

Original article

Elevated Serum Cytokines as Biomarkers for Type 1 Diabetes Mellitus in Diyala Province

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Abstract

The study aims to examine the levels of cytokines in the serum of individuals with type 1 diabetes mellitus and compare these levels to those of healthy controls. This research aimed to assess the levels of some cytokines that includes IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21 and IL-33 in Type I diabetes mellitus. In this study, 60 samples were collected from patients and 30 samples from healthy individuals, collected during the period from the of July 2023 to the March 2024. Results of this study showed a significant increase in the concentration of IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21 and IL-33 in the serum of type 1 diabetes mellitus with the control group there were [10.22±2.065, 73.983±5.117, 35.90±3.343, 3.10±1.612, 19.80±3.433, 20.86±4.010, 70.75±8.57, and 398.71±47.157, respectively] than in healthy groups [6.793±0.924, 47.00±5.535, 20.72±2.534, 1.01±10.597, 10.34±2.036, 10.79±1.818, 44.83±7.201 and 277.59±39.451, respectively]. The results of the current study showed an imbalance in cytokines production that includes IL 4, IL 9, IL 13, IL 35, IL 12, IL 17, IL 21 and IL 33 in type 1 diabetes mellitus [T1DM] patients. The imbalance between pro- and anti-inflammatory cytokines could contribute to pancreatic β -cell destruction, offering insights for potential biomarkers and future therapies.

Keywords: Immune-Mediated Diabetes, Cytokine Imbalance, ELISA.

Introduction

Diabetes represents a complex group of metabolic disorders defined by abnormally high blood sugar levels, which stem from defects in insulin secretion, insulin action, or both. Sustained hyperglycemia is strongly associated with severe, long-term complications, leading to progressive damage, disability, and potential failure of many organs, most particularly the kidneys, nerves, and heart [1]. T1DM is a highly aggressive autoimmune disorder where T-cells relentlessly target and destroy the pancreatic beta cells [β -cells] that produce insulin. This leads to a significant reduction or complete absence of insulin secretion, while the immune system simultaneously generates autoantibodies against the islet cells of Langerhans [2].

Cytokines are proteins produced by various cell types, serve as key immune mediators and regulators [3]. These proteins have a critical role during T1DM development by coordinating the reactions between immune cells and pancreas [β -cells] and this feature employed by scientists as target to suspected treatment development [4]. Cytokines play important roles in the pathogenesis of T1DM, influencing the immune-mediated destruction of pancreatic β -cells. Pro inflammatory cytokines such as IL-1B have role in induces oxidative stress and inflammatory B cells pathways that leading to apoptosis [5]. Anti-inflammatory cytokines such as IL-10 have impartment role as immunoregulatory that can suppresses inflammation and promotes tolerance [6].

Several cytokines have been shown to be elevated in type 1 diabetes mellitus, contributing to both the inflammatory processes and the destruction of pancreatic beta cells. Key cytokines involved include IL-1 β , IL-17, and IFN- γ , each of which influences the immune response and pancreatic function in distinct ways [7]. Proinflammatory and also anti-inflammatory cytokines documented their role in the pathogenesis of T1DM [8]. These cytokines have role in disrupt insulin action in their receptors on cell surface and may finally lead to insulin resistance [IR] [9]. Another study documented that increase level of IL-17 as proinflammatory cytokines, and decrease IL-10 as anti-inflammatory cytokine led to disruptions in the reaction of immune system responses and usually associated with T1DM development [4,10]. IL-35, as member of IL-2 family consider as a powerful inhibitory cytokine has role in T1DM disease [4]. Therefore, the objective of the current study was to assess the levels of certain inflammatory cytokines in T1MD as attempt to understanding the underlining of T1DM development. This research aimed to assess the levels of some cytokines that includes IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21 and IL-33 in Type I diabetes mellitus.

Methods

In this study, 90 samples were collected, 60 samples were collected from patients diagnosed with T1DM and 30 samples were collected from healthy individuals. The patients were diagnosed by a specialist physician at the advisory clinic of Baquba Teaching Hospital, Diyala Province, Iraq, between August 2023 and May 2024. The T1DM group involved of 24 males and 36 females, while the control group included healthy individuals of both sexes. Venous blood samples [5 mL] were drawn from each participant and the samples were processed by centrifugation [3,000 rpm for 5 minutes].

Serum aliquots of 250 μ L were prepared and stored at -20°C until further analysis. Serum levels of inflammatory cytokines [IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21, IL-33] were measured using a Sandwich Enzyme Linked Immunosorbent Assay [ELISA], that procured from a Shanghai-based manufacturer. The Statistical Package for the Social Sciences [SPSS] version 22 was used for Description of quantitative variables as mean, SD and range, Description of qualitative variables as number and percentage, Unpaired t-test was used to compare quantitative variables [11].

Results

As indicated in Table [1], this study comprised 90 samples divided into two groups: 60 samples for type I diabetes and 30 samples for the control group.

Table 1. The gender-based study's distribution

Study groups	Gender	T1DM		P. value
		N	%	
Patients	Female	37	41.1	0.067
	Male	23	25.5	
Controls	Female	19	21.1	0.061
	Male	11	12.2	

The mean serum concentration of IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21 and IL-33 was seen highest in patients with T1D [10.22 \pm 2.065, 73.983 \pm 5.117, 35.90 \pm 3.343, 3.10 \pm 1.612, 19.80 \pm 3.433, 20.86 \pm 4.010, 70.75 \pm 8.57, and 398.71 \pm 47.157, respectively] than in healthy groups [6.793 \pm 0.924, 47.00 \pm 5.535, 20.72 \pm 2.534, 1.01 \pm 10.597, 10.34 \pm 2.036, 10.79 \pm 1.818, 44.83 \pm 7.201 and 277.59 \pm 39.451, respectively [Table 2].

Table 2. Level of study's cytokines in patients with T1DM compared to the control group

Parameter		Patients [60 N]	Control [30 N]	P. value
		[Mean \pm S.D]	[Mean \pm S.D]	
Proinflammatory cytokines	IL-4	10.22 \pm 2.065	6.793 \pm 0.924	0.061
	IL-9	73.983 \pm 5.117	47.00 \pm 5.535	0.094
	IL-13	35.90 \pm 3.343	20.72 \pm 2.534	0.082
	IL-35	3.10 \pm 1.612	1.01 \pm 10.597	0.052
Anti-inflammatory cytokines	IL-12	19.80 \pm 3.433	10.34 \pm 2.036	0.071
	IL-17	20.86 \pm 4.010	10.79 \pm 1.818	0.002
	IL-21	70.75 \pm 8.57	44.83 \pm 7.201	0.002
	IL-33	398.71 \pm 47.157	277.59 \pm 39.451	0.002

Table [2] shown cytokine levels between patients and healthy controls for several cytokines [IL-4, IL-5, IL-13, IL-35, IL-12, IL-17, IL-21, and IL-33]. The Levels of IL-4 are low in both patients and controls, with slightly higher levels in patients. The Patients show a higher level of IL-5 compared to controls, but both are relatively low. Both groups have approximately similar non-significant low levels of IL-12, IL-13, IL-17, and IL-35. In results of IL-21 the patients show slightly elevated levels compared to controls, both are low overall but higher previous ILs mentioned. Finally, IL-33: This cytokine shows the highest levels, significantly elevated in both patients and controls, with patients having higher levels.

The correlations between proinflammatory cytokines [IL-4, IL-9, IL-13 and IL-35] and anti-inflammatory cytokines [IL-12, IL-17, IL-21 and IL-33] in T1DM patients as results shown in table No.3, IL4P has a moderate significant positive correlation with IL35P [r=0.274] and IL21P [r=0.288]. and IL9P exhibits strong positive correlations with IL35P [r=0.395], IL17P [r=0.519], and IL33P [r=0.426], while a strong negative correlation shown with IL12P [r=-0.374]. The negative correlations appeared between IL13P with IL35P [r=-0.347] and IL12P [r=-0.269]. while IL35P shows significant positive correlations with IL9P [r=0.395], IL17P [r=0.406], and IL33P [r=0.387]. IL12P has a strong negative correlation with IL9P [r=-0.374] and IL33P [r=-0.333]. IL17P is positively correlated with IL9P [r=0.519], IL35P [r=0.406], and IL33P [r=0.491]. finally, IL33P shows strong positive correlations with IL9P [r=0.426], IL35P [r=0.387], and IL17P [r=0.491].

In general, the strongest positive correlations are observed between IL-17P and IL-33P [r=0.491] and between IL-9P and IL-17P [r=0.519]. Conversely, there are moderate negative correlations between IL-12P and IL-9P [r=-0.374] and IL-13P and IL-35P [r=-0.347]. These correlations suggest significant interactions between these cytokines in the context of inflammation or immune response.

Table 3. Correlation between proinflammatory and anti-inflammatory cytokines in T1DM.

Cytokines	IL4P	IL9P	IL13P	IL35P	IL12P	IL17P	IL21P	IL33P
IL4P	1	-0.109	0.104	0.274*	-0.016	-0.13	0.288*	-0.044
IL9P	-0.109	1	-0.028	0.395**	-0.374**	0.519**	-0.015	0.426**
IL13P	0.104	-0.028	1	-0.347**	-0.269*	-0.033	0.017	-0.129
IL35P	0.274*	0.395**	-0.347**	1	0.074	0.406**	0.174	0.387**
IL12P	-0.016	-0.374**	-0.269*	0.074	1	0.034	0.071	-0.333**
IL17P	-0.13	0.519**	-0.033	0.406**	0.034	1	0.037	0.491**
IL21P	0.288*	-0.015	0.017	0.174	0.071	0.037	1	-0.12
IL33P	-0.044	0.426**	-0.129	0.387**	-0.333**	0.491**	-0.12	1

*Correlation is significant at the 0.05 level [2-tailed]. ** Correlation is significant at the 0.01 level [2-tailed].

Figure 1 shown the graph presented shows a Receiver Operating Characteristic [ROC] curve, illustrating the diagnostic performance of various cytokines [IL13P, IL35P, IL4P, IL9P] in distinguishing between patients with Type 1 Diabetes Mellitus and healthy controls. IL35P has the best performance, closely following the reference line, indicating high sensitivity and specificity. IL13P has lower sensitivity and specificity compared to IL35P but still shows moderate diagnostic potential. IL9P and IL4P exhibit lower diagnostic accuracy, as indicated by their curves. The Reference Line [diagonal] represents the performance of a random classifier, and the other curves represent how well each cytokine performs relative to this baseline. Due to previous information, IL35P appears to have the highest diagnostic value based on the ROC curve, followed by IL13P, with IL4P and IL9P showing comparatively lower accuracy.

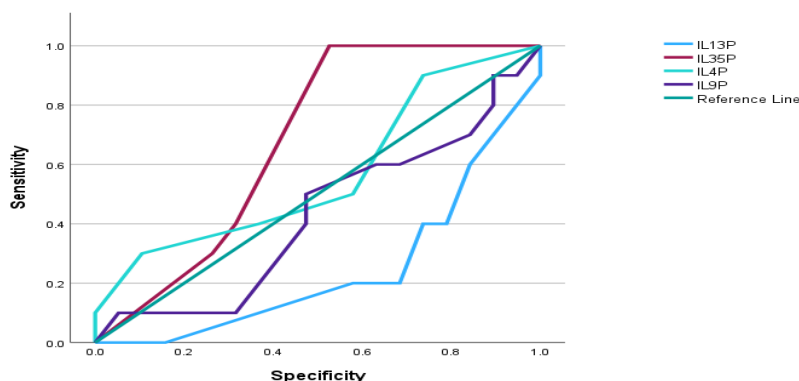
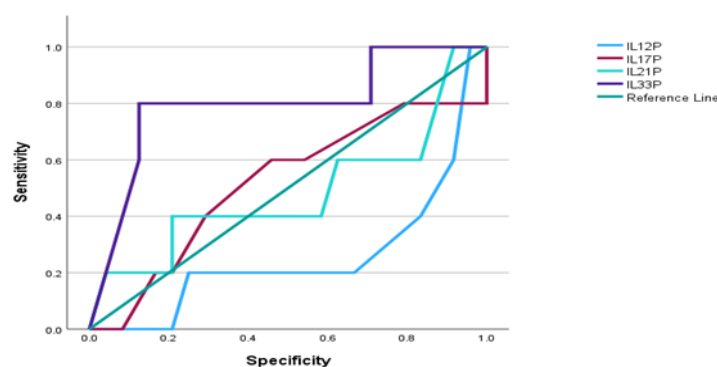
**Figure 1. ROC analysis of proinflammatory cytokines in T1D patients**

Figure 2 shows a Receiver Operating Characteristic [ROC] curve for the cytokines IL12P, IL17P, IL21P, and IL33P, in relation to their ability to distinguish between patients with Type 1 Diabetes Mellitus [T1DM] and healthy controls. IL33P has the best diagnostic performance, with a nearly perfect ROC curve, indicating high sensitivity and specificity. IL17P also performs well, closely following the IL33P curve with good diagnostic accuracy. IL21P shows moderate performance, with its ROC curve indicating a lower balance of sensitivity and specificity compared to IL33P and IL17P. IL12P displays the weakest diagnostic performance, with the curve further from the ideal top-left corner, indicating lower sensitivity and specificity. The Reference Line [diagonal] serves as a baseline, representing a random classifier. In general, IL33P shows the highest diagnostic accuracy, followed by IL17P, while IL12P demonstrates the weakest performance.

**Figure 2. Figure 2: ROC analysis of anti-inflammatory cytokines in T1DM patients**

Discussion

Type 1 diabetes mellitus [T1DM] is a significant autoimmune disorder that predominantly affects individuals with genetic predispositions and is often caused by environmental factors, such as viral infections [12]. It stands as a crucial endocrine condition, leading to the destruction of insulin-producing beta cells within the pancreatic islets [13]. While the exact mechanism which explain the autoimmune reaction that led to T1DM remain unclear. But as believed T-Cells have a vital key role in this mechanism which finally led to beta-cells destruction [14]. Sex hormones also considered as risk factor, which responsible on the increase ratio of diabetes mellitus in females more than males. The behavior of inflammatory cells influenced by sex hormones receptors, and this link shown the correlation between sex hormone and autoimmune development [15]. These autoimmune reactions cause decrease in insulin production due to damage the beta-cells. Pro- and anti-inflammatory cytokines have the vital role in coordinate these reactions [8,16].

Gouda et al documented that several cytokines associated with promote insulin resistance, this study found that increase proinflammatory cytokines act as potential indicator to T1DM development [17]. IL-1 β , IL-2, IL-6, IL-12, TNF- α , IFN- γ , and Interferons level increase in serum of patients with T1DM [18,19]. Through onset and during progressive the T1DM various cytokine such as TGF- β , IL-2 IL-5, IL-4, IL-10, IL-15, IL-33, and IL-35 significantly increase and this may explain the suspect role of these cytokine in T1DM development [20], these findings agree with results of current study.

IL-17 is another cytokine which regulate immune response and their overexpression usually associated with severity of autoimmune development [21]. IL-17 is produced by Th17 cells and has been implicated in the inflammatory process of autoimmune diseases such as T1DM, elevated levels of IL-17 are associated with increased infiltration of immune cells into the pancreatic islets and beta-cell destruction [22]. IL-17 promotes the production of other pro-inflammatory cytokines and chemokines that drive the recruitment of immune cells to the pancreatic islets, contributing to the autoimmune attack [22].

A study agrees with findings of current study found that IL-35 has significant effect as regulator in T1DM development which more common among the children globally [23]. Previous study predicted that IL-35 has protection role against T1DM development through modulating the T and B lymphocytes, and macrophage polarization [24]. Numerous studies have reported an elevated production of IL-17 by T cells in individuals with T1DM, particularly in the early stages of the disease. Children with newly diagnosed or long-standing T1DM [mean age 87 years] exhibited a higher proportion of IL-17-positive T cells compared to age-matched, non-diabetic controls [25]. Additionally, memory T cells from T1D patients demonstrated increased IL-21 production following ex-vivo stimulation when compared to matched controls [26].

There are several studies that discuss the role of cytokines in Type I Diabetes Mellitus [T1DM] in Iraq. Other study focused on understanding the role of cytokines like IFN- γ , IL-10, and IL-6 in the initiation of T1DM, findings emphasized the crucial roles these cytokines may play in the pathogenesis of Type I diabetes [27]. The previous study in Iraq showed a significant increase in the levels of some cytokines [TNF- α and INF- γ] in patient with diabetes mellitus type I compared to the control group [28].

A study conducted by Al-Mashhadani and colleagues focused on the serum levels of interleukins [IL-2, IL-4, IL-6, IL-10] and their relationship with disease progression in T1DM patients [29]. They found that specific cytokines like IL-6 were elevated in patients with Type 1 diabetes mellitus, reflecting an ongoing inflammatory process that might contribute to autoimmune beta-cell destruction.

A previous study in Iraq examined the association between various pro-inflammatory cytokines [such as TNF- α , IL-6, and IL-1 β] and the progression of Type 1 Diabetes in Iraqi children [30]. The results suggested that higher levels of these cytokines correlate with the severity of the disease, and they might be involved in the beta-cell destruction process. This finding is crucial for developing therapeutic interventions targeting these cytokines to prevent or manage T1DM in children. A more recent study looked at the risk of developing T1DM in relation to genetic predisposition and the inflammatory cytokine profile in a cohort of Iraqi patients, this study suggested that cytokine imbalance plays a significant role in the autoimmune attack against pancreatic beta cells, highlighting the importance of managing inflammatory responses in T1DM [31].

Conclusion

This study shows a significant increase in some cytokines in patients with T1DM compared to healthy individuals. Cytokines such as IL-4, IL-9, IL-13, IL-35, IL-12, IL-17, IL-21, and IL-33 are identified as key players in the inflammatory process linked to T1DM. The imbalance between these cytokines may contribute to the autoimmune destruction of pancreatic β -cells, potentially serving as biomarkers for T1DM diagnosis. Future research should investigate cytokine-targeted therapies to restore immune balance and preserve β -cell function.

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Conflicts of Interest. Nil

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المستخلص

تهدف هذه الدراسة إلى فحص مستويات السيتوكينات في مصل الأفراد المصابين بداء السكري من النوع الأول ومقارنة هذه المستويات بمستويات الأفراد الأصحاء. يهدف هذا البحث إلى تقييم مستويات بعض السيتوكينات التي تشمل إنترلوكين-4, إنترلوكين 9, إنترلوكين 13, إنترلوكين 35, إنترلوكين 12, إنترلوكين 17, إنترلوكين 21 وإنترلوكين 33 في مرضى السكري من النوع الأول. تم في هذه الدراسة جمع 60 عينة من المرضى و30 عينة من الأفراد الأصحاء, تم جمعها خلال الفتره من يوليو 2023 إلى مارس 2024. اظهرت نتائج هذه الدراسة زيادة كبيرة في تركيز إنترلوكين-4, إنترلوكين 9, إنترلوكين 13, إنترلوكين 35, إنترلوكين 12, إنترلوكين 17, إنترلوكين 21 وإنترلوكين 33 في مرضى السكري من النوع الأول مقارنة بالأصحاء (2.065±10.22, 5.117±73.983, 3.343±35.90, 1.612±3.10, 3.433 ±19.80, 4.010 ±20.86, 8.57±70.75 و 47.157±398.71 على التوالي مقارنة بالأفراد الأصحاء(0.924±6.793, 5.535±47.00, 2.534±20.72, 10.597±1.01, 2.036±10.34, 1.818±10.79, 7.201±44.83 و 39.451±277.59 على التوالي. اظهرت نتائج الدراسة الحالية خلل في إنتاج السيتوكينات المدروسة في مرضى السكري من النوع الأول. يمكن أن يساهم خلل التوازن بين السيتوكينات المؤيدة والمضادة للالتهابات في تدمير خلايا بيتا البنكرياسية، مما يوفر رؤى حول المؤشرات الحيوية المحتملة والعلاجات المستقبلية.