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# Evaluation of Interleukin-27 as a Cytokine Marker in Type 2 Diabetes Mellitus Associated with Toxoplasmosis in Karbala Governorate

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**Abstract**

**Background and Objective:** Type 2 Diabetes Mellitus (T2DM) is characterized by a state of chronic inflammation and increased risk for certain infections like Toxoplasma gondii. This study set out to investigate the role of interleukin-27 (IL-27), a regulatory cytokine, in this dual-disease milieu.

**Methodology:** 184 participants (diabetic patients with toxoplasmosis and healthy control) were analyzed. Serum measurement of IL-27, Hs-CRP and lipids were done using ELISA and automated systems respectively. Data were analyzed using SPSS (Version 26.0) through t-test, ANOVA and linear regression.

**Results:** All lipid parameters and Hs-CRP were significantly higher in diabetic patients ($P < 0.001$). IL-27 levels were lower than controls (46.63 ± 21.44 ng/ml vs. 50.59 ± 8.50ng/ml), which was not statistically significant ($P = 0.074$). No significant correlation was found between IL-27 and HbA1c ($P = 0.305$), age ($P = 0.917$), or lipids ($P > 0.05$). Also, 50.75% of patients with high Hs-CRP (>3mg/L) had abnormally elevated IL-27 levels.

**Conclusion:** IL-27 may be acting as an independent regulatory mediator across the immune-metabolic axis in diabetic patients with toxoplasmosis. The lack of association of IL-27 with metabolic parameters further alludes to its production being favoured along complex immune-regulatory pathways instead of by the glycaemic state.

**Keywords:** Interleukin-27 (IL-27), Type 2 Diabetes Mellitus (T2DM), Toxoplasma gondii (T. gondii),, High-sensitivity C-reactive protein (Hs-CRP), Glycemic Control (HbA1c).

## Introduction

metabolic disorders and persistent parasitic infections. Toxoplasmosis, triggered by the obligatory intracellular protozoan Toxoplasma gondii, represents a significant immunological challenge due to its ability to maintain life-long encystation within host tissues. In parallel, Type 2 Diabetes Mellitus (T2DM)—distinct from the autoimmune-driven Type 1—functions as a chronic metabolic stressor characterized by systemic insulin resistance and nutrient-induced inflammation (American Diabetes Association [ADA], 2024).

The interaction between T2DM and Toxoplasmosis is characterized by synergistic trade-off of defensive mechanisms of the host. A condition of functional exhaustion in innate immune cells is induced by hyperglycemia, directly leading to the survival and possible reactivation of T. gondii. On the other hand, the chronic expression of parasitic antigens can be a sustained pro-inflammatory stimulus which can exacerbate the metabolic instability of T2DM by disrupting insulin-signaling pathways through a sustained pro-inflammatory response (Boughattas & Bergaoui, 2024).

This biological-parasitic axis gets further adjusted by the biological truth of aging and dyslipidemia. Aging is accompanied by a physiological loss of immune competence, called immunosenescence. This process, together with the lipid abnormalities, which are typical of diabetic patients, specifically, an increase in Total Cholesterol (TC) and Triglycerides (TG) levels, provide an ideal environment to both parasitic persistence and rapid vascular damage (Mizrahi et al., 2023; Ying et al., 2023).

To measure the strength of such multifaceted interaction, it is necessary to assess specific molecular markers, with the first place going to Interleukin-27 (IL-27) and high-sensitivity C-reactive protein (Hs-CRP). IL-27 is a very important member of the IL-12 family, which is a dual-function immunomodulator that can prevent excessive immune-mediated tissue damage during long-term inflammation (Yuan et al., 2023). At the same time, Hs-CRP is the clinical gold standard to measure systemic inflammatory burden and cardiovascular risks associated with it (Pearson et al., 2024). Ultimately, the confluence of parasitic infection, metabolic dysfunction, lipid imbalances, and age-related immune changes creates a complex pathological network. Within this framework, IL-27 emerges as a potential homeostatic regulator that attempts to balance the inflammatory consequences of both T2DM and toxoplasmosis. Therefore, the present study was conducted on a cohort of 184 diabetic patients to evaluate how these variables intersect and influence the immune-metabolic status of individuals facing this dual clinical challenge.

## Materials and Methods

### *3.1. Study Design and Participant Selection*

A case-control clinical study that was an ongoing study was conducted at Al-Imam Al-Hassan (p) Center of Endocrinology and Diabetes, Karbala governorate, Iraq. The recruitment of the patients took a duration of seven months between July of 2025 to January of 2026. One hundred eighty-four (184) subjects were recruited. They were divided into two groups: The Diabetic Group (n=134). These were those people who were diagnosed with T2DM in the clinic. The T2DM definition was fasting blood glucose (FBG) 126mg/dL (7.0mmol/L) and found seropositive to chronic Toxoplasmosis; (Toxoplasma gondii). The Control Group (n=50).

These, were age matched and sex matched healthy volunteers who did not have any metabolic disturbance and were seronegative for T. gondii antibodies. Ethical issues were observed in the study, and the clinical data: Age (<45, 45-64 years, ≥65 and), smoking, medical history were carefully retrieved from the medical archives by a structured interview.

### *3.2. Specimen Handling and Laboratory Processing*

Blood samples (5 ml) were taken out of the participants in the morning hours, after an absolute overnight fast. To enable multifaceted examination, the blood was divided into two different amounts:

EDTA-Coagulated Samples (2 ml): Used to estimate immediately Glycated Hemoglobin (HbA1c).

Non-Coagulated Samples (3 ml): The samples were subjected to natural clotting then centrifuged at 3000 rpm and 10 minutes to isolate the serum.

Interleukin-27 (IL-27) and hs-CRP biochemical assays were performed on frozen aliquots to avoid repeated freeze-thaw cycles, and maintain molecular stability.

### *3.3. Biochemical and Immunological Assays*

Serum IL-27 and high-sensitivity C-reactive protein (Hs-CRP) were quantified using the Enzyme-Linked

Immunosorbent Assay (ELISA) technique, exactly following the protocols laid down by the manufacturer. The metabolic and lipid profiles (including FBG, Total Cholesterol (TC), and Triglycerides (TG)) were assessed with the help of the automated Roche Cobas 6000 diagnostic platform. The clinical interpretation of glycemic control was based on the ADA (2024) criteria (Controlled: <7%; Uncontrolled: ≥7\%), and systemic inflammation was defined with regard to the level of Hs-CRP more than 3.0 mg/L (Pearson et al., 2024). The NCEP ATP III diagnostic thresholds were used to assess lipid status (Ying et al., 2023).

### *3.4. Statistical Analysis*

Data were analysed using IBM SPSS Statistics (Version 26.0). Mean ± Standard Deviation (SD) represented continuous variables; frequency and percentage represented categorical variables. Independent t-test of continuous variables and Pearson Chi-squared test of categorical variables were used to compare the two cohorts. Stratified variables inter-group differences were measured using One-way ANOVA. Bivariate and Multiple Linear Regression models were used to evaluate the degree of predictive relationship of biological factors on IL-27. p-value < 0.05 was accepted statistically significant.

## 4. Results

### *4.1. General Characteristics and Clinical Profiles*

The demographic and clinical comparison between diabetic patients (n=134) and health controls (n=50) revealed significant metabolic disparities. The diabetic cohort exhibited a significantly higher mean age (56.87 ± 10.58 years) compared to the control group (44.62 ± 4.33 years; $P < 0.001$). Regarding glycemic status, the mean HbA1c in the patient group was markedly elevated (7.76 ± 1.66%) with the vast majority (72.39%) demonstrating poor glycemic control (7%).

Systemic inflammatory markers also showed a distinct pattern; Hs-CRP levels were significantly higher in diabetic patients (3.95 ± 3.06 mg/L) than in healthy individuals (2.42 ± 1.53 mg/L; $P < 0.001$). Furthermore, 50.75% of the diabetic subjects presented with high-risk inflammatory status (Hs-CRP ≥ 3 mg/L), whereas only 34.00% of the control group reached this threshold.

**Table 1: Demographic and Clinical Characteristics of the Study Population**

| Characteristics | Diabetic Patients (n=134) | Healthy Controls (n=50) | P-value |
|---|---|---|---|
| Age (Years), Mean (SD) | 56.87 (10.58) | 44.62 (4.33) | <0.001* |
| <45 years, n (%) | 3 (2.24%) | 1 (2.00%) | 0.005* |
| 45-64 years, n (%) | 85 (63.43%) | 46 (92.00%) | |
| >65 years, n (%) | 46 (34.33%) | 3 (6.00%) | |
| Sex, n (%) | | | |
| Male | 45 (33.58%) | 16 (32.00%) | 0.839 |
| Female | 89 (66.42%) | 34 (68.00%) | |
| FBS (mg/dl), Mean (SD) | 150.54 (50.54) | 95.20 (11.99) | <0.001* |
| HbA1c (%), Mean (SD) | 7.76 (1.66) | 5.16 (0.26) | <0.001* |
| Glycemic Control, n (%) | | | |
| Poor Control | 97 (72.39%) | 0 (0.00%) | <0.001* |
| Fair Control | 35 (26.12%) | 0 (0.00%) | |

| | | | |
|---|---|---|---|
| Good Control | 2 (1.49%) | 50 (100%) | |
| Hs-CRP (mg/L), Mean (SD) | 3.95 (3.06) | 2.42 (1.53) | <0.001* |
| <3 mg/L, n (%) | 66 (49.25%) | 33 (66.00%) | 0.042* |
| ≥3 mg/L, n (%) | 68 (50.75%) | 17 (34.00%) | |
| Total Cholesterol (mg/dl) | 175.35 (42.16) | 168.50 (35.66) | 0.273 |
| Triglycerides (mg/dl) | 198.43 (111.12) | 133.06 (67.86) | <0.001* |
| IL-27 (ng/ml), Mean (SD) | 46.63 (21.44) | 50.59 (8.50) | 0.074 |

### *4.2. Serum Interleukin-27 (IL-27) Levels*

The principal interest of the study was the quantitation of serum IL-27. Diabetic patients infected with T. gondii had a lower mean IL-27 concentration (46.63 ± 21.44 ng/ml) as compared to control group (50.59 ± 8.50ng/ml). However, this numerical decline did not reach statistical significance (P = 0.074). In the diabetic group further analysis by stratification showed that the production of IL-27 by the subpopulations was generally consistent. IL -27 production was not significantly affected by sex stratification (P = 0.830) or age groups (P = 0.246) though the production appeared to be modestly upregulated in patients greater than 6 0 years of age. The classical metabolic determinants total cholesterol (P = 0.305), and triglycerides (P = 0.169) also failed to produce a deterministic inf luence on serum IL-27 concentrations

**Table 2:** Stratified Analysis of Serum IL-27 Levels According to Clinical and Demographic Variables

| Variable | Diabetic Patients (n=134) Mean (SD) | P-value | Healthy Controls (n=50) Mean (SD) | P-value |
|---|---|---|---|---|
| Age Groups (Years) | | | | |
| < 45 (Young adults) | 32.83 (12.77) | 0.246 | 54.90 (—) | 0.697 |
| 45 – 64 (Middle-aged) | 45.23 (21.05) | | 50.72 (8.80) | |
| ≥ 65 (Elderly) | 50.10 (22.25) | | 47.20 (1.21) | |
| Sex | | | | |
| Male | 46.07 (22.95) | 0.830 | 48.55 (8.05) | 0.247 |
| Female | 46.91 (20.76) | | 51.56 (8.65) | |
| Hs-CRP (mg/L) | | | | |
| < 3 (Normal/Low Risk) | 45.43 (20.75) | 0.524 | 49.37 (8.22) | 0.157 |
| ≥ 3 (High Risk/Inflammation) | 47.79 (22.18) | | 52.97 (8.78) | |
| Total Cholesterol (mg/dl) | | | | |

| | | | | |
|---|---|---|---|---|
| < 200 (Desirable) | 47.76 (21.77) | 0.305 | 50.65 (8.65) | 0.907 |
| ≥ 200 (High) | 43.43 (20.45) | | 50.24 (8.11) | |
| Triglycerides (mg/dl) | | | | |
| < 150 (Normal) | 43.80 (21.19) | 0.169 | 49.86 (8.67) | 0.354 |
| ≥ 150 (Borderline to High) | 48.92 (21.51) | | 52.31 (8.10) | |

### *4.3. Correlation and Regression Analysis*

To probe predictors of IL-27 modulation linear regression models were created. IL-27 is an IV in our populations of study and exhibited no linear relationship between IL-27 and HbA1c (R = -0.040), P = 0.622 or hs-crp (R= 0.006, P = 0.947). Insinuating that the IL-27 regulatory arms in Diabetic patients co-infected with toxoplasmosis is chiefly determined by the chronicity of the affecting parasite itself and immune responses therein rather than by the classical acute reversible epiphenomena of inflammation and metabolic markers and mediators.

**Table 3:** Serum Interleukin-27 (IL-27) Levels in Diabetic Patients Stratified by Toxoplasmosis Seropositivity and Glycemic Control (HbA1c)

| HbA1c Classification | N | IL-27 (ng/ml) Mean (SD) | P-value |
|---|---|---|---|
| Good Control (< 5.4%) | 2 | 53.05 (37.55) | 0.761 |
| Fair Control (5.4% – 6.4%) | 35 | 48.42 (22.98) | |
| Poor Control (> 6.4%) | 97 | 45.85 (20.79) | |
| Criteria 2: Binary Management Status | | | |
| Controlled Cases (< 7%) | 55 | 49.13 (23.01) | 0.262 |
| Uncontrolled (Bad) Cases (≥ 7%) | 79 | 44.89 (20.24) | |

### *4.4 Linear and multiple regression between IL-37 and other biomedical factors*

To know which of the parameters used in this survey was significantly have a link with the serum IL-27 level in the diabetic patients. We performed linear regression analysis between IL-27 and both the anthropometric and biomedical parameters. The results are presented in Table 4. As shown by linear regression analysis, none of the anthropometric or biomedical parameters were significant predicators of the IL-27 level

**Table 4:** Linear Regression Analysis of Factors Associated with Serum IL-27 Levels

| Predictor Variables | Correlation Coefficient (R) | Lower 95% CI | Upper 95% CI | P-value |
|---|---|---|---|---|
| Age | 0.070 | -0.101 | 0.240 | 0.422 |
| HbA1c (%) | -0.040 | -0.210 | 0.130 | 0.622 |
| hs-CRP (mg/L) | 0.006 | -0.160 | 0.180 | 0.947 |
| Total Cholesterol | -0.120 | -0.280 | 0.050 | 0.178 |
| Triglycerides | 0.040 | -0.130 | 0.210 | 0.629 |

***4.5.CRP and IL-39 in diabetic patients and healthy controls***

In order to assess the association between IL-27 and Hs-CRP, participants were classified according to Hs- CRP cut-off points. The proportion of diabetics with Hs- CRP >3.0 mg/L with abnormal IL-27 (>60 ng/ml) was 50.75% vs. healthy controls (34.00%). Figure1

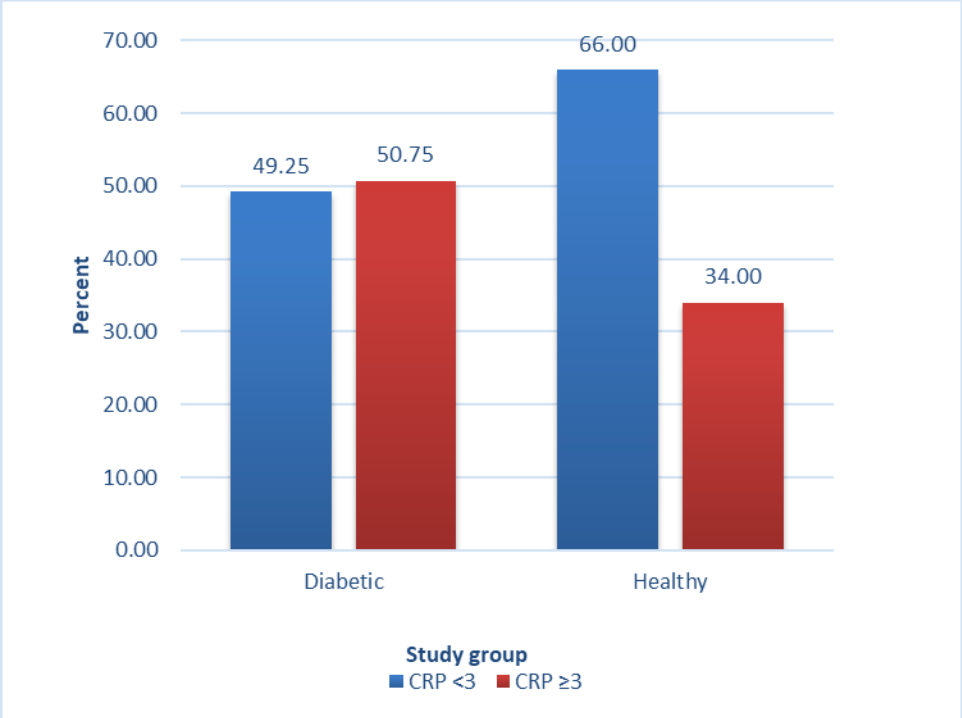


**Fig 1: CRP and IL-39 in diabetic patients and healthy controls**

## Discussion

That patients with T2DM are also co-infected with T. gondii adds complications to the chronic metabolic derangement of diabetes by the host immune-regulatory system. This unique populous demonstrates how a regulatory cytokine, IL-27 behaves all in relation to being hyperglycaemic and being parasitized chronically. The significantly amplified metabolic profiles of diabetic patients compared to controls demonstrate the classically systemic characteristics of T2DM. Poor glycaemic control (>72% of our cohort), signified by the increased HbA1c levels (7.76

±1.66%) and fasting blood sugar of the diabetic amongst other clinical measures, drives chronic low-grade inflammation in the system, which as defined by American Diabetes Association (2024), promotes intracellular pathogens to replicate efficiently (Bacillus, Brucella, Cytomegalovirus, Listeria, Mycobacterium, Plasmodium, Treponema, etc. . .), by hindering the first line of defense - the innate immune response to them.

In line with this, our data also showed a markedly higher systemic inflammatory burden among diabetics; exemplified by significantly elevated Hs-CRP (3.95 ±3.06 mg/L) relative controls ($P < 0.001$). This data is analogous to that of Mizrahi et al. (2023) where they referred to T2DM as "a functional state of metabolic inflammation". Whereby the high glucose environment triggers the release of acute-phase reactants. More impressive however is the suggestion that the presence of T. gondii may act as a "synergistic trigger" of the release of these markers from an already frustrated immune system, due to the lingering conundrum of how to deal with the initially benign parasite, in chronic metabolic disorder. One of the main thrust of this study was the quantification of serum IL-27. Our data showed that the diabetics infected with T. gondii had lower mean IL-27 concentrations (46.63 ±21.44 ng/ml) than the healthy controls (50.59 ±8.50 ng/ml), however the difference was not significant ($P = 0.074$).

Our observation of lower levels of IL-27 in diabetic patients is consistent with data from experimental models that also suggest this cytokine has a protective role (Fujimoto et al. 2015), with IL-27 deficient mice developing more severe hyperglycaemia and islet inflammation, and glucose control can be improved by recombinant IL-27 treatment. Perhaps the lower numbers in our patients reflect less of a regulatory capacity, leaving them more susceptible to the inflammatory damage caused by diabetes and Toxoplasmosis. The lack of significant correlation of IL-27 with lipid profiles ($P > 0.05$) also supports recent clinical observations hinting that IL-27 is more an independent immune-checkpoint than a direct metabolic driver.

By contrast, we do not confirm upregulation of IL-27 in humans, some recent studies have shown increased levels of this cytokine in some diabetic complications. For example, Yuan et al (2023) and others report that serum IL-27 is significantly higher in diabetic retinopathy and diabetic nephropathy, where it was positively correlated with HbA1c and lipid levels. Perhaps this is stage of disease or co-infection dependent, as… in more advanced complications such as retinopathy, IL-27 may be up regulated in localized inflammatory responses, while in our cohorts, the chronic Toxoplasma infection we suspect to be "exhausting" the cytokine response and/or skewing the immune environment towards a Th1 type profile (elevated IFN-gamma) at the expense of regulatory cytokines such as IL-27.

Stratifying by age groups did not indicate any significant difference in IL-27 production across these groups ($p= 0.246$), although the marginal increase with age, particularly in the elderly (≥ 65 years), could be cumulative to immune age-related dysregulation (immunosenescence). Arous et al. (2025), the aging diabetic patients exhibit increasing dysregulation of "helper" cytokines in their fight against chronic parasitic load. Accordingly, also, our diabetic subjects had significantly elevated triglycerides of 198.43 ±111.12 mg/dl (atherogenic lipid profile of T2DM) in agreement with Ying et al. (2023). On the contrary, our results were however opposite to most recent human works, which reported increased IL-27 both as tissue and serum cytokine, particularly in some diabetic complications. Yuan et al. (2023) and others found it significantly increased in serum of patients with diabetic retinopathy and diabetic nephropathy; the cytokine was positively correlated with HbA1c and lipid levels. This discrepancy on the findings is probably explained by the stage of disease/infection or co-infection. In cases of advanced complications of diabetes, such as retinopathy, IL-27 may already be developed as part of disease focused/ localised inflammation, while we think that the chronic Toxoplasma infection in our cohort may be "exhausting" the cytokine probably or skewing the immune event to a Th1-type profile (elevated IFN-gamma) at the expense of regulatory cytokine(s) like IL-27.

The stratified analysis showed no significant age-based disparity in IL-27 production ($P = 0.246$). However, the slight upward trend in elderly patients (≥65 years) may be a compensatory response to immunosenescence. This goes together with the observation of Arous et al. (2025), in which they noted that there is a tendency of altered cytokine profiles in aging diabetic patients when it comes to dealing with chronic parasitic loads. Likewise, the high triglyceride level among our diabetic population (198.43 +111.12 mg/dl) supports the atherogenic lipid profile characteristic of T2DM as Ying et al (2023) discuss.

## Conclusion

The research concludes that although patients with Type 2 Diabetes Mellitus (T2DM) and co-infection by T. gondii experience increased metabolic and inflammatory stress, which is evident in the form of significantly elevated HbA1c, Hs-CRP, and triglycerides. Statistical evidence shows that the concentrations of IL-27 do not vary significantly in relation to the level of glycemic, lipid profiles, or demographics. Hence, IL-27

is an independent regulatory mediator in this population, which is probably regulated by specific immunological mechanisms instead of direct metabolic or acute-phase inflammatory changes.

## Recommendations

To expand on these results, future studies are recommended to use larger cohorts to further prove the use of IL-27 as a stable biomarker in chronic co-morbidities. Research into genetic polymorphisms and receptor expression is needed to comprehend individual variations in immune response, and longitudinal studies are suggested to track changes in cytokine over time. Lastly, there is a potential to explore the possibilities of modulating IL-27 pathways as a possible therapeutic option in the management of chronic inflammation and prevent long-term complication in diabetic patients.

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