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Study of Some Pro- Inflammatory and Anti –Inflammatory Interleukins in Diabetic Patients

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Abstract

The Aim of this research is the evaluation of the roles of IL-38 and IL-39 indicators in pathophysiology of diabetic mellitus type II. This research included Forty-five patients with type II diabetes and, Forty-five non infected. All samples were collected from that attending outpatient's clinics after screening them by a specialist physician in capital Baghdad during time period August to December of 2022. All markers were measured by utilizing enzyme linked immunosorbent assay (ELISA). The results of the current research showed that there were no statistically significant differences (P>0.05) between the study groups according to gender and age. And between the levels of IL-38 and IL-39 in diabetic patients and their gender and age groups. But increased levels of IL-38 and IL-39 were observed in patients with type II diabetes compared to healthy controls. IL-38 was found to have the higher sensitivity and specificity (96% and 95%) compared to IL-39 (80% sensitivity and 75% specificity) at cut-offs (>251.21 and >182.29) . Finally, no significant association (P>0.05) was found between IL-38 and IL-39 in diabetic patients, according to Pearson correlation coefficient results.

Keywords: Diabetic mellitus (DM), Immunity, IL-38 and IL-39.

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دراسة بعض الانترلوكينات البادئة للالتهاب والمضادة للالتهاب لدى مرضى السكري

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الخلاصة

الهدف من هذا البحث هو تقييم دور المؤشرات IL-38 و IL-39 في الفيزيولوجيا المرضية لمرض داء السكري من النوع الثاني. شمل هذا البحث خمسة وأربعين مريضاً مصاباً بالسكري من النوع الثاني وخمسة وأربعين مريضاً غير مصابين. تم جمع العينات من المراجعين للعيادات الخارجية بعد فحصها من قبل طبيب متخصص في العاصمة بغداد خلال الفترة الزمنية من اب إلى كانون الاول من عام 2022. وتم قياس جميع العلامات باستخدام مقايسة الممتز المناعي المرتبط بالإنزيم (ELISA) أظهر البحث الحالي عدم وجود فروق ذات دلالة إحصائية (P>0.05) بين مجموعات الدراسة حسب الجنس والعمر. وبين مستويات IL-38 و IL-39 لدى مرضى السكري حسب الجنس وفئاتهم العمرية. ولكن لوحظت زيادة في مستويات IL-38 و IL-39 في المرضى الذين يعانون من مرض السكري من النوع الثاني مقارنة بالأشخاص الأصحاء. وُجد أن IL-38 يتمتع بحساسية ونوعية أعلى (96% و95%) مقارنةً بـ) IL-39حساسية 80% وخصوصية 75%) عند القطع (< 251.21 و> 182.29). وأخيرا، لم يتم العثور على ارتباط كبير معنوي (P>0.05) بين IL-38 و IL-39 في مرضى السكري، وفقا لنتائج معامل الارتباط بيرسون.

الكلمات المفتاحية : داء السكري ، مناعة ، IL-38 ، IL-39.

Introduction

Around ninety-five percent of the incidences associated with diabetes worldwide are caused by type II diabetes mellitus (T2DM), which is the most prevalent metabolic illness within adults. T2DM having a major influence on health care initiatives and medical practices [1]. The condition is linked to the development of many comorbidities, including retinopathy and neuropathy, which make managing type II diabetes more difficult [2]. Hyperglycemia brought on by abnormalities in insulin production and a proper cellular reaction against insulin are the hallmarks of type II diabetes. The fundamental process of T2DM's complicated pathophysiology remains poorly understood. However, a number of interrelated variables have been found to have an etiological involvement in the condition, such hereditary susceptibility, being overweight, life style, and others [3]. Furthermore, dysregulated immune activities, notably those involving pro- and anti-inflammatory cytokines, have been experimentally linked

to the pathophysiology of type 2 diabetes and its consequences [4]. Strong evidence indicates that pro-inflammatory substances are implicated in resistance to insulin and pancreatic β-cell death, including tumor necrosis factor (TNF)-α, macrophage chemotactic protein-1, interleukin (IL)-1β, and IL-6 [5]. Furthermore, cytokines that are anti-inflammatory, including transforming growth factor-β1 (TGF-β1) and adiponectin, are currently linked to the development of type 2 diabetes (T2DM), and anti-inflammatory treatments are recommended to help patients with T2DM achieve improved glycemic control. It has been shown that pro- and anti-inflammatory cytokines have irregularities in type 2 diabetes and are being linked to an increased risk of the illness [6]. New research on T2DM has shown that IL-38 mediators are linked to the pathophysiology of the (8). it is considered One of the new cytokines of the IL-1family, and thought to play an essential part in controlling the immune system equilibrium and in modulating the etiology of inflammatory disorders [7]., Furthermore, little research has been done on the pathogenic function of IL-38 in diabetic neuropathy (DNP) [9]. Interleukin 39 also has an important role in the etiology of inflammatory disorders in humans. Given that T2DM frequently exhibits minor inflammation [8] As a heterodimer glycoprotein made up of two covalently linked subunits, IL-23p19 and Epstein-Barr virus-induced gene (Ebi3), IL-39 is the most recent member of the IL-12 family of mediators to be found [10]. According to Ecoeur *et al.* [11] IL-39 is a hypothetical cytokine, and the human body is unable to produce it or attribute any biologic function to it. According to the authors' conjecture, IL-39 may be a cytokine that regulates immunity only in mice .Conversely, it has been shown that human serum contains measurable amounts of IL-39 [12]. The study of IL-39 immune-related properties is currently in its early phases. Nevertheless, IL-239 may be implicated in the immunopathogenic pathways underlying systemic lupus erythematosus (SLE) because the pro-inflammatory properties of this interleukin have been demonstrated shown in lupus-like animals [13]. Furthermore, the scientists proposed that IL-39 may serve as a marker for systolic irregularities after finding considerably higher2 levels of the protein in the blood of patients with acute coronary syndrome [14]. IL-39 may be a pertinent cytokine whose harmful significance in illness should be comprehended, and because there is little researches about relation of IL-38

and IL-39 markers with diabetic mellitus, our study aim to evaluate predicting roles of these indicators in pathophysiology of diabetic mellitus.

Materials and Techniques

Collected samples

The conducted investigation was occurred Baghdad during the period from August to December of 2022 Forty five blood samples had from patients suffering from type II diabetes that attending outpatients clinics after screening them by specialist physician . Additionally, 45 blood samples were collected from individuals without disease and considered them as control group. Age and gender of participated were scored in a form.

Techniques

The collected blood were separated using centrifuge (6000 rpm for five minutes) to get the serum. All markers were quantified in all participants by utilizeing enzyme linked immunosorbent assay (ELISA) with kits provided from Bio-Sources International (Camarillo, USA).

Statistical analysis

IL-38 and IL-39 markers were showed as Mean ±SD. Student t test based to mention the large variations of above parameters among all participants. Gender and age groups were mentioned as frequencies and percentages, and the differences between percentages evaluated by Pearson-Chi-square test. Receiver operating characteristic (ROC) curve was based to reveal area under the curve (AUC), cut-off, specificity and sensitivity of conducted parameters. $P \leq 0.05$ was utilized to show statistical differences. Results of current investigation were calculated by SPSS v. 21.0 and Prism v.6 statistical software programs.

Results

1. **Personal features of study groups**

Findings of current research showed no significant differences ($p>0.05$) between study groups based on gender and age groups (table 1).

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Table 1A: shows the Gender between study groups

			Groups		Total	P value
			Control (N=40)	Patients (N=50)		
Gender	Males	N	18	20	38	P>0.05
		%	45.0%	40.0%	42.2%	
	Females	N	22	30	52	
		%2	55.0%	60.0%	57.8%	

Table 1B: shows the age groups between study groups

			Groups		Total	P value
			Control	Patients		
Age groups (years)	≤40	N	12	12	24	P>0.05
		%	30.0%8	24.0%	26.7%	
	41-50	N	14	17	318	
		%	35.0%	34.0%	34.4%	
	51-60	N	12	17	29	
		%	30.0%	34.0%	32.2%	
	>60	N	2	4	6	
		%	5.0%	8.0%	6.7%	

2. Mean values of interleukins within study groups

Our findings presented significant high levels of IL-38 and IL-39 in type II diabetic patients (356.94±58.18 and 247.45±75.14) than controls (209.25± 48.44 and 247.45±75.14) (table 2 and figure 1).

Table 2: comparative levels of IL-38 and IL-39 parameters between research groups

Groups		N	Mean	SD	P value
IL-38 (ng/L)	Control	40	209.25	48.44	P<0.001***
	Patients	50	356.94	58.18	
IL-39 (ng/L)	Control	40	155.14	57.16	P<0.001***
	Patients	50	247.45	75.14	

3. Roc curve of IL-38 and IL-39 indicators

ROC curve outcomes present the IL-38 showed highest sensitivity and specificity (96% and 95%) compared to IL-39 (sensitivity (80%) and specificity (75%)) at cut off (>251.21 and > 182.29) respectively in predicting individuals with diabetes mellitus type II with significant variation (p<0.05) (figure 2).

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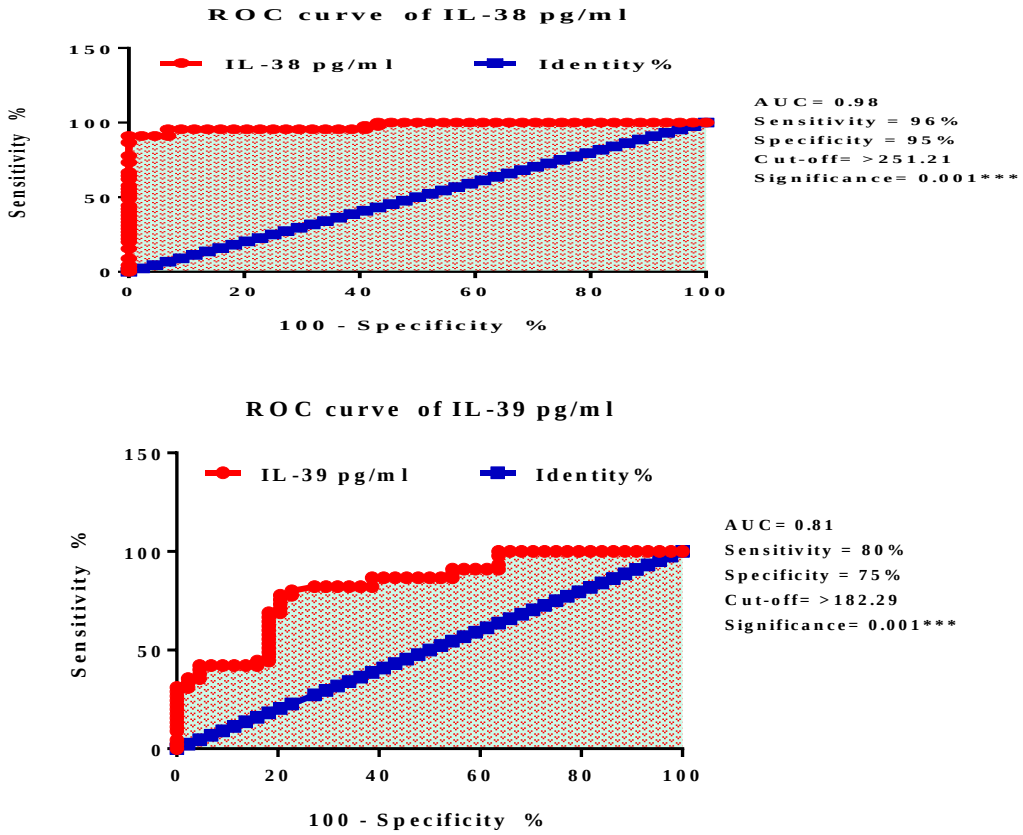

Figure 2: Roc curve of IL-38 and IL-39 indicators

4. Relation of interleukins with gender and age

Depending on correlation between personal features and levels of interleukins in diabetes patients, our outcomes showed no significant differences (p>0.05) between levels of IL-38 and IL-39 and gender as well as age groups in patients with diabetes (table 3).

Table 3A: comparative mean levels of IL-38 and IL-39 markers with gender of diabetes patients

		N	Mean	SD	P value
Gender					
IL-38 (ng/L)	M	20	352.16	59.87	P>0.05
	8F	30	360.13	57.83	
IL-39 (ng/L)	M	20	223.87	83.25	P>0.05
	F	30	263.16	66.04	
	>60	4	287.03	85.24	

Table 3B: comparative mean levels of IL-38 and IL-39 markers with age of diabetes patients

		N	Mean	SD	P value
Age groups (years)					
IL-38 (ng/L)	≤40	12	377.03	53.46	P>0.05
	41-50	17	346.86	40.27	
	51-60	17	355.21	69.66	P>0.05
	>60	4	346.93	89.09	
IL-39 (ng/L)	≤40	12	258.07	85.30	P>0.05
	41-50	17	262.30	60.81	
	51-60	17	215.78	73.85	P>0.05
	>60	4	287.03	85.24	

5. Correlation between interleukins

Based on Pearson correlation coefficient the use to measure type and strong of relationship between quantitative parameters, our outcomes reveal no significant correlation (P>0.05) between IL-38 and IL-39 in diabetes patients (Table 4).

Table 4: Studying of correlation relationship between IL-38 and IL-39 parameters by using Pearson correlation coefficient.

		IL-39 (ng/L)
IL-38 (ng/L)	Pearson Correlation	0.142
	Sig. (2-tailed)	0.326

Discussion

Type II diabetes mellitus is becoming more common in both sexes, however males are often diagnosed with the disease at an earlier stage and with a lower body fat percentage than women. Around 17.7 million men and women globally suffer from diabetes mellitus. When Type II diabetes is diagnosed, women seem to have more risk factors, particularly obesity [15]. The research's findings indicated no variations in the investigated groups' ages or genders, and they disagreed with those of Ali *et al.*, who found that women in the 41–50 age range constituted the majority of diabetes sufferers [6]. However, Kautzky-Willer *et al* [16] found that males in age groups older than 40 represent the majority of people with diabetes. The differences among studies related to chronic disorders, reduce insulin secretion, immune status, organ dysfunction, hormonal abnormalities, obesity, lifestyle, and sample size. As males are more inclined than

women to have gynoid overweight, or android weight gain, as well as greater visceral adiposity, central weight gain may theoretically be linked to a greater likelihood of type II diabetes predominance in men.

Whenever the body cannot make enough insulin, type II diabetes develops. I it is more common in those over 45, being overweight or not getting enough exercise is frequently associated to it as well. Therefore, modifying one's lifestyle to include more activity and a healthier diet can lower the incidence [17] (Table 1).

Nassurat *et al.*, [18] reveal increased values of IL-38 in DM patients than healthy controls, and these outcomes were matched with our research. In contrast, Zhao *et al* [19]. Showed decline levels of IL-38 in DM patients than controls

Cytokine of the IL-1 family, IL-38, was found in higher amounts in T2D patients than in healthy individuals. According to Liu *et al*., [20] kids who had been confirmed to have type II diabetes lately exhibited elevated levels of serum IL-38, especially those that were responsive to insulin treatment. A mice model of type II diabetes was used to study sensitivities to insulin in further detail, and it was suggested that IL-38 might slow the course of T2DM by enhancing insulin sensitivity. Since anti-IL-36 antibodies decreased plasma insulin levels and enhanced the responsiveness to insulin, this outcome might also be obtained by inhibiting the pro-inflammatory properties of IL-36 in these animals [21]. An additional study revealed that senior individuals with T2DM, especially those with diabetic nephropathy (DNP), had considerably higher plasma IL-38 objectives, which were associated positively with tests for liver function, lipids, and HbA1c [20]. A recent research supports the higher levels of IL-38 in DNP and T2DM, yet in DNP clients, IL-38 and WHP had a negative correlation [18]. Contrary to these results, IL-38 levels were higher in patients with T2DM with just asymptomatic TB than in control systems, both with and8 without persistent tuberculosis [22]. Nonetheless, among individuals with gestational diabetes during pregnancy, the link between IL-38 and diabetic was further validated. Those sufferers' placentas underwent immunohistochemically testing, which revealed a 3.3-, 2.6-, and 2.6-fold boost in IL-38 production in the chorionic villi, umbilical artery, and umbilical vein, correspondingly. Consequently, the researchers proposed that this

upregulated expression signifies an anti-inflammatory reaction within the placenta milieu as diabetes during pregnancy develops [23].

The primary goal of the current investigation was to determine the importance of IL-39 as a T2DM indicator because there is a dearth of evidence in this area. The relevance of the data, especially IL-39, in the pathophysiology of type II diabetes was highlighted. According to Nussrat and Ad'hiah [12] T2DM patients' blood levels of IL-39 were substantially greater than those of healthy individuals. These results agreed with what we had found , It was also noteworthy that IL-39 and body mass index (BMI) had a favorable correlation. Unfortunately, there has not been much research done on this kind of cytokine in T2DM, thus this research might be the first to look at blood IL-39 concentrations among individuals with T2DM. Nevertheless, data has been published suggests that IL-39 may have a part in the risk of many illnesses. Since being identified in 2016, IL-39 pro-inflammatory actions are believed to be related to SLE in mice that are susceptible to the disease [24]. Serum amounts of IL-39 were likewise markedly elevated and were correlated with high-sensitivity C-reactive protein (CRP) in individuals with acute coronary syndrome. The possibility of using it as a marker of cardiac dysfunction in the systole was additionally proposed [25]. Contrary findings, nevertheless, were documented in individuals with Hashimoto's thyroiditis and Graves' disease; IL-39 exhibited suppressed quantities but had a favorable correlation with leukocyte counts and CRP, two inflammatory indicators [26]. These data, along with the study's findings, imply that IL-39 is a mediator that is also connected with type 2 diabetes and could serve as a viable sensor for the illness (Table 2).

According to Nassurat *et al*. [18] the elevated levels of IL-38 were very good in differentiating those with T2D versus healthy individuals (AUC = 0.91, sensitivity = 88%, specificity = 92 %). These outcomes were almost identical to our investigation, which found that the AUC of IL-38 was (AUC=0.98, sensitivity=96%, specificity=95%). The authors' higher IL-38 quantities were associated with a 29.97-fold higher incidence of type 2 diabetes. They demonstrated that IL-38 is a significant member of the IL-1 family of mediators linked to T2D risk. According to Nassurat *et al*. [18] this type of cytokine can be viewed as a potential therapy in T2DM.

Nussrat and Ad'hiah, [12] showed the ROC curve analysis reveals that IL-39 was excellent indicator in distinguish between T2DM and healthy (AUC = 0.97, sensitivity = 93%, specificity = 93%). Based on these outcomes, IL-39 could be utilized as a novel predictor of T2DM and/or a therapy site in the disease. These results were higher than our study that showed ROC curve analysis reveal the AUC, sensitivity, and specificity of IL-39 were; 0.81, 80%, and 75% respectively.

The differences in ROC curve analysis among studies related to disease severity, period of disease, and may be due to sample size (Figure 2).

According to relation of IL-38 and IL-39 with gender and age groups of patients, our results not showed significant differences between these interleukins and gender as well as to age, and that refer to nearly immune response in all DM patients.

Nussrat and Ad'hiah, [12] showed high levels of IL-39 in females with T2DM than males due to high hormonal abnormalities that associated with inflammatory response in females than males. These outcomes no similar to our research (Table 3).

The pro- and anti-inflammatory cytokines (IL-39 and IL-38) were investigated in this work. There was a positive correlation with elevated blood levels of both mediators. According to Vasanthakumar and Kallies [27], association patterns suggest that increased quantities of cytokines that are anti-inflammatory are produced in reaction to pro-inflammatory environments, with the aim of reducing the intensity of inflammatory reactions and preserving physiological equilibrium in essential organs. It is important to note that IL-38 also interacted with KPNA7, a gene that codes for a member of the importin alpha group of peptides that helps signal-containing molecules translocate into their nuclei [18]. According to Guo *et al*. [28], importation was shown to be a significant regulator of the transcription factor signaling cascade of nuclear factor kappa B (NF-κB). This process regulates both inflammation and immunity and may be essential to the pathophysiology of illnesses like cardiovascular disorders that result from dysregulated immunological and inflammatory responses [29]. On the other hand, prolonged hyperglycemia may stimulate the pathway of NF-B signaling, which dysregulates the generation of several mediators and inflammatory substances associated in the pathophysiology of type II diabetes [30]. Thus, comprehending the IL-38-NF-κB-KPNA7

interactions axis might be a crucial approach for studies seeking to gain insight into the pathophysiology of type 2 diabetes, and study in this area is definitely welcomed [18] (Table 4).

Conclusions

It was concluded that there is no effect of gender and age on diabetes. Increased levels of pro- and anti-inflammatory interleukins (IL-39 and IL-38) in patients due to inflammation. Anti-inflammatory interleukin (IL-38) was increased due to the effect of pro-inflammatory interleukin (IL39) in reduce the severity of inflammatory reactions and maintaining physiological homeostasis in essential organs. IL-38 is significantly preferred in predicting diabetes compared to IL-39 because it has higher sensitivity and specificity.

References

1. N. A. ElSayed, G. Aleppo, V. R. Aroda, R. R. Bannuru, F. M. Brown, D. Bruemmer, R. A. (2023). Summary of revisions: Standards of Care in Diabetes—2023, Diabetes Care, 46(Supplement_1), S5-S9.
2. J. Goldney, J. A. Sargeant, M. J. Davies, Incretins and microvascular complications of diabetes: neuropathy, nephropathy, retinopathy and microangiopathy, Diabetologia, 66(10), 1832-1845(2023)
3. M. Abdul Basith Khan, M. J. Hashim, J. K. King, R. D. Govender, H. Mustafa, J. Al Kaabi, Epidemiology of type 2 diabetes—global burden of disease and forecasted trends, Journal of epidemiology and global health, 10(1), 107-111(2020)
4. H. Zheng, W. Sun, Q. Zhang, Y. Zhang, L. Ji, X. Liu, S. Zhang, Proinflammatory cytokines predict the incidence of diabetic peripheral neuropathy over 5 years in Chinese type 2 diabetes patients: a prospective cohort study, EClinicalMedicine, 31(2021)
5. S. Nirenjen, J. Narayanan, T. Tamilanban, V. Subramaniyan, V. Chitra, N. K. Fuloria, S. Selvaraj, Exploring the contribution of pro-inflammatory cytokines to impaired wound healing in diabetes. Frontiers in immunology, 14, 1216321(2023)

6. J. Ali, S. M. S. Haider, S. M. Ali, T. Haider, A. Anwar, A. A. Hashmi, Overall clinical features of type 2 diabetes mellitus with respect to gender, Cureus, 15(3), (2023)
7. A. M. Aliyeva, I. E. Baykova, T. V. Pinchuk, I. A. Kotikova, I. G. Nikitin, Interleukin-38 and cardiovascular pathology: literature review, CardioSomatics, (2023)
8. T. V. Velikova, P. P. Kabakchieva, Y. S. Assyov, T. A. Georgiev, Targeting inflammatory cytokines to improve type 2 diabetes control, BioMed research international, (2021)
9. G. Fruehbeck, J. Gomez-Ambrosi, B. Ramirez, A. Mentxaka, A. Rodriguez, S. Becerril, V. Catalan, Increased levels of interleukin-36 in obesity and type 2 diabetes fuel adipose tissue inflammation by inducing its own expression and release by adipocytes and macrophages, Frontiers in Immunology, 13, 832185(2022)
10. M. Abdelkawy, O. G. Shaker, N. A. F. Tarrad, IL-39 and IL-35 gingival crevicular fluid levels in diabetic patients with generalized periodontitis, Clinical Oral Investigations, 28(2), 1-11(2024)
11. F. Ecoeur, J. Weiss, S. Schleeger, C. Guntermann, Lack of evidence for expression and function of IL-39 in human immune cells, Plos one, 15(12), e0242329(2020)
12. S. W. Nussrat, A. H. Ad'hiah, Interleukin-39 is a novel cytokine associated with type 2 diabetes mellitus and positively correlated with body mass index. Endocrinology, diabetes & metabolism, 6(3), e409(2023)
13. Z. Lu, K. Xu, X. Wang, Y. Li, M. Li, Interleukin 39: a new member of interleukin 12 family, Central European Journal of Immunology, 45(2), 214-217(2020)
14. Y. Luo, F. Liu, H. Liu, H. Chen, W. Cheng, S. Dong, W. Xiong, Elevated serum IL-39 in patients with ST-segment elevation myocardial infarction was related with left ventricular systolic dysfunction, Biomarkers in Medicine, 11(6), 419-426(2017)
15. S. Dai, D. Shu, F. Meng, Y. Chen, J. Wang, X. Liu, F. Chen, Higher risk of sarcopenia in older adults with type 2 diabetes: NHANES 1999–2018, Obesity facts, 16(3), 237-248(2023)
16. A. Kautzky-Willer, M. Leutner, J. Harreiter, Sex differences in type 2 2diabetes, Diabetologia, 66(6), 986-1002(2023)

17. P. P. Bhatt, M. S. Sheth, Comparison of fatigue and functional status in elderly type 2 diabetes patients versus age and gender matched individuals, Aging Medicine, (2024)
18. S. W. Nassurat, I. N. Salman, A. H. Ad'hiah, Association of interleukin-36α and interleukin-38 with type 2 diabetes mellitus and diabetic neuropathy, The Egyptian Journal of Internal Medicine, 36(1), 24, (2024)
19. T. Zhao, M. Yu, M. Li, Y. Li, Serum IL-38 levels in patients with type 2 diabetes mellitus, Endokrynologia Polska, 73(6), 988-989(2022)
20. Y. Liu, T. Chen, F. Zhou, D. Mu, S. Liu, Interleukin-38 increases the insulin sensitivity in children with the type 2 diabetes. International Immunopharmacology, 82, 106264(2020)
21. R. Chakraborty, R. Parveen, P. Varshney, P. Kapur, S. Khatoon, N. Saha, N. B. Agarwal, Elevated urinary IL-36α and IL-18 levels are associated with diabetic nephropathy in patients with type 2 diabetes mellitus, Minerva Endocrinology, 46(2), 226-232(2021).
22. X. R. Wang, J. P. Xiao, D. G. Wang, Elevated levels of serum IL 36α in patients with systemic lupus erythematosus, Biomedical reports, 15(3), 1-7(2021)
23. G. Huang, M. Li, X. Tian, Q. Jin, Y. Mao, Y. Li, The emerging roles of IL-36, IL-37, and IL-38 in diabetes mellitus and its complications, Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders), 22(10), 997-1008(2022)
24. X. Wang, Y. Zhang, Z. Wang, X. Liu, G. Zhu, G. Han, R. Wang, Anti IL 39 (IL 23p19/Ebi3) polyclonal antibodies ameliorate autoimmune symptoms in lupus like mice, Molecular Medicine Reports, 17(1), 1660-1666(2018)
25. D. Bastian, X. Sui, H. D. Nguyen, Y. Wu, S. Schutt, L. Tian, X. Z. Yu, Interleukin-23 receptor signaling by interleukin-39 potentiates T cell pathogenicity in8 acute graft-versus-host disease, American Journal of Transplantation, 21(11), 3538-3549(2021)
26. L. Weng, G. Huang, L. Gong, J. Xu, Y. Mao, Y. Li, M. Li, Low levels of serum IL-39 are associated with autoimmune thyroid disease, Journal of clinical laboratory analysis, 36(4), e24284(2022)

27. A. Vasanthakumar, A. Kallies, Interleukin (Il)-33 and the il-1 family of cytokin2es—regulators of inflammation and tissue homeostasis, Cold Spring Harbor perspectives in biology, 11(3), a028506(2019).
28. M. Guo, J. Gao, L. Jiang, Y. Dai, Astragalus Polysaccharide Ameliorates Renal Inflammatory Responses in a Diabetic Nephropathy by Suppressing the TLR4/NF-κB Pathway, Drug Design, Development and Therapy, 2107-2118(2023)
29. A. Matsumori, Nuclear factor-κB is a prime candidate for the diagnosis and control of inflammatory cardiovascular disease, European Cardiology Review, 18, (2023)
30. M. Alrouji, H. M. Al-kuraishy, A. I. Al-Gareeb, A. Alexiou, M. Papadakis, M. S. Jabir, G. E. S. Batiha, NF-κB/NLRP3 inflammasome axis and risk of Parkinson's disease in Type 2 diabetes mellitus: A narrative review and new perspective, Journal of Cellular and Molecular Medicine, 27(13), 1775-1789(2023)