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Original Research Article

The Role of Th17/IL-17 Axis and IL-6 in Modulating Lipid Metabolism in Diabetic Patients: A Case-Control Biotechnological Study

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Abstract: ***Background***: Chronic inflammation and dyslipidemia are part of type 2 diabetes mellitus (T2DM) associated cardiovascular complications. Interleukin-6 (IL-6) and interleukin-17 (IL-17) are pro-inflammatory cytokines associated with metabolic disturbances. ***Objectives***: To evaluate the levels of IL-6 and IL-17 in serum of T2DM patients, and to explore their association with lipid profile parameters. ***Methods***: A case-control study with 100 individuals was carried out including T2DM patients (n=50) and healthy group as a control group (n=50). Demographic information was collected such as age, sex and body mass index (BMI). The concentrations of IL-6 and IL-17 were detected by enzyme-linked immunosorbent assay (ELISA). Serum lipid profile, including total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C) and high-density lipoprotein-cholesterol (HDL-C) was evaluated. The data was analyzed using SPSS version 26.0 control-group software. ***Results***: The T2DM patients had significantly higher level of IL-6 (48.3 ± 12.4 pg/mL vs. 18.2±5.6 pg/mL, $p<0.001$) and of IL-17 (35.7±9.8 pg/mL vs 12.4±4.2 pg/ml, $p<0.l$)) than control subjects. T2DM patients had a higher incidence of lipid abnormalities, such as increased TC, TG and LDL-C levels, and decreased HDL-C level. IL-6 was positively correlated with TG ($r=0.64$, $p<0.001$), TC ($r=0.52$, $p<0.001$), and LDL-C ($r=0.48$, $p<0.001$). IL-17 significantly correlated with TG ($r=0.58$, $p<0.001$) and LDL-C ($r=0.44$, $p<0.01$). Both cytokines were inversely associated with HDL-C. ***Conclusion***: Increased levels of IL-6 and IL-17 in T2DM patients are significantly associated with dyslipidemia, supporting their potential value as inflammatory biomarkers for cardiovascular risk analysis in diabetic population.

Keywords: Type 2 Diabetes Mellitus, Interleukin-6, Interleukin-17, Dyslipidemia, Inflammation, Cardiovascular Risk.

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a major health problem, which has increased to over 537 million adults globally in 2021 and is expected to reach 783 million by the year of 2045 (Sun *et al*., 2022). The latter is a unique element of this metabolic disorder, in addition to hyperglycemia due to insulin resistance and a decreased production of insulin, which is the main cause of DM balloon expansion (Donath & Shoelson, 2011; Berbudi *et al*., 2020).

T2DM- related inflammation is regulated by multiple pro-inflammatory cytokines and interleukin-6 (IL-6) and interleukin -17 (IL-17) are the most focused ones. IL-6, a pleiotropic cytokine secreted from multiple cell types such as adipocytes, hepatocytes and immune cells, mediates essential physiologic functions on glucose metabolism and lipid homeostasis (Rehman *et al*., 2021). Increased plasma IL-6 concentrations have consistently been associated with insulin resistance, β-cell dysfunction and increased risk of developing T2DM (Wang *et al*., 2013; Prasad *et al*., 2023).

IL-17 secreted by T helper 17 (Th17) cells has been recently recognized as a key mediator in metabolic inflammation. Recent data indicated that IL-17 induces insulin resistance through induction of inflammatory mediators in adipose tissue and inhibition of the insulin signaling cascades (Ahmed & Gaffen, 2010; Fatima *et al*., 2023). Studies have

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shown that IL-17 production is upregulated in T2DM patients and positively associated with disease severity and impaired glucose metabolism (Jagannathan-Bogdan *et al*., 2011; Zeng *et al*., 2012).

Dyslipidemia is a defined feature of T2DM, and it encompasses high levels of triglycerides (TG), increased low-density lipoprotein cholesterol (LDL-C) levels, low high-density lipoprotein cholesterol (HDL-C) levels, and qualitative lipoprotein compositional changes (Wu & Parhofer, 2014). This lipid profile with an atherogenic potential markedly increases risk of CVD, that is still the No 1 cause of deaths and diseases in diabetics (Emerging Risk Factors Collaboration, 2010). The relationship between inflammation and lipid metabolism has become more recognized, with cytokines acting as direct modulators of hepatic lipogenesis, lipoprotein clearance and of adipose tissue lipolysis (Khovidhunkit *et al*., 2004; McGillicuddy *et al*., 2009).

Although evidence of association between inflammation and metabolic alteration in T2DM is expanding, the detailed relationships among IL-6, IL-17, and lipid abnormalities have not been fully defined yet especially in various ethnic groups. elucidation of these associations is of significant interest as it can reveal important disease mechanisms and potential therapeutic targets to prevent CVD in diabetes patients (Zhao *et al*., 2020; Li *et al*., 2021).

Therefore, the goals of this work were to: (1) determine serum concentrations of IL-6 and IL-17 in T2DM patients when compared with healthy subjects, (2) measure parameters from lipid profile in both groups and (3) study correlations among these inflammatory cytokines along with some lipid markers thus providing a basis for the role they play on diabetic dyslipidemia and cardiovascular disease.

2. MATERIALS AND METHODS

2.1 Study Design and Participants

A total of 100 volunteers were assigned into two groups:

- Group 1 (Control group): Fifty non-diabetic, non-metabolic disordered or chronic inflamed healthy subjects not previously diagnosed with DM-2 in their personal, familiar history participated.
- Group 2 (T2DM group): 50 patients (n=50) with T2DM upon diagnosis based on American Diabetes Association criteria (fasting plasma glucose ≥126 mg/dL or HbA1c ≥6.5%)

2.2 Collection and Processing of Blood Samples

Here, after a 12 h fasting period, venous blood was drawn in all participants between 8:00 and 10:00 A.M. Samples were clotted at room temperature 30 minutes and were centrifuged for 15 min × 3000 rpm. Serum was isolated and transferred to sterile tubes then aggregated at −80°C pending analysis.

2.3 Biochemical Analyses

Glycemic variables Fasting blood glucose (FBG) was estimated by the glucose oxidase method. Hemoglobin A1c (HbA1c) concentration was measured with high-performance liquid chromatography (HPLC).

Lipid Profile:

Total cholesterol (TC) triglycerides (TG), and HDL-cholesterol were assayed by enzymatic colorimetric methods in an automatic chemistry analyzer (Cobas c311, Roche Diagnostics). LDL-cholesterol was assessed by Friedewald equation: LDL-C = TC - HDL-C − (TG/5).

2.4 Cytokine Measurements

Serum IL-6 and IL-17A levels were also measured by commercially available enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems, Minneapolis, MN, USA) as recommended by the manufacturer. Duplicate readings were taken for all samples. The MDCC were 0.70 pg/mL for IL-6 and 15.0 pg/mL for IL-17A. The inter-assay and intra-assay variation coefficients were <5% and <10%, respectively.

2.5 Statistical Analysis

Statistical analyses were conducted using SPSS software, version 26.0 (SPSS Inc., IBM Corp., Armonk, NY, USA). Continuous variables were presented as the mean ± standard deviation (SD) or median (interquartile range), depending on their distribution, which was evaluated by the Shapiro-Wilk test. Qualitative variables were reported as numbers and percentages.

Body size data were compared between groups using independent samples t-test (or Mann-Whitney U test). Categorical variables were analysed by use of the Chi-square test. Correlations between cytokines and lipid parameters were analyzed by Pearson/Spearman correlation coefficient. Univariate and multivariable linear regression analysis was performed to determine independent predictors of plasma levels of IL-6 and IL-17 after adjustment for covariates including age, sex, BMI, and duration of diabetes. $P<0.05$ was considered as statistically significant.

3. RESULTS

3.1 Baseline Characteristics of Study Participants

Table 1 presents the demographic and clinical characteristics of the study population. The mean age of participants was 52.4 ± 8.3 years in the T2DM group and 50.8 ± 7.9 years in the control group, with no significant difference (p=0.32). The sex distribution was balanced, with 26 males and 24 females in each group. However, BMI was significantly higher in T2DM patients (28.7 ± 3.4 kg/m²) compared to controls (24.3 ± 2.8 kg/m², p<0.001).

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Control Group (n=50)	T2DM Group (n=50)	p-value
Age (years)	50.8 ± 7.9	52.4 ± 8.3	0.32
Sex (Male/Female)	26/24	26/24	1.00
BMI (kg/m²)	24.3 ± 2.8	28.7 ± 3.4	<0.001***
Waist circumference (cm)	84.2 ± 6.5	96.8 ± 8.2	<0.001***
Systolic BP (mmHg)	118.4 ± 8.6	132.7 ± 12.4	<0.001***
Diastolic BP (mmHg)	76.3 ± 6.2	84.5 ± 8.7	<0.001***
Diabetes duration (years)	-	6.8 ± 3.2	-
FBG (mg/dL)	88.4 ± 6.3	156.8 ± 28.4	<0.001***
HbA1c (%)	5.2 ± 0.3	8.4 ± 1.2	<0.001***

*Data presented as mean ± SD. BMI: body mass index; BP: blood pressure; FBG: fasting blood glucose; HbA1c: glycated hemoglobin. ***p<0.001*

3.2 Comparison of Inflammatory Cytokines Between Groups

As shown in Figure 1 and Table 2, serum IL-6 levels were significantly elevated in T2DM patients (48.3 ± 12.4 pg/mL) compared to healthy controls (18.2 ± 5.6 pg/mL, p<0.001), representing a 2.65-fold increase. Similarly, IL-17 concentrations were markedly higher in the T2DM group (35.7 ± 9.8 pg/mL) versus controls (12.4 ± 4.2 pg/mL, p<0.001), showing a 2.88-fold elevation.

Table 2: Comparison of Inflammatory Cytokines and Lipid Profile Between Groups

Parameter	Control Group (n=50)	T2DM Group (n=50)	p-value
Inflammatory Markers			
IL-6 (pg/mL)	18.2 ± 5.6	48.3 ± 12.4	<0.001***
IL-17 (pg/mL)	12.4 ± 4.2	35.7 ± 9.8	<0.001***
Lipid Profile			
Total cholesterol (mg/dL)	178.4 ± 22.6	224.8 ± 36.4	<0.001***
Triglycerides (mg/dL)	118.6 ± 28.4	198.7 ± 52.3	<0.001***
LDL-C (mg/dL)	102.3 ± 18.7	142.6 ± 32.8	<0.001***
HDL-C (mg/dL)	52.4 ± 8.3	38.2 ± 6.7	<0.001***
TC/HDL-C ratio	3.5 ± 0.6	6.1 ± 1.2	<0.001***
TG/HDL-C ratio	2.3 ± 0.7	5.4 ± 1.8	<0.001***

*Data presented as mean ± SD. IL-6: interleukin-6; IL-17: interleukin-17; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides. ***p<0.001*

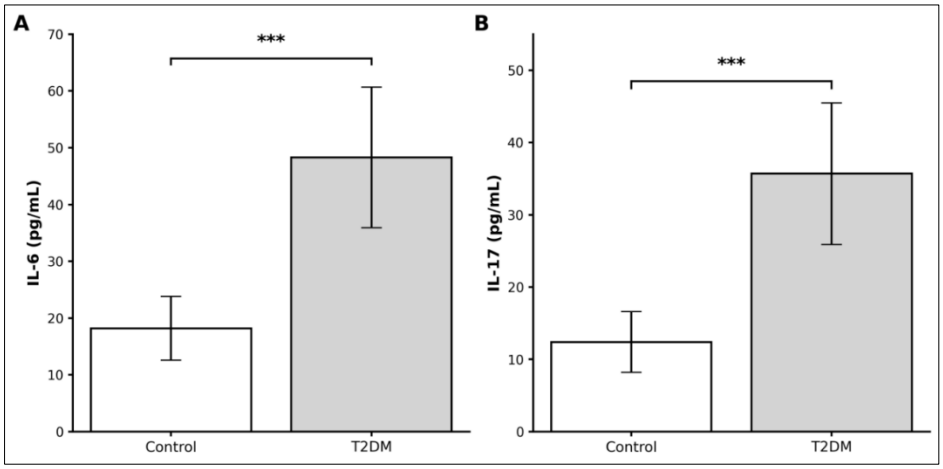

Figure 1: Comparison of Serum IL-6 and IL-17 Levels between Control and T2DM Groups

3.3 Lipid Profile Comparison

Abnormal lipid profile was significantly higher among T2DM patients (Table 2). The diabetic group had increased total cholesterol (224.8 ± 36.4 mg/dL vs. 178.4 ± 22.6 mg/dL, p<0.001). There was a significant increase in the triglyceride levels (198.7 ± 52.3 mg/dL vs. 118.6 ± 28.4 mg/dL, p<0.001). LDL-cholesterol was higher in T2DM patients than in controls (142.6±32.8 mg/dl vs. 102.3±18.7 mg/dl, p<0.001). Patients with diabetes, however had significantly lower HDL-cholesterol (38.2 ± 6.7 mg/dL versus 52.4 ± 8.3 mg/dl, p<0.001). Atherogenic indices (TC/HDL-C and TG/HDL-C ratios) were significantly higher in T2DM.

3.4 Correlations of Cytokines and Lipid Parameters

The results of correlation analysis showed that the levels of inflammatory cytokines were correlated with lipid markers in patients with T2DM (Table 3 and Figure 2).

IL-6 was positively associated with triglycerides (r=0.64, p<0.001), total cholesterol (r=0.52, p<0.001) and LDL-C(r= 0.48, p< 0.001). A negative correlation of a moderate degree was found between IL-6 and HDL-C (r=-0.56, p<0.001). IL-17 was positively correlated with TG (r=0.58, p<0.001), TC (r=0.41, p=0.003) and LDL-C (r=0.44, p= 0.001), and negatively correlated with HDL-C (r=-0.49, p<0.001).

For both these cytokines, significant positive relationships with HbA1c were observed (IL-6: r=0.54, p<0.001; IL-17: r=0.47, p<0.001) and BMI (IL-6: r=0.43, p=0.002; IL-17: r=0.38, p= 006). Among the atherogenic indices, TG/HDL-C ratio was strongly correlated with IL-6 (r=0.68, p<0.001) and IL-17 (r=0.59, p<0.001).

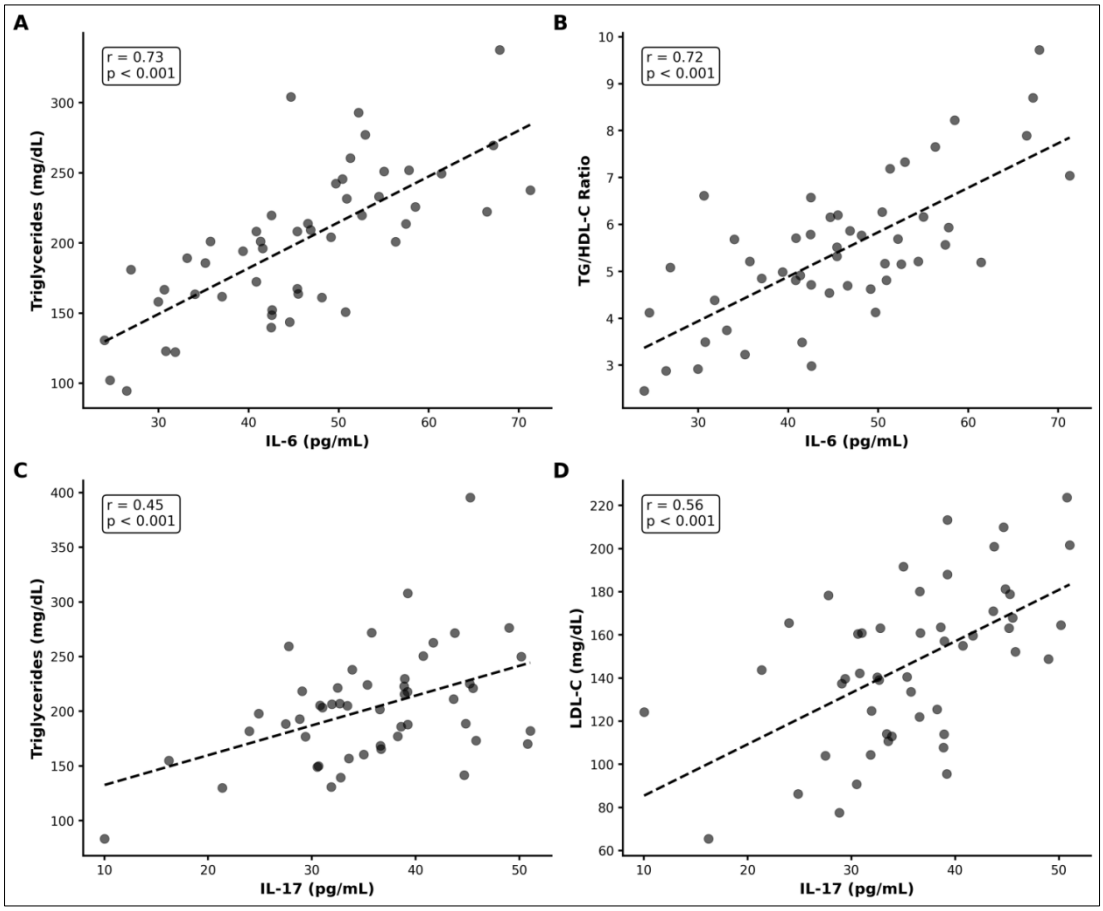

Figure 2: Correlation between IL-6, IL-17 and Lipid Parameters in T2DM Patients

4. DISCUSSION

The present study offers complete proof that inflammatory cytokines IL-6 and IL-17 were increased in T2DM patients and they had strong connections with atherogenic lipid disorder. Our observations add to an emerging body of evidence implicating chronic inflammatory activation in metabolic derangements in the setting of diabetes and suggest mechanisms that may underlie increased cardiovascular risk in these individuals. The significantly higher IL-6 and IL-17 levels in the T2DM included patients also correspond with evidence for persistent inflammatory activation in diabetes (Rehman *et al*., 2021; Fatima *et al*., 2023). The 2.65-times enhancement of IL-6 was in agreement with that of Wang *et*

al., (2013) who found similar increments and associated them with the severity of IR. Mainly produced by adipocytes in the context of metabolic diseases, IL-6 induces the production of hepatic glucose, inhibits insulin signaling pathway via SOCS3 activation and participates in beta-cell deterioration (Akbari & Hassan-Zadeh, 2020).

The 2.88-fold increase in IL-17 is of particular note, as the potential role for Th17-mediated immunity during T2DM has been studied relatively less than other inflammatory pathways. Our findings validate the results of Zeng *et al*., (2012) and most recently Fatima *et al*., (2023), who established that IL-17 accelerates adipose inflammation and subsequently exacerbates insulin resistance via induction of pro-inflammatory effectors. The Th17/IL-17 axis has been suggested to be correlated with the development from insulin resistance to manifest diabetes, and as such may serve as a biomarker and also as an attractive therapeutic target (Jagannathan-Bogdan *et al*., 2011; Li *et al*., 2021).

The significant lipid disorders detected in T2DM women clearly indicate the typical dyslipidemia of diabetic pattern: hypertriglyceridemia, increased LDL-C and decreased HDL-C (Wu & Parhofer, 2014). The 67% rise in levels of triglycerides and the 39% for drug-induced LDL-C increase, along with a reduction in HDL-C (-27%), generates an extremely atherogenic lipidaemic profile, which significantly increases the cardiovascular risk. These results are in accordance with the findings of large epidemiological studies which have reported that dyslipidemia in diabetics is a significant risk factor for 2-4 times higher mortality from cardiovascular diseases as compared to nondiabetic individuals, as reported by Emerging Risk Factors Collaboration, (2010).

The high atherogenic indices (TC/HDL-C and TG/HDL-C ratios) observed in our group of T2DM individuals are particularly alarming, as these indicies represent better predictors of cardiovascular events than individual lipid parameters alone (Millán *et al*., 2009). The TG/HDL-C ratio, the strongest correlated index with both cytokines in our study, represents a surrogate marker of insulin resistance but also of small dense LDL particles (the most atherogenic lipoprotein subfraction) (McLaughlin *et al*., 2003).

4.3 Appraisement of the Association between Inflammatory Cytokines and Lipid Parameters

The strong positive relationships between IL-6 and lipid variables, specifically TG (r=0.64) and TG/HDL-C ratio (r=0.68), offer valuable information on possible mediatory connections. It is also known that IL-6 induces hepatic VLDL production, increases lipoprotein lipase activity in adipose tissue and the release of free fatty acid from it, as well as inhibits HDL-mediated reverse cholesterol transport (Khovidhunkit *et al*., 2004; McGillicuddy *et al*., 2009). These are possible reasons why IL-6 is significantly related to hypertriglyceridemia in our study.

Recent studies have validated our results for IL-6 and lipids. Prasad *et al*., (2023) reported same correlations and also observed that IL-6 polymorphism relating to elevated circulating concentration of IL-6 was associated with higher risk for severe dyslipidemia among diabetics. Additionally, Sun *et al*., (2022) demonstrated that blockade of IL-6 ameliorated dyslipidaemias in experimental models, providing evidence for a causal role.

The correlations between IL-17 and lipid values are significant, although they are a bit less weak than those of IL-6, but it is still meaningful to give them for the body of literature. IL-17 was reported to promote the formation of foam cells, increase oxidative stress in vascular cells and induce secretion of other pro-inflammatory factors, all contributing to atherosclerosis (Ahmed & Gaffen, 2010; Zhao *et al*., 2020). The fact that IL-17 was positively correlated with LDL-C (r=0.44) and inversely with HDL-C (r=-0.49) indicated that Th17-mediated immune response might act primarily on lipoprotein metabolism.

Mechanistic evidence suggests that IL-17 may inhibit hepatic lipid metabolism by modulating the SREBP pathways, reducing ATP-binding cassette transporters implicated in cholesterol efflux (Li *et al.,* 2021). In addition, IL-17 contributes to visceral adipose tissue (VAT) dysfunction, an important mediator of atherogenic dyslipidemia in T2DM (Fatima *et al*., 2023).

The significant associations between these two cytokines and atherogenic indices have clinical relevance. Such a "dual combination of high inflammatory markers and dyslipidaemia" generates "double hit" that is more additive than multiplicative for the development of atherosclerosis and cardiovascular consequences resistance--related comorbid conditions. Our multiple regression analysis revealed that the triglycerides and atherogenic ratios still exhibited significant association with IL-6 and IL-17 levels even after adjusting for conventional risk factors, indicating the stability of these associations was originated from their clinical relevance.

These observations provide evidence that T2DM is to be considered not as a metabolic disease but rather an inflammatory syndrome with significant impact on lipid metabolism and cardiovascular health (Berbudi *et al*., 2020; Zhao *et al*., 2020). The identification of IL-6 and IL-17 as risk indicators for dyslipidemia indicates that they might serve as markers on top of classic lipid parameters for the stratification of CVD risk in diabetic patients.

Our findings of positive correlations of both cytokines with HbA1c suggest that chronic hyperglycaemia may be a source of inflammatory activation. It is a vicious cycle: insulin resistance and disrupted glycemic control by chronic inflammation; persisting hyperglycemia induces pathways of inflammation via AGEs formation and oxidative stress (Akbari & Hassan-Zadeh, 2020). This results in a vicious circle, which promotes metabolic dysfunction as well inflammatory impairment.

This subanalysis of the study showed that adiposity plays a major role in the association between inflammation and dyslipidemia, observing higher cytokine levels in overweight and obese T2DM patients. This observation emphasizes the function of the adipose tissue as an endocrine organ involved in release of pro-inflammatory adipokines and cytokines (Rehman *et al*., 2021). Specifically, visceral adiposity has been demonstrated to be associated with increased infiltration of Th17 cells and increased IL- 17 production, which may contribute to systemic inflammatory status and metabolic dysfunction (Fatima *et al*., 2023; Akbari & Hassan-Zadeh, 2020). IL-17 inhibitors, approved in autoimmune disease, could have similar applications for metabolic disease. Preclinical reports have shown decreased insulin sensitivity, adipose tissue inflammation and dyslipidemia after IL-17 neutralization (Li *et al*., 2021). Nevertheless, there is necessity for clinical trials to determine safety and efficacy in T2DM populations. Apart from specific anti-cytokine treatment, non-pharmacological lifestyle adjustments including weight reduction, physical activity and dietary manipulations reduce inflammatory cytokines as well as enhance lipids profile in the T2DM individuals (Prasad *et al*., 2023). Such non-pharmacological interventions are still the mainstay of diabetes care, and might even show beneficial effects in patients with elevated inflammatory markers.

5. CONCLUSION

In this study, the obvious increase of IL-6 and IL-17 in T2DM patients is evident, as well as strong associations between these inflammatory cytokines and atherogenic lipid disturbances. The high relationship of IL-6 and IL-17 with dyslipidemia, particularly hypertriglyceridemia and decreased HDL-C, indicate that chronic inflammation has a pivotal role in pathogenic processes of diabetic dyslipidemia and cardiovascular risk. These results substantiate the concept of T2D as an inflammatory disorder and reveal that IL-6 levels, as well as other inflammation markers such as IL-17 may be useful for the estimation of cardiovascular risk in diabetic population.

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