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Evaluation of Il-17 in Patients with Type II Diabetes Mellitus

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ABSTRACT: Background: Considering the probable engagement of Interleukin-17 in the development of DM, its possible eligibility as a diagnostic marker should be evaluated.

Objectives: The aim of this study is to find out the role of IL-17 in the pathogenesis and diagnosis of diabetes mellitus.

Methods: This case-control study was carried out at Al-Husseini Teaching Hospital, Karbala, Iraq, during the period from March to September 2024. The study included 50 diagnosed DM patients and 50 healthy controls. IL-17 levels were measured by ELISA using HuamaCount (Germany) kits.

Results: Patients with DM were 48.67 ± 6.44 years old on average. The distribution of their ages was 24% from 35 to 44 years, 26% from 45 to 54 years, 18% from 55 to 64 years, and 32% from 65 to 74 years. For this male-to-female ratio, the DM group was 54:46 as compared to controls, which were 48:52. IL-17 levels were significantly higher in patients with DM (7.33 ± 1.54 pg/ml) than in the controls (5.48 ± 2.44 pg/ml) (P <0.0001). It gave an AUC of 0.63, sensitivity and specificity being 74% and 66% at a cutoff value of 6.33 pg/ml (P = 0.046), thus indicative of IL-17 as a fairly good diagnostic marker for DM.

Conclusions: Elevated IL-17 levels may be involved in the pathogenesis of DM, of potential diagnostic and predictive utility as a biomarker though its modest discriminative ability calls for more research to buttress its usefulness in clinical practice.

KEYWORDS: IL-17, diabetes mellitus, diagnosis, sensitivity, specificity.

INTRODUCTION

Diabetes mellitus is the major global health problem chronic hyperglycemia due to defecting insulin action, insulin secretion or both serves as its functional definition. It is based mainly on two types of conditions, which are type 1 diabetes (T1D), and Type 2 diabetes (T2D). These have independent pathophysiological and immunological mechanisms (ADA, 2015).

Diabetes classification is critical for diagnosis and treatment determination. T1D is typically diagnosed as the autoimmune disease in which most of the time the pancreatic beta cells get damaged. As a result, absolute insulin deficiency arises. In comparison to this, T2D is a type of diabetes that is associated with insulin resistance and there is a relative lack of insulin, also increasingly in obesity and the metabolic syndrome. Some other specific situations are gestational diabetes and latent autoimmune diabetes in adults because of the complexity added to the classification of diabetes (Brophy et al., 2011). The latter is frequently misdiagnosed as LADA-associated T2D because there is a manifestation of insulin resistance preceding the need for insulin treatment due to the autoimmune destruction of beta cells (Brophy et al., 2011).

Diabetes classification is important not just for diagnosis but to appreciate the distinctive immunological modes. While T1D is autoimmune at its core, in T2D there is progressive beta cell dysfunction along with metabolic dysregulation. This difference underlies the growing recognition of the need for individualized treatment that may depend on the immunological roots of the disease. Immunological aspects in diabetes are particularly important for T1D, where the autoimmune response mistakenly identifies beta cells as foreign entities and attacks them. The presence of autoantibodies is a critical diagnostic factor that distinguishes T1D from T2D and LADA (Brophy et al., 2011). Indeed, genetic factors play a major role in the autoimmune reaction typical of T1D, highlighting the importance of studies on genetic and molecular mechanisms responsible for the disease pathogenesis (Kharroubi & Darwish, 2015). Hyperglycemia-induced chronic inflammation is one of the fundamental concepts in the pathogenesis of diabetic cardiovascular and kidney diseases (Tuttle et al. 2014). The relationship between oxidative stress, inflammation, and immune dysfunction is critical because oxidative stress will further fuel chronic inflammation and diminish immune responses in diabetic patients. It is in this relationship that there is an essential requirement for comprehensive strategies that work toward metabolic control together with immunological health (Prietl et al. 2013; Chait & Hartigh, 2020; Berbudi et al. 2020). Pre-existing immune and inflammatory pathways have therefore made hyperglycemia-associated DM a valuable condition through which to assess IL-17 cytokine as a possible newcomer in the pathogenesis of the disease. Despite the continuously growing evidence about IL-17 involvement in diabetes development. First, although the contribution of IL-17 to both T1D and T2D is established, how exactly

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IL-17 causes β-cell apoptosis in T1D has not been adequately addressed (Abdel-Moneim et al., 2028). Future studies are required to fully discern the signaling cascades that drive this mechanism.
The aim of this study is to find out the role of IL-17 in the pathogenesis and diagnosis of diabetes mellitus.

METHODS

Patients and data collection

The case-control study was conducted at Al-Husseini Teaching Hospital, Karbala, Iraq, from March 2024 to September 2024. Fifty diagnosed cases of diabetes mellitus were included in the study; during the same period, fifty apparently healthy individuals were also enrolled as a control. Data concerning general information about the patients were collected from the teaching hospital records. Five cubic centimeters of venous blood samples were collected. The blood samples were allowed to clot in a gel tube for 20 minutes at room temperature. After coagulation, the sera were separated by centrifugation at 2000xg for 20 min, stored at (-20°C). The levels of serum IL-17 were determined using commercial ELISA kits (HuamaCount, Germany) according to their assay procedures for quantitative measurement.

Statistical Analysis

Data were analyzed using SPSS statistics version 25.0 software (SPSS, Chicago). The level of parametric data was checked using the normality test (Shapiro Wilk test). Normally distributed data are presented as mean ± standard deviation and analyzed using an independent t-test. The ROC curve was used to test the predictive ability of IL-17 in the prediction of relapse among breast cancer patients. A value of $p < 0.05$ was considered statistically significant.

The Results

The demographic characteristics of the study participants are presented in Table 1. The mean age of the DM patients was 48.67 ± 6.44 years and the distribution in different age groups were as follows: 24% in the age group of 35–44, 26% in 45–54, 18% in 55–64, and 32% in 65–74 years compared to identical distributions in the control group. The gender distribution of the DM patients is 54% males and 46% females whereas the control group comprises 48% males and 52% females. Thus, the data indicate that there is balanced demographic composition between the DM patients and the controls although there may be slight variations in age and gender distribution.

Table (1) Distribution of DM patients by their demographic data

Items	**Rating**	**DM Patients (N= 50)**		**Control (N= 50)**	
				Freq.	**%**
Age	**35-44**	12	24	13	26
	45-54	13	26	14	28
	55-64	9	18	7	14
	65-74	16	32	16	32
	Mean ± SD 48.67 ± 6.44				
Gender	**Male**	27	54	24	48
	Female	23	46	26	52

The bar chart presents the mean levels of IL-17 (Mean ± SD) in patients and controls (figure 1). Patients had significantly higher levels of IL-17 (7.33 ± 1.54 pg/ml) compared to the controls (5.48 ± 2.44 pg/ml) ($P < 0.0001$). Such a major difference implies that elevated levels of this cytokine may be involved in the pathologic mechanisms acting in the group of patients.

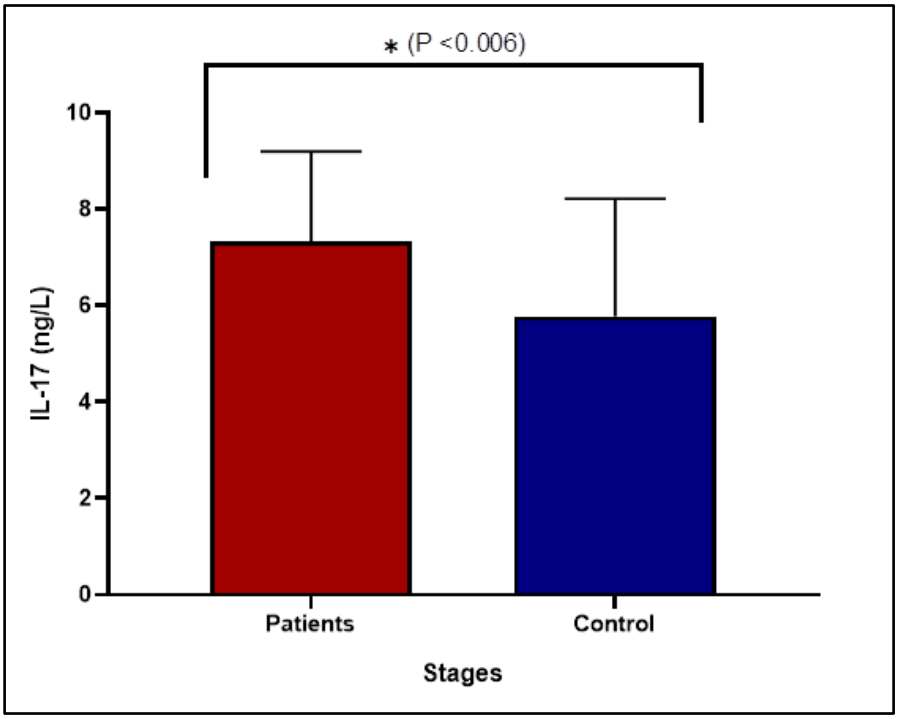

Figure 1. Differences in serum IL-17 between patients and control groups

Table 2. illustrate the diagnostic performance of IL-17 as a biomarker for diabetes mellitus. The area under the curve is 0.63 that uncovers modest discriminative ability. Sensitivity 74% at a cut of 6.33 pg/ml suggests that IL-17 will identify 74% of patients with diabetes correctly. Specificity 66% shows that it will exclude 66% of individuals without diabetes in this study correctly. P-value = 0.046 is the evidence needed for these findings to back IL-17 as a biomarker for DM diagnosis, albeit moderate.

Table (2) Sensitivity and specificity of IL-17 for the diagnosis of DM

Biomarkers	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
IL-17	**0.63**	**0.046**	**6.33**	**0.74**	**0.66**

AUC: Area Under the curve

Discussion

A related study found that IL-17 has linked a major player in T2D-related inflammatory pathways. Upregulated Th17 cell counterparts responsible for IL-17 formation have been detected in T2D patients; hence, shifting the balance further towards a pro-inflammatory T cell phenotype (Al-Fahham et al., 2024). This skewing associates with chronic inflammation and resistance to insulin, the basic characteristics of T2D (Jagannathan-Bogdan et al., 2011). At the cellular level, the interaction of Th17 cells with monocytes is of great importance in maintaining the inflammatory state, indicating then that the intervention targeting this pathway perhaps would restore immune balance and at least alleviate insulin resistance (Li et al., 2019).

Besides IL-17 signaling, IL-17 has also been linked to further prompting an inflammatory milieu in adipose tissue, especially regarding T2D pertaining to obesity. IL-17 and IL-22-producing CD4+ T cells within this tissue reveal their participation in chronic low-grade inflammation further escalating metabolic dysregulation. As such, the relationship between IL-1β and IL-17 is necessarily reciprocal, adding another layer of complexity to this network of related cytokines that could possibly be targeted therapeutically.

Besides, IL-17 has been associated with nonalcoholic fatty liver disease, which generally coincides with T2D. The evidence speaks to the necessity of IL-17 receptor signaling in the development of steatohepatitis, which can enhance metabolic disorders such as diabetes (Daniele et al., 2014). In one study, IL-17A neutralization has ameliorated liver damage in obese animals, thus offering hope that targeting this cytokine could solve several problems at once, including that of diabetes (Daniele et al., 2014). Vitamin D is another regulator of T cell responses since its deficiency results in enhanced generation of Th17 cells responsible for driving inflammation (Bruce et al., 2011). This relationship delineates the importance of vitamin D in preserving immune homeostasis and, thus, a possible role in the pathogenesis of T2D. Further studies should investigate IL-17 and vitamin D supplementation, from a therapeutic point of view in correcting the imbalance of T cell populations to minimize the onset of diabetes. IL-17 has been associated with T1D where it instigates the autoimmune response against pancreatic β-cells. The emergence of IL-17-secreting CD4 T-cells in response to β-cell autoantigens may propose that IL-17 is effectively a biomarker for T1D (Neuhofer et al., 2013). In

addition, IL-17 could cooperate with other pro-inflammatory cytokines to increase β-cell apoptosis, which illustrates its dual effect in the process of inflammation and direct contribution to β-cell dysfunction (Abdel-Moneim et al., 2018).

CONCLUSION

It is suggested that the of activity IL-17 serum levels might have a significant impact on the pathogenesis of diabetes mellitus. This biomarker can also be used in the prediction of and diagnosed with diabetes mellitus.

REFERENCE

1) American Diabetes Association (2015). (2) Classification and diagnosis of diabetes. *Diabetes care*, *38 Suppl*, S8–S16. https://doi.org/10.2337/dc15-S005
2) Abdel-Moneim, A.., Bakery, Heba H., & Allam, G. (2018). The potential pathogenic role of IL-17/Th17 cells in both type 1 and type 2 diabetes mellitus. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 101, 287-292. http://doi.org/10.1016/j.biopha.2018.02.103
3) Al-Fahham Ali, A., Jaffar, A. M., Shubar, S. N. A., & Hadi, H. S. (2024). Structure and physiological significance of IL-17: A review article. *International Journal of Health & Medical Research*, *3*(09), 666–669. doi: 10.58806/ijhmr.2024.v3i09n03.
4) Arif, S.., Moore, F.., Marks, K.., Bouckenooghe, T.., Dayan, C.., Planas, R.., Vives-Pi, M.., Powrie, J.., Tree, T.., Marchetti, P.., Huang, G.., Gurzov, E. N.., Pujol-Borrell, R.., Eizirik, D.., & Peakman, M. (2011). Peripheral and Islet Interleukin-17 Pathway Activation Characterizes Human Autoimmune Diabetes and Promotes Cytokine-Mediated β-Cell Death. Diabetes, 60, 2112 - 2119. http://doi.org/10.2337/db10-1643
5) Basevi, V. (2011). Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*, 34, S62 – S69. http://doi.org/10.2337/dc11-S062
6) Berbudi, Afiat., Rahmadika, N.., Tjahjadi, Adi Imam., & Ruslami, R. (2020). Type 2 Diabetes and its Impact on the Immune System. *Current Diabetes Reviews*, 16, 442 - 449. http://doi.org/10.2174/1573399815666191024085838
7) Brophy, S.., Davies, H.., Mannan, Sopna., Brunt, H.., & Williams, Rhys. (2011). Interventions for latent autoimmune diabetes (LADA) in adults. *The Cochrane database of systematic reviews*, 9, CD006165. http://doi.org/10.1002/14651858.CD006165.pub3
8) Bruce, D.., Yu, Sanhong., Ooi, Jot Hui., & Cantorna, M. (2011). Converging pathways lead to overproduction of IL-17 in the absence of vitamin D signaling. International immunology, 23 8, 519-28. http://doi.org/10.1093/intimm/dxr045
9) Chait, A.., & Hartigh, Laura J. den. (2020). Adipose Tissue Distribution, Inflammation and Its Metabolic Consequences, Including Diabetes and Cardiovascular Disease. *Frontiers in Cardiovascular Medicine*, 7. http://doi.org/10.3389/fcvm.2020.00022
10) Dalmas, E.., Venteclef, N.., Caer, Charles., Poitou, C.., Cremer, I.., Aron-Wisnewsky, J.., Lacroix-Desmazes, S.., Bayry, J.., Kaveri, S.., Clément, K.., André, S.., & Guerre-Millo, M. (2014). T Cell–Derived IL-22 Amplifies IL-1β–Driven Inflammation in Human Adipose Tissue: Relevance to Obesity and Type 2 Diabetes. Diabetes, 63, 1966 - 1977. http://doi.org/10.2337/db13-1511
11) Daniele, Giuseppe., Mendoza, R. G.., Mendoza, R. G.., Winnier, Deidre A.., Fiorentino, T. V.., Zuo, Pengou., Cornell, J.., Andreozzi, F.., Jenkinson, C.., Cersosimo, E.., Federici, M.., Tripathy, D.., & Folli, F. (2014). The inflammatory status score including IL-6, TNF-α, osteopontin, fractalkine, MCP-1 and adiponectin underlies whole-body insulin resistance and hyperglycemia in type 2 diabetes mellitus. Acta Diabetologica , 51 , 123-131 . http://doi.org/10.1007/s00592-013-0543-1
12) Eyerich, K.., Dimartino, V.., & Cavani, A. (2017). IL-17 and IL-22 in immunity: Driving protection and pathology. European Journal of Immunology, 47 . http://doi.org/10.1002/eji.201646723
13) Harley, I. T.., Stankiewicz, T.., Giles, Daniel A.., Softic, S.., Flick, Leah M.., Cappelletti, M.., Sheridan, R.., Xanthakos, S.., Steinbrecher, K.., Sartor, R.., Kohli, Rohit., Karp, C.., & Divanovic, Senad. (2014). IL-17 Signaling Accelerates the Progression of Nonalcoholic Fatty Liver Disease in Mice. Hepatology (Baltimore, Md.), 59, 1830 - 1839. http://doi.org/10.1002/hep.26746
14) Hawkes, J.., Yan, B.., Chan, T.., & Krueger, J. (2018). Discovery of the IL-23/IL-17 Signaling Pathway and the Treatment of Psoriasis. The Journal of Immunology, 201, 1605 - 1613. http://doi.org/10.4049/jimmunol.1800013
15) Ibrahim, S.., Gadalla, Ramy., El-Ghonaimy, Eslam A.., Samir, Omnia., Mohamed, H.., Hassan, Hebatallah., Greve, B.., El-Shinawi, M.., Mohamed, M.., & Götte, M. (2017). Syndecan-1 is a novel molecular marker for triple negative inflammatory breast cancer and modulates the cancer stem cell phenotype via the IL-6/STAT3, Notch and EGFR signaling pathways. Molecular Cancer, 16. http://doi.org/10.1186/s12943-017-0621-z
16) Jagannathan-Bogdan, Madhumita., McDonnell, M.., Shin, Hyunjin., Rehman, Qasim., Hasturk, H.., Apovian, C.., & Nikolajczyk, B. (2011). Elevated Proinflammatory Cytokine Production by a Skewed T Cell Compartment Requires

Monocytes and Promotes Inflammation in Type 2 Diabetes. The Journal of Immunology, 186, 1162 - 1172. http://doi.org/10.4049/jimmunol.1002615

17) Kharroubi, A.., & Darwish, H. (2015). Diabetes mellitus: The epidemic of the century. *World journal of diabetes*, 6 6, 850-67. http://doi.org/10.4239/wjd.v6.i6.850
18) King, A. (2012). The use of animal models in diabetes research. *British Journal of Pharmacology*, 166. http://doi.org/10.1111/j.1476-5381.2012.01911.x
19) Li, Xiaoxia., Bechara, R.., Zhao, Junjie., McGeachy, M.., & Gaffen, S. (2019). IL-17 receptor–based signaling and implications for disease. Nature Immunology, 20, 1594 - 1602. http://doi.org/10.1038/s41590-019-0514-y
20) Mandrup-Poulsen, T.., Pickersgill, Linda., & Donath, M. (2010). Blockade of interleukin 1 in type 1 diabetes mellitus. Nature Reviews Endocrinology, 6, 158-166. http://doi.org/10.1038/nrendo.2009.271
21) Matough, F. A.., Budin, S. B.., Hamid, Z.., Alwahaibi, N.., & Mohamed, J. (2012). The role of oxidative stress and antioxidants in diabetic complications. *Sultan Qaboos University medical journal*, 12 1, 5-18. http://doi.org/10.12816/0003082
22) Nakashima, Taiji., Jinnin, M.., Yamane, Keitaro., Honda, N.., Kajihara, I.., Makino, T.., Masuguchi, S.., Fukushima, S.., Okamoto, Yoshinobu., Hasegawa, M.., Fujimoto, M.., & Ihn, H. (2012). Impaired IL-17 Signaling Pathway Contributes to the Increased Collagen Expression in Scleroderma Fibroblasts. The Journal of Immunology, 188, 3573 - 3583. http://doi.org/10.4049/jimmunol.1100591
23) Neuhofer, A.., Zeyda, M.., Mascher, D.., Itariu, B.., Murano, I.., Leitner, L.., Hochbrugger, E.., Fraisl, P.., Cinti, S.., Serhan, C.., & Stulnig, T. (2013). Impaired Local Production of Proresolving Lipid Mediators in Obesity and 17-HDHA as a Potential Treatment for Obesity-Associated Inflammation. Diabetes, 62, 1945 - 1956. http://doi.org/10.2337/db12-0828
24) Pettersson, U.., Waldén, Tomas B.., Carlsson, P.., Jansson, L.., & Phillipson, M. (2012). Female Mice are Protected against High-Fat Diet Induced Metabolic Syndrome and Increase the Regulatory T Cell Population in Adipose Tissue. PLoS ONE, 7. http://doi.org/10.1371/journal.pone.0046057
25) Prietl, B.., Treiber, Gerlies., Pieber, T.., & Amrein, K. (2013). Vitamin D and Immune Function. *Nutrients*, 5, 2502 - 2521. http://doi.org/10.3390/nu5072502
26) Puchulu, F. (2018). Definition, Diagnosis and Classification of Diabetes Mellitus., 7-18. http://doi.org/10.1007/978-3-319-72475-1_2
27) Tilg, H.., Moschen, A.., & Roden, M. (2017). NAFLD and diabetes mellitus. *Nature Reviews Gastroenterology &Hepatology*, 14, 32-42. http://doi.org/10.1038/nrgastro.2016.147
28) Tuttle, K.., Bakris, G.., Bilous, R.., Chiang, Jane L.., Boer, I. D. de., Goldstein-Fuchs, J.., Hirsch, I.., Kalantar-Zadeh, K.., Narva, A.., Navaneethan, S.., Neumiller, Joshua J.., Patel, U.., Ratner, R.., Whaley-Connell, A.., & Molitch, M. (2014). Diabetic Kidney Disease: A Report from an ADA Consensus Conference. *Diabetes Care*, 37, 2864 - 2883. http://doi.org/10.2337/dc14-1296
29) Wangen, Krankenhaus. (2014). Definition, classification and diagnosis of diabetes mellitus. *Experimental and clinical endocrinology & diabetes: official journal, German Society of Endocrinology [and] German Diabetes Association*, 122 7, 384-6 . http://doi.org/10.1055/s-0034-1366278
30) Wu, Hui., Wu, Michael., Chen, Yi., Allan, C.., Phillips, D.., & Hedger, M. (2012). Correlation between Blood Activin Levels and Clinical Parameters of Type 2 Diabetes. Experimental Diabetes Research, 2012. http://doi.org/10.1155/2012/410579
31) Wu, Ling., Chen, Xing., Zhao, Junjie., Martin, B.., Zepp, J.., Ko, J.., Gu, Chunfang., Cai, Gang., Ouyang, W.., Sen, G.., Stark, G.., Su, Bing., Vines, C.., Tournier, C.., Hamilton, T.., Vidimos, A.., Gastman, B.., Liu, Caini., & Li, Xiaoxia. (2015). A novel IL-17 signaling pathway controlling keratinocyte proliferation and tumorigenesis via the TRAF4–ERK5 axis. The Journal of Experimental Medicine, 212, 1571 - 1587. http://doi.org/10.1084/jem.20150204
32) Yeung, Yiu To., Aziz, F.., Guerrero-Castilla, Angélica., & Arguelles, Sandro. (2018). Signaling Pathways in Inflammation and Anti-inflammatory Therapies. Current pharmaceutical design, 24 14, 1449-1484. http://doi.org/10.2174/1381612824666180327165604