Research Article

Interleukin-39 as an Emerging Biomarker Cytokine in patients with type 2 diabetes Mellitus Diagnosis: Narrative review

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Abstract

It is a worldwide complicated metabolic disorder linked to impaired insulin action, chronic low-grade inflammation, and dysfunctional β-cells. Interleukin-39 (IL-39) has been identified as a new cytokine associated with immune modulation and metabolic dysfunction recently. Recent research has highlighted IL-39 as a biomarker in and an interventional target for T2DM. That review provides a brief of the present evidence on IL-39 biology and its relevance to T2DM pathophysiology.

KEYWORDS: Interleukin 39(IL-39), Diabetes mellitus (T2DM), participants, healthcare

1. INTRODUCTION

1.1. Type 2 diabetes mellitus (T2DM)

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that has attracted considerable global attention from healthcare professionals. Its prevalence is projected to continue increasing over time. It is associated with a high rate of morbidity annually. (Khan et al.). The pathogenicity of T2DM is represented by insulin deficiency and resistance, resulting from disturbances in lipid and glucose metabolism. Hyperglycemia and dyslipidemia are linked to long-term microvascular and macrovascular complications in T2DM patients, including peripheral neuropathy and cardiovascular events. (Galicia-Garcia et al., 2020). T2DM is implicated in a wide range of comorbidities, especially microvascular issues such as peripheral neuropathy and diabetic retinopathy, which limit therapeutic interventions and complicate the effectiveness of chronic disease control strategies (Goldney et al., 2023). Experimentally, researchers have linked immune responses alteration, especially anti- and-pro inflammatory cytokines, to the development of T2DM and its complications (Zheng et al., 2021). Pro-inflammatory factors such as tumour necrosis factor (TNF- α), chemotactic protein secreted by macrophage(IL-1, IL-1β, and IL-6) are implicated in pancreatic β-cell death and insulin resistance (Nirenjen et al., 2023).As well as their effect on acute-phase proteins production that worsens insulin resistance and exaggerates diabetes progression (Elimam et al., 2019). Recently, inflammatory mediators have been investigated as potential therapeutic markers for diabetes and the prevention of chronic complications arising from hyperglycemia.(Velikova et al., 2021).

1.2. Interleukin 39

Interleukin 39 (IL-39) represents one of the most recent emerging cytokines belonging to the IL-12 family (IL-27, IL-23, and IL-35). All members of the IL-12 family share the same heterodimer structure and receptor features; thus, this family potentially overlaps in their biological purposes (Wang et al., 2016). All cytokines inside this family share identical heterodimeric shapes and receptor motifs, suggesting that their biological roles may overlap (Luo et al., 2024).

This innovative cytokine is predominantly generated by lipopolysaccharide-activated B cells, although dendritic cells and macrophages have also been identified as possible sources. IL-39 activates the STAT1 and STAT3 signaling pathways, thereby inducing pro-inflammatory effects by binding to the IL-23R/gp130 receptors (Lu et al., 2020).

Moreover, the researchers suggested that IL-39 could act as a biomarker for systolic abnormalities upon discovering significantly elevated amounts of the protein in the bloodstream of individuals with acute coronary syndrome. There is some disagreement among people about IL-39 secretion. Ecoeur and colleagues reported that, although the IL-23p19 and EBI3 subunits can be co-expressed, IL-39 has not been confirmed as a functional cytokine in humans (Ecoeur et al.,2020). Other authors hypothesized that IL-39 may function as an immunoregulatory cytokine exclusively in mice (Luo et al., 2017). Conversely, detectable concentrations of IL-39 have been proven in serum of human (Yang et al., 2020). Also, IL-39 reported as concanavalin A-induced hepatitis worsening cause (Li et al., 2021).

2. METHODOLOGY

2.1. Search Strategy

PubMed, PubMed, Goggle scholar, and Scopus were explored to perform a comprehensive literature search for English-language papers published between 2016 and 2025. Three researchers separately searched and manually screened for relevant publications on the role of IL-39) in T2DM.

Eligibility Criteria

Studies were chosen based on the following criteria:
• Population: participants with T2DM or in vitro studies examining IL-39 and metabolic inflammation were incorporated for mechanistic elucidation.
• Exposure: Interleukin-39 (IL-39) levels or signaling pathways.
• Study design: experimental studies and observational studies (cross-sectional, case-control, cohort)
• Language: English.

3. RESULTS

A total of 39 search results via database searches. After removing duplicates and finalizing the screening procedure, only three studies concur the inclusion criteria of this review and selected in this qualitative synthesis. The findings of these studies are summarized below. A pivotal 2023 case-control study (n=215) reported a significantly higher median IL-39 concentration at 66 ng/L in T2DM vs. 31 ng/L in controls (level of siginificance is 0.001), with ROC-AUC 0.973 (cut-off 46 ng/L; sensitivity/specificity 93%). Positive correlations existed with BMI (p=0.005, rs=0.27) and HbA1c (p=0.001, rs=0.31), stronger in females and non-neuropathic patients; 91.5% of cases were overweight/obese. No post-2023 T2DM-specific publications or trials were identified, limiting generalizability according to (Nussrat and Ad'hiah, 2023).
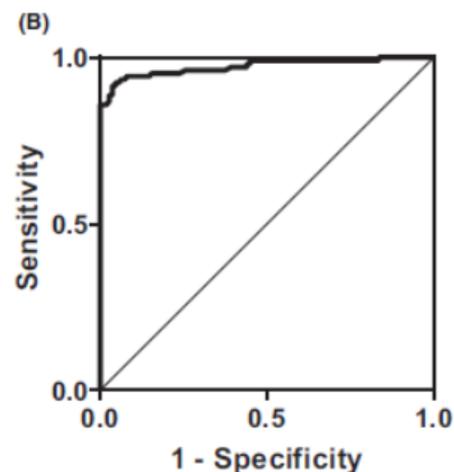

Figure 1 shows the levels of interleukin -39 using ROC curve analysis (Nussrat and Ad'hiah, 2023).

In contrast, in a study conducted by (Adnan and Alwan, 2024) the ROC curve outcomes showed that IL-38 had the highest level of sensitivity (96%) and specificity (95%) compared to IL-39 sensitivity and specificity that was (80% and 75%, respectively) at cutoffs of (>251.21 and >182.29) respectively,

in predicting individuals with T2DM with significant variation (p<0.05) (figure 2). While another study revealed that IL-38 shows lower levels in patients with T2DM in comparison to control group (Zhao et al., 2022).
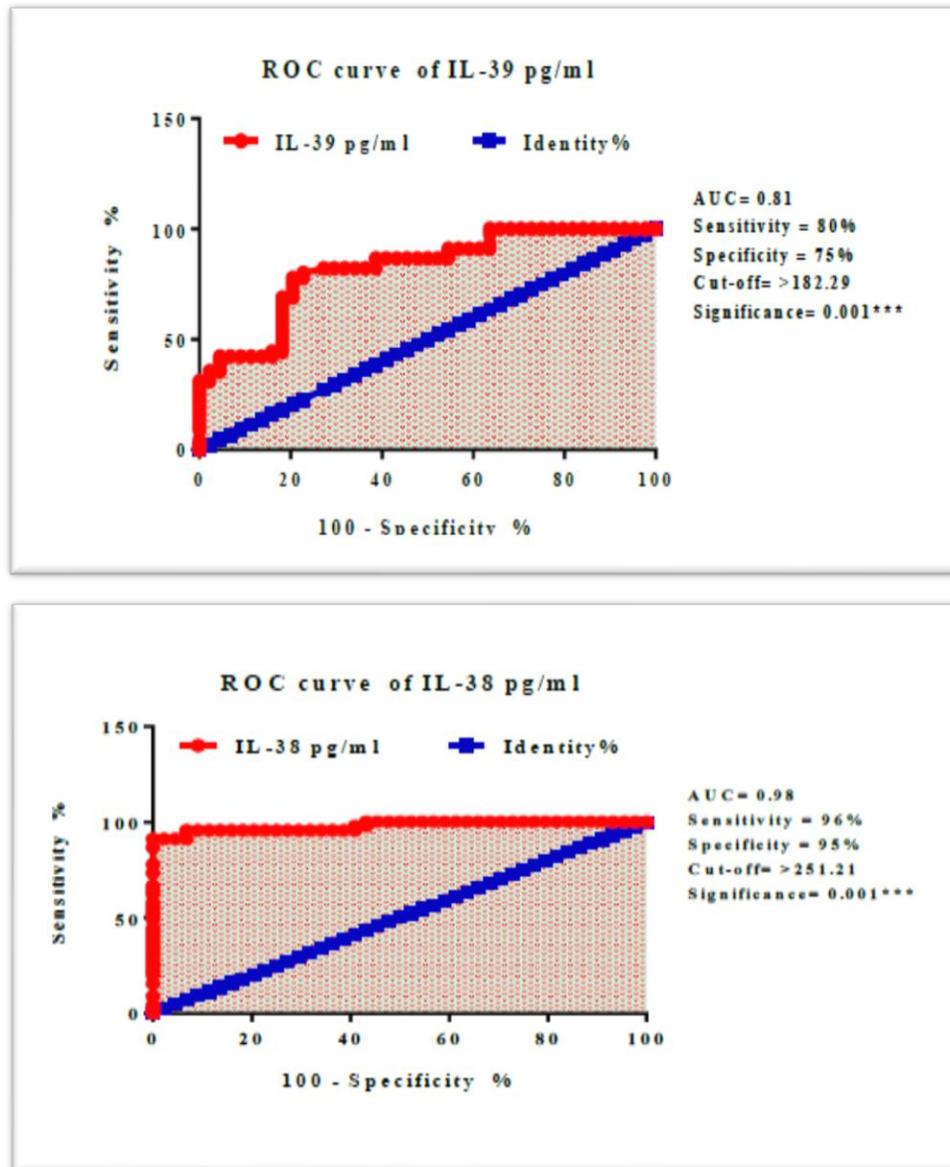

Figure 2: Roc curve of IL-38 and IL-39 indicators (Adnan and Alwan, 2024)

The third study was a case-control conducted on 60 individuals with T2DM and 50 healthy volunteers which revealed a significant association between IL-39 and T2DM. The mean serum level of IL-39 was (87.25 ± 10.24, higher than non-diabetic controls (64.14 ± 2.07), p = 0.03
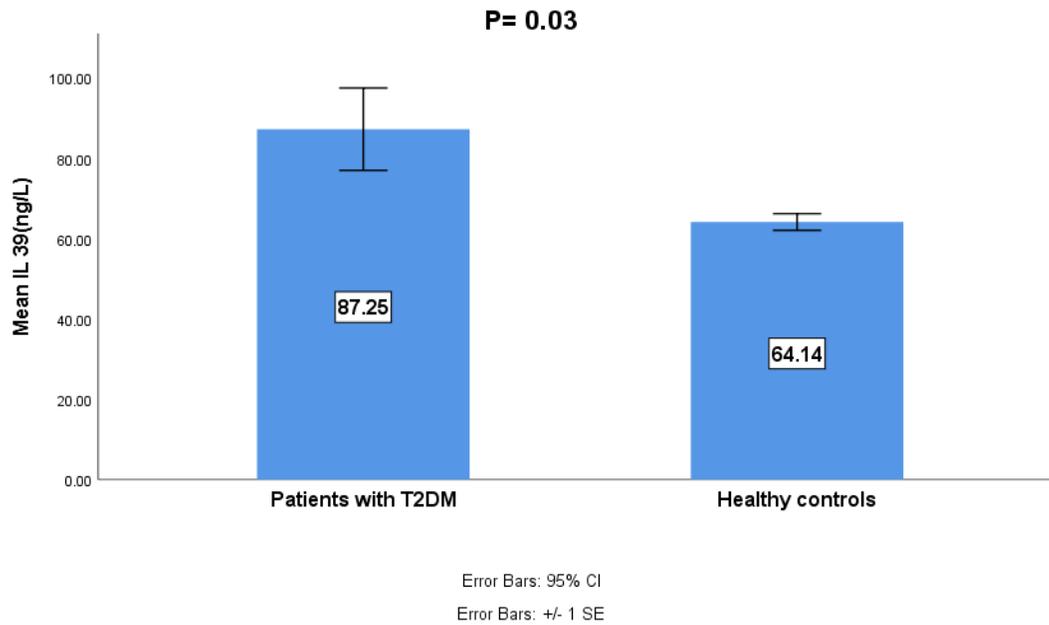
P= 0.03

Figure 3. Mean of IL-39 serum level in patients and controls (Rasheed et al., 2025).

4. CONCLUSION

This review summarises increasing evidence linking interleukin-39 (IL-39) as a possible contribution to the chronic inflammatory state that underpins T2DM. Despite the limited number of available studies only three to date this review represents the first comprehensive synthesis specifically addressing the role of IL-39 in T2DM diabetes mellitus. The lack of study emphasizes the originality of this subject and reveals a significant deficiency in the existing comprehension of inflammatory pathways in diabetes. By consolidating existing evidence, this review provides a valuable foundation for future investigations and draws attention to IL-39 as a promising.

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