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Serum TNF-α and Its Association with Glycaemic Control in Type 2 Diabetes Mellitus: A Comparative Cross-Sectional Study

Mukul Vyas[1], Bhavana Tiwari[2], Rohit Manyal[3], Rajeev Lohokare[4]

[1]PG Resident, Department of Biochemistry, M.G.M. Medical College, Indore, Madhya Pradesh, India.
[2]Assistant Professor, Department of Biochemistry, M.G.M. Medical College, Indore, Madhya Pradesh, India.
[3]Assistant Professor, Department of Biochemistry, M.G.M. Medical College, Indore, Madhya Pradesh, India.
[4]Associate Professor and Head, Department of Biochemistry, M.G.M. Medical College, Indore, Madhya Pradesh, India.

Corresponding Author: Dr. Rajeev Lohokare

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ABSTRACT

Background: Chronic low-grade inflammation is increasingly recognized as an important component of the pathophysiology of type 2 diabetes mellitus (T2DM). Tumor necrosis factor-alpha (TNF-α), a pro-inflammatory cytokine implicated in insulin resistance, may be associated with worsening glycaemic control. This study compared serum TNF-α concentrations between individuals with T2DM and healthy controls and evaluated the association between TNF-α and glycated haemoglobin (HbA1c).

Methods: This comparative case-control study included 120 participants, comprising 60 individuals with T2DM and 60 age- and sex-matched healthy controls. Clinical and biochemical parameters were recorded. HbA1c was measured by ion-exchange high-performance liquid chromatography, while serum TNF-α concentrations were determined using an enzyme-linked immunosorbent assay. TNF-α concentrations were compared between study groups and across HbA1c categories among participants with T2DM. Pearson correlation analysis was used to assess the relationship between TNF-α and HbA1c. Binary logistic regression was performed to identify variables associated with T2DM status. Receiver operating characteristic (ROC) analysis was used to evaluate the discriminatory performance of TNF-α, HbA1c, and their combined model.

Results: Serum TNF-α concentrations were significantly higher in participants with T2DM than in controls (34.8 ± 9.6 vs. 13.7 ± 4.3 pg/mL; $p<0.001$). Among participants with T2DM, mean TNF-α concentrations increased progressively across HbA1c categories, from 21.4 ± 4.2 pg/mL in those with HbA1c of 6.5–7.5% to 45.6 ± 8.5 pg/mL in those with HbA1c >9.5% ($p<0.001$). TNF-α showed a strong positive correlation with HbA1c ($r=0.712$; $p<0.001$). In logistic regression, TNF-α, HbA1c, and BMI were independently associated with T2DM status. ROC analysis demonstrated AUCs of 0.903 for TNF-α, 0.958 for HbA1c, and 0.972 for the combined model.

Conclusion: Serum TNF-α concentrations were elevated in T2DM and were positively associated with HbA1c and worsening glycaemic control. TNF-α may provide complementary information regarding inflammatory activity in T2DM; however, larger prospective and multicentre studies

with independent validation are required before its clinical utility can be established.

Keywords: Type 2 diabetes mellitus; tumour necrosis factor-alpha; HbA1c; glycaemic control; inflammation; insulin resistance.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease marked by persistent hyperglycaemia caused by insulin resistance and inadequate insulin secretion. It is an important cause of illness and death worldwide, and its prevalence continues to increase. Although T2DM is traditionally viewed as a disorder of glucose and lipid metabolism, chronic low-grade inflammation also contributes to its development, progression and related complications.[1]

Tumour necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine involved in the development of insulin resistance.[2] It is produced mainly by macrophages within adipose tissue and by adipocytes. TNF-α can disrupt insulin signalling by promoting serine phosphorylation of insulin receptor substrate-1, thereby reducing the cellular response to insulin.[3] Higher circulating TNF-α concentrations have been reported in individuals with obesity and diabetes, while experimental neutralisation of TNF-α has improved insulin sensitivity in animal models.[4]

Glycated haemoglobin (HbA1c) is widely used to assess average glycaemic control during the preceding two to three months. However, it does not directly reflect the inflammatory changes associated with T2DM. Previous studies have reported a positive association between TNF-α and HbA1c, suggesting that inflammatory activity may increase as glycaemic control worsens.[5]

This study compared serum TNF-α levels between patients with T2DM and healthy controls, examined their relationship with HbA1c, and evaluated the ability of these markers to distinguish between the study groups.

MATERIALS & METHODS

This comparative case–control study was conducted in the Departments of Biochemistry and Medicine at M.G.M. Medical College and its associated hospital in Indore, Madhya Pradesh, India. A total of 120 participants were enrolled, including 60 patients with type 2 diabetes mellitus (T2DM) and 60 age- and sex-matched healthy controls. Patients were recruited from the Medicine Outpatient Department. Individuals without diabetes or any known chronic metabolic or inflammatory disorder were included as controls.

The study protocol was approved by the Institutional Ethics Committee of M.G.M. Medical College, Indore. The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from every participant before enrolment.

Clinical information, including age, sex, duration of diabetes, family history, treatment history and associated medical conditions, was recorded using a structured form. Individuals with type 1 diabetes, active infection, systemic inflammatory or autoimmune disease, malignancy, chronic liver or kidney disease, or pregnancy were excluded. Those receiving corticosteroids, immunosuppressants or systemic anti-inflammatory medication were also excluded.

All participants underwent general and systemic examinations. Body mass index (BMI) was calculated as weight in kilograms divided by height in metres squared. Glycaemic control in patients with T2DM was assessed using HbA1c. Based on their HbA1c levels, patients were divided into four categories: 6.5–7.5%, 7.6–8.5%, 8.6–9.5% and >9.5%.

After an overnight fast, approximately 5 mL of venous blood was collected from each participant under aseptic conditions. Blood for fasting glucose measurement was collected in a fluoride tube, while an EDTA tube was used for HbA1c estimation. Postprandial blood glucose was measured two hours after a standard meal. The

remaining blood was allowed to clot and centrifuged at 3,000 rpm for 10 minutes. The separated serum was transferred into labelled Eppendorf tubes and stored at −20°C until analysis.

HbA1c was measured by ion-exchange high-performance liquid chromatography using the Bio-Rad D-10 Hemoglobin Testing System (Bio-Rad Laboratories, Hercules, CA, USA). The method was certified by the National Glycohemoglobin Standardization Program and traceable to the International Federation of Clinical Chemistry reference system. Serum TNF-α was measured using a commercially available human TNF-α enzyme-linked immunosorbent assay kit according to the manufacturer's protocol. Samples were tested in duplicate, with appropriate quality-control procedures followed throughout the analysis.

Statistical Analysis

Data were entered into Microsoft Excel and analysed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean ± standard deviation, and categorical variables as frequencies and percentages. The independent-samples *t*-test was used to compare continuous variables between patients and controls. Differences in TNF-α across HbA1c categories were examined using one-way analysis of variance, followed by an appropriate post hoc test. The relationship between TNF-α and HbA1c was assessed using Pearson's correlation coefficient. Binary logistic regression was used to examine factors independently associated with T2DM, with findings presented as odds ratios and 95% confidence intervals. Receiver operating characteristic curve analysis assessed the ability of TNF-α and HbA1c, separately and in combination, to distinguish patients with T2DM from controls. A p-value <0.05 was considered statistically significant.

RESULT

The study included 120 participants: 60 patients with type 2 diabetes mellitus (T2DM) and 60 age- and sex-matched healthy controls. Age and sex distribution were comparable between the groups, whereas BMI was higher among patients with T2DM. HbA1c, serum TNF-α, fasting blood glucose and postprandial blood glucose were also significantly higher in the T2DM group (Table 1).

Among patients with T2DM, 14 (23.3%) had an HbA1c of 6.5–7.5%, 18 (30.0%) had 7.6–8.5%, 16 (26.7%) had 8.6–9.5% and 12 (20.0%) had >9.5%. Mean serum TNF-α increased progressively from 21.4 ± 4.2 pg/mL in the lowest HbA1c category to 45.6 ± 8.5 pg/mL in the highest category (p<0.001; Table 2). Serum TNF-α showed a strong positive correlation with HbA1c (r=0.712, p<0.001; Figure 2).

In logistic regression analysis, TNF-α, HbA1c and BMI were independently associated with T2DM status (Table 3). ROC analysis showed an AUC of 0.903 for TNF-α and 0.958 for HbA1c. The combined model had an AUC of 0.972, with 96.7% sensitivity and 93.3% specificity (Table 4; Figure 3).

Table 1. Demographic, clinical and biochemical characteristics of the study groups

Variable	T2DM (n=60)	Controls (n=60)	*p*-value
Age (years)	53.8 ± 8.4	52.6 ± 7.9	0.46
Male, n (%)	36 (60.0)	34 (56.7)	0.71
Female, n (%)	24 (40.0)	26 (43.3)	
BMI (kg/m²)	28.4 ± 3.8	24.3 ± 2.7	<0.001
Duration of diabetes (years)	8.2 ± 4.1	—	—
HbA1c (%)	9.12 ± 1.74	5.24 ± 0.41	<0.001
Serum TNF-α (pg/mL)	34.8 ± 9.6	13.7 ± 4.3	<0.001
Fasting blood glucose (mg/dL)	174.5 ± 48.3	91.2 ± 10.5	<0.001
Postprandial blood glucose (mg/dL)	258.1 ± 71.4	124.5 ± 18.3	<0.001

Data are presented as mean ± SD or n (%). Independent-samples t-test and chi-square test were used as appropriate.

Table 2. Distribution of patients and serum TNF-α levels across HbA1c categories

HbA1c category (%)	Patients, n (%)	Serum TNF-α (pg/mL), mean ± SD	*p*-value
6.5–7.5	14 (23.3)	21.4 ± 4.2	<0.001
7.6–8.5	18 (30.0)	28.7 ± 5.3	
8.6–9.5	16 (26.7)	37.2 ± 6.8	
>9.5	12 (20.0)	45.6 ± 8.5	
Total	**60 (100.0)**	32.66 ± 10.57	
One-way ANOVA. p<0.05 considered statistically significant.			

Table 3. Factors associated with T2DM status in binary logistic regression

Variable	OR	95% CI	*p*-value
Serum TNF-α	1.18	1.10–1.27	<0.001
HbA1c	2.45	1.76–3.61	<0.001
BMI	1.09	1.01–1.18	0.028
Dependent variable: T2DM status. OR, odds ratio; CI, confidence interval.			

Table 4. ROC performance of TNF-α, HbA1c and their combined model

Marker	AUC	Sensitivity (%)	Specificity (%)	Cut-off
Serum TNF-α	0.903	88.3	83.3	21.6 pg/mL
HbA1c	0.958	95.0	91.7	6.55%
Combined model	0.972	96.7	93.3	—

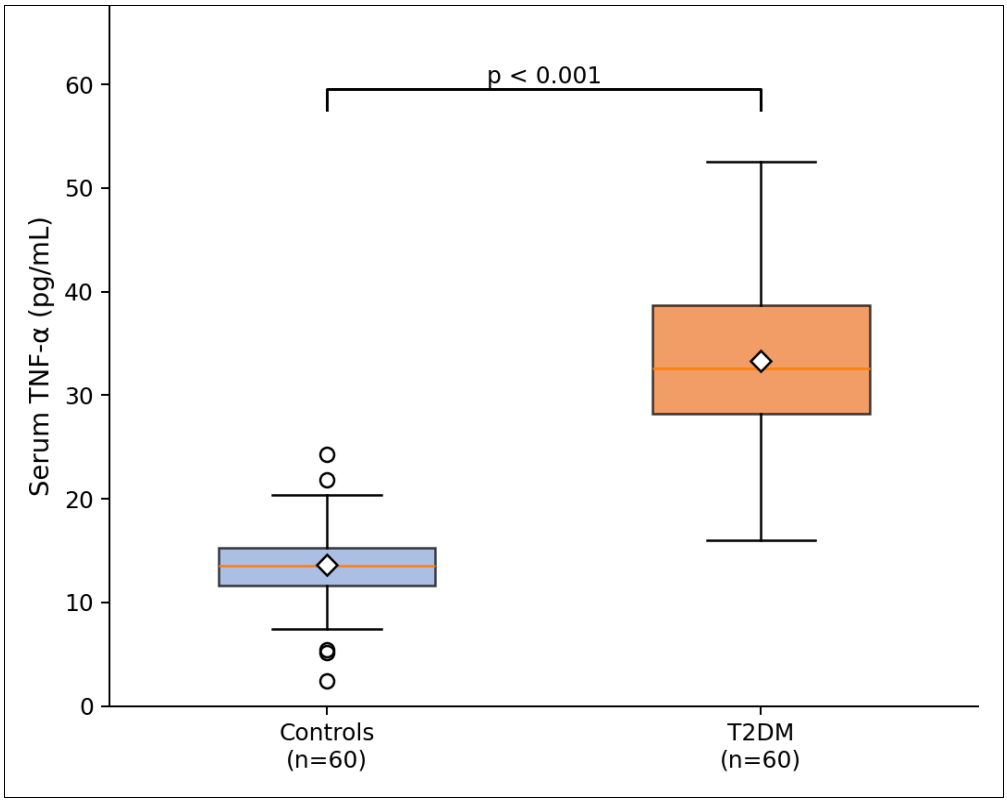

Figure 1. Box plot comparing serum TNF-α concentrations between T2DM patients and healthy controls.

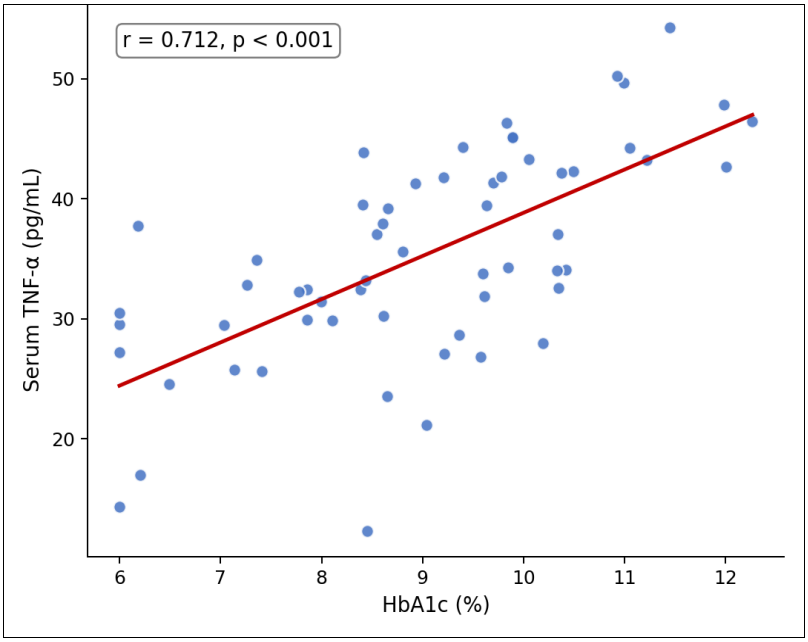

Figure 2. Scatter plot showing a strong positive correlation between serum TNF-α and HbA1c (r = 0.712, p < 0.001).

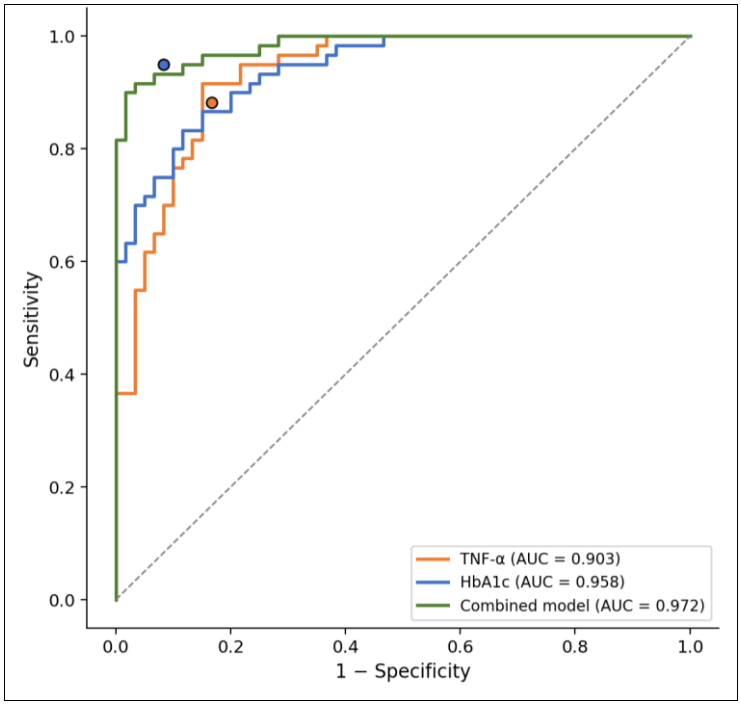

Figure 3. ROC curves demonstrating the diagnostic performance of TNF-α, HbA1c, and the combined model in predicting T2DM.

DISCUSSION

Type 2 diabetes mellitus is associated with persistent low-grade inflammation in addition to impaired glucose metabolism. Inflammatory cytokines may interfere with insulin action and contribute to insulin resistance.[1] TNF-α has received particular attention because it can disrupt insulin signalling through serine phosphorylation of insulin receptor substrate-1, reducing glucose uptake in insulin-sensitive tissues.[3]

In this study, mean serum TNF-α was higher in patients with T2DM than in healthy controls (34.8 ± 9.6 versus 13.7 ± 4.3 pg/mL). TNF-α also showed a strong positive correlation with HbA1c (r=0.712), indicating that higher inflammatory activity

accompanied poorer glycaemic control. Alzamil reported similar elevations in TNF-α among patients with T2DM and found positive correlations with HbA1c and insulin resistance.[4] Although the correlation was stronger in the present study, differences in participant characteristics, glycaemic status and laboratory methods may explain this variation.

Swaroop et al. also found an association between TNF-α and insulin resistance, with adiposity influencing the relationship.[5] In our study, BMI was higher among patients with T2DM and remained associated with T2DM status in regression analysis. This finding is relevant because adipose tissue, particularly when infiltrated by macrophages, is an important source of inflammatory cytokines. Thus, the raised TNF-α concentrations may reflect the combined effects of excess adiposity, inflammation and poor glycaemic control. Elevated circulating TNF-α and other inflammatory mediators have also been reported in different diabetic populations.[6], [7]

Indian studies provide further support for these observations. Bashir et al. reported elevated TNF-α and IL-6 concentrations among patients with T2DM and identified positive associations with insulin resistance.[8] Misra et al. observed increased inflammatory activity in Indian patients with T2DM, particularly among those with macrovascular complications.[9] Arif et al. also found differences in inflammatory biomarkers across prediabetic and diabetic groups and reported useful discrimination on ROC analysis. [10] These findings suggest that systemic inflammation is consistently associated with abnormal glucose metabolism across different Indian populations.

A notable observation in the present study was the progressive increase in TNF-α across HbA1c categories. Mean TNF-α rose from 21.4 ± 4.2 pg/mL among patients with HbA1c of 6.5–7.5% to 45.6 ± 8.5 pg/mL among those with HbA1c above 9.5%. This graded association suggests that worsening glycaemic control may be accompanied by increasing inflammatory burden. Similar relationships between TNF-α, HbA1c and disease severity have been reported in diabetic peripheral neuropathy.[11]

TNF-α remained associated with T2DM after adjustment for HbA1c and BMI. This finding is biologically plausible because TNF-α may impair insulin action through pathways involving adipose tissue and skeletal muscle.[12] Nevertheless, the cross-sectional design cannot determine whether increased TNF-α contributes to hyperglycaemia or develops as a consequence of metabolic disturbance.

ROC analysis showed that TNF-α discriminated patients from controls, although HbA1c had a higher individual AUC. The combined model showed the highest AUC, suggesting that TNF-α may provide inflammatory information alongside glycaemic assessment. However, these results require external validation before clinical application. Genetic variation may also contribute to differences in circulating TNF-α concentrations between individuals. [13]

The study was limited by its single-centre design, modest sample size and cross-sectional assessment. Residual confounding from obesity, treatment, subclinical infection and other inflammatory conditions cannot be excluded. Larger prospective studies are needed to clarify the temporal relationship and determine whether TNF-α offers clinically useful information beyond established markers.

CONCLUSION

Serum TNF-α concentrations were higher in patients with type 2 diabetes mellitus than in healthy controls and showed a positive association with HbA1c. TNF-α also increased across categories of worsening glycaemic control. Although combining TNF-α with HbA1c improved discrimination between the study groups, these findings do not establish causality or immediate clinical utility. TNF-α may serve

as a complementary marker of inflammatory activity in T2DM, but larger prospective and multicentre studies are required to confirm its value in clinical assessment.

Declaration by Authors

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of M.G.M. Medical College, Indore.

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Conflict of Interest: The authors declare no conflict of interest.

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