

# Interleukin-6 May Be Associated with Mitochondrial Dysfunction Through Signal Transducer and Activator of Transcription-3 in Patients with Type 2 Diabetes Mellitus

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**ABSTRACT: Background:** Diabetes mellitus is one of the most prevalent chronic diseases associated with metabolic disorders, characterized by hyperglycemia, which promotes inflammation and cell signaling (e.g., interleukin-6, a cytokine involved in cellular signal transduction pathways) and suppresses mitochondrial function through regulation of signal transducer and activator of transcription-3 (STAT3) levels. The development and progression of diabetic complications are strongly influenced by cellular inflammation, making it a promising therapeutic target for managing diabetes-related complications. **Objective:** The aim of this study is to compare the expression of Signal Transducer and Activator of Transcription 3 and Interleukin 6 between type 2 diabetics and normal healthy controls to determine the role of the pro-inflammatory cytokine Interleukin 6 in the activation of STAT3 associated with mitochondrial dysfunction and their potential as biomarkers of metabolic dysregulation in diabetes. **Methods:** We studied 40 patients with type 2 diabetes and 40 healthy controls. Whole blood was collected in EDTA tubes, and the expression levels of interleukin-6 and STAT3 were analyzed by real-time quantitative PCR. **Results:** Patients with type 2 diabetes had increased levels of interleukin-6 and STAT3 compared with controls. However, there was no statistically significant effect of diabetes on STAT3 expression after adjustment for gender and body mass index. Expression of interleukin-6 was significantly positively correlated with STAT3. **Conclusions:** The level of interleukin-6 was significantly increased in type 2 diabetes compared to controls and remained significant after adjusting for body mass index and gender, indicating its potential utility as a biomarker for type 2 diabetes. Conversely, the increased STAT3 expression became statistically insignificant after adjustment, indicating that STAT3 expression is not an independent biomarker for diabetes. The significant correlation of interleukin-6 and STAT3 may indicate that they play a role in the pathophysiology of type 2 diabetes.

**KEYWORDS:** T2DM; Mitochondria; STAT3; IL-6; Hyperglycemia

## INTRODUCTION

Diabetes mellitus (DM) is a metabolic condition with chronic hyperglycemia resulting from dysfunction in insulin secretion, function, or both [1]. The development of DM involves multifaceted pathophysiological processes, including disrupted autophagy, inflammation, increased oxidative stress, and hemodynamic abnormalities, which contribute to disease progression [2]. Mitochondria act as the major source of energy in mammalian cells and function in controlling cell signaling, reactive oxygen species, cellular proliferation, and apoptosis [3]. There are also an essential role in regulating cellular metabolic homeostasis, so mitochondrial defects have been implicated in metabolic disorders like diabetes [4]. Prolonged exposure to high glucose adversely affects mitochondrial electron transport and stimulates the release of reactive oxygen species, which subsequently damage the mitochondria themselves and mitochondrial DNA, leading to reduced ATP synthesis, apoptosis, and downstream inflammatory promotion of fibrotic signaling pathways involved in disease progression [5].

Circulating Interleukin-6 (IL-6) is a pleiotropic cytokine released by many cells, like stromal cells, neutrophils, and monocytes. It is widely associated with the pathophysiology of Type 2 Diabetes mellitus (T2D); increased IL-6 levels have been associated with the development of inflammatory processes and insulin resistance and act as an independent predictor of T2D [6], [7]. In vitro studies further support this association by indicating that high glucose concentrations can enhance IL-6 production in patients with T2D [8]. Reduction of local and systemic inflammatory responses may be mediated by the control of mitochondrial dynamics and related mechanisms, such as promotion of glucose oxidation and cell differentiation. When exposed to stress, mitochondria exhibit adaptability by modulating division and fusion events and enhancing mitochondrial DNA matrix activities and biogenesis, thereby broadly influencing metabolic homeostasis [9]. Signal Transducer and Activator of Transcription (STAT) proteins are a group of transcription factors responsible for transmitting extracellular signals from the cell surface to the nucleus due to growth factors and cytokines. Following phosphorylation, they regulate expression and control multiple cellular metabolic processes. Signal Transducer and Activator of Transcription-3 (*STAT3*) has diverse roles in inflammation, immune response regulation, and cell survival [10]. IL-6 participates in the trigger *STAT3* signaling pathway as a crucial intracellular signaling cascade [11]. Previous studies have also demonstrated a relationship between chronic inflammation and mitochondria, reporting that IL6 induced suppression of mitochondrial activity by activation of the STAT1/3 axis [12].

*STAT3* in mitochondria (mito*STAT3*) associates with mitochondrial DNA and may directly regulate the transcription of the mitochondrial genome, resulting in increased expression of mitochondrial-encoded transcripts and supporting oxidative metabolic activity [13]. The available evidence identifies *STAT3* as a trigger of metabolic network regulation, focusing on the possible interaction of *STAT3* with processes that maintain mitochondrial function, including regulation of the electron transport chain, reactive oxygen species production, the maintenance of cellular calcium, and the suppression of the opening of the mitochondrial permeability transition pore [14]. In addition to its traditional role in cytoplasm-to-nucleus translocation during cytokine-mediated signaling, mitochondrial *STAT3* may contribute to the regulation of cellular energy metabolism, mainly by affecting the mitochondrial electron transport chain. Although the structural basis for its mitochondrial effects and functional activity remains unclear [15]. In this context, the current study was designed to investigate the correlation between IL-6 and *STAT3* and their potential involvement in the pathway linked to mitochondrial dysfunction in patients with T2D, as well as to evaluate the role of these factors in the diabetic-associated metabolic dysregulation.

## MATERIALS AND METHODS

### Collection of Blood Samples

The current study was conducted in Basrah province, Iraq, from February to August 2025. A total of 80 consenting subjects participated in this study and were divided into two groups: patients (with a diagnosis of T2D) and controls, forty subjects in each group (participants had no acute or chronic inflammatory diseases during the study period). Three to five ml of whole blood was obtained in the morning after an overnight fast and drawn into EDTA-containing tubes and cooled on ice, and all samples were kept at -80 °C until subsequent analysis.

### Total RNA Extraction

Total RNA samples were isolated from blood with an RNA purification kit from Geneaid. According to the manufacturer's instructions, RNA quality was verified by 260/280 nm ratio measurement using NanoDrop LITE (MECASYS Co., Korea). Secondly, reverse transcription and cDNA were synthesized from the extracted total RNA using UniScript (Genes and Biotech) (Cat. No. SR512).

### Quantitative Real-Time PCR

Real-time quantitative PCR (qPCR) was performed on a QuantStudio™ system (Thermo Fisher Scientific, USA) with SYBR Green qPCR Master Mix (Takara). The cycling conditions were initial denaturation at 95 °C for 35 s, followed by 40 cycles comprising 95 °C for 5 s and 60 °C for 35 s. Specificity of the primers was confirmed by melting curve analysis ranging from 59 to 95 °C with a temperature increment of 0.075 °C/s. Expression levels were normalized using  $\beta$ -actin as the internal reference gene. and calculated using the  $2^{-\Delta Ct}$  method. All primers were synthesized by Macrogen (Korea); the primer sequences are shown in Table 1. Relative expression levels of IL6 and target genes

were quantified by applying the  $2^{-\Delta\Delta C_t}$  comparative method [16], wherein  $\Delta\Delta C_t$  was calculated as the  $\Delta C_t$  of the experimental group minus the  $\Delta C_t$  of the control group, each of  $\Delta C_t$  being derived from the subtraction of the mean of the housekeeping gene  $C_t$  value from the mean target gene  $C_t$  value within the corresponding group. All RT-qPCR experiments were analyzed in triplicate in a 96-well plate.

**Table 1.** The primer sequences used for RT-qPCR

| Gene                            | Forward                 | Reverse                  |
|---------------------------------|-------------------------|--------------------------|
| <i>IL-6</i>                     | ACTCACCTCTTCAGAACGAATTG | CCATCTTTGGAAGGTTTCAGGTTG |
| <i>STAT3</i>                    | CAAAGAAAACATGGCTGGCA    | TGAAACCCATGATGTACCCTT    |
| <i><math>\beta</math>-actin</i> | AAGTACTCCGTGTGGATCGG    | AAAGCCATGCCAATCTCATC     |

## Statistical Analysis

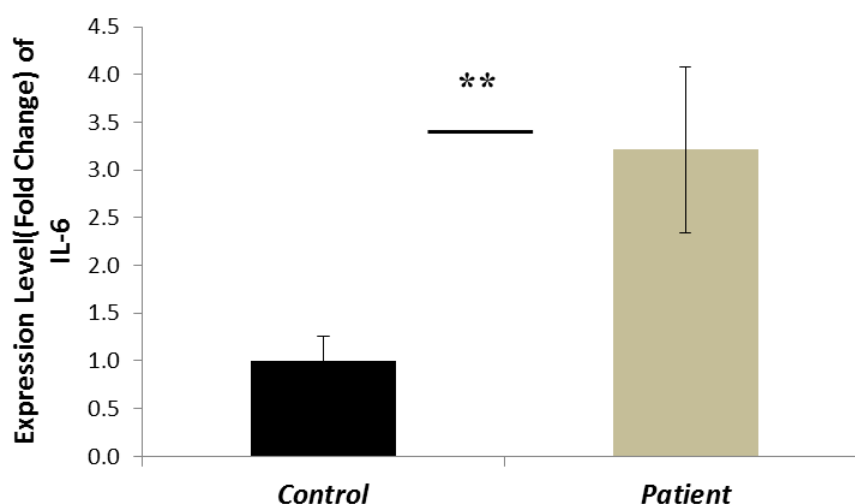
All statistical data and figures are reported as means $\pm$ standard error derived from at least three separate experiments. Statistical significance has been assessed via an independent samples t-test in SPSS. Gender and body mass index (BMI) were employed as covariates throughout the ANCOVA analysis. Pearson's correlation was used to detect the association between gene expressions. Differences were considered statistically significant at a p-value<0.05.

## RESULTS AND DISCUSSION

This study included 80 samples. The control group was constituted by 40 healthy individuals, including 20 (50%) males and 20 (50%) females, and 40 subjects with diabetes, 20 (50%) men and 20 (50%) women. BMI was assessed and recorded for all participants. The mean of BMI was  $34.54\pm 9.1$  for the diabetes group and  $23.57\pm 3.8$  for the control group.

### Expression of IL-6

Figure 1 shows an upregulation of IL-6 expression level in the patient group, with a 3.21-fold increase compared with the control group (1-fold). Consistently, the independent samples t-test showed that the mean  $\Delta C_t$  value was significantly lower in the patients ( $2.32\pm 0.41$ ) than in the control group ( $4.05\pm 0.34$ ,  $P<0.001$ ), indicating higher IL-6 expression in the patient group. Since  $\Delta C_t$  values are inversely related to gene expression, lower values indicate higher expression.



**Figure 1.** The comparison expression level of IL-6 control vs. patient groups showed a significant increase in the patient group ( $P<0.000$ )

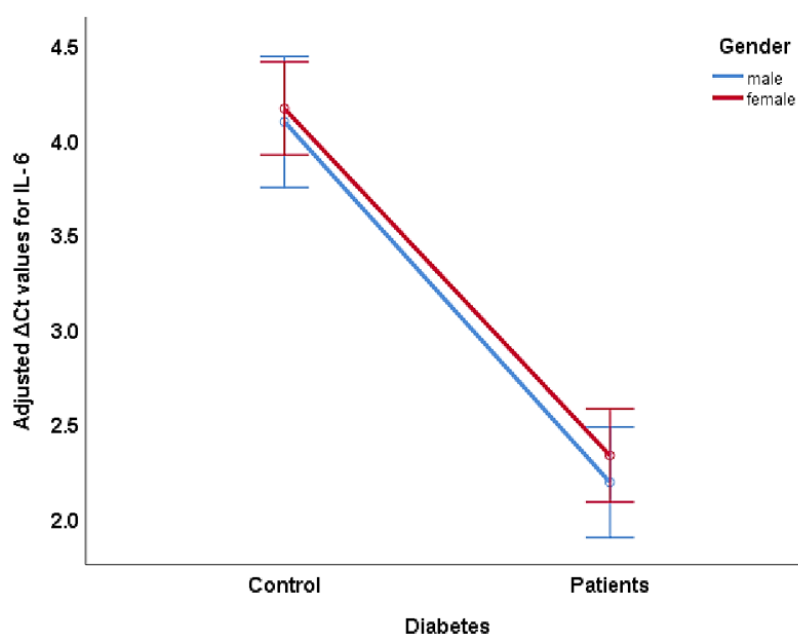
The analysis of covariance (ANCOVA) (Table 2) demonstrated a statistically significant effect of diabetes status on IL-6 gene expression ( $F=5.14$ ,  $P=0.03$ , Partial  $\eta^2=0.14$ ). In contrast, neither gender ( $F=0.72$ ,  $P=0.40$ ) nor BMI ( $F=3.10$ ,  $P=0.09$ ) showed significant effects. Furthermore, no significant effects of interaction were observed between diabetes status and gender ( $P=0.81$ ) or between gender and BMI ( $P=0.10$ ).

**Table 2.** ANCOVA for effects of diabetes, gender, and BMI on IL-6 gene expression

| Variables                | df | F    | P-value | Partial $\eta^2$ |
|--------------------------|----|------|---------|------------------|
| Diabetes                 | 1  | 5.14 | 0.03    | 0.14             |
| Gender                   | 1  | 0.72 | 0.40    | 0.02             |
| BMI                      | 1  | 3.09 | 0.09    | 0.09             |
| Diabetes $\times$ Gender | 1  | 0.06 | 0.81    | 0.00             |
| Gender $\times$ BMI      | 1  | 0.54 | 0.47    | 0.02             |
| Diabetes $\times$ BMI    | 1  | 0.00 | 0.10    | 0.00             |

\* Partial  $\eta^2$  refers to the effect size

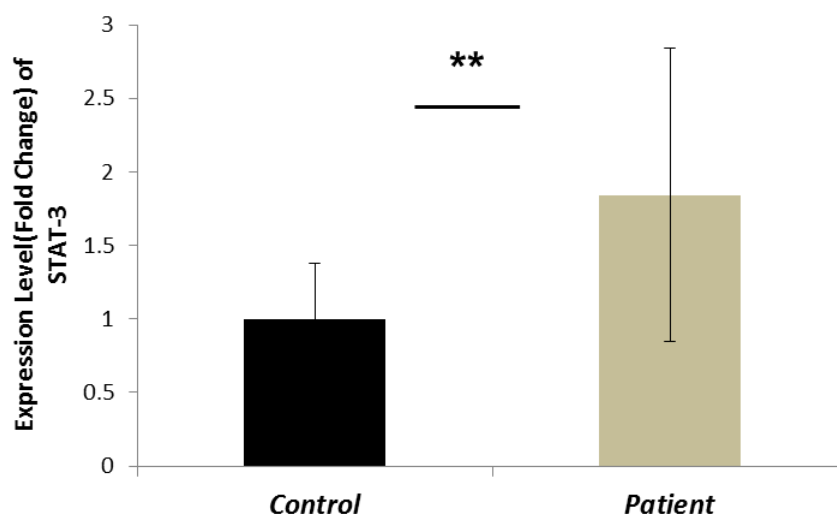
Figure 2 illustrates the adjusted mean  $\Delta Ct$  values for IL-6, which were lower in the patient group than in the controls in both males and females, corresponding to a higher IL-6 expression in the patient group. A similar pattern was observed across both sexes. The error bars indicate the variability of the adjusted estimate and show some overlap between groups. Since  $\Delta Ct$  values are inversely related to gene expression, lower  $\Delta Ct$  values mean higher expression.



**Figure 2.** Adjusted mean  $\Delta Ct$  values for IL-6 according to diabetes status (control vs. patients) and gender. Data are presented as adjusted means  $\pm$  standard error, and confidence intervals are derived from ANCOVA. Note:  $\Delta Ct$  values are inversely related to gene expression: lower values indicate higher gene expression

### Expression of *STAT3*

Figure 3 revealed an upregulation of *STAT3* expression level in the patient group, with an unadjusted fold change of 1.84-fold compared with the control group (1-fold). An independent t-test showed that the  $\Delta Ct$  value was significantly lower in the patient group ( $-0.30 \pm 0.68$ ) than in controls ( $0.58 \pm 0.5$ ,  $P < 0.001$ ), indicating higher *STAT3* expression in the patient group. Since  $\Delta Ct$  values are inversely related to gene expression, lower  $\Delta Ct$  values mean higher expression.



**Figure 3.** Comparison of *STAT3* expression levels between control and patient groups showed a significant increase in the patient group ( $P < 0.001$ )

After adjustment for gender and BMI using ANCOVA (Table 3), results showed no statistically significant effects of diabetes status on *STAT3* ( $P = 0.598$ ). Similarly, neither gender ( $P = 0.167$ ) nor BMI ( $P = 0.869$ ) showed significant effects on *STAT3*, indicating that *STAT3* gene expression did not differ significantly according to these variables. All interaction effects were also not statistically significant, including diabetes  $\times$  gender ( $p = 0.609$ ), gender  $\times$  BMI ( $P = 0.215$ ), and diabetes  $\times$  BMI ( $P = 0.951$ ). Furthermore, partial  $\eta^2$  values indicated very small effect sizes, ranging from 0.000 to 0.057. Overall, these results indicate that the diabetes status, gender, BMI, and their interaction did not significantly influence *STAT3* gene expression in the studied sample.

**Table 3.** ANCOVA for effects of diabetes, gender, and BMI on *STAT3* gene expression

| Variables                | df | F     | P-value | Partial $\eta^2$ |
|--------------------------|----|-------|---------|------------------|
| Diabetes                 | 1  | 0.283 | 0.598   | 0.009            |
| Gender                   | 1  | 2.000 | 0.167   | 0.057            |
| BMI                      | 1  | 0.028 | 0.869   | 0.001            |
| Diabetes $\times$ Gender | 1  | 0.267 | 0.609   | 0.008            |
| Gender $\times$ BMI      | 1  | 1.600 | 0.215   | 0.046            |
| Diabetes $\times$ BMI    | 1  | 0.004 | 0.951   | 0.000            |

\* Partial  $\eta^2$  refers to the effect size

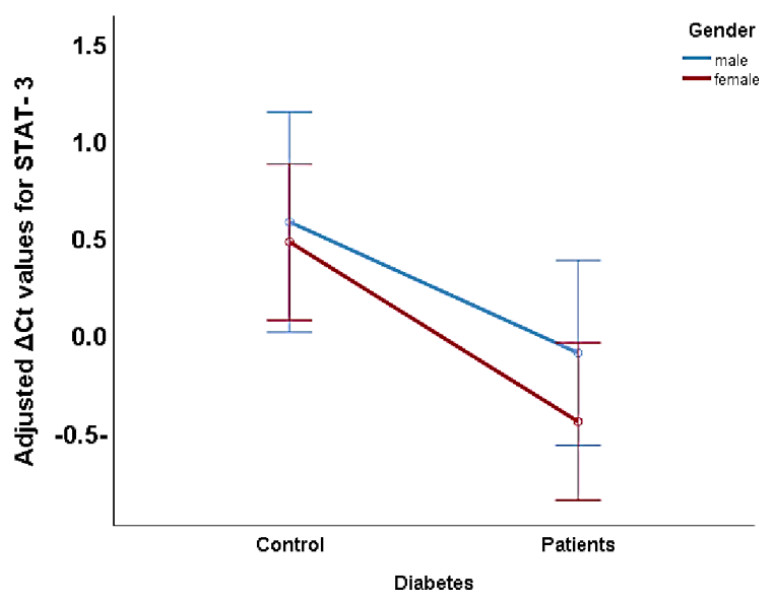
Figure 4 illustrates the adjusted mean  $\Delta Ct$  values for *STAT3* according to diabetes status and gender after adjustment for BMI. The adjusted  $\Delta Ct$  values were lower in the patient group than in the control group for both males and females, indicating higher *STAT3* expression in the patient group. Females demonstrated slightly lower adjusted  $\Delta Ct$  values than males in both groups, corresponding to slightly higher *STAT3* expression. The parallel pattern of the lines suggests no significant interaction effect between diabetes status and gender on *STAT3* expression, consistent with the ANCOVA analysis. The error bars indicate variability within groups and show substantial overlap. Since  $\Delta Ct$  values are inversely related to gene expression, lower  $\Delta Ct$  values mean higher expression.

## Correlation Analysis

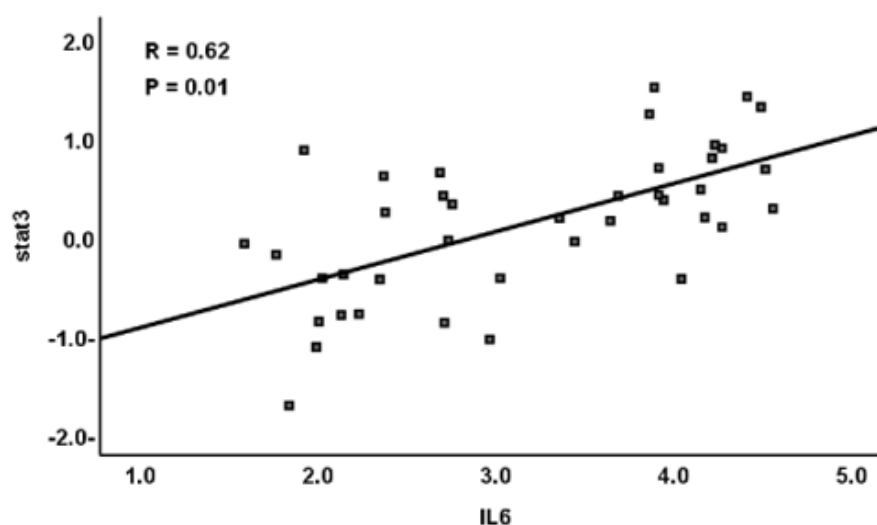
Figure 5 shows significant positive correlations between levels of IL-6 and *STAT3* with a Pearson's correlation coefficient of  $R = 0.62$  ( $p < 0.01$ ).

A hallmark of the pathogenic processes of diabetes is elevated levels of inflammatory factors, which contribute to the initiation and progression of the disease and are linked by disruption of mitochondrial

function in T2D [17].



**Figure 4.** Adjusted mean  $\Delta C_t$  values for *STAT3* according to diabetes status (control vs. patients) and gender; data are presented as adjusted means  $\pm$  standard error and confidence intervals derived from ANCOVA. Note:  $\Delta C_t$  values are inversely related to gene expression: lower values indicate higher gene expression



**Figure 5.** Pearson's correlation analysis between the expression levels of IL-6 and *STAT3*

The present results revealed a significant upregulation of the expression level of the proinflammatory cytokine IL-6 in the patient group compared with the control group; therefore, the observed overexpression of IL-6 suggests its possible involvement in disease pathogenesis and highlights its potential value as a biomarker associated with disease. Similar findings were obtained [18]: increased IL-6 concentrations have been identified in patients with T2D, suggesting an association between IL-6 and hyperglycemic status. This relation is further corroborated by the positive correlation between IL-6 and triglyceride-rich lipoproteins, which have been associated with an increased risk of cardiovascular complications in diabetic individuals with diabetes. Furthermore, [19] noted that hyperglycemia, a hallmark of diabetes, is linked with IL-6 concentrations, which are characteristic of diabetes. IL-6 may be involved in the inflammatory processes contributing to insulin resistance, a key precursor to type 2 diabetes, indicating its role in metabolic dysfunction [20]. IL-6 is involved in the regulation

of glucose homeostasis and metabolic pathways in pancreatic cells, and dysregulation of these processes may result in hyperglycemia and either directly or indirectly promote diabetes [21]. Previous publications have also shown that IL-6 may be implicated in enhancing cellular senescence and may inhibit mitochondrial function and oxidative phosphorylation in primary human retinal endothelial cells [22].

The current study showed that neither gender nor BMI had a significant effect on IL-6 expression, suggesting that the observed changes were primarily associated with diabetes related metabolic disturbances rather than gender or BMI. Furthermore, the absence of significant interaction effects indicates that the impact of diabetes on the pro-inflammatory cytokine IL-6 is consistent across gender and BMI levels. These findings are consistent with the participation of IL-6 as a pro-inflammatory cytokine in diabetes, and previous studies have revealed that elevated IL-6 levels are linked with suboptimal glycemic control and increased BMI [23]. In addition, [24] showed that BMI plays a vital role in chronic inflammation and demonstrates a threshold effect, with its pro-inflammatory effect appearing to be greater in females compared with males. Importantly, although *STAT3* expression was significantly upregulated in the patient group in the unadjusted analysis, there was no statistical difference in the levels of *STAT3* after covariate correction (sex and BMI), and this result suggests that increased *STAT3* gene levels may be influenced by these covariates and should therefore be interpreted cautiously. An alternative possible explanation is that the relatively modest sample size utilized in this study may have been insufficient to confer statistical power to find reliable biological differences; adjustment for additional covariates in a small study can reduce the statistical power to detect true effects [25].

Previous studies have reported that *STAT3* is an important component of inflammatory and metabolic signaling pathways that contribute to diabetes. Dysregulation of *STAT3* signaling may contribute to the pathogenesis of T2D by affecting immune cell responses, chronic inflammation, insulin sensitivity, and glucose homeostasis [26]. Alterations in *STAT3*-related signaling have also been associated with glucose homeostasis impairment and insulin resistance in diabetes-related metabolic disorders [27]. In addition, exposure to high glucose has been reported to stimulate inflammatory responses and lead to mitochondrial dysfunction, activating apoptosis via the IL-6/ *STAT3* pathway [14]. *STAT3* has been reported to be involved in the interaction between mitochondria and endoplasmic reticulum in inflammatory conditions, providing new approaches to targeting *STAT3* activation and mitochondrial function in disease-related processes [28]. Similar findings were obtained by [29], who described *STAT3* as a promoter for the metabolic network, particularly via interactions with pathways implicated in the homeostasis of mitochondrial functions, including modulation of the electron transport chain and reactive oxygen species. Moreover, [30] reported that the activation of the *STAT3* signaling pathway was associated with mitochondrial dysfunction characterized by elevated mitochondrial fission, reduced mitophagy, and defective mitochondrial quality management. The results of the present study revealed a positive correlation between IL-6 and *STAT3* expression. Previous studies have reported that increased IL-6 expression may enhance *STAT3* signaling and may be associated with mitochondrial dysfunction, abnormal energy metabolism, and oxidative stress [31]. High glucose levels significantly increased cytokines, such as IL-6, and remarkably upregulated *STAT3* in comparison with normal glucose conditions [32]. A previous study [33] demonstrated that IL-6 signaling is triggered due to the engagement of the IL-6 receptor and gp130 co-receptor, causing activation of Janus kinases (JAKs), which phosphorylate *STAT3*, enhancing its dimerization and nuclear translocation to modulate the transcription of genes involved in immune responses, inflammation, and metabolic homeostasis. In addition, elevated IL-6 expression was associated with *STAT3* activation in diabetic patients [34]. The present research has significant limitations, including the relatively small sample size and the lack of direct assessments of mitochondrial function or *STAT3* protein activation. Therefore, the observed associations should be regarded with caution, so future mechanistic studies with larger longitudinal cohorts and functional analyses are required to evaluate the viability of IL-6 and *STAT3* as biomarkers and to enhance precision medicine strategies in T2DM.

## CONCLUSION

The study demonstrates that elevated IL-6 expression is associated with T2D, independent of gender and BMI, suggesting its potential as a biomarker for T2D. In contrast, although increased *STAT3* expression was observed in T2D patients, it showed no significant effect after adjusting for gender and BMI, indicating that *STAT3* may not serve as an independent biomarker for T2D. A significant positive correlation between IL-6 and *STAT3* suggests a potential interaction between these signaling pathways in T2D. Further studies with larger sample sizes and direct assessments of mitochondrial activity are recommended to clarify the roles of IL-6 and *STAT3* in the metabolic

dysregulation associated with diabetes.

## SUPPLEMENTARY MATERIAL

*None.*

## AUTHOR CONTRIBUTIONS

*Azhar A. Ameen: Methodology, Investigation; Visualization; Data curation; Formal analysis; Writing – review & editing.*

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## DATA AVAILABILITY STATEMENT

*Data are available from the authors upon reasonable request.*

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## CONFLICTS OF INTEREST

*The author declares no conflicts of interest.*

## DECLARATION OF GENERATIVE AI USE

*The author declares that no generative AI or AI-assisted technologies were used in the preparation of this manuscript.*

## ETHICAL APPROVAL

*The study protocol was authorized by the Ethics Committee of the University of Basrah, Iraq (7/54/1776).*

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