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Low level of IL1F10 gene expression encoding interleukin-38 is a marker associated with risk of diabetes patients

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Abstract

Diabetes is a common metabolic disorder and a leading cause of physical disability worldwide. It is also classified as an autoimmune disorder characterized by chronic low-grade inflammation, with cytokines playing a role in the disease process and insulin resistance. This research aims to analyze *IL1F10* gene expression, which encodes the anti-inflammatory interleukin-38, in diabetic patients to understand its role in inflammatory and insulin-resistance pathways. Quantitative polymerase chain reaction (qPCR) was used to measure gene expression based on fold change. The results showed a decrease in *IL1F10* expression in diabetes patients compared to control groups (median [interquartile range: 25-75%]) (0.097 [0.018-1.819]). *IL1F10* expression was significantly affected by disease duration and treatment status only. Disease duration showed a marked reduction in the expression level of newly diagnosed patients compared to other groups [3.846 (1.427-5.910) *vs*. 0.384 (0.010-1.169); 0.058 (0.021-2.134); and 0.059 (0.018-0.803); *p*-value = 0.007, respectively]. While treatment status showed a marked increase in the expression level of untreated patients compared to those treated [3.846 (1.819–5.910 *vs*. 0.056 (0.018–0.754); $p < 0.001$, respectively]. ROC curve analysis demonstrated the reliability of *IL1F10* expression in differentiating between diabetic patients and control groups (area under the curve = 0.696; probability <0.001). Finally, the expression of *IL1F10* mRNA is down-regulated in diabetic patients and is only significantly affected by disease duration and treatment status, and can be considered a potential risk factor for diabetic patients.

Keywords: *IL1F10* gene, interleukin-38, diabetes

Introduction

Diabetes is a heterogeneous metabolic disorder, characterized by an increase in blood sugar levels due to an imbalance in insulin secretion, a defect in insulin action, or both (Punthakee *et al*., 2018) . According to the International Diabetes Federation, the global prevalence of diabetes was estimated at 9.3% in 2019, affecting 463 million people. Furthermore, the prevalence of diabetes is projected to rise to 10.2% (578 million) by 2030 and to 10.9% (700 million) by 2045 (Lu *et al*., 2023) . Although most autoimmune diseases are more common in females, there are no clear sex differences in the incidence of type 1 diabetes

in children. In some population groups, such as older males of European descent (over 13 years old), they may be more likely to develop type 1 diabetes than females (male to female ratio 3:2). Globally, one in 11 adults has diabetes90 %of them are infected with type 2 (Sapra *et al*., 2019) .Clinical recognition of diabetes dates back to antiquity, with early descriptions documented by ancient Egyptian, Indian, and Greek physicians who noted the characteristic symptoms of polyuria and wasting. However, a modern scientific understanding of its pathogenesis only began to take root in the late 19th and early 20th centuries. Joseph von Mering demonstrated that removing the pancreas from canine models of fatal diabetes established the organ's central regulatory role. This paved the way for the massive isolation of insulin by Frederick Banting and Charles Best in 1921, a breakthrough that essentially transformed diabetes from a fatal to a chronic diagnosis (Donath & Shoelson, 1995). Over the following decades, research shifted from basic metabolic observation toward immunometabolic. By the late 20th century, foundational studies had established that type 2 diabetes is not simply a metabolic defect, but a chronic, low-grade inflammatory disorder driven by immune system activation and cytokine stress (Donath & Shoelson, 1995). Twenty-first-century genetic exploration has revealed complex cytokine networks that regulate these processes.

Cytokines are a group of proteins used in cellular signaling, and they are likely to predict the development of diabetes complications. Cytokines are part of the inflammatory processes involved in the development of diabetes (Abu Siyam, 2024) .Within the Interleukin-1 (IL-1) cytokine family, first discovered in 2001 a new member known as Interleukin-38 (IL-38), encoded by the *IL1F10* gene, has recently emerged located on chromosome 2q14.1, acts as an anti-inflammatory cytokine (Chen *et al*., 2023). It plays a pivotal role in mitigating the low-grade inflammation associated with type 2 diabetes and insulin resistance by binding to receptors such as IL-36R and IL1RAPL1. It does this by interacting with various receptors, such as IL-36R and IL-1RAPL1, thereby inhibiting the expression of inflammatory pathways (NF-κB and JNK) and preventing the destruction of pancreatic beta cells (Klejbuk & Strączkowski, 2024; Al-Obaidi & Al-Bayati, 2025) .However, the role of IL-38 in type 2 diabetes has not yet been determined (Zhao *et al*., 2022) .Some recent studies have indicated an increase in IL-38 levels in patients with type 1 diabetes, and it can be used as a biomarker for diabetes (Wagner *et al*., 2026; Nassurat *et al*., 2024) . Another study indicated a direct correlation between IL-38 levels and insulin resistance (Klejbuk & Strączkowski, 2024) .Meanwhile, another study found decreased IL-38 levels in patients with type 2 diabetes (Zhao *et al*., 2022). In recent years, the population of the Middle East, especially in Iraq, has witnessed a sharp increase in the spread of metabolic disorders, driven by a complex interaction of genetic predisposition, the transformation of nutritional patterns, and social and economic changes(Ahdi *et al*., 2023). Despite the increasing burden of diabetes in the region, genetic and genetic contributions to inflammatory foundations remain unstable. Specifically, the *IL1F10* gene expression profile and its anti-inflammatory product, IL-38, were not distinguished within the Iraqi clinical regiment. Investigating these molecular differences in a local context is necessary to understand the dynamics of population diseases and assess whether the term *IL1F10* can serve as a viable regional biological sign (Al-Rubaie *et al*., 2024; Nassurat *et al*., 2024).

This study aims to evaluate the gene expression level of *IL1F10* encoding interleukin-38 in Iraqi diabetic patients and to investigate its relationship to inflammatory pathways and insulin resistance. The study also seeks to determine the extent to which this gene expression is affected by the patients' demographic and clinical variables, such as age, sex, family history, disease duration, body mass index (BMI), and treatment status, to assess its efficacy and discriminatory capacity as a biomarker for diagnosing the disease or distinguishing diabetic patients from healthy individuals.

Materials and Methods

2.1. Subjects

This case-control study included 100 participants, equally divided into a diabetic group (n=50) and a healthy control group (n=50). Participants were recruited from the National Diabetes Center at Al-Mustansiriya University in Baghdad, Iraq, between October 2025 and March 2026. Patients were diagnosed clinically and laboratory-based according to the American Diabetes Association (ADA) criteria. The eligibility criteria for the patient group consisted of adults (aged ≥ 18 years) of both sexes who consented to participate. Pregnancy, malignancies, and co-existing chronic or infectious diseases were excluded from the study. The control group, on the other hand, comprised healthy volunteers with no clinical signs of diabetes, malignancies, or chronic diseases. A standardized case report form was used to document demographic and clinical data, including age, sex, age at onset, disease duration, body mass index (BMI), and medications used. Informed and signed consent was obtained from all participants prior to the study's commencement.

2.2. RNA extraction

RNA was extracted from peripheral blood (PB) samples treated with TRIzol reagent using the EasyPure Blood RNA kit and according to the manufacturer's instructions (TransGen Biotech, China). The purity of the extracted RNA was then assessed using a NanoDrop spectrophotometer (Quawell, USA), with absorbance values ranging from 1.8 to 2.0 (260/280), confirming the quality and purity of the isolated samples according to the manufacturer's standards.

2.3. *IL1F10 expression*

To assess *IL1F10* mRNA gene expression levels in peripheral blood (PB) cells, the TransScript Green one-step kit (TransGen Biotech, China) was used according to the manufacturer's instructions. The 2−ΔΔCt method was applied to calculate the relative dopancy change in gene expression, using the GAPDH gene as a housekeeping gene for calibration. The forward and reverse primers for *IL1F10* are 5′-AAGGTCCCCATTTTCCTGG-3′ and 5′- AGAAGGTGAAGCGTGTGG-3′, and *GAPDH* as 5'-GAAATCCCATCACCATCTTCCAGG-3' and 5'-GAGCCCCAGCCTTCTCCATG-3' (Bashi and Ad'hiah *et al*., 2026). The qPCR reaction mix was prepared in a final volume of 20 μL and contained reverse transcriptase (0.4 μL), extracted RNA (4 μL), forward and reverse primers (1.5 μL each), SuperMix (6 μL), reference dye (0.5 μL), and nuclease-free water (6.1 μL). The thermal cycling protocol consisted of a 5-minute initial cycle at 45°C for cDNA synthesis, followed by a 30-second amplification cycle at 95°C, and then 30 repeat cycles including: 95°C for 5 seconds, 60°C for 1 minute, and 72°C for 40 seconds. The reactions were performed using the Mx3005P QPCR" system and the data were analyzed using the MxPro" software (Strtagene USA), as shown in Figure (1) the amplification plots and cleavage curves for the *IL1F10* gene. To measure the gene expression level of *IL1F10*, the threshold cycle (Ct) value was determined for the target gene and the reference gene GAPDH in patients and a control group. The values of ΔCt for the two groups were calculated by subtracting the Ct value of the reference gene from the value of the target gene, and then the value of ΔCt for the control group was subtracted from the value for the patient group to obtain ΔΔCt applying the equation ($2^{-\Delta\Delta Ct}$) the relative fold change was estimated (Bashi and Ad'hiah *et al*., 2025). A value of 1.0 was adopted as the baseline for gene expression in healthy individuals; Thus, values of ($2^{-\Delta\Delta Ct}$) that exceed 1.0 were considered evidence of increased gene expression (Up-regulation), while values less than 1.0 reflected a decrease in it (Down-regulation).

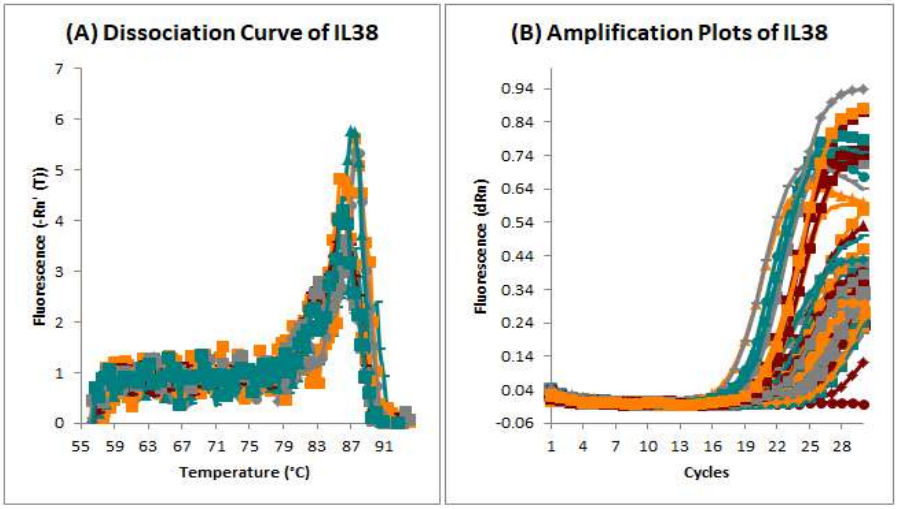

Fig. 1: Dissociation curves (**Plots A**) and amplification plots (**Plots B**) of IL38 mRNA expression, respectively generated based on the dRn fluorescence signal. Amplification plots followed a smooth pattern, and in the dissociation curve, single peaks were observed.

2.4. Statistical analysis

Qualitative data were expressed as mean ± standard deviation and/or number (%). Quantitative data (gene expression) was expressed as median and interquartile range (IQR: 25–75%) using the $2^{-\Delta\Delta Ct}$ method according to a normality test that showed nonparametric distribution. Significance was assessed using Mann-Whitney U test (for comparison of two groups) or Kruskal-Wallis test (for comparison of more than two groups). A probability (p) < 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 27.0 software (Armonk, NY: IBM Corp) and GraphPad Prism software version 9.2.0 (San Diego, CA, USA).

Results

3.1. Baseline demographics and clinical characteristics of patients

This study included 100 participants, divided into two groups: 50 diabetic patients and 50 healthy individuals. The mean age of diabetic patients was 48 ± 13 years, while the mean age of healthy individuals was 37 ± 12 years, indicating no statistically significant difference between the two groups (P=0.126). However, the distribution of age groups differed significantly between the two groups ($p < 0.001$), with a higher proportion of controls under 45 years of age (72.0%) and a greater number of patients in the older age groups (46-60 years: 38.0%; >60 years: 20.0%). There was no statistically significant difference in the gender distribution between the patients and the control group ($p < 0.122$). In the patient group, females comprised 60.0% and males 40.0%, while in the control group, females comprised 44.0% and males 56.0%. 72% of patients reported a positive family history of the disease. The mean duration of the disease was 8 ± 8 years, with most patients (54%) having experienced the disease for more than 5 years. The mean BMI was 31.18 ± 5.44 kg/m², with 58% of patients being obese (BMI ≥ 30 kg/m²) and 40% being overweight (BMI 25.0–29.9 kg/m²). Regarding treatment status, 82% of patients were receiving treatment, while 18% were not (Table 1).

3.2. *IL1F10* gene expression and clinical characteristics

Fold change ($2^{-\Delta\Delta Ct}$) analysis revealed that *IL1F10* gene encoding IL-38 (median [IQR]) were downregulated expression level in all DM patients compared to HC [0.097 (0.018-1.819)]; as shown in Figure 2 (Plot A). *IL1F10* expression was significantly associated with disease duration and treatment

status only. For disease duration, the highest level of *IL1F10* expression was observed in newly diagnosed patients, while expression was significantly reduced in patients with disease for ≤ 1 years, 2-5 years, and > 5 years [3.846 (1.427-5.910) compared to 0.384 (0.010-1.169); 0.058 (0.021-2.134); and 0.059 (0.018-0.803); *p*-value = 0.007, respectively]. Furthermore, *IL1F10* expression levels were significantly higher in untreated patients compared to treated patients [3.846 (1.819–5.910 *vs*. 0.056 (0.018–0.754); $p < 0.001$, respectively], indicating a marked increase in *IL1F10* gene expression in newly diagnosed and untreated cases. In contrast, there was no statistically significant association between *IL1F10* expression and age group, sex, family history, and BMI ($p = 0.393$, 0.961, 0.864 and 0.722, respectively) as shown in Table 2.

Table 1: Baseline characteristics and labertory data of diabetes patients and healthy controls.

Characteristic; mean ± SD or n (%)		Patients; n = 50	HC; n = 50	*p*-value
Age; years		48±13	37±12	0.126
Age group; years	≤45	21 (42.0)	36 (72.0)	**<0.001**
	46–60	19 (38.0)	14 (28.0)	
	> 60	10 (20.0)	0 (0.0)	
Gender	Male	20 (40.0)	28 (56.0)	0.122
	Female	30 (60.0)	22 (44.0)	
Family history	Yes	36 (72.0)	NA	NA
	No	14 (28.0)		
Disease duration; years		8±8	NA	NA
Disease duration group; years	ND	7 (14.0)	NA	NA
	≤ 1	4 (8.0)		
	2-5	12 (24.0)		
	> 5	27 (54.0)		
BMI; kg/m2		31.183±5.435	NA	NA
	18–24.9	1 (2.0)	NA	NA
	25.0–29.9	20 (40.0)		
	≥ 30	29 (58.0)		
Medication	Untreated	9 (18.0)	NA	NA
	Treated	41 (82.0)		

SD: Standard deviation; HC: Healthy controls; BMI: Body Mass Index; NA: Not Detectable; *p*: Two-tailed probability (significant *p*-value is indicated in bold).

Table 2: The expression level of *IL38* gene classified by clinical characteristics of diabetes patients.

Characteristic		*Il38* expression		*p*-value
		Median	IQR 25–75	
Age group; years	≤45	0.699	0.036-2.319	0.393
	46–60	0.059	0.015-1.530	
	> 60	0.061	0.018-1.408	
Gender	Male	0.108	0.019-1.674	0.961
	Female	0.078	0.018-1.883	
Family history	Yes	0.078	0.018-1.903	0.864

	No	0.169	0.030-.803	
Disease duration group; years	ND	3.846	1.427-5.910	**0.007**
	≤ 1	0.384	0.010-1.169	
	2-5	0.058	0.021-2.134	
	> 5	0.059	0.018-.803	
BMI; kg/m2	18–24.9	0.060	0.060-0.060	0.722
	25.0–29.9	0.078	0.016-1.469	
	≥ 30	0.118	0.021-1.923	
Medication	Untreated	3.846	1.819-5.910	**<0.001**
	Treated	0.056	0.018-0.754	

SD: Standard deviation; HC: Healthy controls; BMI: Body Mass Index; NA: Not Detectable; *p*: Two-tailed probability (significant *p*-value is indicated in bold).

3.5. ROC curve analysis

ROC curve analysis showed that *IL1F10* expression reliably distinguished diabetic patients from healthy individuals, with an AUC of 0.696 (95% CI: 0.592–0.800; $p < 0.001$). The sensitivity and specificity of *IL1F10* expression at a cut-off value of 19.44 (Youden index = 0.24) were 62% each. ROC curve analysis indicates the ability of a test to differentiate between patients and healthy individuals by calculating the AUC as shown in Figure 2 (Plot B). An AUC value ranges from 0.5 to 1.0. An AUC value of 0.5 means the indicator being tested is not useful in differentiating between patients and healthy individuals, while an AUC value of 1.0 indicates optimal discrimination ability. An AUC value greater than 0.6 is generally considered clinically useful.

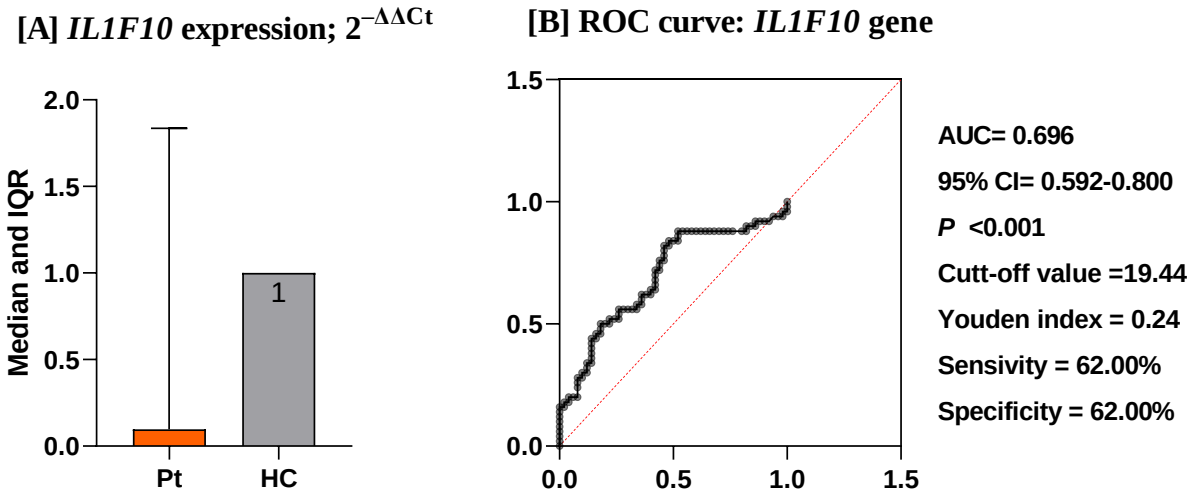

Fig. 2: [A] Dot plots showing *IL38* gene expression in DM patients. Expression were given as median and IQR {(0.097 (0.018-1.819)}.The value of the controls (HC) is 1.0. Plot [**B**] shows the receiver operating characteristic (ROC) curve analysis of *IL38* expression in DM patients *versus* HC. The estimated area under the curve (AUC) and 95% confidence interval (CI) were 0.696 and 0.592-0.800, respectively, indicating the potential for *IL38* expression in differentiating between DM patients and HC.

Discussion

In this study, the importance of *IL1F10* gene expression in diabetic patients and in the pathophysiology of the disease was evaluated. The results showed a decrease in *IL1F10* expression in diabetes patients

compared to control groups (0.097 [0.018-1.819]). *IL1F10* expression was significantly affected by disease duration and treatment status only. Disease duration showed a marked reduction in the expression level of newly diagnosed patients compared to other groups [3.846 (1.427-5.910) *vs*. 0.384 (0.010-1.169); 0.058 (0.021-2.134); and 0.059 (0.018-0.803); *p*-value = 0.007, respectively]. While treatment status showed a marked increase in the expression level of untreated patients compared to those treated [3.846 (1.819–5.910 *vs*. 0.056 (0.018–0.754); $p < 0.001$, respectively]. ROC curve analysis demonstrated the reliability of *IL1F10* expression in differentiating between diabetic patients and control groups (area under the curve = 0.696; probability <0.001).

However, a very large statistical difference ($p < 0.001$) emerged when participants were divided into three age groups; the largest proportion of healthy individuals (72%) was clustered in the younger group (45 years). This distribution is consistent with the epidemiological reality of diabetes in the Middle East and Iraq, where incidence rates increase sharply with age due to the accumulation of metabolic risk factors and declining pancreatic beta-cell efficiency (International Diabetes Federation [IDF], 2025). On the other hand, females constituted 60% of the patient group, and statistical analysis did not show any significant difference in distribution between the sexes (p = 0.122), thus eliminating any significant statistical bias that might result from hormonal differences (Saber & El-Houssinie, 2025). The results also showed that the majority of patients (72%) had a positive family history of the disease, a high percentage that confirms the pivotal role of heredity and genetic kinship in increasing susceptibility to the disease within the Iraqi population (Nassurat *et al*., 2024). With an average total duration of infection of (8) years, the study population represents a category suffering from chronic low-grade and long-term inflammation (Todd *et al*., 2025).

The results using RT-qPCR showed a decrease in *IL1F10* expression in diabetes patients compared to control groups (0.097 [0.018-1.819]). This variability reflects the ongoing global debate surrounding the precise role of *IL1F10* in metabolic disorders. Some studies suggest that its serum levels are low in type 2 diabetic patients, indicating a failure of regulatory mechanisms to suppress chronic inflammation (Zhao *et al*., 2022). Conversely, other research suggests that its elevation represents a compensatory response to protect pancreatic beta cells by blocking inflammatory pathways such as NF-κB and JNK (Chen *et al*., 2023; Klejbuk & Strączkowski, 2024). This overlap and individual variability explain the wide error range in our results and the lack of a statistically significant difference between the two groups. Despite the physiological and immunological changes associated with aging and variations in sex hormones, gene expression remained stable, suggesting that it is subject to stable epigenetic regulatory mechanisms in peripheral lymphocytes rather than changing demographic factors (Saber & El-Houssinie, 2025). Hence, *IL1F10* expression was significantly affected by disease duration and treatment status only. Disease duration showed a marked reduction in the expression level of newly diagnosed patients compared to other groups [3.846 (1.427-5.910) *vs*. 0.384 (0.010-1.169); 0.058 (0.021-2.134); and 0.059 (0.018-0.803); *p*-value = 0.007, respectively]. While treatment status showed a marked increase in the expression level of untreated patients compared to those treated [3.846 (1.819–5.910 *vs*. 0.056 (0.018–0.754); $p < 0.001$, respectively]. Markedly elevated levels of the protein *IL1F10* in newly diagnosed, untreated patients indicate an initial compensatory immune response aimed at suppressing active inflammation and protecting tissues. Conversely, the lower levels observed in other groups are attributed to the success of medical treatment in curbing the inflammatory triggers that originally drove its production (Mora *et al*., 2026). Other study which proves that standard diabetes drugs (such as metformin or oral hypoglycemic agents), although effective in controlling glucose levels and improving insulin receptor sensitivity, do not have the ability to directly stimulate or suppress the transcriptional machinery of the *IL1F10* gene in lymphocytes (Hassan & Ali, 2025). The combined results confirm that IL-38 gene expression is an independent and stable trait, but this stability and lack of correlation with different clinical parameters

represents a major limitation that completely restricts the possibility of using this gene as a reliable dynamic biomarker to predict the course of diabetes or monitor treatment response in current medical practice (Radhi *et al*., 2026).

IL1F10 expression levels were not associated with the length of time the disease lasted or the genetic background, indicating that the disruption of the *IL1F10* transcriptional pathway is not due to the gradual deterioration of metabolic mechanisms, but may represent a constant biological feature in these patients from the early stages (Todd *et al*., 2025). One of the most notable clinical findings was the sharp increase in body mass index (BMI) among the patient group, with a mean of 31.183 kg/m², classifying 58% as obese (BMI < 0.05). Physiologically, obesity is a chronic, low-grade inflammatory condition in which adipose tissue secretes cytokines that increase insulin resistance (Brix *et al*., 2026). However, gene expression did not show any significant regulatory response based on BMI (p = 0.722). This is scientifically explained by the fact that immune cells extracted from peripheral blood (Peripheral blood mononuclear cells) may not accurately reflect the local molecular changes taking place within the adipose tissue microenvironment, where anti-inflammatory cytokines are locally suppressed by severe oxidative stress associated with obesity (Brix *et al*., 2026; Todd *et al*., 2025). As for the therapeutic condition, receiving medical treatment in (82%) did not change gene expression (p = 0.383), reflecting that the conventional treatments used (such as metformin or insulin), despite their metabolic role, do not have a direct or immediate effect on the transcriptional control mechanism of the *IL1F10* gene in peripheral lymphocytes (Klejbuk & Strączkowski, 2024). Taken together, the results confirm that the stable expression of the *IL1F10* gene and its lack of correlation with different clinical and demographic parameters significantly limit its potential use as a biomarker for diagnosing diabetes. Gene expression showed no significant change between different age groups (p =0.393) or between males and females (p =0.961). Although aging is usually associated with “inflammation” and a change in the immune response between the sexes due to hormones, the stability of IL-38 expression suggests that the transcriptional mechanism of this gene is governed by a stable inherent genetic regulation that is not affected by transient physiological variables associated with age or sex, which is supported by recent research indicating the stability of gene expression of some regulatory cytokines in Middle Eastern populations (Al-Mhanna & Al-Saeed, 2024).Despite variations in disease history, gene expression of IL-38 was not affected by family history of the disease (p = 0.864) . This independence means that the disruption or stability of the IL-38 transcriptional pathway does not represent a direct response that worsens or increases with the progression of diabetes over time or with a familial genetic charge, but rather a stable transcriptional characteristic that persists from the early stages of the disease, thus weakening the gene's role as an indicator of disease progression (Mousa *et al*., 2025). Despite the prevalence of morbid obesity in the study sample, gene expression did not show any significant differences based on body mass index (p = 0.722). This is partly explained by the fact that examining gene expression in peripheral blood does not necessarily reflect the "local" immune activity occurring within the adipose tissue microenvironment; Anti-inflammatory cytokines are suppressed locally by severe oxidative stress resulting from the enlargement of fat cells, without this effect being clearly visible in the general blood circulation (Kamil & Jassim, 2026).

ROC curve analysis demonstrated the reliability of *IL1F10* expression in differentiating between diabetic patients and control groups (area under the curve = 0.696; probability <0.001). This result is consistent with recent proteomic and genetic studies that have confirmed that anti-inflammatory regulatory cytokines achieve clinically acceptable areas under the curve (AUC) when tested in the blood due to the overlap of inflammatory pathways with other metabolic diseases such as obesity, making them reliable and independent diagnostic indicators (Hameed & Al-Rubaie, 2025; Kadhim *et al*., 2025).

Conclusion

In conclusion, the expression of *IL1F10* mRNA is down-regulated in diabetic patients, and this can be considered a reliable indicator associated with an increased risk of developing the disease. *IL1F10* expression was only significantly affected by disease duration and treatment status. ROC curve analysis demonstrated the reliability of *IL1F10* expression in differentiating between diabetic patients and control groups (area under the curve = 0.696; p <0.001). Hence, more functional and experimental investigations are needed to validate the pathophysiological and clinical role of *IL1F10* expression in diabetes disease.

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