

# EXPRESSION LEVELS OF miR-146A AND miR-155 AND THEIR ASSOCIATION WITH INTERLEUKIN-6 IN TYPE 1 DIABETES



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**Abstract.** *Background.* Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by the immune-mediated destruction of pancreatic beta cells, leading to insulin deficiency. Inflammatory cytokines, particularly interleukin-6 (IL-6), play a central role in this pathological process by promoting pro-inflammatory immune responses. Recent evidence highlights the involvement of microRNAs, especially miR-146a and miR-155, in regulating immune cell activation and cytokine signaling pathways. Dysregulation of these microRNAs may disrupt immune homeostasis and contribute to the progression of T1DM. This study aimed to investigate the expression levels of miR-146a and miR-155 in patients with T1DM and to examine their association with serum IL-6 concentrations. *Materials and methods.* This case-control study included 150 participants, comprising 100 individuals diagnosed with T1DM and 50 healthy controls. Peripheral blood samples were collected to evaluate fasting blood glucose, glycated hemoglobin, and IL-6 levels using an enzyme-linked immunosorbent assay. Quantitative real-time polymerase chain reaction was used to assess the expression of miR-146a and miR-155, normalized to miR-16 as the internal control. *Results.* The results revealed significantly elevated levels of fasting blood glucose, glycated hemoglobin, and IL-6 in patients compared to controls ( $p < 0.0001$ ). Additionally, miR-146a expression was increased by a 3.1-fold change, and miR-155 showed a 1.58-fold increase in patients with T1DM compared to healthy individuals. *Conclusions.* The significant overexpression of microRNAs miR-146a and miR-155, in parallel with elevated serum levels of the pro-inflammatory cytokine IL-6, highlights their crucial role in the immunopathogenesis of T1DM. These findings suggest that miR-146a and miR-155 may act as key regulators in modulating immune responses, contributing to the autoimmune destruction of pancreatic beta cells. Moreover, the combined assessment of these microRNAs and IL-6 may serve as valuable molecular biomarkers for early diagnosis, disease prognosis, and the development of novel immunomodulatory therapeutic strategies in T1DM management.

**Key words:** miR-146a, miR-155, T1DM, IL-6, microRNAs.

## УРОВНИ ЭКСПРЕССИИ miR-146A И miR-155 И ИХ АССОЦИАЦИЯ С ИНТЕРЛЕЙКИНОМ-6 ПРИ САХАРНОМ ДИАБЕТЕ 1 ТИПА

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**Резюме.** *Введение.* Сахарный диабет 1 типа (СД1) — хроническое аутоиммунное заболевание, характеризующееся иммуноопосредованным разрушением  $\beta$ -клеток поджелудочной железы, приводящим к дефициту инсулина. Воспалительные цитокины, в частности интерлейкин-6 (IL-6), играют центральную роль

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в этом патологическом процессе, стимулируя провоспалительные иммунные реакции. Последние данные свидетельствуют об участии микроРНК, особенно miR-146a и miR-155, в регуляции активации иммунных клеток и эффектов цитокинов. Нарушение регуляции указанных микроРНК может нарушать иммунный гомеостаз и способствовать прогрессированию СД1. Целью данного исследования было изучение уровней экспрессии miR-146a и miR-155 у пациентов с СД1 типа и их взаимосвязи с уровнем IL-6 в сыворотке крови. **Материалы и методы.** В исследовании «случай–контроль» приняли участие 150 человек, включая 100 человек с диагнозом СД1 и 50 здоровых лиц контрольной группы. От пациентов с СД1 были получены образцы периферической крови для определения уровня глюкозы в крови натощак, гликированного гемоглобина и IL-6 методом иммуноферментного анализа. Для оценки экспрессии miR-146a и miR-155 использовалась количественная полимеразная цепная реакция в реальном времени, нормализованная по уровню miR-16 в качестве внутреннего контроля. **Результаты.** В ходе исследования обнаружено достоверное повышение уровня глюкозы в крови натощак, гликированного гемоглобина и IL-6 у пациентов по сравнению с контрольной группой ( $p < 0.0001$ ). Кроме того, экспрессия miR-146a увеличилась в 3.1 раза, а экспрессия miR-155 — в 1.58 раза у пациентов с СД1 по сравнению со здоровыми людьми. **Выводы.** Достоверное усиление экспрессии микроРНК miR-146a и miR-155, наряду с повышенным уровнем провоспалительного цитокина IL-6 в сыворотке крови, подчеркивает их ключевую роль в иммунопатогенезе СД1, свидетельствуя о том, что miR-146a и miR-155 могут выступать в качестве ключевых регуляторов иммунного ответа, способствуя аутоиммунному разрушению  $\beta$ -клеток поджелудочной железы. Более того, комбинированная оценка уровня miR-146a и miR-155 и IL-6 может служить значимыми молекулярными биомаркерами для ранней диагностики, прогнозирования заболевания и разработки новых иммуномодулирующих терапевтических стратегий при лечении СД1.

**Ключевые слова:** miR-146a, miR-155, сахарный диабет 1 типа, IL-6, микроРНК.

## Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder that typically manifests during childhood or adolescence and requires lifelong insulin therapy to effectively manage blood glucose levels. It is characterized by insufficient insulin secretion and persistent hyperglycemia, resulting from the complete or partial destruction of pancreatic beta cells [1].

Despite advances in treatment, T1DM remains a major global health concern [2]. This is due to its diverse range of triggers, including genetic, biological, and environmental factors. Moreover, T1DM can develop as a result of autoimmunity, in which immune cells function abnormally—an essential hallmark of the disease [16].

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that initiates a cascade of immune responses leading to inflammation [13, 29]. The infiltration of immune cells into the islets of Langerhans is associated with increased pancreatic inflammation and involves four key immune cell types: macrophages, B lymphocytes, T lymphocytes, and dendritic [10, 26]. Therefore, increased concentrations of IL-6 molecules and an inflammatory response characterize this immunological disease [7].

Additionally, the issue worsens because of ongoing inflammation, which causes more beta cells in the pancreas to die; this factor is crucial in determining how severe the disease becomes [21]. Nitric oxide and increased endoplasmic reticulum stress are mechanisms that contribute to the worsening of the condition and may contribute to diabetes-related compli-

cations [3]. A recent study indicates that T1DM alters immune system functionality [34].

Post-transcriptional regulatory mechanisms are essential for this process to function effectively [5]. MicroRNAs are single-stranded RNA molecules that regulate gene expression but without protein synthesis at post-transcriptional levels. MicroRNAs such as miR-155 and miR-146a regulate cytokines and NF- $\kappa$ B during inflammatory responses [15, 27]. Given their role in autoimmunity in both innate and adaptive responses, it is evident that they play a significant part in these processes [14]. One of the primary functions of miRNA-146a is to inhibit inflammation in the body [28, 31]. Two critical components of the NF- $\kappa$ B signaling cascade are TRAF6 and IRAK1 [33]. MiR-146a influences the immune system by reducing the concentrations of TRAF6 and IRAK1 [17]. The effect inhibits inflammatory signals from intensifying and prevents them from becoming overly active [24]. Conversely, microRNA-155 activates immune cells, including macrophages, dendritic cells, and T lymphocytes, which exacerbates the inflammatory response [31].

Compromised microRNAs can induce cytokine imbalances and exacerbate tissue damage within the immune system. This current imbalance may exacerbate the illness and increase the likelihood of autoimmune reactions by accelerating the demise of pancreatic beta cells. Give an overview of how miR-146a, miR-155, and IL-6 could be helpful in understanding the molecular processes involved in type 1 diabetes. While IL-6 is known for worsening the disease, it's important to recognize that miR-146a and miR-155 are important for keeping the immune system in equilibrium.

## Materials and methods

This case-control study included 150 participants (100 T1DM patients with a mean age of  $12.02 \pm 4.89$  years and 50 healthy controls with a mean age of  $12.52 \pm 5.59$  years; overall mean age  $12.19 \pm 5.12$  years), whose blood samples were collected from multiple sources, including the National Center for Diabetes Treatment and Research at Al-Mustansiriyah University and a private diagnostic laboratory in Baghdad, Iraq, to ensure representative sampling and proper clinical characterization of both cases and controls.

**Inclusion and Exclusion Criteria.** Participants in the patient group met WHO diagnostic criteria for T1DM, while those with other types of diabetes, comorbid autoimmune disorders, active infections, or chronic diseases were excluded. Control subjects were recruited based on negative personal and familial histories of autoimmune or metabolic disorders.

**Ethical Considerations.** The study protocol received formal approval from the Institutional Review Board of the Genetic Engineering and Biotechnology Institute at the University of Baghdad on 1/11/2024 (Project No. 826823). Written informed consent was obtained from all participants' parents or legal guardians in accordance with international ethical guidelines for pediatric research.

**Blood Collection and Processing.** Following a 12-hour overnight fast, venous blood samples (5 mL) were collected from all participants under standardized aseptic conditions. The samples were immediately aliquoted into: first, EDTA-containing tubes (2 mL) for molecular analyses and HbA1c quantification; and second, sterile serum separator tubes (3 mL). The serum tubes were allowed to clot at room temperature for 15 minutes before centrifugation at 1000g for 5 minutes. The resulting serum was aliquoted into sterile microvials and stored at  $-20^{\circ}\text{C}$  until subsequent analysis of IL-6 and fasting blood glucose levels.

**Biochemical Analyses.** Fasting blood sugar (FBS) levels and hemoglobin A1c (HbA1c) percentages were quantified for all study participants. FBS concentrations were determined enzymatically using the COBAS INTEGRA 311 clinical chemistry analyzer (Roche Diagnostics). HbA1c measurement was performed via turbidimetric inhibition immunoassay (TINIA) methodology on a COBAS c 111 analyzer (Roche Diagnostics), with photometric detection at 546 nm. Both assays were conducted following the manufacturer's protocols with appropriate quality control measures.

**Immunoassay test.** Serum IL-6 concentrations were determined using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human IL-6 ELISA Kit, Cat. No. E-EL-H0109, Elabscience Biotechnology Inc.) according to the manufacturer's protocol. The sandwich ELISA as-

say was performed with strict adherence to quality control measures, including duplicate measurements of all samples and inclusion of standard curve calibrators with each assay run.

**Molecular testing.** Total RNA was extracted from serum samples using TRIzol™ LS Reagent (Invitrogen, Cat. No. 10296028) following the manufacturer's protocol. The extraction procedure involved sequential phase separation with chloroform, RNA precipitation with isopropanol, and purification through 75% ethanol washes. The resulting RNA pellet was resuspended in nuclease-free water (Thermo Scientific, Cat. No. AM9937). RNA concentration and purity were assessed using a Quantus™ Fluorometer (Promega) with the QuantiFluor® RNA System.

**Reverse Transcription.** Complementary DNA (cDNA) was synthesized from total RNA using the AddScript Reverse Transcriptase Kit (Microgen, Korea) according to the manufacturer's protocol in a 20  $\mu\text{L}$  reaction volume, ensuring complete conversion of all mRNA into cDNA. The thermal cycling conditions consisted of an annealing step at  $25^{\circ}\text{C}$  for 5 minutes, followed by extension at  $37^{\circ}\text{C}$  for 30 minutes, enzyme inactivation at  $92^{\circ}\text{C}$  for 5 minutes (1 cycle), and a final hold at  $4^{\circ}\text{C}$  for 10 minutes.

Complementary DNA (cDNA) synthesized from RNA served as the template for quantitative real-time PCR (qRT-PCR) analysis using miRNA-specific primers. The 20  $\mu\text{L}$  reaction mixture contained 10  $\mu\text{L}$  of 2.5 $\times$  reaction mix (including dNTPs and reverse transcriptase), 1  $\mu\text{L}$   $\text{MgCl}_2$ , 1  $\mu\text{L}$  each of forward and reverse primers, 3  $\mu\text{L}$  cDNA template, and 4  $\mu\text{L}$  nuclease-free water. Thermal cycling conditions consisted of initial denaturation at  $95^{\circ}\text{C}$  for 5 minutes, followed by 45 cycles of denaturation ( $95^{\circ}\text{C}$ , 20 seconds), annealing ( $60$ – $65^{\circ}\text{C}$ , 20 seconds), and extension ( $72^{\circ}\text{C}$ , 20 seconds). miRNA-16 expression served as the endogenous control for normalization, while relative quantification of miRNA-146a and miRNA-155 expression between patient and control groups was determined using the  $2^{-\Delta\Delta\text{Ct}}$  method (Table 1).

## Results

In this study, a highly significant elevation in FBS levels was revealed among T1DM patients, indicating ( $243.48 \pm 106.42$ ) compared to controls ( $95.96 \pm 6.56$ ) ( $p < 0.000$ ). Additionally, significantly higher levels of HbA1c were observed in T1DM patients ( $9.75 \pm 2.18$ ) than in controls ( $4.90 \pm 0.56$ ) ( $p < 0.000$ ) (Table 2).

The concentration of IL-6 was significantly higher ( $p < 0.01$ ) in patients with T1DM compared to apparently healthy (control) participants. The IL-6 concentration in T1DM patients was ( $31.42 \pm 3.81$ ), while it was ( $20.55 \pm 2.13$ ) in the control group, as shown in Table 3.

According to the findings of the current study, the expression level of miRNA-146 was significantly

elevated among individuals with T1DM compared to healthy individuals. The study revealed a significant increase in miRNA-146 expression in blood samples obtained from diabetic patients. The fold change in miRNA-146 expression among T1DM patients (fold change 3.1) was substantially higher than that observed in the controls (fold change 1), as depicted in Table 4. Similarly, the investigation of miRNA-155 expression indicated a marked increase among individuals with T1DM compared to healthy individuals. The research found that blood samples taken from diabetic individuals with type 1 had significantly higher levels of miRNA-155 expression, with a fold change of 1.5 in T1DM patients compared to 1 in controls (Table 5).

## Discussion

The study results showed an increase in serum levels of IL-6, an inflammatory cytokine, in the T1DM patient group compared to the healthy (non-diabetic) group. Regarding miRNA-146a and miRNA-155, both showed significantly elevated expression levels in T1DM patients.

Individuals were categorized into diabetic and non-diabetic groups based on their HbA1c levels. The range of HbA1c (5.7–6.4%) was used to identify intermediate hyperglycemia and distinguish between individuals with and without diabetes. This range was chosen because HbA1c shows less day-to-day variability compared to glucose levels and is consid-

**Table 1. Primers utilized for miRNA-146, miRNA-155 and mirna16gene expression**

Primer	Sequence (5'→3' direction)	Length (bp)
<b>miR-16-1</b>		
Forward	GGTTTTTTTTAGCAGCACGTAAT	24
Reverse	GTGCAGGGTCCGAGGT	17
RT	GTTGGCTCTGGTGCAGGGTCCGAGGTATTCGCACCAGAGCCAACCGCCAAT	50
<b>miR-155</b>		
Forward	TTAATGCTAATCGTGATAGGGGTT	24
RT	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAACCCC	46
<b>miR-146a</b>		
Forward	TGAGAACTGAATCCATGGGTT	24
RT	GTCGTATCCAGTGCAGGGTCCGAGGTATTCGCACTGGATACGACAACCCA	50
<b>Universal reverse</b>		
Reverse	CCAGTGCAGGGTCCGAGGTAT	21

**Table 2. Comparison between patients and control in FBS (mg/dL) and HbA1c (%)**

		N	Mean	Std. Deviation	Std. Error	t-test	
						t-value	p-value
FBS	Control	50	95.96	6.56	0.93	95.579	0.000
	Patients	100	243.48	106.42	10.64		
HBA1C	Control	50	4.90	0.56	0.08	238.758	0.000

**Table 3. Comparison of IL-6 levels between study groups**

		N	Mean	Std. Deviation	Std. Error	t-test	
						t-value	p-value
IL-6	Control	50	20.55	2.13	0.30	350.865**	0.0001
	Patients	100	31.42	3.81	0.38		

**Table 4. Levels of miRNA146a expression in the patients and control groups**

Groups	Means Ct of miRNA-146a	Means Ct of miRNA-16	Mean ΔCt	ΔΔCt Calibrator	2 <sup>-ΔΔCt</sup>	Experimental group/control group	Fold of gene
Control	13.7018	20.846	-7.1442	0	1	1	1
Patients	13.74015	22.517	-8.77685	-1.63265	3.10	3.100906445	3.1

**Table 5. Comparison between patients and control groups regarding miRNA155 fold expression levels**

Groups	Means Ct of miR-155	Means Ct of miR-16	Mean ΔCt	ΔΔCt Calibrator	2 <sup>-ΔΔCt</sup>	Experimental group/control group	Fold of gene
Control	9.76175	20.846	-11.084	0	1	1	1
Patients	10.77213	22.517	-11.7446	-0.66062	1.58	1.580805	1.58

ered indicative of T1DM. The findings, as presented in Table 5, revealed a significant increase in the levels of hemoglobin A1c and fasting blood sugar among patients compared to controls.

When it comes to the development or worsening of T1DM, both genes and the immune system are important, including family history, an imbalance of certain immune cells, loss of tolerance in the body, and interactions between different signaling proteins [25]. These factors contribute to the damaging of pancreatic beta cells due to increasing inflammation reactions. IL-6, important pro-inflammatory cytokines, secreted by macrophages and T cells. The study demonstrates the elevation of these signaling molecules correlates with insulinitis inflammation by enhancing the immune responses, as T1DM is characterized by the destruction of insulin-producing beta cells in the pancreas [9]. The current finding a line with Chen et al. (2017), who demonstrates the increasing serum levels of IL-6 in the T1DM group with an absence of correlation between this elevation and other factors such as age, ethnicity, and disease duration, suggesting that IL-6 may inherently influence the onset of T1DM [6]. In addition to Hundhausen et al. (2016), concluded that the increased sensitivity of T-cells (helper and cytotoxic) responses to IL-6 in T1DM enhances the activity of signal transducer and activator of transcription 3 (STAT3) and STAT1 signaling proteins, due to increased expressers of IL-6R on their surface. Suggests that if T1DM diagnosis is earlier, the higher the activation of STAT3 in response to IL-6 [12]. This means that IL-6 signaling problems might be most severe early in the disease and could be useful as an early marker of T1DM progression [7].

The study suggests that the elevation in miRNA-146a levels may result from heightened inflammation, thus increasing the risk of diabetes-related complications, including diabetic retinopathy, cardiovascular disease, and nephropathy [18]. The lab experiment by Kamali et al. (2016) found that when blood sugar levels are high, the risk of diabetes complications goes up because inflammation increases and miRNA-146 levels rise, which affects NF- $\kappa$ B activity by blocking certain inflammatory signaling molecules like IRAK1 and TRAF6 [15]. Additionally, a study by Mohammed et al. (2022) who reported that miRNA-146a was increased in recently diagnosed patients with T1DM [19]. However, Yang et al. (2015) studied the expression level of miRNA-146a in PBMCs and showed that the expression level of miRNA-146a decreased over a long-time undergoing insulin therapy [32]. T1DM patients, even with well-controlled glucose levels, also reported that the low level of miRNA-146a increases the appearance of autoantibodies, specifically, glutamic acid decarboxylase antibody. Reveals that the improper regulation of miRNA-146a contributes to the permanent autoimmune dysregulation observed in individuals with T1DM.

The study reveals that miRNA-155 facilitates inflammation and immunological reactions and hence plays an important role in the etiology of autoimmune diabetes mellitus. This is backed up by Mostahfezian et al. (2019) who found higher levels of this miRNA in the blood cells of T1DM patients [20].

According to Mohamed found that a specific genetic change, called rs767649, is linked to higher levels of miRNA-155 and the development of T1DM [19]. This suggests that genetic factors, especially SNPs, significantly affect the susceptibility to T1DM by potentially altering the expression levels and functionality of miRNA155 [4]. The study on T2DM conducted by Polina et al. (2019) who indicates that patients exhibit lower levels of miRNA-155 in their plasma [22]. The findings indicate that the expression level of miRNA155 is influenced by two factors: the sample type and the type of diabetes.

The findings of elevated levels of both miRNA-155 and miRNA-146a in T1DM indicate their potential as biomarkers for the diseases. Notably, García-Díaz et al. (2018) [8] reported in Chilean T1D patients a significant increase in miR-155, alongside a reduction in miR-146a, and uniquely identified miR-155's association with autoimmunity (ZnT8) and inflammatory markers (vCAM) highlighting its potential as a mediator of immune activation in T1D.

Complementing this, Ghaffari et al. (2023) [9] reviewed the broader metabolic context of miR-146a across both type 1 and type 2 diabetes. They found that downregulation of miR-146a is linked to the progression of diabetic complications such as nephropathy, neuropathy, impaired wound healing, olfactory dysfunction, cardiovascular disorders, and retinopathy suggesting a protective role of miR-146a within diabetic pathology.

Furthermore, the therapeutic landscape is enriched by Cho et al. (2025) [7], whose recent review underscores the dual significance of miRNAs including miR-146a and miR-155 as both diagnostic biomarkers and promising therapeutic targets in T1DM. They emphasize how miRNA modulation could pave the way to preserving  $\beta$ -cell function and targeting underlying pathogenic mechanisms.

MiRNA-155, miRNA-146a, and IL-6: These molecules could show when the disease starts or gets worse, might be good options for new treatments because they help control the immune system, and could be used as indicators of the diseases.

## Conclusion

This study demonstrates that pediatric patients with T1DM exhibit markedly elevated fasting blood glucose, HbA1c, and IL-6 levels, alongside significant overexpression of miR-146a (3.1-fold) and miR-155 (1.58-fold) compared with healthy controls. These findings may support the role of miR-146a and miR-155 as key molecular regulators in the inflamma-

tory and autoimmune processes underlying T1DM. The concurrent elevation of IL-6 further reinforces the involvement of pro-inflammatory cytokine signaling in disease progression. Future research should validate these findings in larger and more diverse cohorts and explore the clinical utility of microRNA modulation as part of personalized T1DM management.

## Additional information

**Competing interests.** The authors of this work declare no competing interests whatsoever.

**Data availability.** The study data is available upon request.

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