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Genetic Polymorphism of the IL-6 Gene and Its Association with the Risk of Type 2 Diabetes Mellitus: A Genetic and Biochemical Study

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Abstract

T2DM is a complex disorder linked to inflammation. IL-6 is an important pro-inflammatory mediator that contributes to poor insulin sensitivity and β-cell dysfunction. The association between the -174 G/C (rs1800795) polymorphism in IL-6 and the risk of T2DM is not consistent across populations. This study tested the association of this polymorphism with the susceptibility of T2DM and the correlation between the polymorphism and several metabolic and inflammatory parameters.

We conducted a case-control study with 200 T2DM patients and 200 age- and sex-matched controls. Genotyping was done using PCR-RFLP. Fasting plasma glucose levels, HbA1c, fasting insulin levels, HOMA-IR, lipid analyses, and serum IL-6 concentrations were determined.

The frequency of the C allele was significantly higher in T2DM compared to the control group (32.5% vs 20.5%, p<.001). Compared to the GG genotype, the CC genotype was identified to be an independent risk factor for T2DM (adjusted OR=4.02, p<.001), while the GC genotype identified a lesser degree of risk (OR=1.67, p=.015). A gene dosage effect for serum IL-6 levels was identified; CC homozygotes had the highest IL-6 levels (6.5±2.1 pg/mL), followed by GC (5.2±1.7), and GG (3.9±1.3; p<.001). In addition, the C allele was identified as an independent risk factor for elevated HbA1c, a higher HOMA-IR, and an atherogenic lipid profile. The polymorphism was confirmed to be an independent predictor of T2DM using multivariable regression analyses. In addition, IL-6 levels had a positive correlation with HbA1c (r=.46) and HOMA-IR (r=.58). Subgroup analysis of the C allele demonstrated

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exacerbation of obesity's effects on insulin resistance, indicating a significant gene-environment interaction.

In conclusion, the IL-6 -174 G/C polymorphism is a strong genetic risk factor for T2DM. The pro-inflammatory C allele elevates systemic inflammation, fostering insulin resistance, poor glycemic control, and dyslipidemia. These findings support integrating IL-6 genotyping into personalized diabetes risk assessments and prevention strategies.

Keywords: Type 2 Diabetes Mellitus, Interleukin-6, IL-6 -174 G/C Polymorphism, rs1800795, Insulin Resistance.

1. Introduction

One of the biggest challenges in the healthcare sector today is Type 2 diabetes mellitus (T2DM). In 2021, an estimated 537 million adults had diabetes, and projections suggest that this figure will grow to 783 million by 2045, with more than 90% of these projected cases classified as T2DM (International Diabetes Federation, 2015). T2DM is a chronic metabolic disorder characterized by an ongoing decrease in glycemic control due to both insulin resistance and progressive deterioration of pancreatic β-cell function (American Diabetes Association, 2012; Gaulton, 2017). Many factors contribute to increasing the incidence of T2DM, including lifestyle changes, an aging population, and genetic susceptibility (Fuchsberger et al., 2016).

For many years, T2DM was thought to be the result of two primary pathways – glucotoxicity and lipotoxicity. Recently, however, new evidence suggests that chronic, low-grade systemic inflammation is not only the result of insulin resistance but that it is also a key factor in the development of insulin resistance and β-cell dysfunction (Tsalamandris et al., 2019). In addition, adipose tissue surrounding the abdomen has recently been identified as an active endocrine organ capable of secreting various bioactive substances known as adipocytokines. In cases of obesity, hypertrophied adipocytes and infiltrating macrophages in adipose tissue produce large amounts of pro-inflammatory cytokines (e.g., TNF-

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α, IL-1β, and IL-6) that create a state of systemic inflammation (Pickup et al., 1997; Tsalamandris et al., 2019).

Of these, one stands out, with a unique and complex position: IL-6. It is a pleiotropic cytokine produced by immune cells, endothelial cells, fibroblasts, and adipocytes, and is thought to be produced from up to 30% of circulating levels from adipose tissue in obese individuals (Akbari & Hassan-Zadeh, 2018). The influence of IL-6 on glucose metabolism is complex and situation-dependent. In an acute context IL-6 can increase glucose uptake in contracting skeletal muscle but in chronic elevations as would be seen in obesity and T2DM, the overall metabolic effects are deleterious. Chronically elevated IL-6 is known to inhibit the insulin signaling cascade, though this mechanism is not fully understood, but it is known to induce suppressor of cytokine signaling 3 (SOCS3) which binds to and promotes degradation of insulin receptor substrate-1 (IRS-1), thus impairing insulin mediated suppression of hepatic glucose output (Edgerton et al., 2017). Within skeletal muscle, IL-6 inhibits insulin stimulated glucose disposal, through down-regulation of the expression of glucose transporter type 4 (GLUT-4) and key components of the insulin receptor pathway. Moreover, IL-6 was shown to directly trigger apoptosis in pancreatic β-cells, thereby contributing to a decrease in the number of functional β-cells (Böni-Schnetzler et al., 2018).

Because of its central role in the pathogenesis, the genes regulating IL-6 expression are excellent candidate susceptibility genes for T2DM. The short arm of chromosome 7 at position 7p21 is the location of the human IL-6 gene (Bosgana et al., 2025). A common single nucleotide polymorphism (SNP; guanine (G) to cytosine (C) substitution at position -174, which is located in the promoter region, has been well studied. This polymorphism is a functional one. Initial in vitro analyses with reporter gene constructs showed that the basal and stimulated transcriptional activity was higher for the -174 G allele than for the C allele (Alhilali et al., 2025). Interestingly, however, many in vivo clinical studies have

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found that carriers of the C allele have elevated circulating levels of both IL-6 and C-reactive protein (CRP), which may be due to compensatory dysregulation in response to chronic inflammatory stimuli or due to other interacting regulatory variants (Vozarova et al., 2003; Huth et al., 2006).

The relationship between the IL-6 -174 G/C polymorphism and T2DM susceptibility has been studied in a number of ethnic groups, but the results have been inconsistent. A seminal study showed a C allele association with a higher risk of T2DM in both Pima Indians and Caucasians (Vozarova et al., 2003). This was further supported by a large collaborative meta-analysis of 21 studies that confirmed a small but statistically significant positive association between the C allele and the risk for T2DM (Huth et al., 2006). Further support has been found in subsequent studies of the Ethiopian, Pakistani, Greek, and Mexican populations (Ayelign et al., 2021) and others have reported no association possibly due to different allele frequencies, linkage disequilibrium patterns or environmental factors like diet, obesity or physical activity (Lara-Gómez et al., 2019; Haghnazari, L., & Sabzi, 2021).

In addition to disease susceptibility, the polymorphism has also been linked to severity and complications of diabetes (Nadeem et al., 2017; Plataki et al., 2018). Experimental data have been associated with the C allele with increased risk of diabetic nephropathy, retinopathy, and cardiovascular disease in T2DM, supporting the hypothesis of a genetically determined enhanced inflammatory state, which leads to micro- and macrovascular diabetic damage (Ghavimi et al., 2016; Fathy et al., 2019; Martínez-Ramírez et al., 2021). Moreover, the combination of the IL-6 genotype with other inflammatory gene polymorphisms like those of the tumor necrosis factor alpha (TNF-α) and interleukin 1 beta (IL-1β) has been found to have a synergistic effect on the risk of T2DM and its complications, underscoring the polygenicity of inflammatory susceptibility (Campos et al., 2019; Cirelli et al., 2020).

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Even with all these publications, there is no study that simultaneously investigates the genetic association of the IL-6 -174 G/C polymorphism to the risk of T2DM, quantifies its effects on a large set of metabolic parameters such as serum IL-6, glycemic control, insulin resistance and lipid profile, and models the gene–environment interaction with obesity. Therefore, the present investigation was designed with the following specific aims: (i) genotype/allele frequency distribution of the IL-6 -174 G/C polymorphism in a well-characterized case-control cohort; (ii) estimation of the risk of T2DM associated with the different genotypes using robustly adjusted statistical models; (iii) detailed metabolic/ inflammatory characterisation of the biochemical consequences of each genotype; and (iv) investigation of the potential interaction between the IL-6 genotype and obesity on the level of insulin resistance. The integrated genetic and biochemical approach is proposed to gain insight of the molecular pathways from a common genetic variant to the clinical manifestation of T2DM.

2. Materials and Methods

2.1 Study Design and Population

An 18-month long careful design, the research was completed from a case-control basis collecting data from a hospital setting. Prior to commencing with the project, the study design (protocol) was validated by ethics and research boards and every participant provided consent to participate. Patients enrolled were between 35–70 years old who had been seen in the outpatient endocrinology offices or their respective primary care office and were recruited from their endocrinology provider. Participants were separated into two study groups:

Case Group (n=200): Patients that were diagnosed as having Type 2 Diabetes Mellitus (T2DM) according to the American Diabetes Association (ADA) criteria: HbA1c $\geq$ 6.5%, or 2-hour plasma glucose during 75g oral glucose tolerance test (OGTT) $\geq$ 200 mg/dL, or fasting plasma glucose (FPG) $\geq$ 126 mg/dL, or a random plasma glucose (RPG)

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≥ 200 mg/dL in the presence of classic hyperglycemic symptoms (American Diabetes Association, 2012).

Control Group (n=200): Healthy volunteers, matched for age (± 3 years) and sex, with no personal or first-degree family history of diabetes. All controls had an FPG < 100 mg/dL and HbA1c < 5.7%.

2.2 Exclusion Criteria

Patients were excluded from this study if they had any of the following conditions: type 1 diabetes mellitus, maturity-onset diabetes of the young (MODY), gestational diabetes, acute or chronic inflammatory or infectious diseases (such as rheumatoid arthritis, systemic lupus erythematosus, active tuberculosis, and chronic hepatitis C), severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2), hepatic dysfunction, current use of systemic corticosteroids, immunosuppressive agents, or anti-inflammatory therapy (including high-dose statins that could influence IL-6 levels), history of major surgery or trauma within 3 months, or pregnancy or lactation.

2.3 Anthropometric and Clinical Data Collection

Data were gathered using a uniform questionnaire which included demographic information, personal and family history, diabetes duration, and lifestyle factors. Participants wore light clothing with no shoes on when anthropometric measurements were taken. Body weight was measured to the nearest 0.1 kg, and height to the nearest 0.1 cm. BMI was calculated as body weight (kg) / body height^2 (m^2). Waist circumference was taken at the middle of the distance between the lower costal margin and the iliac crest with a non-stretchable measuring tape. BP was taken with a calibrated sphygmomanometer following a seated rest of at least 10 minutes.

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2.4 Sample Collection and Biochemical Analysis.

Venous blood was collected from each subject on an overnight fast (10-12 hours). The blood was allocated into three types of vacutainer tubes:

- EDTA tube (3 mL): For DNA extraction and HbA1c analysis. Aliquots of whole blood were collected and frozen at -20°C for molecular analyses.
- Fluoride oxalate tube (2 mL): The plasma was separated after the tube was centrifuged at 3000 rpm for 10 minutes and measured for FPG using glucose oxidase-peroxidase method and an automated analyzer.

Clotted for 30 minutes, centrifuged at 3000 rpm for 15 minutes and aliquots of the separated serum were obtained (plain serum separator tube, 10 mL). Lipid profile (total cholesterol [TC], triglycerides [TG] and high-density lipoprotein cholesterol [HDL-C]) was measured by standard enzymatic colorimetric methods with a fresh aliquot. The Friedewald formula was used to calculate low-density lipoprotein cholesterol (LDL-C): LDL-C = TC – HDL-C – (TG/5). A chemiluminescent immunoassay was used to measure serum insulin. The rest of the serum samples were then stored at -80 C for batch analysis of IL-6.

The level of IL-6 was measured in serum by a commercial high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit, following the manufacturer instructions. The dynamic range of the assay was 0.7 pg/mL; the intra-assay and inter-assay coefficients of variation were <8% and <10%, respectively. The Homeostasis Model Assessment (HOMA-IR) index, which was defined as fasting insulin (µIU/mL) × FPG (mg/dL) / 405 (Diniz et al., 2020), was used to estimate insulin resistance.

2.5 Genotyping of the IL-6 -174 G/C Polymorphism (rs1800795)

Peripheral blood leukocytes were used for the extraction of genomic DNA with a commercial wizard genomic DNA purification kit (Takawira et al., 2022). Using a spectrophotometer, the quality and concentration of extracted DNA was determined by measuring absorbance at 260 nm and 280 nm. The A260/A280 ratio of 1.7 to 1.9 was used as an indicator of

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high purity DNA. The integrity of DNA was also verified by electrophoresis in 1% Agarose gel.

We genotyped the IL-6 -174 G/C polymorphism using a well-established PCR-RFLP assay. The following primers were used to amplify a 525 base pair (bp) region of the IL-6 promoter:

· Reverse: 5'-ACA GTA GTA GTA GTA GTA GTA GTA GTA-3'

· Reverse: 5’-CTG ATT GGA AAC CTT ATT AAG-3’

The PCR was performed in 25 µL reaction volume containing: 100 ng genomic DNA, 1X PCR buffer, 1.5 mM $MgCl_2$, 200 mM dNTPs, 0.4 mM of each primer and 1.0 U Taq DNA polymerase. The amplification conditions were: an initial denaturation for 5 minutes at 95°C, followed by denaturation at 95°C for 45 seconds, annealing at 55°C for 45 seconds and extension at 72°C for 60 seconds with 35 cycles and a final extension at 72°C for 10 minutes. To confirm the PCR product was run on a 2% agarose gel.

Genotyping was done by digesting 10 µL of the PCR product with 5 U of the restriction enzyme SfaNI (HpyCH4IV) for 16 hours at 37°C. The restriction fragments were then separated on a 3% agarose gel and stained with ethidium bromide which was then viewed under UV light. The -174 G allele is uncut and results in only one 525 bp band. The -174 C allele forms a restriction site, which gives rise to two fragments of 311 and 214 bp. Thus, the three genotypes were identified as: a single 525 bp band for GG homozygotes; three bands (525, 311, 214 bp) for GC heterozygotes; and two bands (311, 214 bp) for CC homozygotes. Twenty percent of the samples were randomly selected for repeat genotyping and 100% of those samples were concordant for quality control.

2.6 Statistical Analysis

All the analyses were carried out using IBM SPSS Statistics Version 26.0 (IBM Corp., Armonk, NY). Prior to conducting any comparative analyses, the normality of each continuous variable (i.e. normality) was evaluated using Shapiro-Wilk's test. Variables that were normally

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distributed were reported as the mean ± SD while categorical variables were reported as both count and percentage of frequency. Within the control group, the distribution of genotypes was evaluated by means of a chi-square (χ^2) goodness-of-fit test, to determine whether observation of the genotype counts were consistent with the predictions according to Hardy-Weinberg equilibrium (HWE). Two-sample Student's t-test was used when two independent groups (the two groups of Participants (cases; controls)) needed to be compared across normally-distributed continuous measures. For comparisons involving three groups of genotypes, we used a one-way analysis of variance (ANOVA) procedure and followed up with post-hoc pairwise group comparisons only when the omnibus F-test yielded statistically significant results adjusting for multiple comparisons using the Bonferroni correction procedure to control for family-wise error rate. To compare the distribution of the various genotypes and alleles accordingly within each population (i.e., patients and controls), the distributions of each group (genotype and allele) were analysed using the Pearson chi-square (χ^2) test of independence on the relevant corresponding contingency tables. The strength of the association between the IL-6 genetic polymorphism and the likelihood of developing T2DM was assessed using odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated from binary logistic regression analyses conducted in two stages: first a crude model that included only the genetic variable, and second, an adjusted model that included covariates consisting of Age, biological sex, body mass index (BMI), and documented family history of diabetes. In addition to the above analyses assessing the relationship between genetic polymorphisms and the likelihood of developing diabetes, stratified analyses were conducted using a general linear model (GLM) framework that included an interaction term in order to assess if the effect of IL-6 genotype in relation to measures of insulin resistance was modified by obesity status. Finally, the nature and strength of the linear correlation between serum

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IL-6 levels and measures of glycemia and HOMA-IR were evaluated using Pearson's product-moment correlation coefficient. A criterion of $p < 0.05$ (two-tailed) was used as the cutoff for determining whether each hypothesis was statistically significant.

3. Results

3.1 Baseline Characteristics of the Study Population

In the final analysis, there were a total of 400 participants, with 200 participants included in the type II diabetes (T2DM) group and 200 participants included in the control group. Table 1 summarizes the demographic, anthropometric and biochemical characteristics of the two groups. At a mean age of 54.8 (T2DM) vs. 53.5 (controls) years, there was no statistically significant difference between the two group. in terms of sex ($p = 0.551$) or age ($p = 0.163$) All metabolic and inflammatory parameters were statistically significantly higher in individuals with T2DM. BMI was significantly higher in the diabetic group (29.6 ± 4.8 vs. 25.2 ± 3.5 kg/m², $p<0.001$). The biochemical profile of T2DM patients was characterized by severe hyperglycemia (FPG: 168.5 ± 42.3 vs. 88.7 ± 9.8 mg/dL; HbA1c: 8.2 ± 1.6 vs. 5.1 ± 0.4%, both $p<0.001$), marked insulin resistance (HOMA-IR: 4.5 ± 2.1 vs. 1.2 ± 0.5, $p<0.001$), a pro-atherogenic lipid profile, and nearly three-fold higher serum IL-6 levels (4.8 ± 1.9 vs. 1.7 ± 0.8 pg/mL, $p<0.001$).

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Table (1) Baseline Demographic, Anthropometric and Biochemical Characteristics of the Study Participants.

Parameter	T2DM Patients (n=200)	Controls (n=200)	Test Statistic (t/χ^2)	P-value
Age (years)	54.8 ± 9.5	53.5 ± 9.1	1.397	0.163
Gender (Male/Female), n	112/88	106/94	0.368	0.551
BMI (kg/m ²)	29.6 ± 4.8	25.2 ± 3.5	10.485	<0.001
Waist Circumference (cm)	102.5 ± 12.8	90.3 ± 10.5	10.424	<0.001
FPG (mg/dL)	168.5 ± 42.3	88.7 ± 9.8	26.011	<0.001
HbA1c (%)	8.2 ± 1.6	5.1 ± 0.4	26.604	<0.001
Fasting Insulin (µIU/mL)	10.8 ± 4.2	5.4 ± 2.1	16.264	<0.001
HOMA-IR Index	4.5 ± 2.1	1.2 ± 0.5	21.619	<0.001
Total Cholesterol (mg/dL)	215.4 ± 40.2	186.5 ± 32.5	7.908	<0.001
Triglycerides (mg/dL)	195.3 ± 75.5	115.6 ± 45.2	12.812	<0.001
HDL-C (mg/dL)	38.5 ± 8.2	49.8 ± 11.5	-11.328	<0.001
LDL-C (mg/dL)	136.2 ± 35.8	112.1 ± 28.9	7.404	<0.001
Serum IL-6 (pg/mL)	4.8 ± 1.9	1.7 ± 0.8	21.249	<0.001

Data are presented as mean ± SD or number. P-values from independent t-test for continuous variables and chi-square test for gender.

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3.2 Genetic Analysis: Genotype and Allele Frequencies

Hardy-Weinberg equilibrium was satisfied as indicated by an insignificant chi-square = 0.84, p = 0.36, indicating this is a valid control sample for the purpose of determining the distribution of IL-6 -174 G/C genotypes. The allele/genotype distribution for T2DM and control groups can be found in Table 2. The T2DM and control groups showed statistically significant differences between these genotype distributions (chi-square = 14.56, df = 2, p<0.001). The homozygous CC genotype had a higher occurrence in the T2DM (12.0%) than in controls (4.0%), similarly with the GC genotype (T2DM 41.0%; controls 33.0%). The appearance of the mutant C allele was overrepresented in the T2DM (32.5%) as compared to the controls (20.5%) with statistical significance (p<0.001).

Table (2) Genotype and Allele Frequencies of the IL-6 -174 G/C (rs1800795) Polymorphism.

Genotype/Allele	T2DM Cases (n=200)	Controls (n=200)	χ^2	P-value
GG	94 (47.0%)	126 (63.0%)		
GC	82 (41.0%)	66 (33.0%)	14.56	<0.001
CC	24 (12.0%)	8 (4.0%)		
G Allele	270 (67.5%)	318 (79.5%)	14.93	<0.001
C Allele	130 (32.5%)	82 (20.5%)		

(HWE for controls: χ^2=0.84, p=0.36.)

3.3 Risk Assessment for Type 2 Diabetes Mellitus

The use of binary logistic regression helped determine the direction and strength of the association between genotype and T2DM; this is outlined in Table 3. In the non-adjusted models, individuals with the GC genotype had an approximately 1.67 times greater risk of developing T2DM (95% CI: 1.10-2.52, p=0.015) and CC genotype carriers had a 4.02 times greater risk of T2DM (95% CI: 1.73-9.33, p<0.001) when compared to those with the GG wild-type allele. In the dominant model (GG vs. GC

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and CC), the odds of T2DM were 1.93 (95% CI: 1.30-2.85, p<0.001) for the C allele homozygous and heterozygous compared to individuals who are GG homozygotes. After accounting for demographic factors (age, sex, BMI, family history of diabetes) in Model 1, the genetic associations remained significant. The addition of waist circumference to Model 1 (Model 2) led to a modest attenuation of the odds ratios; however, this attenuation was not complete, which supports the hypothesis that some of the genetic risk for T2DM is associated with obesity. In the fully-adjusted model, carriers of the C allele (i.e., GC and CC) were at a 1.71 (95% CI: 1.12-2.62, p=0.013) times higher risk for T2DM, which further supports the classification of the IL-6 polymorphism as an independent risk factor for T2DM.

Table (3) Logistic Regression Analysis for the Risk of T2DM According to IL-6 -174 G/C Genotype.

Genetic Model	Crude OR (95% CI)	P-value	Adjusted OR Model 1* (95% CI)	P-value	Adjusted OR Model 2** (95% CI)	P-value
GG (Reference)	1.00 -	-	1.00 -	-	1.00 -	-
GC	1.67 (1.10-2.52)	0.015	1.54 (1.01-2.37)	0.046	1.48 (0.95-2.32)	0.081
CC	4.02 (1.73-9.33)	<0.001	3.76 (1.58-8.95)	0.003	3.21 (1.30-7.93)	0.011
Dominant (GC+CC vs. GG)	1.93 (1.30-2.85)	<0.001	1.83 (1.21-2.76)	0.004	1.71 (1.12-2.62)	0.013
C Allele (vs. G Allele)	1.87 (1.35-2.58)	<0.001	-	-	-	-

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*(Model 1: Adjusted for age, sex, and BMI. / *Model 2: Adjusted for age, sex, BMI, waist circumference, and family history of diabetes.)*

3.4 Biochemical Correlates of the IL-6 Genotype in the Total Study Population

To understand the biochemical consequences of this polymorphism independent of disease status, all 400 participants were stratified by genotype and their metabolic parameters compared (Table 4). A clear gene-dosage effect was observed across the GG, GC, and CC genotypes. Serum IL-6 levels showed a stepwise increase from 2.3 ± 1.2 pg/mL in GG individuals to 3.5 ± 1.9 pg/mL in GC and 5.1 ± 2.5 pg/mL in CC homozygotes ($p<0.001$). A similar pattern was observed for FPG, HbA1c, and HOMA-IR, with CC individuals exhibiting the most adverse metabolic profile. Even among non-diabetic controls (data not shown in table, but confirmed via stratified analysis), CC carriers had higher IL-6 levels and HOMA-IR than GG carriers, indicating that the genetically determined inflammatory predisposition exists in the pre-diabetic state. The lipid profile also deteriorated across genotypes, with CC carriers having significantly higher triglycerides and lower HDL-C.

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Table (4) Comparison of Biochemical Parameters Across IL-6 -174 G/C Genotypes in the Entire Study Cohort (N=400).

Parameter	GG (n=220)	GC (n=148)	CC (n=32)	F-statistic (ANOVA)	P-value
Serum IL-6 (pg/mL)	2.3 ± 1.2	3.5 ± 1.9	5.1 ± 2.5	58.32	<0.001
FPG (mg/dL)	115.2 ± 38.5	135.8 ± 45.2	158.4 ± 52.1	18.79	<0.001
HbA1c (%)	6.1 ± 1.5	6.9 ± 1.8	7.5 ± 2.1	19.85	<0.001
HOMA-IR	2.2 ± 1.5	3.3 ± 2.1	4.5 ± 2.6	33.45	<0.001
Total Cholesterol (mg/dL)	198.5 ± 38.2	205.6 ± 39.8	215.4 ± 42.5	3.88	0.021
Triglycerides (mg/dL)	143.2 ± 58.5	168.4 ± 72.3	188.2 ± 80.1	11.52	<0.001
HDL-C (mg/dL)	45.2 ± 10.5	42.1 ± 9.8	38.5 ± 8.8	9.36	<0.001
LDL-C (mg/dL)	122.5 ± 30.8	130.2 ± 33.5	136.8 ± 35.2	4.56	0.011

(Data are mean ± SD. P-values from one-way ANOVA. Post-hoc Bonferroni tests confirmed significant differences between all genotype pairs for IL-6, FPG, HbA1c, HOMA-IR, and TG (p<0.05).)

Data are mean ± SD. P-values from one-way ANOVA. Post-hoc Bonferroni tests confirmed significant differences between all genotype pairs for IL-6, FPG, HbA1c, HOMA-IR, and TG (p<0.05).

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3.5 Stratified Analysis of the Impact of Genotype on Biochemical Parameters Within the T2DM Group

To isolate the effect of the polymorphism specifically in the diabetic state, we analyzed the 200 T2DM patients stratified by genotype (Table 5). Within the diabetic group, the IL-6 genotype continued to exert a significant influence. CC homozygotes had markedly higher IL-6 levels (6.5 ± 2.1 pg/mL) than GG patients (3.9 ± 1.3 pg/mL). This translated to significantly worse glycemic control (HbA1c: 9.1 ± 1.7% vs. 7.6 ± 1.4%, $p<0.001$) and greater insulin resistance (HOMA-IR: 5.7 ± 2.4 vs. 3.8 ± 1.7, $p<0.001$). Interestingly, even after adjusting for BMI and duration of diabetes in an ANCOVA model, the differences in HbA1c and HOMA-IR between genotypes remained statistically significant ($p=0.012$ and $p=0.004$, respectively), suggesting a direct effect of the genetic variant on disease severity beyond its association with obesity.

Table (5) Biochemical and Clinical Parameters in T2DM Patients Stratified by IL-6 -174 G/C Genotype.

Parameter	GG (n=94)	GC (n=82)	CC (n=24)	P-value
Serum IL-6 (pg/mL)	3.9 ± 1.3	5.2 ± 1.7	6.5 ± 2.1	<0.001
HbA1c (%)	7.6 ± 1.4	8.4 ± 1.5	9.1 ± 1.7	<0.001
HOMA-IR Index	3.8 ± 1.7	4.8 ± 2.1	5.7 ± 2.4	<0.001
Total Cholesterol (mg/dL)	208.5 ± 38.9	220.1 ± 39.5	226.3 ± 42.1	0.031
Triglycerides (mg/dL)	181.2 ± 70.5	204.5 ± 76.1	218.8 ± 80.2	0.022
HDL-C (mg/dL)	40.2 ± 8.5	37.5 ± 7.8	36.1 ± 7.1	0.018
LDL-C (mg/dL)	130.5 ± 34.2	139.8 ± 35.1	145.2 ± 38.5	0.045
Duration of Diabetes (years)	6.5 ± 5.2	7.1 ± 5.8	7.8 ± 6.1	0.553

(P-values from one-way ANOVA.)

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P-values from one-way ANOVA.

4.6 Correlation and Interaction Analyses

A comprehensive Pearson correlation analysis was performed to delineate the interrelationships among the key inflammatory and metabolic markers (Table 6). In the T2DM group, serum IL-6 exhibited a strong positive correlation with HOMA-IR ($r = 0.58$, $p < 0.001$), indicating that elevated IL-6 is tightly coupled with the degree of insulin resistance. IL-6 also correlated significantly with HbA1c ($r = 0.46$, $p < 0.001$), FPG ($r = 0.41$, $p < 0.001$), and triglycerides ($r = 0.32$, $p < 0.001$), while showing a negative correlation with HDL-C ($r = -0.27$, $p < 0.001$). The strong correlation between HOMA-IR and both HbA1c (r=0.52) and triglycerides (r=0.38) underscores the central role of insulin resistance in driving both hyperglycemia and diabetic dyslipidemia.

Table (6) Pearson Correlation Coefficients Between Serum IL-6, Insulin Resistance, and Metabolic Parameters in T2DM Patients.

Variable	IL-6	HOMA-IR	HbA1c	FPG	TG	HDL-C
IL-6 (pg/mL)	1	0.58**	0.46**	0.41**	0.32**	-0.27**
HOMA-IR		1	0.52**	0.48**	0.38**	-0.35**
HbA1c (%)			1	0.71**	0.15*	-0.12
FPG (mg/dL)				1	0.12	-0.09
TG (mg/dL)					1	-0.45**
HDL-C (mg/dL)						1

*(**$p < 0.001$, *$p < 0.05$.)*

Finally, the co-hort was divided according to the polymorphism [GG vs. C allele carriers] and obesity categories [non-obese: BMI < 30 kg/m2, obese: BMI ≥ 30 kg/m2] to investigate the gene-environment interaction between the polymorphism and obesity. This general linear model showed a significant interaction effect between genotype and obesity on HOMA-IR ($p = 0.018$). The difference in HOMA-IR between GG and C

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allele carriers was smaller in nonobese individuals (2.1 ± 0.9 vs. 2.8 ± 1.2, p=0.04). In the obese sub-group, though, the HOMA-IR was significantly greater with the C allele (3.9 ± 1.8 vs. 5.8 ± 2.3, p<0.001). This shows that the genetically driven pro-inflammatory environment potentiates the insulin resistance of obesity-induced inflammation, resulting in a greater insulin resistance than either alone.

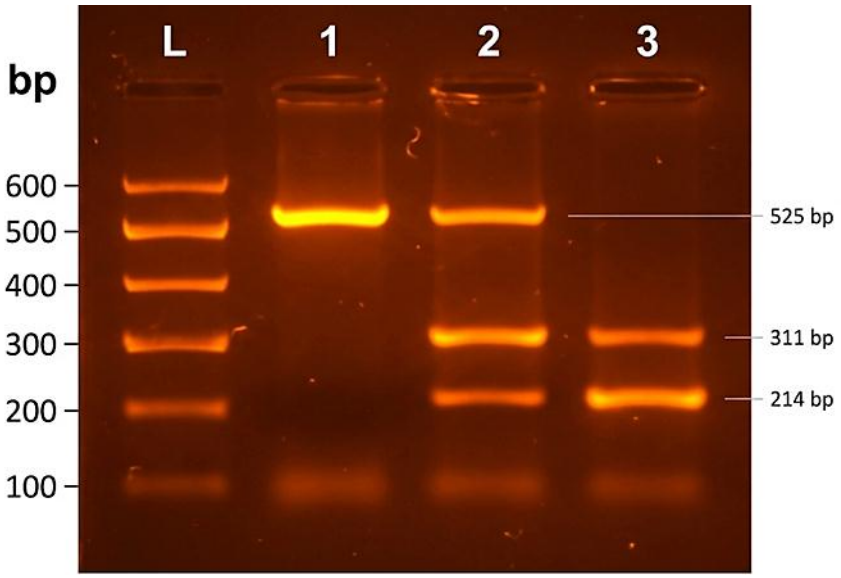

Figure (1) Agarose Gel Electrophoresis of PCR-RFLP Products for Genotyping the IL-6 -174 G/C (rs1800795) Polymorphism.

Figure 1 show banding pattern which is used to differentiate the three IL-6 genotypes is illustrated. The 100 bp DNA molecular weight marker is Lane M. A single uncut 525 bp fragment is shown as the homozygous GG genotype in lane 1. The heterozygous GC genotype is represented in Lane 2, having three bands at 525, 311 and 214 bp. Lane 3 is homozygous CC genotype with two bands at 311 and 214 bp, denoting that the restriction enzyme has digested the entire sample. This figure validates the PCR-RFLP method's specificity for the polymorphism.

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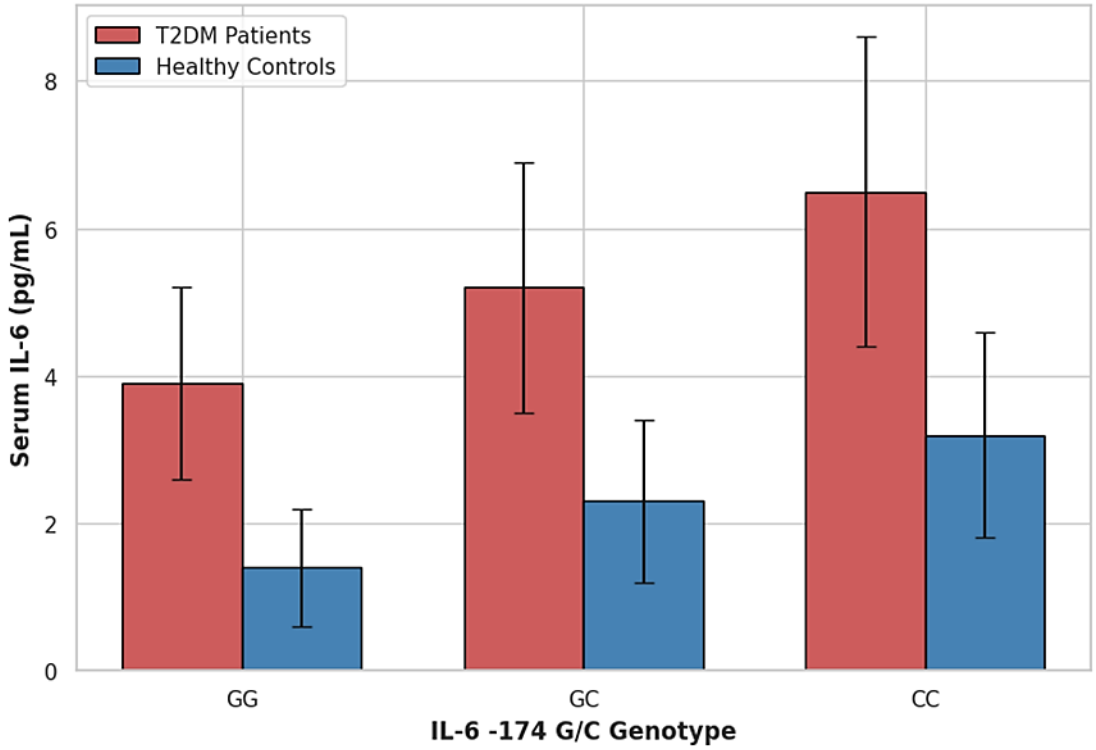

Figure (2) Comparison of Mean Serum IL-6 Levels Across IL-6 -174 G/C Genotypes.

Figure 2 shows the mean (+/- SD) serum IL-6 (pg/mL) levels for each genotype group in the T2DM case (red bar) and control (blue bar) groups. The figure shows that, in both groups,that the gene dosage effect (CC homozygotes have the highest IL-6 levels) exists. Finally, the chart also reveals that the levels of IL-6 are significantly elevated in diabetic patients vs healthy control subjects for all genotypes, indicating the synergistic action of genotype and disease state on systemic inflammation Figure 3 is a scatter plot in which the individual data points of the 200 patients with T2DM appear on the chart with the serum IL-6 level on the x-axis, and the HOMA-IR index on the y-axis. Overlaid are a linear regression line (solid line) and 95% confidence interval (dashed lines). The plot demonstrates a significant positive linear correlation ($r = 0.58$, $p < 0.001$), with more insulin resistance being associated with higher levels

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of circulating IL-6. All points are coloured by genotype: CC carriers (red dots) are grouped in the upper right quadrant, corresponding to the highest IL-6 and highest HOMA-IR.

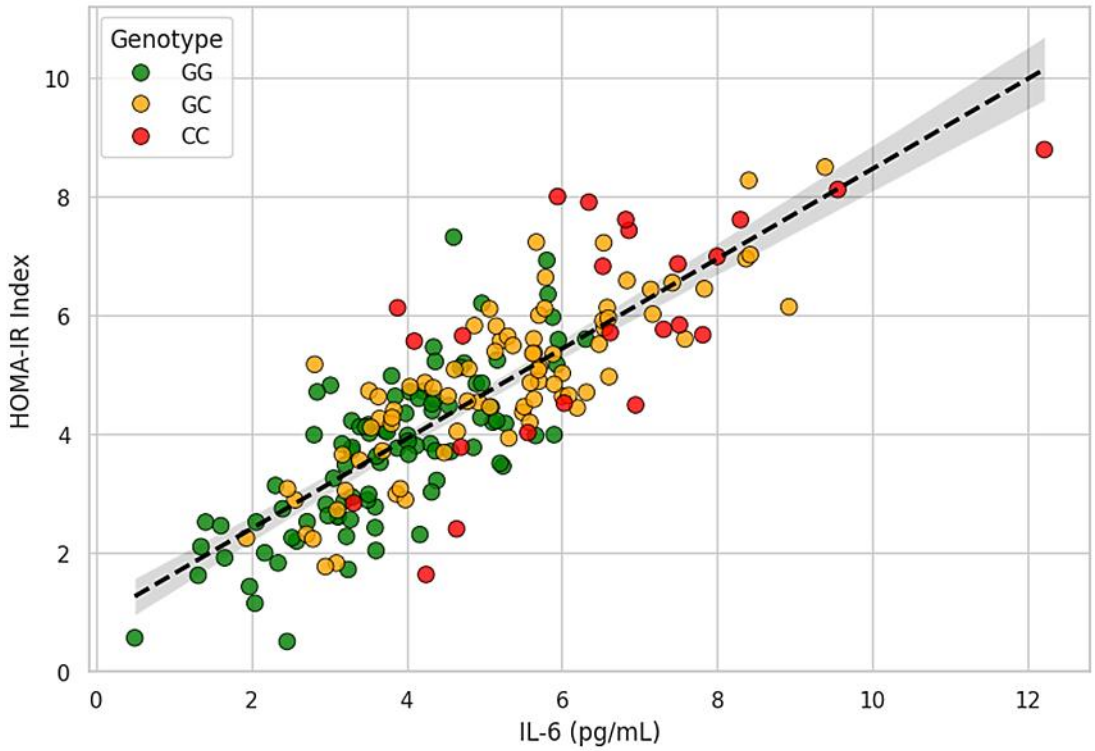

Figure (3) Scatter Plot Illustrating the Correlation Between Serum IL-6 Levels and HOMA-IR Index in Type 2 Diabetic Patients.

4. Discussion

This genetic and biochemical analysis strongly indicates that the IL-6 −174 G/C (rs1800795) promoter polymorphism is an important and independent risk factor for type 2 diabetes mellitus (T2DM) based on a well-established inflammatory pathway. The mutant C allele was significantly overrepresented among T2DM patients, and a clear gene-dose effect on the risk of developing the condition was convincingly demonstrated. The risk of developing T2DM was four times greater in patients carrying the homozygous CC genotype than in those harboring the wild-type GG genotype (OR = 4.02), which points directly to the

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substantial biological impact of this common variant in the pathogenesis of a complex multifactorial disease defined under the latest diagnostic criteria (American Diabetes Association, 2025). Moreover, after rigorous multivariable adjustment controlling for established confounding factors—including chronological age, sex, body mass index (BMI), and family history of diabetes—the association between the IL-6 −174 G/C polymorphism and T2DM persisted as a significant, robust, and independent predictor of disease susceptibility.

The extensive biochemical profiling performed in the present study represents a central strength and novelty of our work, directly linking the underlying genetic architecture to the clinical metabolic phenotype at an intricate mechanistic level. Circulating serum IL-6 levels exhibited a significant, step-wise escalation from the GG wild-type to the GC heterozygous and CC homozygous genotypes, evident across the entire cohort and particularly pronounced within the diabetic group. This observation aligns with a growing body of *in vivo* clinical and translational investigations demonstrating that the −174 G/C polymorphism functions as a quantitative trait locus regulating systemic IL-6 production in humans (Çelik et al., 2024; Król-Kulikowska et al., 2024; Ołdakowska et al., 2022). Although early *in vitro* transient transfection experiments initially suggested that the G allele was a stronger transcriptional activator (Olivieri et al., 2003; Huth et al., 2006; Alhilali et al., 2025), clinical real-world findings across diverse metabolic cohorts demonstrate that the chronic, low-grade inflammatory microenvironment characteristic of obesity and T2DM fundamentally alters promoter regulation. Under sustained metabolic stress, complex epigenetic remodelling—such as altered promoter methylation and chromatin accessibility—combined with the recruitment of stress-activated transcription factors (such as NF-κB and AP-1), results in paradoxically augmented basal and stimulated transcription from the C allele in key metabolic tissues (Indumathi et al., 2022; Tarfeen et al.,

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2023; Zuo et al., 2025). As hypertrophic and hypoxic adipocytes expand, the innate capacity of C allele carriers to secrete disproportionately higher levels of IL-6 establishes a self-perpetuating vicious cycle between immune hyper-reactivity, systemic inflammation, and metabolic deterioration (Bojarczuk et al., 2024; Koc et al., 2023).

This pathological cycle is further supported by the robust positive correlation identified between circulating serum IL-6 and the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR; $r = 0.58$, $p < 0.001$), corroborating the classical model where hyper-interleukinemia acts as a primary driver of systemic insulin resistance (Bashir et al., 2022; Ul Islam Hashmi et al., 2025). Mechanistically, chronic exposure to elevated IL-6 triggers the hyperactivation of the suppressor of cytokine signaling 3 (SOCS3) pathway within hepatic and peripheral target tissues (Asif et al., 2025; Koc et al., 2023). SOCS3 directly associates with both the insulin receptor (IR) β-subunit and insulin receptor substrate-1 (IRS-1), physically occluding phosphorylation motifs and targeting these essential signaling intermediates for ubiquitin-proteasome degradation. The resulting abrogation of downstream PI3K/Akt signaling prevents insulin-mediated suppression of hepatic gluconeogenesis, driving persistent hepatic glucose output and overt fasting hyperglycemia (Edgerton et al., 2017). This cascade directly explains the notable parallel elevations observed between serum IL-6, fasting plasma glucose (FPG), and glycated hemoglobin (HbA1c) in our study cohort, confirming that inflammatory tone correlates with glycemic dysregulation (Bashir et al., 2022; Çelik et al., 2024). Furthermore, carriage of the risk C allele was accompanied by a typical atherogenic dyslipidemic profile, marked by hypertriglyceridemia and depleted high-density lipoprotein cholesterol (HDL-C). In adipose tissue, IL-6-induced insulin resistance prevents the physiological suppression of hormone-sensitive lipase (HSL), leading to uncontrolled lipolysis and an unregulated efflux of free fatty acids (FFAs)

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into the splanchnic and systemic circulation. This excessive flux of FFAs accelerates hepatic very-low-density lipoprotein (VLDL) synthesis and stimulates cholesteryl ester transfer protein (CETP) activity, replacing cholesteryl esters with triglycerides in core HDL particles—a mechanism that significantly elevates cardiovascular vulnerability and premature subclinical atherosclerosis among diabetic carriers of the C allele (Posadas-Sánchez et al., 2024; Tabrez et al., 2022; Zuo et al., 2025).

A compelling dimension of our findings is the statistically significant gene-environment interaction uncovered between the IL-6 genotype and adiposity. The detrimental impact of the C allele on insulin resistance was substantially amplified in overweight and obese individuals compared to their lean counterparts. This observation indicates that individuals carrying the risk genotypes (GC or CC) not only have a higher baseline risk for developing diabetes, but also exhibit an exaggerated, hyper-responsive diabetogenic phenotype when exposed to excess adiposity. In other words, excess adipose accumulation exacts a steeper metabolic toll in C allele carriers than in homozygous GG individuals. These findings are in complete agreement with recent large-scale evidence: Bojarczuk et al. (2024) demonstrated in a comprehensive meta-analysis that the IL-6 rs1800795 C variant significantly interacts with adiposity to increase metabolic susceptibility, while Koc et al. (2023) showed that both rs1800795 and the adjacent promoter variant rs1800796 independently associate with adverse body composition and clinical obesity phenotypes. Hence, this gene-adiposity synergy identifies a distinct clinical sub-population that is exceptionally vulnerable to weight gain and would derive maximal clinical benefit from early, targeted weight-reduction and anti-inflammatory lifestyle interventions.

An expanded comparative analysis with contemporary worldwide literature underscores both universal patterns and population-specific nuances. The association between the IL-6 −174 C allele and T2DM risk observed in our cohort closely mirrors recent global data synthesized by

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Harun-Or-Roshid and Mollah (2023, 2024). In their extensive meta-analyses comprising up to 149 case-control investigations across multiple ancestries, the mutant C allele of rs1800795 consistently emerged as a major genetic determinant elevating overall susceptibility to metabolic disorders, with a documented elevated risk for T2DM under both dominant and allelic models (Harun-Or-Roshid & Mollah, 2023, 2024). In Middle Eastern and North African cohorts, our findings correspond with recent reports from Saudi Arabia by Elssaig et al. (2024), who confirmed that the mutant C allele of rs1800795 was significantly enriched in obese T2DM patients compared to healthy controls ($p = 0.002$), and by Khdair et al. (2023) in a Jordanian population, which demonstrated the strong contribution of IL-6 promoter variants to diabetes predisposition. Parallel investigations in Egypt by Motawea et al. (2025) similarly established that functional variations across the IL-6 promoter region—specifically the rs1800796 hotspot—correlate with elevated circulating IL-6 and severe glycemic deterioration in diabetic cohorts. In West India, Dabhi et al. (2024) observed that cytokine promoter alterations, including the IL-6 −634 C/G locus, are accompanied by marked hyper-interleukinemia in T2DM patients with and without secondary microvascular complications. Furthermore, comparative analyses across African ancestral backgrounds reveal intriguing genomic architecture: Obirikorang et al. (2024) identified independent associations between IL-6 rs1800795 and rs1800796 polymorphisms and T2DM in a Ghanaian case-control population, while Gondo et al. (2025) confirmed that variations across IL-6 and *IL-6R* loci correlate with systemic inflammatory burdens and metabolic syndrome traits in Central Africa. In Mexican cohorts, Posadas-Sánchez et al. (2024) demonstrated that IL-6 promoter polymorphisms correlate with adverse cardiometabolic profiles, and Król-Kulikowska et al. (2024) reported in European subjects that single nucleotide polymorphisms in

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IL6 directly govern the secretion dynamics of both IL-6 and regulatory islet hormones (insulin and glucagon).

Nevertheless, subtle disparities in effect sizes across the literature warrant consideration. While our observed odds ratio (OR = 4.02 for the CC genotype) represents a robust effect, other cohorts—such as select East Asian populations or specific isolated Iranian cohorts—have occasionally documented weaker associations or lack of statistical significance (Harun-Or-Roshid & Mollah, 2024). These regional discrepancies are largely explained by substantial cross-ethnic differences in baseline minor allele frequencies (MAFs), which vary widely between Caucasian, African, and Asian populations, as well as distinct dietary patterns (such as omega-6 to omega-3 polyunsaturated fatty acid ratios), ambient physical activity levels, and complex polygenic backgrounds that may buffer or magnify single-locus genetic risks (Bojarczuk et al., 2024; Harun-Or-Roshid & Mollah, 2023). In addition, differences in clinical inclusion criteria—such as strict exclusion of acute systemic inflammatory confounders versus inclusion of multi-morbid diabetic patients suffering from end-stage diabetic foot ulcers (Zhao et al., 2022) or severe respiratory infections (Cekin et al., 2025)—can alter observed effect magnitudes across clinical cohorts.

The clinical and translational implications of these findings are broad. Because the IL-6 −174 G/C polymorphism directly mirrors circulating cytokine levels and correlates with HOMA-IR, this variant could serve alongside serum IL-6 as part of an integrative multi-marker panel for precision risk stratification during the asymptomatic, pre-diabetic stage. Using straightforward, cost-effective molecular screening platforms (such as PCR-RFLP or allele-specific PCR), clinicians could identify genetically susceptible individuals before the clinical manifestation of beta-cell exhaustion. Identifying individuals carrying the C allele who harbor heightened sensitivity to adipose tissue expansion allows for targeted, aggressive lifestyle modifications and earlier pharmacological

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management. Beyond risk prediction, our data provide support for personalized immunometabolic pharmacotherapy in T2DM. Because the IL-6 signaling pathway is directly targetable, therapeutic modalities that inhibit classical or trans-signaling pathways (such as monoclonal antibodies targeting the IL-6 receptor, or downstream JAK/STAT and SOCS3 inhibitors) could have clinical utility. While broad-spectrum anti-cytokine therapies carry immunological risks, genotype-guided stratification may isolate a specific subset of insulin-resistant, C-allele-carrying diabetic patients who exhibit hyper-inflammatory signaling and would derive the most favorable benefit-to-risk ratio from pathway-specific anti-inflammatory therapeutics (Asif et al., 2025).

Notwithstanding these insights, several methodological considerations must be acknowledged. First, the cross-sectional, case-control design inherently precludes the establishment of definitive longitudinal causality; prospective, well-characterized cohort studies will be necessary to confirm the temporal predictive power of the IL-6 −174 G/C polymorphism for incident T2DM. Second, while the sample size was fully powered to detect primary genetic and biochemical associations, larger multi-center cohorts are needed to evaluate higher-order gene-gene and gene-diet interactions. Third, while our study focused on the functional −174 G/C promoter variant, extensive evidence indicates that adjacent regulatory polymorphisms (such as rs1800796, rs1800797) and key missense variants in the cognate receptor gene (IL6R, notably Asp358Ala; rs2228145) actively modulate soluble IL-6 receptor shedding and trans-signaling intensity (Gondo et al., 2025; Karcıoğlu Batur et al., 2022). Comprehensive haplotype construction encompassing both *IL6* and IL6R loci will provide a more granular picture of individual inflammatory risk. Finally, although IL-6 was mapped against key glycemic and lipid indices, concurrent quantification of interconnected regulatory cytokines—such as TNF-α, adiponectin, and vitamin D endocrine axes (Bashir et al., 2022; Indumathi et al., 2022; Tarfeen et al.,

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2023; Ul Islam Hashmi et al., 2025)—in future studies will help fully delineate the systemic network driving metabolic dysfunction in type 2 diabetes.

5. Conclusions

The present study clearly shows that the IL-6 gene's -174 G/C (rs1800795) polymorphism in the promoter region is a strong genetic risk factor for type 2 diabetes mellitus. The C allele is found in a significantly higher frequency in the disease and has a dose-dependent effect on the disease and is a predictor of the severity of the metabolic phenotype independently of other risk factors This linkage is clarified by the clear, genetically determined biochemical gradient of the C allele that leads to higher serum levels of IL-6, which are strongly and positively correlated with insulin resistance, hyperglycemia and atherogenic dyslipidemia. Importantly, the genetic risk is greatly exacerbated by obesity, identifying a strong gene-environment interaction. These results have strengthened the inflammatory hypothesis of T2DM at the molecular level and warrant further studies to support the integration of IL-6 genotyping and systemic inflammatory profiling for personalized risk assessment and therapeutic decisions for the prevention and management of type 2 diabetes.

Recommendations

Based on these results, further studies are needed to confirm these findings by moving to large-scale prospective cohort studies with multi-ethnic populations to establish temporal causality between the IL-6 −174 G/C polymorphism and occurrence of type 2 diabetes mellitus and to evaluate the presence of these allele frequencies in other populations. Combining this variant with other pro-inflammatory metabolic variants (TNF-α, CRP, TCF7L2) and advanced statistical techniques such as Mendelian randomization and machine learning will significantly improve the predictive power of multi-locus polygenetic risk scores. At the same time, detailed functional, transcriptomic and epigenetic studies may be required to identify the downstream molecular mechanisms

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related to increased IL-6 and the dysfunction of insulin signaling and receptor dynamics in specific tissues. To take these genetic discoveries and make them the basis for personalised, genotype-driven preventive and therapeutic approaches, sufficiently powered investigations of these interactions between genes and the environment (e.g., diet and physical activity), sex- and age-specific dimorphisms, and vascular complications are required, in addition to randomized controlled trials of pharmacogenomic responses to standard antidiabetic therapies compared with targeted anti-IL-6 biologics.

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التعدد الشكلي الجيني لجين IL-6 وعلاقته بخطر الإصابة بداء السكري من النوع الثاني: دراسة جينية وكيميائية حيوية

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مستخلص البحث:

داء السكري من النوع الثاني اضطراب معقد مرتبط بالالتهاب. يُعدّ الإنترلوكين-6 وسيطًا التهابيًا هامًا يُسهم في ضعف حساسية الأنسولين واختلال وظائف خلايا بيتا. لا يوجد اتساق في العلاقة بين تعدد الأشكال الجينية - 174 G/C (rs1800795) في جين الإنترلوكين-6 وخطر الإصابة بداء السكري من النوع الثاني بين مختلف المجموعات السكانية. هدفت هذه الدراسة إلى اختبار ارتباط هذا التعدد الجيني بالاستعداد للإصابة بداء السكري من النوع الثاني، بالإضافة إلى العلاقة بينه وبين العديد من المؤشرات الأيضية والالتهابية.أجرينا دراسة حالة-مراقبة شملت 200 مريضًا بداء السكري من النوع الثاني و200 شخص من مجموعة المراقبة متطابقين في العمر والجنس. تم تحديد النمط الجيني باستخدام تقنية تفاعل البوليميراز المتسلسل مع تحليل تعدد أطوال قطع التقييد .(PCR-RFLP) تم قياس مستويات سكر الدم الصائم، والهيموجلوبين السكري (HbA1c)، ومستويات الأنسولين الصائم، ومؤشر مقاومة الأنسولين(HOMA-IR) ، وتحليل الدهون، وتركيز الإنترلوكين-6 في المصل.كان تردد الأليل C أعلى بشكل ملحوظ لدى مرضى داء السكري من النوع الثاني مقارنة بمجموعة المراقبة (32.5% مقابل 20.5%، .(p<0.001بالمقارنة مع النمط الجينيGG ، تبين أن النمط الجيني CC عامل خطر مستقل للإصابة بداء السكري من النوع الثاني (نسبة الأرجحية المعدلة = 4.02، قيمة(p < 0.001 ، بينما أظهر النمط الجيني GC درجة أقل من الخطر (نسبة الأرجحية = 1.67، قيمة .(p = 0.015 كما لوحظ تأثير جرعة الجين على مستويات إنترلوكين-6 في الدم؛ حيث سجل الأفراد متماثلو الزيجوت CC أعلى مستويات إنترلوكين-6 (6.5 ± 2.1 بيكوغرام/مل)، يليهم الأفراد متماثلو الزيجوت(1.7 ± 5.2) GC ، ثم الأفراد متماثلو الزيجوت1.3 ± 3.9) GG ؛ قيمة .(p < 0.001 بالإضافة إلى ذلك، تبين أن الأليل C عامل خطر مستقل لارتفاع مستوى الهيموغلوبين السكري(HbA1c) ، وارتفاع مؤشر مقاومة الأنسولين(HOMA-IR) ، وظهور صورة دهنية مُسببة لتصلب الشرايين. وقد تم تأكيد أن تعدد الأشكال الجينية يُعد مؤشرًا مستقلاً للإصابة بداء السكري من النوع الثاني باستخدام تحليلات الانحدار متعدد المتغيرات. بالإضافة إلى ذلك، أظهرت مستويات إنترلوكين-6 ارتباطًا إيجابيًا مع الهيموجلوبين السكري (HbA1c) (r=0.46)ومؤشر مقاومة الأنسولين (HOMA-IR) (r=0.58). وأظهر تحليل المجموعات الفرعية للأليل C تفاقم تأثيرات السمنة على مقاومة الأنسولين، مما يشير إلى تفاعل جيني بيئي هام.

في الختام، يُعد تعدد الأشكال الجينية IL-6 -174 G/C عامل خطر وراثي قوي للإصابة بداء السكري من النوع الثاني. ويؤدي الأليل C المُحفز للالتهاب إلى زيادة الالتهاب الجهازي، مما يُعزز مقاومة الأنسولين، وضعف التحكم في مستوى السكر في الدم، واضطراب شحوم الدم. وتدعم هذه النتائج دمج تحديد النمط الجيني لإنترلوكين-6 في تقييمات مخاطر الإصابة بداء السكري الشخصية واستراتيجيات الوقاية منه.

الكلمات المفتاحية: داء السكري من النوع الثاني؛ إنترلوكين-6؛ تعدد الأشكالG/C 174 -IL-6 ؛ rs1800795؛ مقاومة الأنسولين.