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Evaluation of IL-6, IL-10, and TNF-α as Predictive Inflammatory Biomarkers in Type 2 Diabetes and Early Nephropathy

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Abstract

Low-grade chronic inflammation is central to the pathogenesis of Type 2 diabetes and early diabetic nephropathy; therefore, the predictive biomarkers of the early renal and metabolic dysfunction could be cytokines like IL-6, TNF-α and IL-10. This study intended to assess the IL-6, IL-10, and TNF-al levels in Type 2 diabetes mellitus patients and to determine their possible application as predictive inflammatory biomarkers of early diabetic nephropathy. The study was a case-control study with 150 participants (100 patients with T2DM and 50 control), who admitted to Al-Habbobi Teaching Hospital, Iraq for the period extended January 2024 to February 2025. Diabetic patients were categorized into two groups first with nephropathy and the second without. Diagnosis was based on American Diabetes Association criteria (ADA) criteria and nephropathy was based on microalbuminuria and eGFR. Fasting blood sampling and clinical assessment were done. The biochemical parameters were automatically measured and level of IL-6, IL-10, and TNF-α were measured using ELISA. Ages and sex of T2DM patients were similar to the controls but with greater BMI, blood pressure, HbA1c, and lower eGFR. Inflammatory imbalance was manifested by a high level of IL-6, TNF-α, and CRP and a decrease in IL-10. Patients with nephropathy at an early stage possessed increased pro-inflammatory indicators and ACR with reduced IL-10. There was a positive correlation between IL-6 and TNF-α and HbA1c and ACR and negative correlation between eGFR. Regression analysis revealed that IL-6, TNF-α, HbA1c and BMI were independent predictors of early nephropathy. In conclusion, high IL-6 and TNF-α and low IL-10 are indications of chronic inflammatory responses that lead to insulin resistance, endothelial dysfunction, and early kidney damage in T2DM. These cytokines alone foresee nephropathy because of their effects on oxidative stress, mesangial expansion, and glomerular permeability.

Keywords: Type 2 Diabetes Mellitus; IL-6; TNF-α; IL-10; Early Diabetic Nephropathy.

Introduction

Type 2 diabetes mellitus (T2DM) is a long term metabolic disease where the person is constantly experiencing hyperglycemia due to insulin resistance and the gradual degeneration of beta cells in the pancreas. It is one of the largest international health issues

which face a soaring prevalence rate and a dramatic morbidity and mortality (1). Diabetic nephropathy is one of the microvascular outcomes of this disease and is one of the most severe long-term complications that occur and is a primary cause of end-stage renal disease in the global arena. Historically, hyperglycemia, hemodynamic changes, and metabolic imbalance were believed to be the major causes of diabetic kidney damage. Nevertheless, there is an increasing body of evidence showing that chronic low-grade inflammation is the pivotal factor with regard to the onset and course of T2DM and its renal complications (2, 3).

Inflammation in T2DM is currently the accepted persistent immune-metabolic imbalance caused by dysfunction of adipose tissue, oxidative stress, and end-products of advanced glycation (AGE) build-up. Increased adipose tissue has adipocytes and infiltrating macrophages that secrete pro-inflammatory cytokines that disrupt insulin signaling pathways. Two of these interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) have proven to be important mediators of systemic insulin resistance (4, 5). TNF-α suppresses phosphorylation of the insulin receptor substrate (IRS) and interferes with the PI3K/Akt- signal transduction, which inhibits glucose uptake in peripheral tissues. Likewise, IL-6 is a stimulation of gluconeogenesis in the liver and the increase of C-reactive protein (CRP) production strengthens the systemic inflammation. Continuous increase in these cytokines is a cause of not only metabolic dysregulation but also endothelial dysfunction and vascular injury (6). On the contrary, interleukin-10 (IL-10) is an anti-inflammatory cytokine affecting immune responses by inhibiting the production of pro-inflammatory cytokines and macrophage activation. The protective role of IL-10 is in the preservation of the state of immunity and the avoidance of excessive tissue damage (7). Individuals with metabolic syndrome and T2DM have been found to have low quantities of IL-10, implying that they do not regulate anti-inflammatory functions. The low proportion of anti-inflammatory to pro-inflammatory cytokines is thus regarded as one of the manifestations of metabolic inflammation and could be taken as an early sign of the disease evolution (8, 9).

Once regarded as a result of hyperglycemia neglecting the role of comorbid factors, diabetic nephropathy is now considered an inflammatory-mediated disease, as it is initially manifested by microalbuminuria and progressive loss of glomerular filtration rate (GFR). Hyperglycemia triggers oxidative stress, mitochondrial dysfunction, and nuclear factor-kappa B (NF- κB) activation that stimulates inflammatory cytokine transcription in tissue in the kidney (10). High IL-6 and TNF-α levels stimulate mesangial cell growth, deposition of the extracellular matrix, podocyte apoptotic processes, and hyperpermeable glomerules, leading to albuminuria and structural damage of renal tissue (11). Additionally, intrarenal hemodynamic alterations are worsened by the action of inflammatory cytokines and speed up the process of nephron loss. In contrast, sufficient anti-inflammatory responses with the participation of IL-10 can reduce inflammation in the kidneys and delay the development of the disease (12).

Early detection of patients who have the risk of developing nephropathy is still one of the leading clinical challenges. In spite of the popularity of albumin/creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) as commonly used indicators of renal function, those in the majority of cases represent an indication of pre-existing renal damage as opposed to early signs of inflammatory changes (13). Thus, the discovery of predictive inflammatory biomarkers would enhance risk stratification and make it easier to intervene with therapy early. Some of the researches have also risen the amount of IL-6 and TNF-α in diabetic kidney disease patients and lower concentrations of IL-10 have been correlated with greater renal impairment. However, the extent of prediction of these cytokines on early nephropathy remains to be established in addition to their potential to

be independently linked to metabolic parameters, particularly in other population groups (14, 15). Moreover, the interplay between the glycemic regulation and the obesity, systemic inflammation, and renal failure demonstrate the drug effect of diabetic complication. Inflammatory activation is enhanced by bad glycemic control (high HbA1c) and body mass index (BMI) only enhances the release of cytokines by the adipose tissue. This results in an inflammatory cascade which culminates in a vicious cycle of metabolic stress and renal injury. This cytokine-mediated process is one avenue that can be investigated to offer new data on effective anti-inflammatory therapies to avoid renal risk among patients with T2DM (16, 17). In that respect, the evaluating of IL-6, IL-10, and TNF-α as inflammatory prognostic biomarkers in T2DM and early nephropathy has high clinical value. Evaluation of their correlation with glycemic control, indices of renal functionality and albuminuria could be more insightful in evaluating the inflammatory processes underlying diabetic renal damage. Moreover, their independent predictive value may be established, which will justify their possible application as early diagnostic and prognostic predictors (18). Accordingly, the present study was designed to investigate the serum levels of IL-6, IL-10, and TNF-α in patients with Type 2 Diabetes Mellitus (T2DM), assess their correlation with the early onset of nephropathy, and determine their potential utility as predictive inflammatory biomarkers of diabetic renal disease.

Materials and Methods

Ethical approval

The human ethics committee of Al-Habbobi Teaching Hospital approved this study. All the participants involved in this study were informed verbally. They also requested to sign a written consent form, and also assured that the information would remain confidential.

Study design

A case–control study was conducted at the Al-Habbobi Teaching Hospital, Iraq, between January 2024 and February 2025, to evaluate IL-6, IL-10, and TNF-α as predictive inflammatory biomarkers in Type 2 Diabetes Mellitus (T2DM) and early nephropathy. The study included 150 participants divided into 100 T2DM patients and 50 healthy individual, who age- and sex-matched to serve as a control group. The diabetic group was further categorised into patients without nephropathy (n = 60) and those with early nephropathy (n = 40). The diagnosis of T2DM was made by the American Diabetes Association criteria and relied on fasting plasma glucose of 126mg/dl and HbA1c of 6.5 per cent and 2hour glucose of 200mg/dl or clinical diagnosis. The case of early diabetic nephropathy was determined through the existence of microalbuminuria (30-300 mg/g albumin-to-creatinine ratio) and maintenance of renal dynamic (eGFR 60 mL/min/1.73 m2) obtained with the help of a CKD-EPI formula. The inclusion criteria were adults aged 35 to 70 years with T2DM 3-years duration and three-month stable treatment and exclusion criteria were type 1 diabetes, acute or chronic inflammatory diseases, autoimmune disorders, malignancy, chronic liver disease, advanced renal failure, recent infection, or corticosteroid or immunosuppressive drug use. A thorough clinical assessment was done, including anthropometric dimensions and blood pressure measurement. Samples were taken following an overnight fast (8-12 hours) and an aseptic venous sampling of 8-10 mL of blood; samples of HbA1c were collected in EDTA

samples, whereas serum samples were centrifuged and stored in -20 o C. Automated biochemical measurements were used to measure fasting blood glucose, creatinine, and CRP, and urinary albumin and creatinine were measured to calculate Albumin-to-creatinine ratio (ACR). The serum levels of IL-6, IL-10, and TNF-α were measured using commercially available ELISA kits as per instructions of the manufacturer and all the samples were measured in duplicate.

Statistical analysis

Statistical test was done in SPSS version 26; continuous variables were also represented as mean SD, frequency and percentage as categorical variables, independent t-tests were used to compare groups, Pearson coefficient was used to determine correlation, and multivariate logistic regression was used to determine the independent predictors of early nephropathy. A p-value of less than 0.05 was taken to be statistically significant.

Results

Comparison of Demographic Profile, Metabolic Parameters, and Renal Function between Study Groups

As demonstrated in Table 1, there were no significant differences in age ($p = 0.312$) or sex distribution ($p = 0.642$) between T2DM patients and controls, which means that there is adequate group matching. Nevertheless, BMI, systolic blood pressure and HbA1c were found to be much higher in T2DM patients in comparison with controls (all $p < 0.001$). Also, the overall renal performance was observed to be lower in diabetic group as the values of eGFR were lower ($p < 0.001$). The average patient age with diabetes was 8.7 years. These results prove that there are metabolic and early renal changes in the T2DM cohort.

Table.1: Baseline Demographic and Clinical Characteristics of T2DM Patients and Healthy Controls

Variable	T2DM Patients (n=100)	Controls (n=50)	p-value
Age (years)	55.8 ± 8.9	54.2 ± 9.1	0.312
Male, n (%)	58 (58%)	27 (54%)	0.642
Female, n (%)	42 (42%)	23 (46%)	
BMI (kg/m²)	30.6 ± 4.3	27.4 ± 3.8	<0.001
Duration of Diabetes (years)	8.7 ± 3.5	N/A	N/A
Systolic BP (mmHg)	138.4 ± 14.2	122.6 ± 11.5	<0.001
HbA1c (%)	8.4 ± 1.2	5.3 ± 0.4	<0.001
eGFR (mL/min/1.73m²)	78.6 ± 14.5	96.8 ± 10.7	<0.001

Differences in Circulating Pro- and Anti-Inflammatory Markers Between Study Groups

In table 2, the level of pro-inflammatory cytokines was significantly higher in T2DM patients than in controls. IL-6 levels were markedly higher in the diabetic group (8.92 ± 2.31 pg/mL vs. 3.84 ± 1.12 pg/mL, $p < 0.001$), as were TNF-α levels (14.75 ± 3.64 pg/mL

vs. 7.42 ± 2.01 pg/mL, $p < 0.001$). Similarly, CRP concentrations were significantly increased among patients (6.8 ± 2.9 mg/L vs. 2.4 ± 1.3 mg/L, $p < 0.001$). In contrast, the anti-inflammatory cytokine IL-10 was significantly lower in T2DM patients compared to controls (4.26 ± 1.05 pg/mL vs. 5.12 ± 1.18 pg/mL, $p = 0.002$). These results reveal the existence of a strong inflammatory disproportion in patients with T2DM.

Table. 2: Comparison of Inflammatory Biomarkers Between T2DM Patients and Healthy Controls

Biomarker	T2DM Patients (n=100)	Controls (n=50)	p-value
IL-6 (pg/mL)	8.92 ± 2.31	3.84 ± 1.12	<0.001
IL-10 (pg/mL)	4.26 ± 1.05	5.12 ± 1.18	0.002
TNF-α (pg/mL)	14.75 ± 3.64	7.42 ± 2.01	<0.001
CRP (mg/L)	6.8 ± 2.9	2.4 ± 1.3	<0.001

Comparison of Cytokine Levels and Albuminuria Between Diabetic Patients With and Without Early Nephropathy

Table. 3 shows that the level of pro-inflammatory cytokines was significantly higher in T2DM patients with early nephropathy than those without nephropathy. IL-6 levels were markedly elevated in the early nephropathy group (10.45 ± 2.41 pg/mL vs. 7.85 ± 1.98 pg/mL, $p < 0.001$), as were TNF-α levels (16.89 ± 3.54 pg/mL vs. 13.42 ± 3.11 pg/mL, $p < 0.001$). Conversely, the anti-inflammatory cytokine IL-10 was significantly reduced in patients with early nephropathy (3.79 ± 0.88 pg/mL vs. 4.58 ± 0.97 pg/mL, $p = 0.001$). Additionally, albumin/creatinine ratio was substantially higher in the nephropathy group (74.2 ± 18.9 mg/g vs. 18.6 ± 6.4 mg/g, $p < 0.001$). These results indicate that dysregulation of inflammation is closely linked with early renal involvement of T2DM.

Table. 3: Inflammatory Biomarkers According to Early Nephropathy Status in T2DM Patients

Variable	Without Nephropathy (n=60)	Early Nephropathy (n=40)	p-value
IL-6 (pg/mL)	7.85 ± 1.98	10.45 ± 2.41	<0.001
IL-10 (pg/mL)	4.58 ± 0.97	3.79 ± 0.88	0.001
TNF-α (pg/mL)	13.42 ± 3.11	16.89 ± 3.54	<0.001
Albumin/Creatinine Ratio (mg/g)	18.6 ± 6.4	74.2 ± 18.9	<0.001

Association of IL-6, IL-10, and TNF-α with Glycemic Control, Renal Function, and Inflammatory Markers

Table 4 demonstrates significant correlations between inflammatory biomarkers and key metabolic and renal parameters in T2DM patients. IL-6 showed strong positive correlations with HbA1c ($r = 0.54$), ACR ($r = 0.59$), and CRP ($r = 0.63$), and a significant negative correlation with eGFR ($r = -0.47$) (all $p < 0.001$). TNF-α exhibited a similar pattern, positively correlating with HbA1c ($r = 0.48$), ACR ($r = 0.61$), and CRP ($r = 0.57$), while negatively correlating with eGFR ($r = -0.52$) (all $p < 0.001$). Conversely, IL-10 was negatively correlated with HbA1c, BMI, ACR, and CRP and positively correlated with

eGFR, which implies its protective effect. The results indicate the close association between inflammatory imbalance, glycemic dysregulation, and early renal impairment in T2DM.

Table. 4: Pearson Correlation between Inflammatory Biomarkers and Clinical Parameters in T2DM Patients

Variable	IL-6 (r)	p-value	IL-10 (r)	p-value	TNF-α (r)	p-value
HbA1c	0.54	<0.001	-0.32	0.002	0.48	<0.001
BMI	0.41	<0.001	-0.21	0.034	0.36	0.001
eGFR	-0.47	<0.001	0.29	0.004	-0.52	<0.001
ACR	0.59	<0.001	-0.38	<0.001	0.61	<0.001
CRP	0.63	<0.001	-0.35	<0.001	0.57	<0.001

Independent Predictors of Early Renal Impairment Based on Inflammatory and Metabolic Parameters

Table. 5 shows the multivariate logistic regression analysis which was used to identify the independent predictors of early nephropathy in T2DM patients. IL-6 was significantly associated with increased risk, with each 1 pg/mL increase raising the odds by 42% (OR = 1.42, 95% CI: 1.21–1.67, $p < 0.001$). Similarly, TNF-α independently increased nephropathy risk (OR = 1.36, 95% CI: 1.18–1.58, $p < 0.001$). In contrast, IL-10 demonstrated a protective effect, as higher levels were associated with reduced risk (OR = 0.74, 95% CI: 0.59–0.92, $p = 0.008$). Among metabolic parameters, HbA1c (OR = 1.58, $p = 0.002$) and BMI (OR = 1.12, $p = 0.011$) were also significant predictors. These results verify that early diabetic kidney damage is caused by pro-inflammatory cytokines and inadequate diabetes glycemic control.

Table. 5: Multivariate Logistic Regression Analysis for Prediction of Early Nephropathy in T2DM Patients

Variable	OR	95% CI	p-value
IL-6 (per 1 pg/mL increase)	1.42	1.21 – 1.67	<0.001
TNF-α (per 1 pg/mL increase)	1.36	1.18 – 1.58	<0.001
IL-10 (per 1 pg/mL increase)	0.74	0.59 – 0.92	0.008
HbA1c	1.58	1.19 – 2.09	0.002
BMI	1.12	1.03 – 1.22	0.011

Discussion

The present study has also brought out the apparent presence of inflammatory imbalance in patients with type 2 diabetes mellitus (T2DM) particularly among individuals with early nephropathy. The baseline description made the patients and the controls similar in terms of age and sex that minimized the demographic confounding. However, T2DM patients had much higher BMIs, systolic blood pressure, and lower HbA1c and lower eGFR. The findings are congruent with the established metabolic phenotype of T2DM in

which gluttony, high blood pressure, and persistent hyperglycemia are all conditions that result in microvascular damage and renal failure (19). High BMI the group of the current study would be an indicator of exaggerated adipose tissue inflammatory signaling, a key factor in insulin resistance of the system and vascular pathology (20). The finding of the current study showed high levels of IL-6 and TNF-α in T2DM patients as opposed to control with significantly low levels of IL-10. The results obtained align with the earlier works that have shown increased pro-inflammatory cytokine in T2DM (21,22). The IL-6 is a multifunctional cytokine that is involved in the production of hepatic CRP, endothelial malfunction, and insulin resistance. Unremitting hyperglycemia facilitates the formation of advanced glycation end-products (AGE), oxidative stress, and the activation of NF-κB, resulting in prolonged IL- 6, TNF-α production (23). TNF-α in this case upsets the signaling of insulin receptors by increasing serine phosphorylation of insulin receptor substrate-1 (IRS-1), thus worsening insulin resistance (24). The reduction in the IL-10, which is an anti-inflammatory cytokine, is observed and it indicates poor regulation of the immune functions in diabetes patients. The IL-10 naturally suppresses the effects of macrophage activation and pro-inflammatory cytokine release and thus, its depletion can allow the uncontrolled inflammatory development (25).

The subgroup analysis showed that patients who had early nephropathy had significantly higher levels of IL-6 and TNF-α and lower levels of IL-10. This is consistent with findings that diabetic nephropathy is not only a hemodynamic disease but it is also an inflammatory disease which includes glomerular and tubular damage caused by cytokines (26). The IL-6 leads to the growth of mesangial cells and the extracellular matrix, whereas TNF-α elevates podocyte death and glomerular perm-selectivity (27). The high albumin/creatinine ratio (ACR) in the nephropathy group is also a significant indicator of the presence of connections between inflammation and renal damage. The same results were also indicated by Tayeh *et al.*, (2016), who established that higher levels of IL-6 in circulation were predictors of diabetic kidney disease development (28). On the other hand, other studies have also established lesser linkages between IL-6 and early nephropathy. Differences in the period of disease, glycemic control, sample size or sensitivity of the assay could explain such discrepancies (29).

A correlation analysis of the variables of the current study revealed high positive correlations among IL-6/ TNF-α, HbA1c, BMI, ACR and CRP and negative with eGFR. These findings support the assumption that systemic inflammation is strongly connected with inadequate glycemic regulation and renal failure. Persistent hyperglycemia facilitates the overproduction of reactive oxygen species (ROS) in the mitochondria, triggers inflammatory transcription factors (NF-κB and AP-1), and enhances expression of cytokines (30). The fact that the correlation with CRP is positive also supports the effect of IL-6 on the induction of hepatic acute-phase response. The IL-10 negatively correlates with HbA1c or ACR, which implies that the lack of anti-inflammatory activity can promote the onset of renal damage. This is in accordance with a study that had shown that less IL-10 production predisposes macrophage invasion and glomerular inflammation (31).

The IL-6 and TNF-alpha were the independent predictors of early nephropathy, which remained after the adjustment of HbA1c and BMI. These results are consistent with the past reports which indicated that inflammatory factors are independent predictors of renal deterioration in T2DM (32). The observed odds ratios of 1.42 for IL-6 and 1.36 for TNF-α per unit increase suggest a significant association with early nephropathy, highlighting their potential clinical relevance as inflammatory markers rather than definitive predictive biomarkers. Surprisingly, IL-10 also played a protective role, which is in line with the research indicating that an increase in the IL-10 concentration is linked with a slow pace

of diabetic kidney disease development (33). Nevertheless, other studies have not been able to verify the protective effect of IL-10 (34). This variability could either indicate heterogeneity of patterns of immune response, genetic polymorphism on production of the cytokines or could be due to stage of nephropathy at the time of enrolment.
The systemic inflammatory milieu is further supported with the high CRP levels in T2DM patients. A product of IL-6 stimulation, CRP is also involved in endothelial dysfunction decreasing the bioavailability of nitric oxide and promoting vascular rigidity (35). This impairment of the vessels probably increases the rate of glomerular ischemia and nephron loss. The interaction of metabolic stress, oxidative damage and immune response, therefore, seems to be key in the pathogenesis of diabetic nephropathy (36). Altogether, the evidence of this study confirmed the idea evidence confirms the idea that the nephropathy at the early stage of diabetic patients is a condition of increased inflammatory stimulation and the lack of anti-inflammatory control. The findings of the current study agree with previously published study (37), which further validates the use of the inflammatory hypothesis in diabetic renal disease. The reported differences in certain contradictory studies could be attributed to differences in the population traits, ethnicity, used therapeutic regimens, and the laboratory procedures. Notably, the limitation to causal determination exists because of the cross-sectional character of most studies, including the results of the current study (38).

Conclusion

In conclusion, the results of the current study approved that IL-6 and TNF-alpha are significantly increased and independently associated with early nephropathy in T2DM, however, IL-10 is protective. These results revealed to the mechanistic contribution of cytokine-based inflammation to diabetic renal disease and indicated the possible application of inflammatory biomarkers in the early risk stratification and specific therapeutic treatment.

Declarations

Acknowledgment
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Ethics statement
This study was conducted in accordance with the ethical standards and guidelines outlined in the journal's "Ethics Approval" section. Informed consent was obtained from all participants prior to sample collection.

Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests
The authors declare that they have no competing interests.

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Authors' Contributions
SMH: designed the study, performed the statistical analysis, and drafted the manuscript. NHK: contributed to patient recruitment and sample collection, and performed the laboratory assays. All authors read and approved the final manuscript.

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