Role of the *IL-10* gene and its genetic variations in the development of diabetes mellitus in women

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Abstract. Interleukin (IL)-10 is a key anti-inflammatory cytokine that plays a critical role in immune regulation and the pathogenesis of chronic metabolic diseases. Genetic polymorphisms in the *IL-10* gene, particularly at rs1800896, can affect cytokine expression and consequently, disease susceptibility. The present study aimed to investigate the association between the *IL-10* gene polymorphism (rs1800896) and the development of diabetes mellitus in women using tetra-primer amplification refractory mutation system-polymerase chain reaction (tetra-ARMS-PCR) and sequencing analysis. The present study was a case-control study conducted on healthy women and those with diabetes. The *IL-10* gene polymorphism (rs1800896) was investigated using tetra-ARMS-PCR. The results were confirmed by DNA sequencing technology by measuring the nucleotide sequencing for the amplified pieces. In the women with diabetes, three *IL-10* genotypes (AA, AG and GG) were detected, whereas only the AA genotype was found in the healthy controls. The GG genotype appeared in 14% of the women with diabetes and in 0% of the controls. The frequency of AG genotype appearance was 6% in diabetic women vs. 0% in controls. The frequency of the mutant G allele was 17% in women with diabetes and 0% in the controls (odds ratio, 5.8) which indicates a significant association with diabetes. Sequencing analysis revealed additional nucleotide variations, including transversions and deletions. On the whole, the present study found that there was a significant association between the *IL-10* gene polymorphism (rs1800896) and diabetes mellitus in women. The presence of the G allele may play a potential role as a genetic marker for disease vulnerability, suggesting the impact of immune regulation in the pathogenesis of diabetes.

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Introduction

Diabetes mellitus (DM) is a chronic metabolic disease that is characterized by a sustained high blood sugar level due to a disruption in insulin secretion or/and action. The prevalence of DM is continuously increasing at a rapid rate; thus, this poses a critical public health concern. According to the World Health Organization, there were >537 million adults with DM in 2021, a number which is prone to increase to 643 million by the year 2030 (1). Type 1 DM is caused by autoimmune pancreatic β-cell destruction, whereas type 2 DM results from insulin resistance, obesity and chronic low-grade inflammation (2). Evidence suggests a crucial role of immune and inflammatory signaling pathways in the development of both types of DM, addressing the relevance of cytokine regulation in the development and progression of disease; this is a promising field which warrants investigation (3).

Interleukin (IL)-10 is an anti-inflammatory cytokine that is produced from different immune cells such as T-regulatory cells, monocytes and macrophages. It plays an essential role in immune regulation via attenuating pro-inflammatory actions and maintaining immune homeostasis (4). As regards DM, IL-10 can potentially protect against β-cell destruction in type 1 DM and modulate systemic inflammation. Research has concluded that exogenous IL-10 can improve insulitis and delay the onset of type 1 DM in mice (5). Additionally, a previous study demonstrated an association between high IL-10 levels, and improved insulin sensitivity and glycemic control in humans with obesity-induced insulin resistance (6).

Previous studies have found a strong association between the expression of specific genes and the prevalence of certain diseases (7,8). The expression levels and functional activity of IL-10 may be influenced by genetic variations in the *IL-10* gene, particularly single nucleotide polymorphisms (SNPs) in the promoter region. Research has investigated polymorphisms, including-1082A>G, -819C>T and -592C>A in different populations and found that these variants can regulate IL-10 transcription and, consequently, influence cytokine levels and immune responses (9). Previous studies have examined the association between *IL-10* gene polymorphisms and susceptibility to type 1 DM and type 2 DM, and reported inconsistent results. Some reports have illustrated a protective effect of high *IL-10*-producing genotypes (10,11), whilst other studies

have shown no significant associations or even an elevated risk of disease with certain alleles (12,13).

The gene-environment interaction is potentially complex in the pathogenesis of diabetes as different contradictory findings across different ethnic groups and geographic regions have been reported. These discrepancies may be due to a variety of factors, such as genetic background, lifestyle, comorbidities and sample size variability (14,15). In addition, the functional results of *IL-10* polymorphisms *in vivo* are not yet completely understood. In addition, the mechanisms through which these genetic variations may affect other pro-inflammatory and anti-inflammatory cytokines and consequently, influence the immune milieu in patients with diabetes, remain to be determined (16).

Due to the increasing evidence implicating the association between inflammation and the onset and progression of DM (17,18), studying the genetic basis of key immunoregulatory markers, such as *IL-10* could enhance the understanding of the mechanisms of the disease, and could potentially lead to the identification of novel biomarkers or therapeutic targets. The present study aimed to investigate the role of *IL-10* gene variations in the development of DM and to determine the nucleotide sequencing of this gene in Iraqi women.

Subjects and methods

Study design. The present study was a case-control study that included 45 women between the ages of 31 and 74 years. The participants were divided into two groups as follows: 15 Healthy women serving as the control group and 30 women diagnosed with DM. The subjects of the study resided in Mosul, Iraq, and the study was conducted during the period from December, 2024 to February, 2025. The subjects in the control group were selected to match the cases in terms of age (Table I). The participants were further screened to exclude individuals with a family history of diabetes, autoimmune diseases, or chronic inflammatory conditions and those using medications to minimize potential confounding bias. The present study was conducted with the authorized approval from the Collegiate Committee for Medical Research Ethics at the University of Mosul, Mosul, Iraq (CCMRE-PHA-25-4). All participants provided written informed consent.

Collection of blood samples and DNA extraction. Blood specimens were obtained from all subjects using EDTA tubes. DNA was isolated from whole blood samples using a Whole Blood Genomic DNA Extraction kit (AddBio Inc.) following the manufacturer's instructions. The extracted DNA quality was assessed by measuring the absorbance at 260 and 280 nm using a nanodrop spectrophotometer (Thermo Fisher Scientific, Inc.). DNA was obtained from the blood of all 45 samples and thereafter preserved at -20˚C for use in further experiments.

Tetra-primer amplification refractory mutation system-polymerase chain reaction (tetra-ARMS-PCR). The DNA concentration in each sample was modified using TE buffer solution (10 mM Tris-HCl with 1m M EDTA•Na_2) (Bioneer Corporation) to achieve 25 ng/μl for PCR amplification. In total, four primers were used for primer reactions, including F-outer and R-outer throughout the gene. The forward outer-reverse inner primers are used for the mutant allele, in place of those for the normal allele. Nucleic acid from each sample was combined with suitable primers for the specific mutations and master mix components to create the PCR reaction mixture in 0.2-ml PCR tubes. The mixture was rapidly centrifuged at 3,000 x g for 1 min at room temperature to yield the ideal components. The PCR tubes were subjected to cycling in a thermocycler using tailored protocols for specific mutations. The reaction product (at 2% concentration) was introduced into the wells of a prepared agarose gel following the injection of a DNA ladder from Bio-Lab Ltd. into designated wells. Following 40 min of electrophoresis for sample migration, the bands were visualized using a horizontal gel electrophoresis system (BiocomDirect). Tetra-ARMS-PCR was used to evaluate the genetic variation of the *IL-10* gene at the locus (rs1800896).

Determination of genetic variation of the IL-10 gene in situ (rs1800896) using tetra-ARMS-PCR. The detection of the A à G mutation in the *IL-10* gene at the rs1800896 site was performed by the addition of 4 μl (100 nanograms) of template DNA to the contents of the master mix (Macrogen) which contains 1 μl (10 picomol) of each mutation-specific primer for the *IL-10* gene (Table II) (19). Subsequently, a multiplication reaction was performed on the reaction mix using the thermocycler and according to the special program for the reaction presented in Table III. Using the gradient program in the thermocycler device (GeneAmp PCR System 9700, Applied Biosystems, Thermo Fisher Scientific, Inc.), the optimal temperature for the primer bonding was deduced and the gradient was ±5. Following this, 2% agarose gel (AddBio) was used to separate the PCR reaction.

DNA Sanger sequencing technology of the IL-10 gene. The sequence of the nitrogenous bases of the gene under investigation was ascertained, and the results of the PCR reaction were directed to the aforementioned gene using the primers of the resultant bands. The 3130 Genetic Analyzer (supplied by Applied Biosystems, Hitachi, Ltd.) was used to determine the gene sequences in the 30 DNA samples. The gene sequences were compared with those recorded in the National Centre for Biotechnology Information (NCBI).

Statistical analysis. Statistical analysis was conducted by calculating confidence intervals (CIs) value, P-values and odds ratios (ORs) using MedCalc statistical software, version 20.009 https://www.medcalc.org. The association between genotypes or alleles and DM was evaluated using Fisher's exact test. The sample size for genotype and allele frequency comparisons was n=30 patients and n=15 controls. A value of $P<0.05$ was considered to indicate a statistically significant difference and 95% CI values were calculated for all ORs. The following frequencies were calculated based on the following dependency: Allelic frequency of the normal allele=2 (number of homozygous individuals) + (number of heterozygous individuals)/2 (total number), e.g., frequency of G=(2xGG + AG)/(2 x total sample size). The allelic frequency of the mutant allele=2 (number of heterozygotes) + (number of heterozygotes)/2(total number).

Table I. Demographic characteristics of the study participants.

Variable	Diabetic group (n=30)	Control group (n=15)
Age, years (mean ± SD)	54.2±9.1 years	52.7±8.4 years
BMI (mean ± SD)	31.4±4.6 kg/m^2	28.2±3.9 kg/m^2
Family history of DM (%)	20 (66.7%)	3 (20.0%)
Hypertension (%)	16 (53.3%)	4 (26.7%)

BMI, body mass index; DM, diabetes mellitus.

Table II. Primers used for detection of the genetic variation at rs1800896.

Locus	Primer	Sequence	Band size	Annealing
rs1800896 for *IL-10*	F-outer	5'-GAATTTGGTTTCCTCACCCTACTG-3'	390 bp	61˚C
	R-outer	5'-CTGAAGAAGTCCTGATGTCACTGC-3'		
	F-inner	5'-TTTCCTCTTACCTATCCCTACTTCCACT-3'	190 bp	
	R-inner	5'-AAGACAACACTACTAAGGCTTCTTTGGTAG-3'	250 bp	

Table III. Thermocycling conditions used in ARMS-PCR technique for the detection of the mutation at rs1800896.

No.	Stage	locus	Temperature	Time	Cycle number
1	Initial denaturation	For all sites	95˚C	6 min.	1
2	Denaturation	For all sites	95˚C	45 sec.	35
3	Annealing	(rs1800896)	61˚C	1 min.	
4	Extension	For all sites	72˚C	1 min.	
5	Final extension	For all sites	72˚C	5 min.	1
6	Stop reaction	For all sites	4˚C	5 min.	1

ARMS-PCR, amplification-refractory mutation system-polymerase chain reaction.

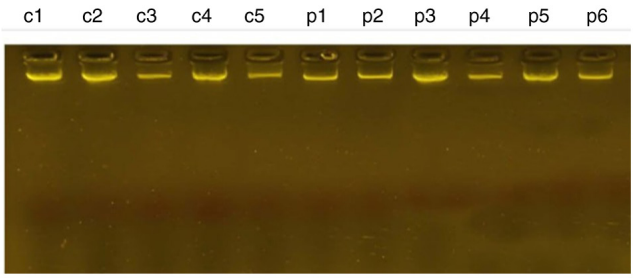

Figure 1. Genomes extracted from blood samples and separated by agarose gel electrophoresis at a concentration of 1%. Lanes c1-c5 represent control samples; and lanes p1-p6 represent patient samples.

Results

DNA extraction from blood samples. The genome packages were extracted from blood samples and illustrated in Fig. 1. The concentration ranged from (50-125 ng/μl) and the purity of the DNA sample ranged between (1.5-1.7).

Determination of genetic variations of the IL-10 gene in situ (rs1800896) using tetra-ARMS-PCR. The expression of the *IL-10* gene (rs1800896) on chromosome 1 and its variations in both healthy women and in those with diabetes were investigated using tetra-ARMS-PCR. The PCR reaction revealed that there was a genetic variation of the *IL-10* gene in women with diabetes, which appeared as three genotypes AA, AG and GG; however, in the control samples, there was only one genotype (Fig. 2).

The percentage of allelic observations and the frequency of the different genotypes of the *IL-10* gene at rs1800896 are presented in Table IV. The results for women with diabetes revealed that the frequency of the mutant genotype GG was the highest in women with diabetes at 13.3% compared with the mutant genotype in the control group at 0%, while the percentage of the normal genotype AA was the lowest in women with diabetes, at 80%, compared to 100% in the control group. The percentage of the variant genotype AG was 6% in the patient group in comparison to 0% in the control group. The percentage of the allelic frequency observed for the mutant G allele was high in the patient group (16.7%) compared

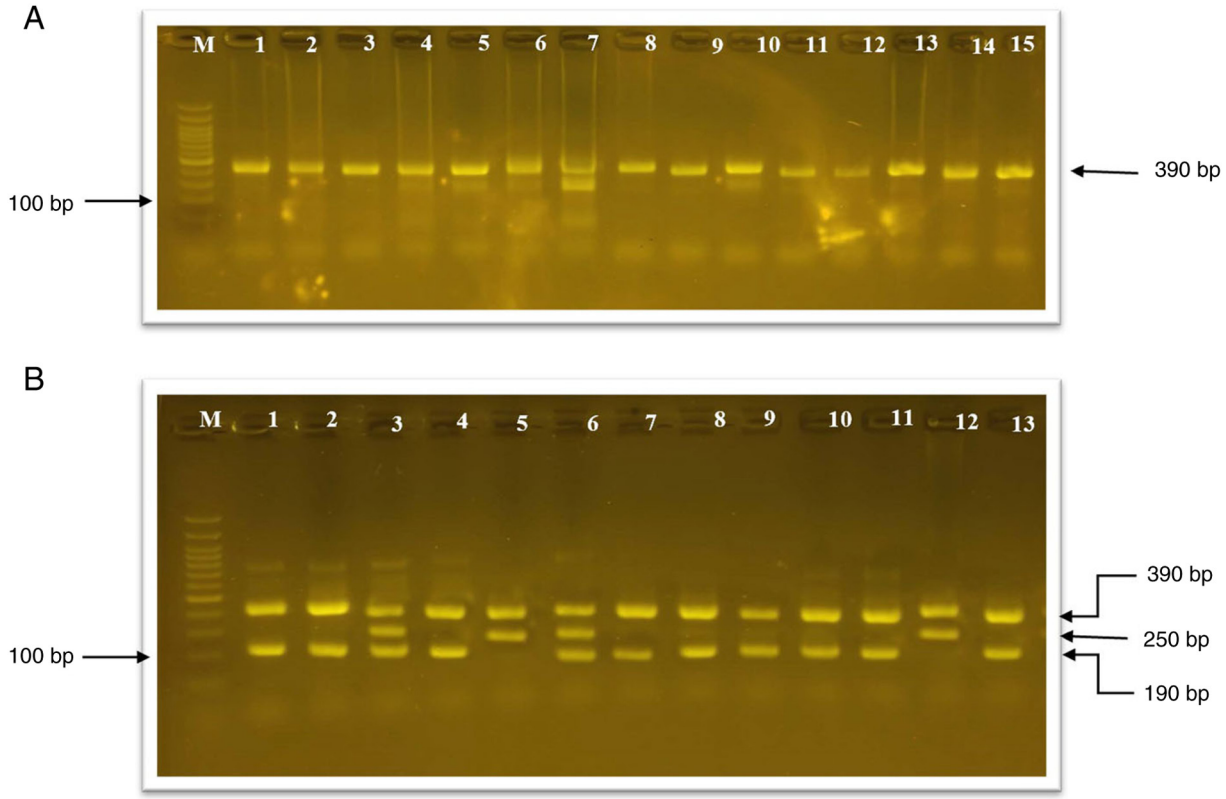

Figure 2. Product of the PCR reaction of the genetic variation (rs1800896) of the *IL-10* gene. Lane M represents the ladder with a size of 100 bp. (A) The results of the control samples demonstrating a reaction containing one band of 390 bp in size for the main gene. (B) The results of the patient samples demonstrating a reaction containing three bundles, the first with a size of 390 bp for the main gene, the second with a size of 190 bp for the natural allele, and the third bundle with a size of 250 bp for the mutant allele.

to the control group (0%). By contrast, the percentage of the normal allele in patients was 83%, in comparison with that of the control group, which was 100%.

DNA sequencing technology for IL-10 gene. The results of DNA sequencing technology for the amplified *IL-10* gene revealed that there were differences in the number of nucleotides, as illustrated in Fig. 3. DNA sequencing confirmed the presence of the rs1800896 (A>G) polymorphism in the promoter region of the *IL-10* gene. The variation was identified in yhr AA, AG and GG genotypes. The SNP is located at position chr1:206946930 (GRCh38) and may influence *IL-10* transcriptional activity due to its regulatory location.

In addition, the Sanger sequencing analysis revealed varied types of genetic mutations and their locations on the *IL-10* gene after comparing them with the gene sequences at the NCBI site (Table V). In addition, a representative sequencing chromatogram illustrated in Fig. S1.

Discussion

The present study examined the association between *IL-10* gene polymorphism at rs1800896 and the incidence of DM in women, particularly genotype and allele frequencies in diabetic vs. healthy individuals. The present study identified a clear distinction in the distribution of *IL-10* genotypes and alleles between diabetic and non-diabetic women by using tetra-ARMS-PCR and Sanger sequencing, which suggests a potential genetic predisposition influenced by *IL-10* polymorphisms.

The present study found that three genotypes AA (wild-type), AG (heterozygous) and GG (homozygous mutant) are present among women with diabetes, whereas only the AA genotype was observed in the control group, underscoring a significant genetic variation in the patient population. Notably, the GG genotype was limited to the diabetic patients (13.3%), and the AG genotype was also detected only in the diabetic group (6.7%), whereas this was absent in the control group. These findings are in accordance with those in the study by Zietz *et al* (20), which linked *IL-10* gene polymorphisms with an altered immune regulation and an elevated risk of metabolic disorders, including type 2 DM. The rs1800896 polymorphism, which occurs in the promoter region of the *IL-10* gene on chromosome 1q31-32, can affect transcriptional activity and cytokine expression levels (21). Notably, chronic low-grade inflammation is associated with the incidence of type 2 DM, whereas IL-10 plays a crucial role as an anti-inflammatory mediator.

The findings of the present study about allele frequency support the hypothesis of a genetic predisposition. The mutant G allele was absent in the healthy individuals, while it was noted in 16.7% of the patients with diabetes. The absence of this genotype in healthy individuals highlights its possible contribution to disease vulnerability, particularly as regards the allele-level data. The findings of the present study are consistent with those of the study by Van Exel *et al* (6), which

Table IV. Distribution of allelic viewing and genotype of the *IL-10* gene at the locus (rs1800896) among the group of controls and women with diabetes.

Comparison	Patients (n=30), n (%)	Controls (n=15), n (%)	OR	95% CI	P-value[a]
AA vs. (AG + GG)	24 (80.0)	15 (100.0)	0.00	Not estimable	0.1575
AG vs. (AA + GG)	2 (6.7)	0 (0.0)		Not estimable	0.5455
GG vs. (AA + AG)	4 (13.3)	0 (0.0)		Not estimable	0.2847
A vs. G	A=50 (83.3) G=10 (16.7)	A=30 (100.0) G=0 (0.0)	0.00	Not estimable	0.0273

The A allele is the normal allele, whilst the G allele is the mutant allele. [a]Data were analyzed using Fisher's exact test.

Table V. Types and locations of mutations in the *IL-10* gene in patients with diabetes.

ID sequence	Nucleotide	Location	Mutation type	Identity (%)	Gaps (%)
LC801126.1	T→G	507	Transition	88	0
LC801126.1	T→A	514	Trans version	88	0
LC801126.1	C→A	515	Transition	88	0
LC801126.1	T→-	516	Deletion	88	0
LC801126.1	A→N	518		88	0

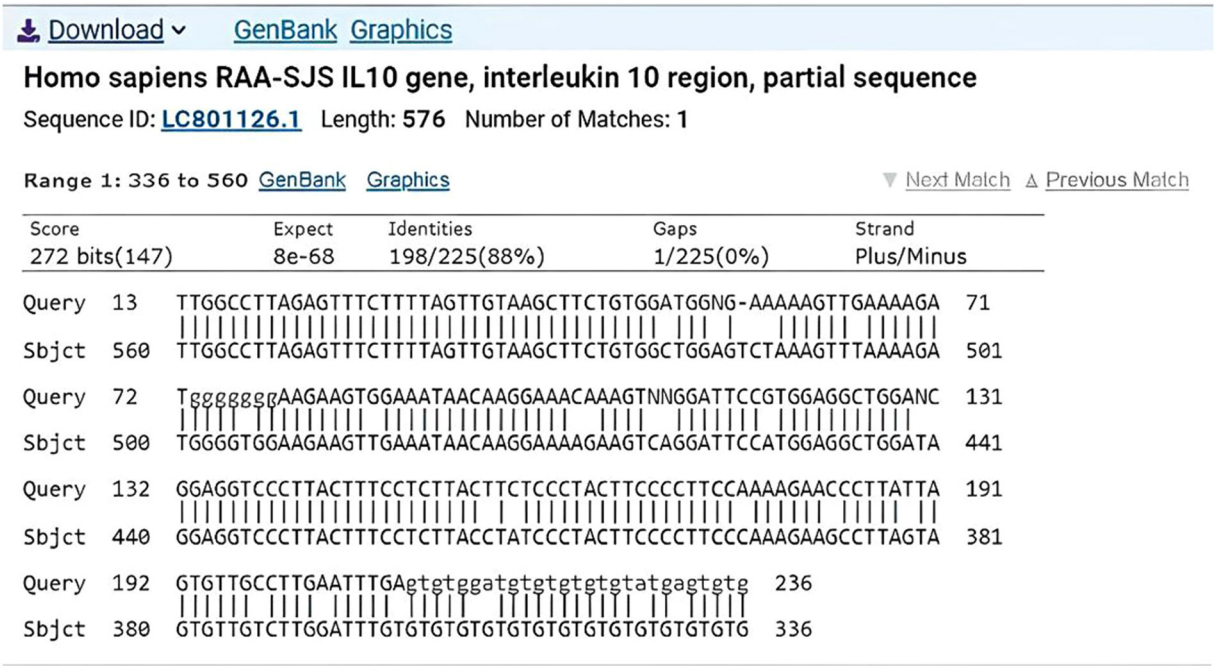

Figure 3. The results of matching between the sequences of the original *IL-10* gene at the NCBI site compared to the studied nucleotide sequence.

demonstrated a positive association between *IL-10* gene variants and the incidence of metabolic syndrome and type II DM, and a negative association between IL-10 expression and insulin resistance and systemic inflammation. In addition, Pociot and Lernmark (22) examined the factors affecting the genetic architecture of diabetes and reported a significant role in inflammatory gene polymorphisms, including *IL-10*. Notably, a substantial link has been reported between DM and inflammation, and a number of anti-diabetic drugs have anti-inflammatory effects that aid in ameliorating diabetes-related complications (23).

As regards sequencing analysis, the present study revealed nucleotide differences and different types of genetic variations, such as transversions and deletions in comparison with the reference *IL-10* sequence provided by NCBI. These multiple point mutations and structural variability in the *IL-10*

gene could influence transcription factor binding or mRNA stability, ultimately affecting cytokine production. Due to these probabilities, further functional studies are required to investigate the precise impact of the mutations observed.

Previous studies have reported conflicting results about the role of the G allele at rs1800896. For instance, studies revealed that an elevated *IL-10* secretion may play a protective role in autoimmune and inflammatory conditions (24,25). However, the present study demonstrated that the high frequency of the G allele in patients with diabetes does not play a protective role; instead, it reflects an adaptive or dysregulated immune response in attempting to counterbalance systemic inflammation.

This dual effect of *IL-10* has been noted in other chronic diseases, in which an increased *IL-10* production may inhibit essential immune activation, leading to metabolic dysfunction (26). The discrepancies among different studies may be potentially due to that various factors can modulate the effect of *IL-10* polymorphisms, such as gene-environment interactions, ethnic backgrounds of the populations studied, dietary habits and lifestyle factors.

The present study has certain limitations which should be mentioned. The present study had a relatively small sample size and only focused on a single SNP. This was due to the costly materials and techniques used and that the study was self-funded. Increasing the sample size, adjusting for environmental, clinical and metabolic variables, and including additional *IL-10* polymorphisms or other cytokine genes could provide a more comprehensive understanding of genetic vulnerability to DM. The functional consequences of these genetic variations are recommended to be investigated via correlating genotypic data with IL-10 serum levels and some clinical indicators (e.g., HbA1c and HOMA-IR). Inflammatory status activation and estimation can differ between different genders (27,28). Although the present study focused exclusively on women to control for the impact of sex hormones on immune regulation and cytokine gene expression, future studies including both sexes are recommended for the generalizability and expansion of these results.

In conclusion, the present study revealed a potential link between the *IL-10* gene polymorphism (rs1800896) and the disruption in glucose homeostasis (DM) in women and suggested that the presence of the G allele and GG genotype may be regarded as a risk factor. However, functional validation and clinical correlation analyses are required to confirm these findings. In addition, these results highlight the significance of inflammation and immune regulation in the pathogenesis of DM and support the inclusion of immunogenetic profiling in future risk assessment and therapeutic strategies.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AAA and SSIB designed the study. SJS performed the experiments. AAA and SSIB were involved in the writing of the draft of the manuscript. SSIB and SJS confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Collegiate Committee for Medical Research Ethics (CCMRE-PHA-25-4). All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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