0.001*	4.18 (1.92 – 9.10)

HWE: p-value for Hardy-Weinberg, If P < 0.05 - not consistent with HWE. OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit, ®: reference group, χ^2: Chi-square test, p: p-value for comparing between the studied groups, *: Statistically significant at p ≤ 0.05

Table 3 Haplotype frequency in the two study groups

Haplotype between IL-6 and IL-8	Haplotype frequencies (%)		p	OR (95%CI) (LL – UL)
	Negative control (n = 100)	DM (n = 100)		
CC	84 (84%)	45 (45%)	--	--
CT	9 (9%)	17 (17%)	0.005*	3.526 (1.455 – 8.546)
GC	6 (6%)	23 (23%)	<0.001*	7.156 (2.716 – 18.851)
GT	1 (1%)	15 (15%)	0.001*	28.0 (3.582 – 218.891)

OR: Odds ratio, CI: Confidence interval, LL: Lower limit, UL: Upper Limit
*: Statistically significant at p ≤ 0.05

Correlation analysis

Statistical correlations between IL-6rs1800795 and IL-8 rs7306 polymorphisms and sugar profile among diabetic patients did not show any significant association (Table 4, 5). Thus, they do not have any effect on DM severity.

Table 4 Relation between IL 6rs1800795 and sugar picture in DM group (n= 50)

Mean ± SD	IL 6rs1800795			F	p
	CC (n= 18)	CG (n= 26)	GG (n= 6)		
RBS (mg/dl)	367.6 ± 58.4	362.9 ± 49.7	352.3 ± 54.7	0.184	0.833
HBA1C (%)	7.9 ± 0.5	7.9 ± 0.5	7.7 ± 0.6	0.746	0.480
FBS (mg/dl)	227.7± 40.3	220.5 ± 29.3	202.7 ± 34	1.211	0.307
PPBG (mg/dl)	360.4 ± 75.8	371.2 ± 67.6	332.5 ± 84.7	0.708	0.498

F: F for ANOVA test, p: p-value for association between different categories

Table 5 Relation between IL 8 rs2227306 and sugar picture in DM group (n= 50)

Mean ± SD	IL 8 rs2227306			F	p
	CC (n= 22)	CT (n= 24)	TT (n= 4)		
RBS (mg/dl)	356.7 ± 48.7	370.4 ± 58.5	357 ± 40.7	0.412	0.665
HBA1C (%)	7.9 ± 0.5	7.9 ± 0.5	7.8 ± 0.5	0.136	0.873
FBS (mg/dl)	216.5 ± 27.8	223.7 ± 39.3	228.3 ± 41.2	0.340	0.713
PPBG (mg/dl)	359.2 ± 68.5	365.3 ± 79	365.8 ± 65.3	0.043	0.958

F: F for ANOVA test, p: p-value for the association between different categories

4. DISCUSSION

Diabetes mellitus type 1 is considered the second most frequent chronic disease and the most common endocrine-metabolic disorder in childhood (Álvarez-Casaño et al., 2021). There are a lot of vascular complications associated with T1DM as diabetic retinopathy (DR), diabetic nephropathy (DN), diabetic neuropathy (DPN) and altered wound healing. These complications increase the burden of T1DM and cause early mortality (Borilova-Linhartova et al., 2018).

It is well known that chronic inflammation and destruction of pancreatic β-cells are important causes of the development of T1DM (Haghnazari and Sabzi, 2021; King et al., 1998). IL-6 is a pleiotropic inflammatory cytokine that participates in the pathogenesis of several metabolic and autoimmune diseases through its pro and anti-inflammatory effects (Qu et al., 2014).

In DM, it was found that IL-6 facilitated micro-and macro-vascular tissue damage, changed insulin secretion directly or through stimulation of free fatty acid production and altered homeostasis of glucose (Erbağci et al., 2001). In addition, a persistent increase in IL-6 levels was reported to cause insulin resistance by ruining insulin receptor phosphorylation and inducing SOCS-3 expression, a potential inhibitor of insulin signaling (Rehman et al., 2017). Moreover, it was reported that SNP of the pro-inflammatory IL-6 coordinates the phases of wound healing in diabetic foot and has been connected to various diabetic complications (Djuric et al., 2010; Dhamodharan et al., 2015). Karahmet et al., (2021) have stated that IL-6 levels are markedly associated with neuropathy among patients with DM; particularly young patients.

Cimini et al., (2017) have accomplished a cross-sectional study to evaluate the levels of IL-8 and IL-6 in T2DM and correlate between IL-8 levels, the clinical and biochemical parameters among these patients. They found that serum levels of IL-8 were significantly higher among diabetic patients in comparison with non-diabetic subjects. In addition, there was a statistically significant correlation between increased IL-8 concentration and higher IL-6, TNF-α, FBG and HbA1c concentrations.

Genetic discrepancies in the genes encoding these inflammatory cytokines might converse susceptibility to DM and/or its complications by altering these cytokines' function and/or expression (Ahluwalia et al., 2009). Thus, the current study aims to evaluate the role of IL-6 rs0795 and IL-8 rs7306 SNP in T1DM. The study enrolled 50 patients with DM-1 and 50 non-diabetic healthy controls without any statistically significant difference between the studied groups regarding gender and age (P=0.841 and 0.363, respectively).

Genotypic and allelic distribution of IL-6 rs0795 SNP showed a higher incidence of CG and GG genotypes among DM-1 patients than in control groups (P=0.003* and <0.001*, respectively). Patients carrying G allele are at 8 times more susceptible to DM than those carrying C allele (38% vs. 7%; OR = 8.25; 95% C.I. = 3.45 – 19.73; p <0.001*). There is a statistically significant relation between IL-6 rs0795 G and the occurrence of type 1 DM. However, correlations analysis does not reveal any association between IL-6rs1800795 SNP and sugar picture among diabetic patients. Thus, they did not have any effect on the severity of DM.

In accordance with our results, Dhamodharan et al., (2015) reported that interleukin-6, tumor necrosis factor-alpha (TNF-α) and the chemokine stromal cell-derived factor (SDF-1/CXCL12) is well-categorized SNP which has formerly been allied to several diabetic complications. They have assessed the association of these SNP with diabetic complications and correlated them with the serum levels of IL-6 along with other serum biomarkers including adiponectin, leptin and high-sensitivity C-reactive protein among Indian population. They noticed that IL-6 rs0795 C allele conferred resistance to T2DM but not its complications. This is because IL-6 orchestrates the physiological wound healing process because it controls the immune cells, keratinocytes, fibroblasts and endothelial cells which clear the bacteria, perform re-epithelialization, restore dermal matrix and ensure angiogenesis, respectively.

Contrary to the results of the current study, Haghnazari and Sabzi (2021) have accomplished a cross-sectional study to determine the role of IL-6rs1800795 variants in DM. Their results showed that the dominant form of IL-6rs1800795 SNP (GC + CC vs. GG) (OR= 1.381; P = 0.364) and C vs. G alleles (OR= 0.734; P = 0.304) may increase the risk of DM type 1, but they were not statistically significant. They concluded that IL-6 rs0795 alleles do not show marked differences between DM type 1 and control

groups. Thus, it does not increase the risk of developing DM among the Kermanshah province population, Iran. This difference may be attributed to different ethnic groups or diet habits.

Regarding the role of IL-8 in T1DM, it is known that IL-8 is a potent chemo attractant and activator to neutrophils which is implicated in the initiation and augmentation of inflammatory reactions (Borilova-Linhartova et al., 2018). It was reported that neutrophils have a major role in the pathogenesis of T1DM (Ahmadi et al., 2013; Harsunen et al., 2013; Valle et al., 2013; Ismail et al., 2016). Moreover, IL-8 receptors (CXCR1/2 chemokine receptors) have been identified as "master regulators" of diabetes pathogenesis (Citro et al., 2014; Haurogné et al., 2015).

On the other hand, Purohit et al., (2015) have performed large-scale studies to find the cytokines and/or chemokine that may have role in T1DM. They measured thirteen serum cytokines and chemokine in 4424 persons using multiplex immunoassays. They found that serum levels of IL8 and other cytokines were markedly decreased among T1DM patients in comparison with the normal controls. They postulated that IL-8 has a protective effect against the development of DM as it reduces the monocytes' migration to pancreatic islets by decreasing their expression of CD11b (Sanda et al., 2010). Another study has shown that recombinant IL-8 inhibits the leukocytes' adhesion to endothelial cells and so attenuates inflammation at the vessel wall (Gimbrone et al., 1989).

This change in serum IL-8 levels is most probably controlled by genetic mutation of IL-8 gene or gene polymorphism. Thus, we aimed to determine the role of IL-8 SNP on T1DM. Genotypic discrimination of IL-8 rs7306 SNP showed a higher occurrence of CT and TT genotypes among DM-1 patients than controls (P <0.001*). Patients carrying IL-8 rs7306 T are 4.18 times more susceptible to DM-1 than C allele. There is a statistically significant relation between IL-8 rs7306 SNP, particularly T allele and the occurrence of type 1 DM. However, correlations analysis does not reveal any association between IL-8 rs7306 SNP and sugar picture among diabetic patients. Ahluwalia et al., (2009) have found that IL-8 rs4073AA genotype is associated with a higher risk of DN. They explained that the presence of IL8 rs4073 (T/A) variant in the regulatory region and so it will regulate IL8 gene expression.

Shen and Liu, (2021) have described some facts regarding the role of IL-6 and IL-8 gene polymorphism in the tendency to micro vascular complications in patients with (DM). They reported that the frequencies of IL-6-572G/C (IL-6 rs1800796 SNP) were higher among patients with diabetic nephropathy while IL-8−251 A/T (IL-8 rs4073 SNP) was associated with diabetic retinopathy. So, they suggested that IL-6 and/or IL-8 polymorphisms may affect the occurrence of diabetic complications.

Finally, evaluation of the haplotypes frequency of both cytokines in the current study declared a higher risk of developing DM-1 when IL-6 rs0795 G and IL-8 rs7306 T alleles are present together in the same patient OR = 28.0; 95% CI = 3.582 – 218.891; p =0.001*. This could provide a clue of genetic risk factors for DM-1 and can be used as diagnostic tests for DM-1, particularly in high-risk families. Also, further studies on larger scales are recommended to investigate the role of these inflammatory cytokines in the occurrence and pathogenesis of DM-1.

Limitations of the study

The small sample size is the main limitation of the study and further research on a larger sample is recommended.

5. CONCLUSION

IL-8rs2227306 T and IL-6 rs0795 G alleles frequency is very high among T1DM patients. They could be risk factors for DM-1, particularly if presented together but did not have any effect on the severity.

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Author contributions

Study design, collection of data and samples, methodology, writing and editing were performed by Dr Eman Rashwan.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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