Original Article

DOI: 10.7860/JCDR/2025/79192.21383

Biochemistry Section

Association of Serum Interleukin-6 and Erythrocyte Sedimentation Rate with Glycemic Control and Body Mass Index in Type 2 Diabetes Mellitus: A Comparative Cross-sectional Study

ROSMI JOHNACHAN[1], DIANA MARIAM[2], SIBIYA ODAYAPPURATH[3]

ABSTRACT

Introduction: Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder marked by insulin resistance and persistent hyperglycaemia. Increasing evidence indicates that low-grade systemic inflammation contributes to its development and progression. Interleukin-6 (IL-6), a proinflammatory cytokine, serves as a potential marker of metabolic and vascular complications. Similarly, elevated Erythrocyte Sedimentation Rate (ESR) reflects ongoing inflammation and correlates with poor glycaemic control.

Aim: To assess and compare serum IL-6 and ESR levels in patients with T2DM and healthy controls, and to evaluate their correlation with glycaemic indices and Body Mass Index (BMI).

Materials and Methods: This comparative cross-sectional study included 66 participants: 33 diagnosed T2DM patients (on treatment for 2-5 years) and 33 age and sex-matched healthy controls. Fasting Blood Sugar (FBS), Glycated Haemoglobin (HbA1c), ESR, BMI, and serum IL-6 were measured. IL-6 levels were estimated using sandwich Enzyme Linked Immunosorbent Essay (ELISA). Statistical analysis was performed using the Mann-Whitney U test and Spearman's correlation, with $p<0.05$ considered significant.

Results: T2DM patients showed significantly higher mean FBS (132.7 mg/dL), HbA1c (7.56%), ESR (25.76 mm/hr), IL-6 (103.0 pg/mL), and BMI (25.70 kg/m^2) compared to controls ($p<0.001$ for all). A weak but statistically significant positive correlation was found between IL-6 and BMI ($\rho=0.38$, $p=0.03$). HbA1c also showed a positive trend with ESR. Although IL-6 levels were higher in patients with longer diabetes duration, the difference was not statistically significant.

Conclusion: To conclude, IL-6 and ESR levels were significantly elevated in T2DM, indicating a strong inflammatory component in the disease. IL-6 showed a positive correlation with BMI, supporting its role in obesity-related inflammation. These findings highlight the potential utility of IL-6 as a biomarker for monitoring inflammation and disease progression in T2DM.

Keywords: Body mass index, Erythrocyte sedimentation rate, Glycated haemoglobin A, Hyperglycaemia, Inflammatory markers, Proinflammatory cytokines, Vascular inflammation

INTRODUCTION

Diabetes Mellitus (DM) is a multifactorial metabolic disorder marked by chronic hyperglycaemia resulting from defects in insulin secretion, insulin action, or both [1]. Chronic elevation in blood glucose is associated with progressive damage, dysfunction, and failure of vital organs such as the eyes, kidneys, nerves, heart, and vasculature [1,2]. Among the two major clinical types of DM, T2DM is the most prevalent, accounting for more than 90% of all cases globally [3,4]. It is primarily characterised by insulin resistance, usually accompanied by a relative insulin deficiency [5]. The disease develops insidiously, with patients often remaining undiagnosed for years until complications manifest.

According to the International Diabetes Federation, the global burden of diabetes was estimated at 415 million in 2015, with projections indicating a rise to 642 million by 2040 [6]. India faces an alarming surge in prevalence, with an estimated 79.4 million cases expected by 2030, largely attributable to rapid urbanisation, sedentary lifestyles, and genetic predisposition [7,8]. Inflammation plays a pivotal role in the pathogenesis and progression of T2DM and its associated microvascular and macrovascular complications.

Interleukin-6 (IL-6), a pleiotropic proinflammatory cytokine, has gained attention for its central role in inflammatory and immune responses. It is secreted by various cells including adipocytes, fibroblasts, endothelial cells, monocytes, and activated leukocytes [8]. The IL-6 gene encodes this cytokine, which functions as a primary mediator of the acute-phase inflammatory response and is involved in the transition from acute to chronic inflammation [9].

In T2DM, chronic hyperglycaemia triggers oxidative stress and inflammation, leading to endothelial dysfunction and vascular damage. Elevated IL-6 levels have been positively correlated with insulin resistance and have been proposed as a predictive biomarker for the onset of diabetes and its complications, including diabetic retinopathy, nephropathy, and neuropathy [10-12]. IL-6 induces hepatic production of C-reactive Protein (CRP) and other acute-phase proteins, thereby perpetuating systemic inflammation [13]. Moreover, the ESR, a non specific marker of inflammation, has been reported to be higher in individuals with T2DM, further highlighting the inflammatory milieu associated with the disease [9]. Comparative studies assessing IL-6 and ESR levels in diabetics and healthy individuals can help elucidate the role of systemic inflammation in T2DM pathogenesis and complications. Thus, the present study aims to evaluate and compare the levels of IL-6 and ESR in patients with T2DM and healthy controls, thereby exploring their potential as markers for disease severity and progression.

MATERIALS AND METHODS

The present comparative cross-sectional study was conducted over a period of one year at the Government Medical College,

Kozhikode, Kerala, India. The primary objective was to assess and compare selected inflammatory and glycaemic parameters among T2DM patients and healthy controls. The study was conducted after Institutional Ethical Committee clearance (ref no. GMCKKD/RP2017/EC/185) and informed consent from study participants.

Sample size calculation: Sample size was calculated using the formula:

$$\frac{(Z\alpha+Z\beta)^2\times SD^2\times 2}{d^2}$$

SD from the reference study=2.35+0.51=1.43 [5]

Hence, substituting the values in equation with (for 80% power and 5% level of significance)=32.71 was the calculated sample size for the present study.

Where:

- SD (Standard Deviation) from a reference study was taken as 1.43
- Zα+Zβ=2.8 (for 80% power and 5% level of significance)
- d (mean difference to be detected)=1

Thus, a total of 33 subjects per group was included, making the overall sample size 66 participants.

Inclusion and Exclusion criteria: The study included diagnosed Type 2 Diabetes Mellitus (T2DM) patients of both sexes, aged 30-65 years, undergoing treatment for 2-5 years and attending the outpatient department. Age and sex-matched healthy, non diabetiglobal check individuals were recruited as controls from hospital staff and visitors who provided informed written consent. Exclusion criteria for cases included acute illness, coronary artery disease, hepatic dysfunction, chronic kidney disease, pregnancy, malignancy, substance abuse, or inflammatory disorders. Controls unwilling to provide consent were excluded.

A non probability consecutive sampling technique was used. Diabetic patients were recruited from the Internal Medicine outpatient department, and controls from hospital staff and attendees.

- **Group 1 (Cases):** 33 patients with T2DM on treatment for 2-5 years.
- **Group 2 (Controls):** 33 age and sex-matched healthy non diabetic individuals.

Study Procedure

After obtaining written informed consent, participants were interviewed and examined for demographic and clinical details. Venous blood (5 mL) was collected between 8:00 AM and 10:00 AM after an overnight fast of 12 hours using standard aseptic venipuncture into plain vacutainers without anticoagulant. Samples were allowed to clot and centrifuged at 1500 rpm for 15 minutes to separate serum. One millilitres was used for immediate analysis, and the remainder stored at -80°C for IL-6 estimation. Body Mass Index was calculated as weight (kg) divided by height squared (m^2).

Fasting Blood Sugar (FBS): Fasting blood sugar was estimated using the Glucose Oxidase-Peroxidase (GOD-POD) method. In this enzymatic assay, glucose is oxidised to gluconic acid and hydrogen peroxide, which reacts with 4-aminoantipyrine and phenol in the presence of peroxidase to form a red quinoneimine dye. Absorbance was measured at 505 nm. Glucose concentration was calculated as (Absorbance of Sample/Absorbance of Standard)×100. The reference range for fasting glucose is 70-105 mg/dL [14,15].

Glycated Haemoglobin (HbA1c): HbA1c levels were measured using the Turbidimetric Inhibition Immunoassay (TINIA) on the Cobas e 311 analyser. The assay involves red cell lysis, antibody binding to HbA1c, and competitive inhibition by polyhapten. Immune complexes were quantified turbidimetrically. Results were expressed as HbA1c (%)=(HbA1c/Hb)×91.5+2.15. The normal range is 4.8-5.9% [2,15-17].

Erythrocyte Sedimentation Rate (ESR): ESR was measured using the Westergren method. Two milliliters of venous blood were mixed with 0.5 mL of 3.8% sodium citrate. The anticoagulated sample was drawn into a Westergren tube, and erythrocyte sedimentation was recorded after one hour. Normal values: 0-15 mm/hr for men, 0-20 mm/hr for women [18].

Interleukin-6 (IL-6): IL-6 levels were measured using a sandwich ELISA on a Multiscan FC microplate reader. Serum IL-6 bound to monoclonal capture antibodies, followed by biotinylated detection antibodies and streptavidin-HRP. TMB substrate produced a blue colour that turned yellow upon stopping the reaction and was read at 450 nm. The assay was sensitive to 2 pg/mL, with no cross-reactivity with IL-1, IL-10, or TNF-α [8-12]. Serum was stored at -70°C. Reference IL-6 range: <5-10 pg/mL [8,9].

STATISTICAL ANALYSIS

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 22.0. Quantitative variables were expressed as mean and standard deviation, and categorical variables as frequencies and percentages. The Mann-Whitney U test compared continuous variables, while the Chi-square test assessed categorical differences, including gender and blood pressure. Spearman's correlation analysed associations between serum IL-6 and study parameters. A p-value <0.05 was considered significant. Spearman's ρ values were interpreted by standard correlation strength categories.

RESULTS

The study included 66 participants, 33 type 2 diabetics on oral hypoglycaemics and 33 age and sex-matched controls. The mean age of participants in the case group was 51.2 years (±6.2), while that of controls was 48.3 years (±4.2). The difference in age distribution between groups was not statistically significant (p=0.06), indicating appropriate age matching. Regarding gender, 33.3% of cases and 27.3% of controls were male, while females comprised 66.7% and 72.7% of the respective groups. The gender distribution also showed no statistically significant difference (p=0.59) [Table/Fig-1].

Variables	Category	Cases (n=33)	Controls (n=33)	p-value	Statistical test
Age (years)	Mean±SD	51.2±6.2	48.3±4.2	0.06	Mann-Whitney U test
	Range	32-61	39-55		
Gender	Males	11 (33.3%)	9 (27.3%)	0.59	Chi-square test
	Females	22 (66.7%)	24 (72.7%)		

[Table/Fig-1]: Age and gender distribution among study subjects.

[Table/Fig-2] shows statistically significant differences between cases and controls across all biochemical and inflammatory parameters. Mean FBS was higher in diabetics (132.70 mg/dL) than controls (96.61 mg/dL; p<0.001). Mean HbA1c was 7.56% in cases and 4.58% in controls (p<0.001), indicating poor glycaemic control in cases. ESR and IL-6 were significantly elevated in cases (25.76 mm/hr and 103.00 pg/mL) compared to controls (8.67 mm/hr and 14.18 pg/mL), with p<0.001 for both parameters. BMI was also higher in cases (25.70 vs. 20.82 kg/m^2; p<0.001).

[Table/Fig-3] illustrates the distribution of participants based on blood pressure status, comparing diabetic cases and healthy controls. A distinct difference was observed between groups. Among cases, 57.6% had stage I hypertension, 39.4% were prehypertensive, and only 3.0% had normal blood pressure. In contrast, 69.7% of controls were prehypertensive, 24.2% had normal blood pressure, and only 6.1% had stage I hypertension. This difference was statistically highly significant (χ^2=21.984, p<0.001), indicating a strong association between type 2 diabetes and elevated blood pressure.

Parameters	Group	N	Mean	SD	Mean difference	Z-value	p-value	Statistical test
FBS (mg/dL)	Cases	33	132.70	36.10	36.09	-5.352	<0.001*	Mann-Whitney U test
	Controls	33	96.61	6.24				
HbA1c (%)	Cases	33	7.56	0.90	2.97	-7.001	<0.001*	Mann-Whitney U test
	Controls	33	4.58	0.18				
ESR (mm/hr)	Cases	33	25.76	17.66	17.09	-4.856	<0.001*	Mann-Whitney U test
	Controls	33	8.67	2.81				
BMI (kg/m²)	Cases	33	25.70	2.19	4.88	-5.688	<0.001*	Mann-Whitney U test
	Controls	33	20.82	2.65				
IL-6 (pg/mL)	Cases	33	103.00	52.06	88.82	-6.489	<0.001*	Mann-Whitney U test
	Controls	33	14.18	13.44				

[Table/Fig-2]: Comparison of FBS, HbA1c, ESR, BMI, and Interleukin-6 levels between cases and controls.
*p<0.001 denotes statistically highly significant results

Blood pressure category	Cases (n=33)	Controls (n=33)	Chi-square (χ^2) value	p-value	Statistical test
Normal	1 (3.0%)	8 (24.2%)	**21.984**	**<0.001***	Chi-square test
Prehypertension	13 (39.4%)	23 (69.7%)			
Stage I hypertension	19 (57.6%)	2 (6.1%)			

[Table/Fig-3]: Distribution of study subjects based on blood pressure status.
*p<0.001 denotes statistically highly significant difference

[Table/Fig-4] presents a comparison of FBS, HbA1c, ESR, BMI, and IL-6 levels among diabetic patients based on diabetes duration (2-3 years vs. 3-4 years). Mean values of FBS (142.06 mg/dL), HbA1c (7.80%), ESR (27.88 mm/hr), and IL-6 (115.06 pg/mL) were higher in the 3-4 year group compared to the 2-3 year group, but differences were not statistically significant (p>0.05). BMI was comparable between both duration groups. These findings suggest a trend without statistical confirmation.

[Table/Fig-5] shows the correlation between serum IL-6 levels and study parameters, FBS, HbA1c, ESR, and BMI using Spearman's correlation test for cases and controls. Among diabetic cases, a statistically significant weak positive correlation was observed between IL-6 and BMI (ρ=0.38, p=0.03), suggesting that higher BMI is associated with increased IL-6. Weak, non significant positive correlations were also found between IL-6 and FBS, HbA1c, and ESR. In controls, none of the correlations reached statistical significance, although ESR and BMI showed near significant weak correlations with IL-6 (p=0.06). IL-6 was more closely associated with inflammation and adiposity in diabetics than controls.

[Table/Fig-6] presents a scatterplot of BMI (Kg/m²) versus IL-6 (pg/mL) in diabetic cases. Each dot represents a participant, with BMI on the x-axis and IL-6 on the y-axis. IL-6 levels ranged from near 0 to over 200 pg/mL, with BMI values from 19 to 31 Kg/m². A trend line indicates a slight upward trajectory, supporting the significant correlation seen in [Table/Fig-5]. [Table/Fig-7] displays a scatterplot illustrating the relationship between HbA1c levels (%) and ESR levels (mm/hr) in the case group. Each point represents a type 2 diabetic individual, with HbA1c on the x-axis and ESR on the y-axis. The data distribution shows a moderately rising trend, reflected by the upward slope of the line of best fit. This suggests a positive correlation, indicating that individuals with higher HbA1c levels tend to exhibit elevated ESR, a marker of inflammation. Although the association is modest, the visual trend supports the link between poor glycaemic control and increased inflammatory status. Despite inter-individual variability, the overall pattern highlights the role of chronic hyperglycaemia in contributing to low-grade systemic inflammation among diabetic patients, reinforcing the need for effective glycaemic regulation in managing T2DM and its associated inflammatory burden.

None of the comparisons across duration groups (2-3 years vs. 3-4 years) showed a statistically significant difference (p>0.05) for any parameter, although values for FBS, HbA1c, ESR, and IL-6 tended to be higher in the group with a longer disease duration.

Parameter	DM duration	N	Mean	SD	Mean difference	Z-value	p-value	Statistical test
FBS (mg/dL)	2-3 years	16	122.75	28.92	-19.31	-1.532	0.13	Mann-Whitney U test
	3-4 years	17	142.06	40.37				
HbA1c (%)	2-3 years	16	7.29	0.67	-0.51	-1.865	0.06	Mann-Whitney U test
	3-4 years	17	7.80	1.03				
ESR (mm/hr)	2-3 years	16	23.50	21.32	-4.38	-1.553	0.12	Mann-Whitney U test
	3-4 years	17	27.88	13.70				
BMI (kg/m²)	2-3 years	16	25.58	1.23	-0.24	0.214	0.22	Mann-Whitney U test
	3-4 years	17	25.82	2.85				
IL-6 (pg/mL)	2-3 years	16	90.18	46.47	-24.89	-0.901	0.37	Mann-Whitney U test
	3-4 years	17	115.06	55.47				

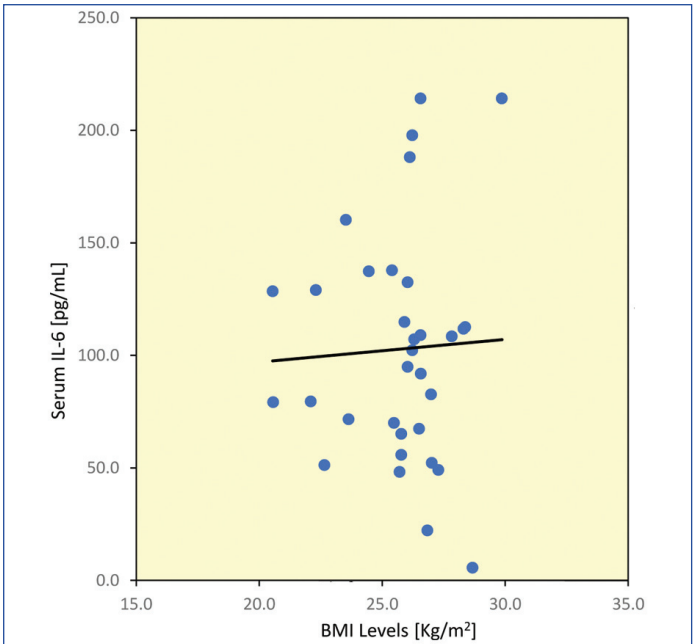
[Table/Fig-4]: Comparison of FBS, HbA1c, ESR, BMI, and IL-6 levels based on duration of Diabetes Mellitus (2-3 years vs. 3-4 years).

IL-6	Parameter	FBS	HbA1c	ESR	BMI
Cases	Correlation coefficient (ρ)	0.16	0.24	0.24	0.38
	p-value	0.37	0.18	0.18	0.03*
Controls	Correlation coefficient (ρ)	0.06	0.146	0.34	0.36
	p-value	0.76	0.418	0.06	0.06

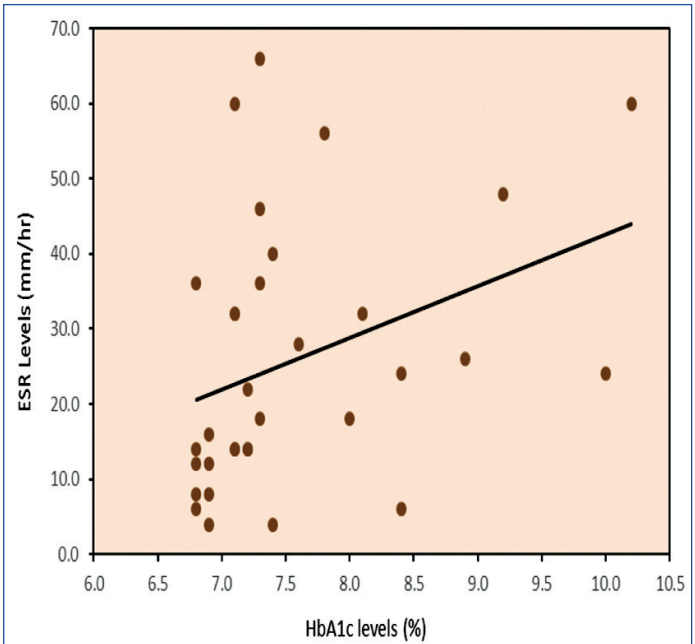
[Table/Fig-5]: Correlation between serum IL-6 and other study parameters in cases and controls (Spearman's Correlation Test).
*p<0.05 indicates statistically significant correlation

DISCUSSION

Diabetes Mellitus (DM) is increasingly recognised as a chronic low-grade inflammatory condition, where hyperglycaemia contributes to a proinflammatory milieu. This leads to the progression of microvascular complications such as nephropathy, retinopathy, and neuropathy. Mechanisms underlying this process include insulin resistance, elevated adipokines, Advanced Glycation End-products (AGEs), oxidative stress, and hypoxia, all of which potentiate



[Table/Fig-6]: Scatterplot depicting the relationship between BMI levels and Serum IL-6 levels in case group.



[Table/Fig-7]: Scatterplot depicting the relationship between HbA1C levels and ESR levels in cases.

inflammation [11]. In the present comparative cross-sectional study involving 66 subjects (33 cases with T2DM and 33 healthy controls), significantly higher levels of serum IL-6, ESR, FBS, HbA1c, and BMI were observed in the diabetic group compared to controls. The mean age was 51.2 years in cases and 48.3 years in controls, with no significant difference in age or gender distribution. This study demonstrated significantly elevated serum IL-6 levels in T2DM patients (mean 103.00 pg/mL) compared with healthy controls (14.18 pg/mL; p<0.001), accompanying raised ESR, BMI, FBS, and HbA1c. These findings align strongly with previous comparative studies and meta-analyses linking IL-6 with metabolic dysregulation and chronic inflammation in diabetes.

Afzal N et al., reported mean IL-6 concentrations of approximately 18 pg/mL in patients with T2DM without retinopathy and around 32 pg/mL in those with diabetic retinopathy, compared to ~8 pg/mL in healthy controls, indicating progressive IL-6 elevation with microvascular involvement [19]. In contrast, the present study observed substantially higher mean IL-6 levels (~103 pg/mL), which may reflect a more advanced inflammatory burden, greater metabolic derangement, or differences related to ethnicity, sample matrix (serum vs. plasma), or assay sensitivity. Similarly, Reddy VKK et al., noted IL-6 elevations ranging between 20-40 pg/mL in T2DM individuals with and without nephropathy, highlighting the cytokine's association with diabetic kidney disease [20]. The higher IL-6 levels seen in the current group were likely due to a strong inflammatory response in Indian patients attending a tertiary care center which was worsened by long-standing diabetes. Population-level variation was further illustrated by Phosat C et al., who reported IL-6 levels in the 5-10 pg/mL range among rural Thai T2DM patients, reinforcing the heterogeneity in IL-6 response across geographic and genetic contexts [21]. Jin Z et al., through a comprehensive umbrella review, confirmed a consistent trend of IL-6 elevation across diabetic populations, regardless of clinical phenotype [22]. In concordance, Bowker N et al.,'s meta-analysis documented a 1.5- to 2-fold rise in IL-6 among T2DM patients versus healthy individuals, further validating its relevance as a biomarker of systemic inflammation [23]. Bara Jk et al.,'s 2025 meta-analysis further substantiated IL-6's role as a mediator of chronic low-grade inflammation contributing to β-cell dysfunction and insulin resistance, thus reinforcing the cytokine's dual diagnostic and pathogenic relevance in T2DM and its complications [24].

Genetic predisposition appeared to play a contributory role in IL-6 elevation among individuals with T2DM. Obirikorang C et al., identified a significant association between the IL-6 -174 G/C (rs1800795) polymorphism and increased T2DM susceptibility [25]. Similarly, Ayelign B et al., demonstrated that this variant correlated with both elevated IL-6 concentrations and heightened T2DM risk in Ethiopian subjects [26]. Although the present study did not assess genetic polymorphisms, the markedly high IL-6 levels (mean ~103 pg/mL) may partly reflect underlying, population-specific genetic influences that enhance cytokine expression. Rodrigues KF et al., further supported this concept by reporting that IL-6 and TNF-α gene variants were significantly associated with circulating IL-6 levels and obesity in Brazilian individuals, indicating a gene inflammation metabolism axis relevant to T2DM pathophysiology [27]. These findings highlighted the importance of host genetic factors in modulating inflammatory responses.

In the present study, IL-6 showed a statistically significant but weak positive correlation with BMI (ρ=0.38, p=0.03), while correlations with FBS, HbA1c, and ESR were positive but not statistically significant. These findings are in line with those of Rodrigues KF et al., [27], who reported a significant association between IL-6 levels and BMI in Brazilian patients with type 2 diabetes. Their study highlighted that increased adiposity, particularly visceral fat, contributes to elevated IL-6 levels, reflecting a proinflammatory state. This supports the biological mechanism whereby adipose tissue acts as an active endocrine organ secreting IL-6, thereby promoting systemic inflammation and insulin resistance. Todingan M et al., observed higher IL-6 levels in uncontrolled versus controlled T2DM cases in Indonesia (~40 pg/mL vs. ~18 pg/mL), which aligned with the elevated IL-6 in the current study, despite a non significant HbA1c correlation possibly due to therapeutic variations or limited HbA1c variability [28]. Ghalaut RS et al., further demonstrated a stepwise increase in IL-6 and TNF-α across diabetic nephropathy stages, reinforcing this inflammatory trajectory [29].

In this study, the mean ESR in the T2DM group (25.76 mm/hr) was significantly higher than in controls (8.67 mm/hr), supporting the presence of low-grade chronic inflammation. This finding aligned with Aslan Sirakaya H et al., who reported parallel increases in ESR and IL-6 in diabetic ketoacidosis patients, correlating with disease severity and adverse outcomes [30]. Similarly, Phosat C et al., demonstrated elevated ESR, CRP, and IL-6 in T2DM subjects, reinforcing the systemic inflammatory state associated with diabetes [21]. Although ESR is a non specific marker, its elevation in this cohort affirms its practical utility as an accessible indicator of inflammation.

Additionally, subgroup analysis comparing T2DM duration of 2-3 versus 3-4 years revealed a non significant upward trend in FBS, HbA1c, ESR, and IL-6 levels. This observation mirrored Bara JK et al.'s findings of progressive inflammatory marker elevation with increasing disease duration, often becoming statistically significant beyond five years [24], suggesting that this study reflects an early-to-mid inflammatory stage.

The role of IL-6 as a mediator of both microvascular and macrovascular complications in diabetes has been well-established. Bahrami HSZ et al., in the Thousand and 1 Study, identified significant associations between elevated IL-6 levels and subclinical left ventricular dysfunction in type 1 diabetic patients, highlighting its contribution to early cardiac involvement [31]. Although the present study did not include cardiac imaging, the markedly elevated IL-6 levels and a high prevalence of hypertension among diabetic participants suggest a possible early stage of vascular injury. Alhamawi RM et al., further elaborated on IL-6's dualistic role in diabetic nephropathy, showing that while IL-6 may initially trigger protective immune responses, its sustained overexpression contributes to glomerular injury and fibrosis, exacerbating renal dysfunction [32]. Moreover, Elssaig EH et al., demonstrated that TNF-α and IL-6 gene polymorphisms significantly influenced the development of diabetic complications in Sudanese patients [33], further supporting the pathophysiological link between proinflammatory cytokines and end-organ damage. These findings underscore IL-6 not only as a biomarker but also as a potential effector in the progression of diabetic vasculopathy.

Several inter-related mechanisms may underlie the observed findings. Adiposity-driven inflammation is a major contributor; wherein increased BMI enhances IL-6 secretion from adipocytes and infiltrating macrophages. Hyperglycaemia, through glucotoxic effects, stimulates the generation of reactive oxygen species and activates inflammatory cascades that further elevate IL-6 production. Genetic predisposition also plays a role, as polymorphisms in the IL-6 promoter region have been associated with enhanced transcriptional activation. Additionally, IL-6 contributes to insulin resistance by disrupting insulin signaling via the Suppressor of Cytokine Signaling 3 (SOCS3) and JAK-STAT pathways. IL-6 thus, functions as both a marker and mediator of T2DM. Meta-analyses by Bowker N et al., and Bara JK et al., have shown that IL-6 levels predict the onset and severity of T2DM [23,24]. The observed positive correlation between IL-6 and BMI in the current study reinforces the concept that obesity-induced inflammation is central to the pathophysiology of T2DM. Furthermore, the findings align with those of Afzal N et al., who reported stage-specific increases in IL-6 levels with diabetic complications, supporting the interpretation that elevated IL-6 may reflect early microvascular damage [19]. While absolute IL-6 values differ among studies, the relative ranking remains consistent healthy controls exhibit the lowest levels, followed by T2DM without complications, and then T2DM with complications. The present study reports one of the highest mean IL-6 levels to date (~103 pg/mL), which may be attributed to methodological differences such as the use of serum over plasma, variations in assay sensitivity, geographic or genetic influences, and participant characteristics including age and disease duration. These factors collectively justify the elevated IL-6 values and reaffirm its role in the inflammatory landscape of T2DM.

Hence, the study reinforced IL-6 as a useful biomarker of inflammation in T2DM. Elevated IL-6 appeared to predict early complications, and targeting it through anti-inflammatory measures such as weight loss, physical activity, or pharmacological agents (e.g., IL-6 inhibitors) showed potential benefits. IL-6 and ESR were significantly elevated in T2DM subjects, with IL-6 showing a weak but significant correlation with BMI. The magnitude of IL-6 elevation in this Indian cohort exceeded previous reports, indicating possible ethnic or genetic factors. These results supported IL-6's role as both a biomarker and mediator in diabetes-related inflammation.

Limitation(s)

The cross-sectional design precluded causal inference, and the relatively small sample size reduced statistical power and generalisability. IL-6, being a non specific inflammatory marker, might have been elevated due to factors unrelated to diabetes. The study did not include genotyping, which could have clarified associations with IL-6 promoter polymorphisms, nor were additional proinflammatory markers like CRP, TNF-α, or IL-1β assessed. Uncertainity regarding the exact duration of diabetes in some participants hindered a clear interpretation of disease progression. Moreover, the single-centre sampling introduced potential selection bias, and the high absolute IL-6 values observed may limit comparability with other studies. Future longitudinal research with larger, more diverse cohorts is needed to delineate the temporal dynamics of IL-6 and its role in beta cell dysfunction, insulin resistance, and diabetic complications.

CONCLUSION(S)

The present study demonstrated that serum IL-6 levels were significantly elevated in patients with T2DM compared to healthy controls, suggesting that IL-6 may be an important inflammatory mediator contributing to the disease process. Higher IL-6 levels observed in patients with poorer glycaemic control indicate a possible role in the development of chronic complications associated with diabetes. Similarly, ESR levels were markedly elevated in diabetic individuals, especially among those with uncontrolled diabetes, further reinforcing the association between systemic inflammation and glycaemic status. These findings support the potential use of IL-6 as a biomarker for predicting diabetes and its complications. However, since IL-6 is a non specific marker, its role should be interpreted alongside other clinical and biochemical parameters. Further research is needed to better understand the contribution of IL-6 in the pathogenesis and progression of diabetes and to explore its utility in clinical risk stratification and monitoring of diabetic complications.

REFERENCES

[1] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2004;27 Suppl 1:S5-S10. Doi: 10.2337/diacare.27.2007.s5. PMID: 14693921.

[2] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S13-S28. Doi: 10.2337/dc19-S002. PMID: 30559228.

[3] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-51. Doi: 10.1016/S0140-6736(17)30058-2. Epub 2017 Feb 10. Erratum in: Lancet. 2017;389(10085):2192. Doi: 10.1016/S0140-6736(17)30539-1. PMID: 28190580.

[4] Vijayakumar G, Arun R, Kutty VR. High prevalence of type 2 diabetes mellitus and other metabolic disorders in rural Central Kerala. J Assoc Physicians India. 2009;57:563-67. PMID: 20209716.

[5] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1(Suppl 1):S62-69. Doi: 10.2337/dc10-S062. Erratum in: Diabetes Care. 2010;33(4):e57. PMID: 20042775; PMCID: PMC2797383.

[6] Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: Global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011;94(3):311-21. Doi: 10.1016/j.diabres.2011.10.029. Epub 2011 Nov 12. PMID: 22079683.

[7] Herman WH. The global burden of diabetes: An overview. Diabetes mellitus in developing countries and underserved communities. 2017:01-05.

[8] Rose-John S. Interleukin-6 family cytokines. Cold Spring Harb Perspect Biol. 2018;10(2):a028415. Doi: 10.1101/cshperspect.a028415. PMID: 28620096; PMCID: PMC5793756.

[9] Vidhate DA, Thomas J, Gupte AM. Association of IL-6 with diabetes mellitus in Indian population from Navi Mumbai. International Journal of Recent Trends in Science and Technology. 2013;8(2):100-02.

[10] Saxena M, Agrawal CG, Srivastava N, Banerjee M. Interleukin-6 (IL-6)-597 A/G (rs1800797) & -174 G/C (rs1800795) gene polymorphisms in type 2 diabetes. Indian J Med Res. 2014;140(1):60-68.

[11] Nguyen DV, Shaw LC, Grant MB. Inflammation in the pathogenesis of microvascular complications in diabetes. Front Endocrinol (Lausanne). 2012;3:170.

[12] Joshi SV, Tambwekar SR, Khadalia K, Dhar HL. Role of inflammatory marker Interleukin 6 (IL-6) and insulin in diabetes and diabetic neuropathy. Bombay Hosp J. 2008;50(3):466-71.

[13] Singh VP, Bali A, Singh N, Jaggi AS. Advanced glycation end products and diabetic complications. Korean J Physiol Pharmacol. 2014;18(1):01-14. Doi: 10.4196/kjpp.2014.18.1.1. Epub 2014 Feb 13. PMID: 24634591; PMCID: PMC3951818.

[14] Saudek CD, Herman WH, Sacks DB, Bergenstal RM, Edelman D, Davidson MB. A new look at screening and diagnosing diabetes mellitus. J Clin Endocrinol Metab. 2008;93(7):2447-53. Doi: 10.1210/jc.2007-2174. Epub 2008 May 6. PMID: 18460560.
[15] Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, et al. Tests of glycemia in diabetes. Diabetes Care. 2004;27(7):1761-73. Doi: 10.2337/diacare.27.7.1761. PMID: 15220264.
[16] American Diabetes Association. Standards of medical care in diabetes--2014. Diabetes Care. 2014;37 Suppl 1:S14-80. Doi: 10.2337/dc14-S014. PMID: 24357209.
[17] Sacks DB, Arnold M, Bakris GL, Bruns DE, Horvath AR, Lernmark Å, et al. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. Diabetes Care. 2023;46(10):e151-e199. Doi: 10.2337/dci23-0036. PMID: 37471273; PMCID: PMC10516260.
[18] Jameson JL, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J, editors. Harrison's Manual of Medicine. 20th ed. New York: McGraw-Hill Education; 2020.
[19] Afzal N, Anjum R, Nadeem A, Javed K, Shahzad F, Kashif M, et al. Serum level of il-6 in patients of type-ii diabetes mellitus with and without retinopathy: A comparative study. Bangladesh Journal of Medical Science. 2017;16(4):525-29.
[20] Reddy VKK, Shiddapur G, Jagdale N, Kondapalli MP, Adapa S. Investigating Interleukin-6 levels in type 2 diabetes mellitus patients with and without diabetic nephropathy. Cureus. 2024;16(8):e67014. Doi: 10.7759/cureus.67014. PMID: 39280507; PMCID: PMC11402502.
[21] Phosat C, Panprathip P, Chumpathat N, Prangthip P, Chantratita N, Soonthornworasiri N, et al. Elevated C-reactive protein, interleukin 6, tumor necrosis factor alpha and glycemic load associated with type 2 diabetes mellitus in rural Thais: A cross-sectional study. BMC Endocr Disord. 2017;17(1):44. Doi: 10.1186/s12902-017-0189-z. PMID: 28716139; PMCID: PMC5512726.
[22] Jin Z, Zhang Q, Liu K, Wang S, Yan Y, Zhang B, et al. The association between interleukin family and diabetes mellitus and its complications: An overview of systematic reviews and meta-analyses. Diabetes Res Clin Pract. 2024;210:111615. Doi: 10.1016/j.diabres.2024.111615. Epub 2024 Mar 19. PMID: 38513987.
[23] Bowker N, Shah RL, Sharp SJ, Luan J, Stewart ID, Wheeler E, et al. Meta-analysis investigating the role of interleukin-6 mediated inflammation in type 2 diabetes. EBioMedicine. 2020;61:103062. Doi: 10.1016/j.ebiom.2020.103062. Epub 2020 Oct 21. PMID: 33096487; PMCID: PMC7581887.
[24] Bara JK, Gandhi P, Verma P. Revisiting the markers interleukin-6 and glucagon-like peptide-1 for targeting low-grade inflammation in type 2 diabetes: A meta-analysis and our lab experience. Acta Diabetol. 2025;62(6):811-18. Doi: 10.1007/s00592-024-02398-8. Epub 2024 Oct 30. PMID: 39476149.
[25] Obirikorang C, Lokpo SY, Owiredu WKBA, Ahenkorah-Fondjo L, Osei-Yeboah J, Duedu KO, et al. Association between Interleukin-6 gene polymorphism (rs1800795 and rs1800796) and type 2 diabetes mellitus in a Ghanaian population: A case-control study in the Ho municipality. Biomed Res Int. 2024;2024:3610879. Doi: 10.1155/2024/3610879. PMID: 38707766; PMCID: PMC11068456.
[26] Ayelign B, Negash M, Andualem H, Wondemagegn T, Kassa E, Shibabaw T, et al. Association of IL-10 (-1082 A/G) and IL-6 (-174 G/C) gene polymorphism with type 2 diabetes mellitus in Ethiopia population. BMC Endocr Disord. 2021;21(1):70. Doi: 10.1186/s12902-021-00738-1. PMID: 33858419; PMCID: PMC8051082.
[27] Rodrigues KF, Pietrani NT, Bosco AA, Campos FMF, Sandrim VC, Gomes KB. IL-6, TNF-α, and IL-10 levels/polymorphisms and their association with type 2 diabetes mellitus and obesity in Brazilian individuals. Arch Endocrinol Metab. 2017;61(5):438-46. Doi: 10.1590/2359-3997000000254. Epub 2017 Feb 16. PMID: 28225860; PMCID: PMC10522244.
[28] Todingan M, Muhiddin R, Kurniawan LB. IL-6 levels analysis controlled in type 2 diabetes mellitus patients and uncontrolled. INDONESIAN Journal of Clinical Pathology and Medical Laboratory. 2023;29(2):175-79.
[29] Ghalaut RS, Dalal D, Kumar H, HK A, Ghalaut VS. The role of pro-inflammatory cytokines–tumor necrosis factor-alpha and interleukin 6–in the evolution of diabetic nephropathy: A comparative study. Natl J Physiol Pharm Pharmacol. 2023;13(4):744-47.
[30] Aslan Sirakaya H, Sipahioglu H, Cetinkaya A, Aydin K. Relationship between inflammatory markers (IL-6, Neutrophil-lymphocyte ratio, and C-reactive protein-Albumin ratio) and diabetic ketoacidosis severity: Correlation with clinical outcomes. Medicina (Kaunas). 2025;61(2):321. Doi: 10.3390/medicina61020321. PMID: 40005437; PMCID: PMC11857497.
[31] Bahrami HSZ, Jørgensen PG, Hove JD, Dixen U, Rasmussen LJH, Eugen-Olsen J, et al. Association between interleukin-6, suPAR, and hsCRP with subclinical left ventricular dysfunction in type 1 diabetes: The Thousand & 1 study. Diabetes Res Clin Pract. 2025;222:112071. Doi: 10.1016/j.diabres.2025.112071. Epub 2025 Mar 3. PMID: 40043809.
[32] Alhamawi RM, Mohammedsaeed W, Aljumaa M. Interleukin 6: Friend or foe in diabetic nephropathy? Arch Med Sci. Doi. 2025;10.
[33] Elssaig EH, Ali AE, Alsubai MA, Alnour TM, Ahmed-Abakur EH, Yousif A, et al. Impact of tumor necrosis factor-α and interleukin 6 polymorphisms on type 2 diabetes mellitus Sudanese patients. Italian Journal of Medicine. 2025;19(2):1967.

PARTICULARS OF CONTRIBUTORS:
1. Assistant Professor, Department of Biochemistry, Government TD Medical College, Alappuzha, Kerala, India.
2. Consultant Biochemist, Department of Biochemistry, Aswini Diagnostic Services, Kozhikode, Kerala, India.
3. Assistant Professor, Department of Biochemistry, Government Medical College, Manjeri, Malappuram, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Rosmi Johnachan,
Pulickal House, Thathampally PO, Alappuzha, Kerala, India.
E-mail: rosmijohnachan19@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 08, 2025
- Manual Googling: Jul 13, 2025
- iThenticate Software: Jul 15, 2025 (11%)

ETYMOLOGY: Author Origin

EMENDATIONS: 4

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 07, 2025**
Date of Peer Review: **Jul 02, 2025**
Date of Acceptance: **Jul 17, 2025**
Date of Publishing: **Aug 01, 2025**