Egyptian Journal of Medical Microbiology Volume 34 / No.4 / October 2025 137-144 Online ISSN: 2537-0979

ORIGINAL ARTICLE

Expression of miR-181a1-3p and its Correlation with TGF-β1 and Chromogranin A in Patients with Type 1 Diabetes Mellitus

[1]Zaid A. Twayej*, [2]Mayyada F. Darweesh
[1]Laboratory Department, Immunology and Serology Unit, Alfurat Al-awsat Hospital, Najaf, Iraq.
[2]Department of Biology, Faculty of Science, University of Kufa, Najaf, Iraq.

Key words:
T1DM, Chromogranin A, TGF- β 1, MiR-181a-1-3-p

Corresponding Author:
Zaid Ali Twayej
Laboratory Department, Immunology and Serology Unit, Alfurat Al-awsat Hospital, Najaf, Iraq
ztwyj77@gmail.com

ABSTRACT

Background: *Type 1 Diabetes (T1DM) is a prevalent chronic illness, especially in children and teenagers. This rising incidence indicates the necessity of effective control and research.* ***Objective:*** *This study is designed to investigate the role of MiR-181a-1-3p, TGF- β 1 and Chromogranin A(CgA) levels in the development of T1DM.Methodology:- The control case study involved 120 participants, of whom 40 were apparently healthy controls group and 80 T1DM patients diagnosed by a specialist in the Diabetic Department / Al-sader Medical City in AL- Najaf Al-Ashraf province from October 2023 till the end of February 2024. Blood sample was collected from all participants to detect TGF- β 1 and CgA serum level by enzyme linked immunosorbent assay (ELISA) and MiR-181a-1-3-p by the reverse transcription polymerase chain reaction (RT-PCR). On the other hand, the anti-GAD65 and C-peptide diagnosis was conducted by (automatid Snibe MAGLUMI X3).* ***Results:*** *The results showed that serum TGF- β 1 was significant in the healthy controls (735.37±103.41), which is significantly higher than (322.54 ±69.72) ng/ml patients. Meanwhile, there was a marked increase in the serum level of CgA in T1DM patients compared to control groups (1260.21 ± 850.21; 439.47±202.05) ng /ml. The expression of MiR-181a-1-3p was significantly higher in the control group than the patients group. The serum level of anti-GAD antibodies among patients with T1DM was significantly higher than in healthy controls (P<0.001) (375.01; 5.66 U/ml). All patients showed decreased serum level of C-peptide compared healthy controls. Conclusions: Finally, both miRNA181a-1-3-p. and serum level of TGF- β 1 were considered prognosis marker in T1DM especially when corelated with Chromogranin A to detect disease progressive.*

INTRODUCTION

Type 1 Diabetes Mellitus is a chronic hyperglycemic disease, which results from autoimmune destruction for pancreatic β-cells causing little or no insulin production leading to lifelong insulin treatment. It is associated with various complication, such as nephropathy, retinopathy and neuropathy[1]. In 2021, T1D involved 8.4 million individuals, of which 18% (1.5 million) were younger than 20 years old, meaning that about 1 in 6 people with T1DM are childen or adolescent [2]. Serum biomarkers, including C-peptide and insulin Autoantibodies (IAA), Glutamic Acid Decarboxylase (GAD), insulinoma-associated antigen-2 (IA-2), Islet cell antibodies (ICA) and Zinc Transporter Protein (ZnT8A) autoantibodies are used to diagnose type 1 diabetes, although they often indicate a late stage of the illness when the majority of the pancreatic β-cells have been gone. Since T1D is becoming more commonplace globally, prognostic biomarkers are desperately needed to forecast the onset or progress of T1D [3]. Chromogranin A is an important soluble protein produced by neuroendocrine cells, functions as a useful biomarker in clinical practice as well as a regulator of hormone release and neuron peptides. A study suggested that increased CgA levels are correlated with diabetic complications, such as autonomic neuropathy [4]. Autoreactive T cells directed toward β-cell antigens Chromogranin A plays a central role in the destruction of β-cells in human (T1DM) byCD4 T cell clones. (ChgA) is one of the

autoantigen types found in islet beta cell and nerves system[5]. Transforming growth factor beta (TGF-β) is a cytokine that inhibits immune responses, suppresses the functions of diabetogenic, proinflammatory Th1 cells, which are connected to the autoimmune mortality of beta cells. It promotes the generation of T reg cells that maintain tolerance and prevent autoimmunity[6]. Micro-RNAs play a crucial role in regulating immune responses and inflammation, and its dysregulated expression has been observed in various autoimmune and inflammatory diseases[7]. MiR-181a-3p may modulate inflammatory responses that lead to beta-cell death by influencing the production of cytokines and other immune-related molecules and has potential roles in the T1D pathogenesis and progression[8] Therefore, the current study aims to explore the impact of MiR-181a-3p.

METHODOLOGY

Patients and control characterization

This case-control study involved 120 participants, of whom 80 were diagnosed with Type 1 Diabetes and 40 were healthy controls. The patients' age ranged from 3-17 years from both sexes. The patients were selected from the Diabetic Center in Al-Sader Medical City in AL- Najaf Al-Ashraf province from October 2023 till the end of February 2024. Their diagnoses were based on clinical, and serological parameters.

Sample Collection

About 3 ml venous blood sample was collected from each patient and control subject. Of this, an aliquot blood sample (2.5 ml) was placed into a gel tube for serum separation, used for measuring TGF-B and CgA level by ELISA kits (BT- LAB, China). A second aliquot blood sample (0.5 ml) was transferred into an Eppendorf tube containing 0.5 ml triazole and immediately stored at -80 C◦ until use for assessment of miRNA-181a-1-3-p by RT-PCR. Total RNA was extracted from whole blood using commercial kits (TransZol™ miRNA, Trans, China), following the manufacturer's protocol. Primers for miR-181a-1-3-p, and U6 calibrators were designed by a biotechnology company (Macrogen Inc., Korea).

The sequence of the miR-181a-1-3-p primers was F: GAACATTCAACGCTGTCGGT -R: GTTAGCCATAGGGTACAATCAACG

The expression of U6, as an internal control, was used for the normalization of miRNA expression. The first Step of the reverse transcription quantitative polymerase chain reaction (RT-qPCR) reaction was prepared according to Promega company and the thermocycling conditions were: One cycle of reverse transcription at 37℃ for 15 minutes, then one cycle of RT inactivation at 95 ℃ for 10 minutes.

This was followed by 40 cycles each included denaturation at 95 ℃ for 10 sec, then annealing at 58 ℃ for 30 sec and extension at 72 ℃ for 30 sec.

Gene expression (gene fold) relative quantification value was calculated according to the method described by 10 relative quantification (RQ) = 2-(ΔΔCT). First, the gene fold was determined for each triplicated sample by obtaining the CT (cycle threshold) average value from the real-time PCR equipment. Next, the ΔCT value was computed for each sample in the following manner: Δ CT = CT (tested miRNA181a) – CT (reference gene U6). ΔΔ CT = Δ CT (tested sample) – Δ CT (reference gene), fold gene expression RQ = 2-(ΔΔCT).

Ethical approval

The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Medicine, Kufa University (H K/1070, dated October 2023). It was performed with patients' consent both verbally and analytically before sampling.

Statistical Analysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20. They are expressed as means ± standard deviation (SD). The statistical analyses were performed through an independent T-test, one-way ANOVA, the receiver operating characteristic (ROC) curve analysis.

RESULTS

Demographic distribution of T1D patients and healthy

This case-control study involved 120 participants, of whom 80 were patients with Type 1 Diabetes, and 40 were controls. The results of incidence ratio according to sex were equal 40 (50%) cases for female: male patients. The age range of patients between 3-17. The results showed no significant difference between patients and healthy group, and the range of healthy group was 3-16. The female: male ratio was equal 20 subject for each group. The mean age of Type 1 diabetic (T1DM) patients was (11.19± 3.58) years and (10.0±2.84) years of healthy group. The mean duration of Type 1 diabetic disease was (4.95± 3.21) years, as shown in Table 1.

Mean titer of Anti –GAD IgG and C-peptide in the patients withT1D and Healthy control

The results show that the mean titer of Anti –GAD IgG was significantly higher in (T1DM) patients (375.01±238.43) while in healthy (5.66±1.95) with P<0.05. The mean titer of C-peptide was significantly higher in healthy (2.91±0.73) than (T1D) in patients (0.64±0.29) with P<0.05, as shown in Table 2.

Evaluation Serum Level of TGF- β 1 in T1DM patients

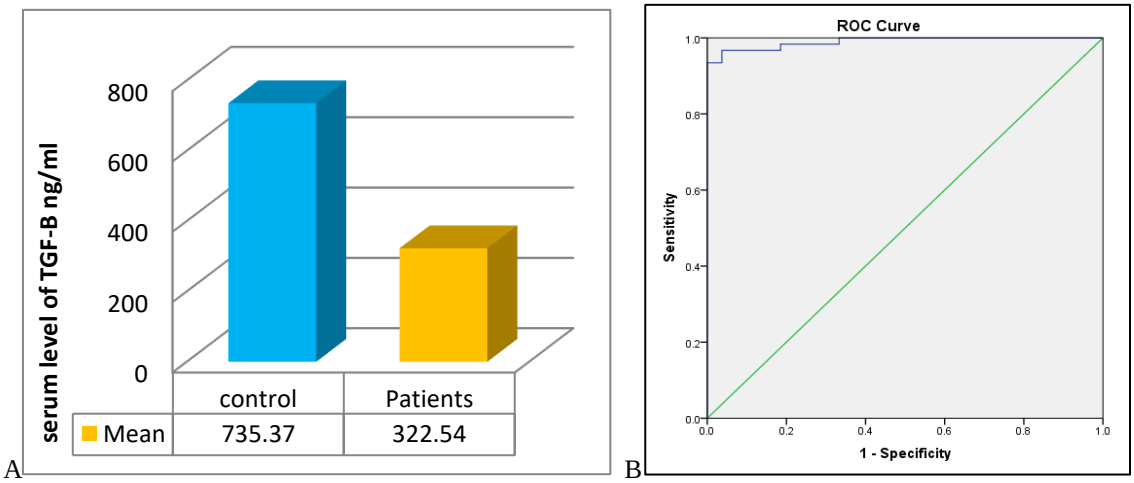
The results show that concentration of TGF-β1 in healthy controls (735.37 ± 103.41) was significantly higher (p < 0.001) than(T1DM) patients (322.54 ±69.72) ng/ml, as shown in figure 1. In addition, by ROC analysis, it is shown that TGF-B1 gave AUV value0.999 (sensitivity 93 %, specificity 100 %), Table 3.

Table 1: Distribution of study subjects according to age, gender and duration of disease.

Characters		DM1 patients N=80	%	Healthy Group N=40	%
Sex		40	50	20	50
		40	50	20	50
Age range		3-17		3-16	
Mean(years)		11.19± 3.58		10.0 ± 2.84	
Total		80	100	40	100
Duration of disease	Under 5 years	60	75		
	Upper 5 years	20	25		
	mean	(4.95± 3.21)			

Table 2: Mean titer of and Anti –GAD IgG and C-peptide inT1DM patients and healthy groups

Parameters	T1DM (Mean±SD)	Healthy (Mean±SD)	p- value
Anti –GAD IgG	**375.01±238.43**	**5.66±1.95**	P<0.05
C-peptide	**0.64±0.29**	**2.91±0.73**	P<0.05



A B

Fig. 1: A-Serum level of TGF- β 1 B- ROC curve of TGF- β 1 inT1DM Patients and control

Table 3: TGF-β1 sensitivity and specificity in T1DM patients and control

AUC	P-value	Cut off	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.990	**0.001**	**423.87**	**0. 976**	**1.000**	**93 %**	**100 %**

Estimation TGF- β1 serum level in Type 1 diabetic patients according to duration of disease.

The current study showed significant TGF- β1 difference between Type 1 diabetic patients depending on the duration of disease and control group, as shown in Figure 2. The TGF- β1 concentration was significantly decreased in patients more than 5 years (299.59± 80.71) ng/ml compared to patients of less than 5 years (525.82 ± 52.40) ng/ml and (735.37 ± 103.41) in control.

Evaluation Serum Level of Chromogranin A in T1DM patients

In the current study, there was a marked increase in the serum level of CgA in T1DM patients (1260.21 ± 850.21) ng /ml, which is significantly higher (P=0.001) compared to healthy control groups (439.47 ± 202.05) ng/ml, as shown in Figure 3-A. In ROC analysis, TD1 patients gave AUV value 0.999 (sensitivity 100%, specificity 90%) and the cutoff value was (671.76), as shown in Figure 3-B and Table 4.

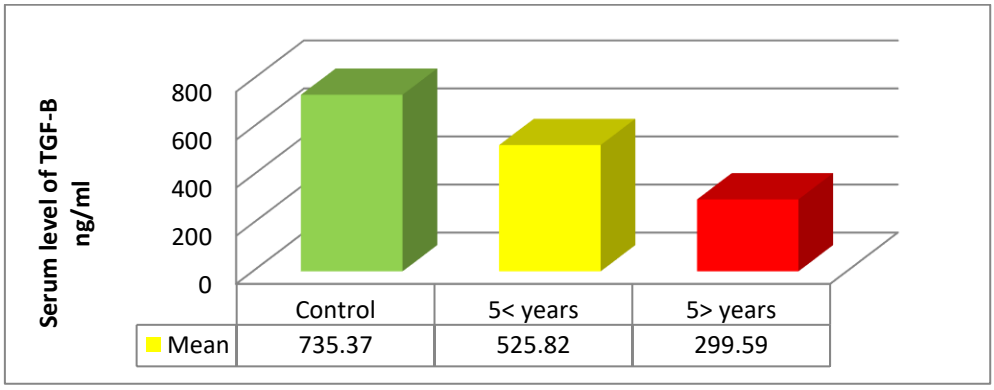


Fig. 2: Serum level of TGF- β depend on duration of disease and healthy groups

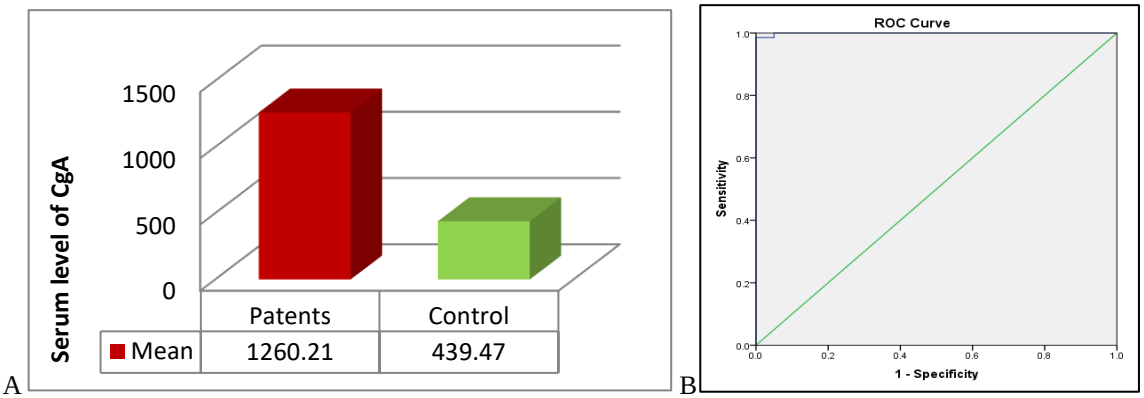


Fig. 3: A-Serum level of CgA B- ROC curve of CgA inT1DM Patients and control

Table 4: CgA sensitivity **and specificity in T1DM patients and control**

AUC	P-value	Cut off	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.999	**0.001**	**671.76**	**0. 997**	**1.000**	**100 %**	**90 %**

Estimation CgA serum level in Type 1 diabetic patients according to duration of disease.

The current study showed significant difference in CgA between Type 1 diabetic patients depending on duration of disease and control. The CgA concentration was significant in patients T1DM (under 5 years) (1039.90 ± 357.61) ng/ml. Mean while, it was (3211.47 ± 1324.88) ng/ml in (upper 5 years) and in control it was (439.47 ± 202.05).

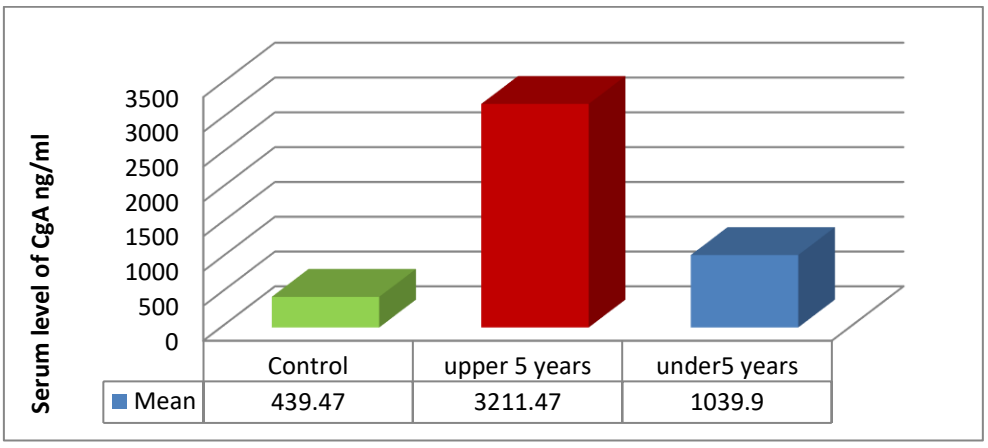


Fig. 5: Serum level of CgA in T1DM depend on duration of disease and healthy groups

MiR-181a 1-3-p expression in Diabetic mellitus type 1 patients and controls

The results of microRNA-181a 1-3-p expression in patients with diabetic mellitus Type 1 was (0.58 ± 0.10) fold change compared to control subjects (1.0± 0.12) fold change, as shown in Figures 5-A and 5-B. There was highly significant difference in miRNA-181a 1-3-p among study groups (P< 0.001). The clinical significance of miRNA-181a 1-3-p in the T1DMpatients is illustrated in Table 5. The receiver operating characteristics (ROC) curve of Figure 6 shows the sensitivity 76% and specificity 100 % of miRNA-181a 1-3-p, cutoff value was 0.70 , AUC 0.87 and (95%CI= 0.63–1.00).

MiR-181a1-3p gene expression in patients with T1DM according to duration of disease.

The results of miR-181a1-3-p gene expression showed significant up-regulation (P<0.05) in TD1 patients (5< years) (fold change 0. 717 ± 0.071), when compared to T1DM patients (5>years) (fold change 0.557 ± 0.078) and healthy control (fold change 1± 0.128), as shown in Figure 7.

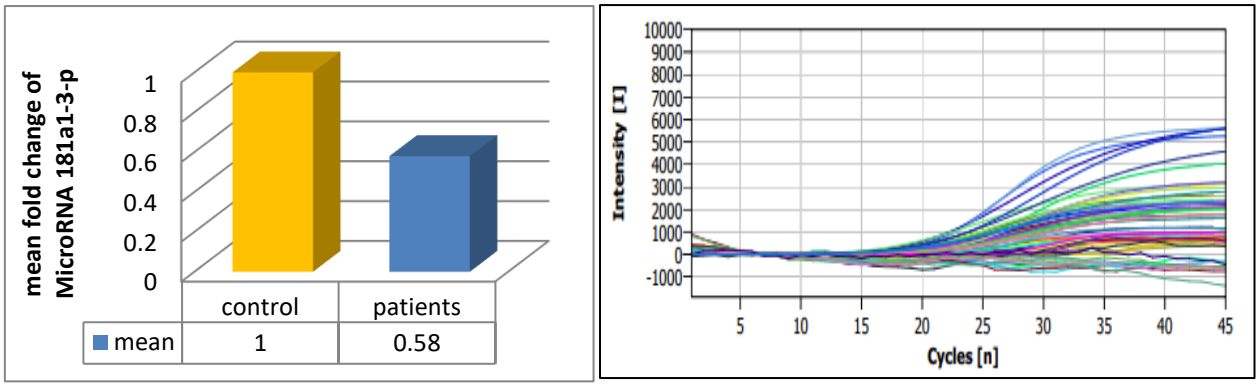


Fig. 5: A. Mean of the miR-181a 1-3-p fold change in T1DM patients and controls. B. RT-PCR images show Ct value of microRNA-181a 1-3-p genes

Table 5: Sensitivity and specificity of miRNA-181a 1-3-p in T1DM patients.

AUC	P-value	Cut off	Asymptotic 95% Confidence Interval		Sensitivity	Specificity
			Lower Bound	Upper Bound		
0.87	0.001	0.70	0.63	1.00	76%	100%

AUC, area under the curve, **spec**. specificity, **sense**. Sensitivity,
CI: Confidence interval, values were significant at P< 0.05.

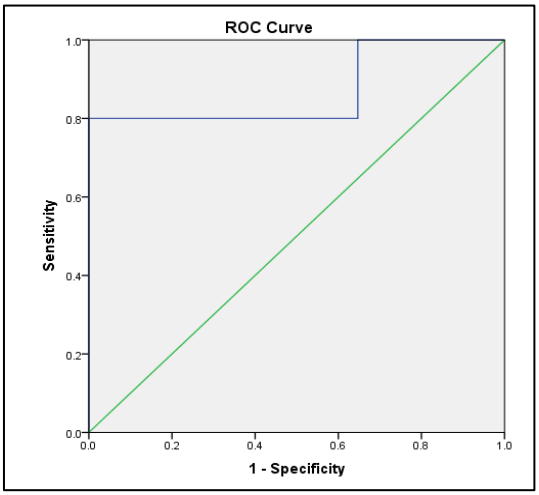


Fig. 6: Receiver operating characteristic (ROC) curve for miRNA-181a1-3p in T1DM patient

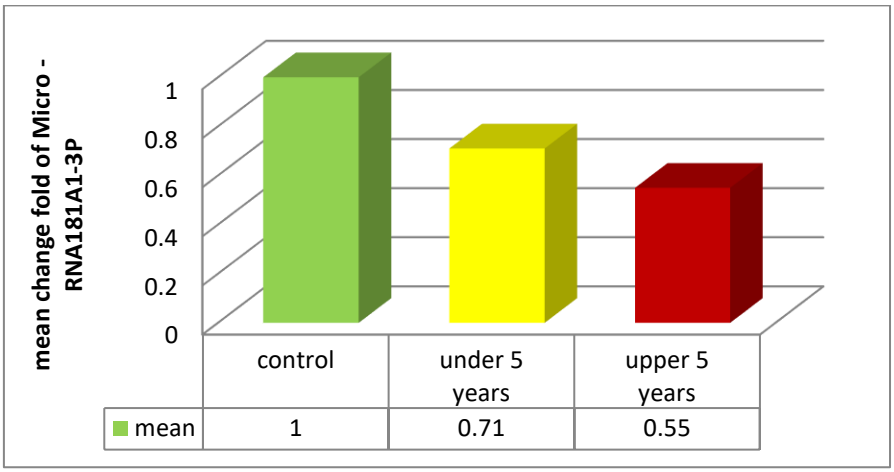


Fig. 7: Mean fold change of miR-181a1-3p depend on duration of disease and control groups

DISCUSSION

According to this study, there were as many females as men, and the average age of T1DM patients was 11.19± 3.58 years, with a range of 3–17 years. This study integrates previous results, which showed that males recorded 38 (50.7%), compared to females 37(49.3). All patients were under the age of 18 years with a mean 10.56(2.61). The age of onset ranged from 1 to 10 years with a mean of 4.38 years and the duration of disease was more than 4 years[9].

Another study reported the same results, where the mean age of patients with diabetes and controls was 10.0 ± 3.73 and 8.68 ± 3.1 years, respectively, with no significant difference (P= 0.069). The mean age at onset and disease duration was 7.08±2.93 years and 3.0±2.61 years, respectively, with 76.19% of the patients having a disease duration of less than 5 years[10].

The results in the current study showed decreased level of TGF-β1, which plays a key role in regulating immune response, whereas decreased level leads to elevated level of proinnflammatory cytokines and prograssion of T1DM disease. This agrees with the result of CD *et al.* [11] who observed that T1DM patients had decreased concentration of TGF-B1 in peripheral blood compared to the healthy control group[11]. Also, a study by Ninić et al. [12] indicated that gene expression had downregulation of TGF-β1 in PBMC of T1DM adolescents. TGF-β1 mRNA downregulation may be useful for predicting early complecation of disease[12]. Wadai [13] confirmed that decreased concentration of TGF-β1 serum level leads to persistent inflammation and subsequent abnormal immune response causing antagonistic effect on the T1DM development[13]. In another study by Chen, *et al.* [14] observed that TGF-β1 release plays a vital role with cytokine that modulates immune responses for maintaining immune homeostasis due to their potent immunosuppressive functions[14].

Furthermore, Singh,*et al.*, [15] Al-Muhanna et al [16] established that decreased levels of TGF-B1 is associated with breakdown of immune tolerance through suppressive function of regulatory T cells, allowing autoreactive T cells to proliferate and target self – antigen such as Anti-GAD65[17] . Mellitus et al ,mentioned that T1DM complications can be detected in adolescents after five-years duration of T1DM indicating that prolonged period of disease with persestance decreased TGF-β1 leads to complecations such as nephropathy and cardiovascular disease.

Moreover, Finnson et al [18] observed that serum TGF-β levels decreased significantly and in the T1DM group, especially those diagnosed for more than 5 years. They explained that the process of differentiation of CD4+ T cells into helper T cells 1 (Th1) and 2 (Th2) is inhibited by the TGF-β signal; therfore, decreased level leads to conteneous activation of t-cell, which halmarks of autoimmunity[18]. The results in the current study agrees with the result of Watanabe et al. [19] who found that serum CgA levels rise as the disease progresses, which may indicate the presence of autoimmune processes affecting the pancreas . According to prior study, CgA is an autoantigen, which implies that immune responses against it might activate autoreactive T cells and contribute to the pathophysiology of T1DM [20].

Similarly, Kinsley et al. [21] showed that T1DM patients had much greater blood CgA levels than healthy controls. The rise may be a sign of continued autoimmune destruction of pancreatic beta cells and coincides with greater disease activity. Ebert,*et al* [22] detected that TIDM patients had increased CgA in the autoimmune, compared with the non- autoimmune. Also, Ioannidis,*et al* [23]confirmed that increased concentration of CgA leads to increased Pro- inflammatory and subsequent abnormal

immune response, which in turn causes beta-cell damage and promotes disease progression.

On the other hand, elevated serum levels of CgA have been reported in TIDM patients relative to healthy control groups [24]. In this study, the results are in line with Herold et al (2020), who showed that the serum levels of CgA in newly-diagnosed Type 1 diabetes patients were significantly higher than the healthy controls, suggesting that these CgA cleavage products contribute to the pathogenesis of Type 1 diabetes. This work indecates that decreased expresion of miR-181a-1-3p in T1DM patients, which influence the balance between regulatory T cells (Tregs) and effector T cells, affecting the autoimmune response [25].

In consistent results, Assmann et al [26] found that miR-181a-1-3p has role in cytokine-mediated beta-cell destruction. Liu *et al* [27] demonstrated that the expression level of *miR-146a*, and *miR-181a* are decreased levels of serum in autoimmune diabetes. Loss of *miR-181a* increases the reactivity of peripheral T cells against self-antigens, indicating its essential role in modulation of T-cell activity, and the imbalance between pro- and anti-inflammatory processes could be attributed to the dysregulation of these miRNAs, since the targets of these miRNAs are linked to the control of Th1/Th17 and the differentiation of T-reg cells . In same vein Gordino,*et al* [28] estabilised that the downregulation of miR-181a-1-3p has been associated with increased levels of pro-inflammatory cytokines, such as IL-6 and TNF-a, which can exacerbate beta-cell damage and promote disease progression. Furthermore, they showed that miRNA-181a-1-3p is implicated in the development of immunopathogenesis in T1DM patients via stimulating the process of differentiation and development of T lymphocytes[29] .

Scherm and Daniel [30] further showed that miR-181a-3p influences T cell activation and the balance between effector T cells and regulatory T cells (Tregs). Decreased levels of miR-181a-3 can promote T cell activation while inhibiting Treg induction, potentially exacerbating autoimmune responses against pancreatic β-cells. According to disease duration. Santos *et al* [31] found that miR-181a-1-3p is differentially expressed in various periods of disease of T1DM, suggesting that the period of disease affect miRNA with potential role in disease progression. Finally, Zhang et al [32] showcased that miR-181a-1-3p is correlated with the presence of islet autoantibodies and beta cell function, indicating its relevance to the disease early stages and duration of diabetes.

CONCLUSION

As a potential target for therapeutic intervention and a measure of disease activity, chromogranin A , TGF-B is recognized as a significant role player in the pathophysiology of Type 1 diabetes.

REFERENCES

1. Handelsman Y, Butler J, Bakris G, DeFronzo R, Fonarow G, Green J, Grunberger G, Januzzi J, Klein S, Fonseca V. Early intervention and intensive management of patients with diabetes, cardiorenal, and metabolic diseases. J Diabetes Complications. 2023 ;37(2):108389. doi: 10.1016/j.jdiacomp.2022.108389.
2. Neama N, Darweesh MF and Al-Obiadi A. Prevalence and antibiotic susceptibility pattern in diabetic foot ulcer infection with evaluation role of biomarker IL-12 in disease. Biochem. Cell. Arch.2018; 18 (2): 2321-28.
3. Dakroub A, Dbouk A, Asfour S, Nasser A, El-Yazbi, Sahebkar A, Eid A, Eid AH. C-peptide in diabetes: A player in a dual hormone disorder? Journal of cellular physiology 2024 ; 45(3): 264-272.
4. Ebert A, König J , Frommer L, Schuppan, D, Kahaly G. Chromogranins serves as novel biomarker of endocrine and gastric autoimmunity. J. Clin. Endocrinol. Metab. 2020, 105, dgaa288.
5. Srivastava N, Hu H, Vomund A, Peterson O, Baker R, Haskins K, Unanue ER. Chromogranin A deficiency confers protection from autoimmune diabetes via multiple mechanisms. Diabetes. 2021 ;70(12), 2860-2870.
6. Mansor M R and Alammar M H.Evaluation of miRNA-155 expression in patients with Alzheimer's disease. Egyp.J. of Med Micro.2024;33(4). DOI: 10.21608/ejmm.306484.1283
7. Almousawy AJ, Darweesh MF. Prognostic Value of miRNA-155 and Tumor Necrosis Factor-Alpha in Rheumatoid Arthritis Disease. EJMM. 2024; 34(1).
8. Abdulla NY, Motaweq ZY, Alrufaie ZM, Zghair LS. Phenotypic and Genotypic Study of Biofilm Formation in Multidrug Resistance Bacteria Isolated from Diabetes Patients. AIP Conference Proceedings .2024;3092(1).
9. Al-Husseini R. M. Impact of interleukin-1 beta gene allelic polymorphisms in diabetic and non-diabetic hemodialysis Iraqi patients. Systematic Reviews in Pharmacy.2020; 11(12), 63-6.
10. Hussein D and Darweesh M F. Role of EBV infection in Type-1 Diabetic nephropathy pathogenesis with related to IL-12 level in patients. BIO Web of Conferences.2023; 65(05041).
11. Miličić T, Jotić A, Marković I, Popadić D, Lalić K, Uskoković V, Lukić L, Maćešić M. Changes in CD4+CD25 T cells and TGFβ1 levels in different stages of adult-onset type 1 diabetes. J Med Biochem. 2024 ;43(6):915-926.

12. Abass RJ, Sharba IR. GDF-15 A potential Biomarker of Diabetic Nephropathy in Iraq Patients with Chronic Kidney Disease. Trop J Nat Prod Res. 2020;4(12):1081-1087.
13. Chen S, Meng X, Wang H, Jiang M, Shen X, Wang and Wang C. Analysis of frequency changes in CD8+ regulatory T cell subsets in peripheral blood of individuals with type 1 diabetes." Diabetology & Metabolic Syndrome. 2024; 16: 305.
14. Singh B, Krawetz R, De Lima R, Mukherjee P, Chaturvedi E, Lee-Chan E and Summers K. Role of TGF-β in self-peptide regulation of autoimmunity. Archivum Immunologiae et Therapiae Experimentalis. 2018; 66: 11-19.
15. Al-sabti KH, Shabaa RA.Evaluation of antifungal drug resistance among *Candida albicans* isolated from clinical specimens.*Microbial Biosystems*.2025; 10(1) 206-214. doi: 10.21608/mb.2025.302765.1123
16. Mellitus W, Irawan R, Endaryanto A, and Rochmah N. The Role of TGF-β in the Pathogenesis of Type 1 Diabetes. International Journal of Scientific Advances. 2022; 3(2).
17. Jumaah HS, Ali AJM. miR-762 as biomarker in Graves' ophthalmopathy patients. Rend.Fis Acc.Lincei .2025; 35, 733–739. doi.org/10.1007/s12210-024-01263-8 .
18. Watanabe T. The Emerging Roles of Chromogranins and Derived Polypeptides in Atherosclerosis, Diabetes, and Coronary Heart Disease. International Journal of Molecular Sciences. 2021; 22(11):6118. https://doi.org/10.3390/ijms22116118.
19. Goetze J, Hilsted L, Rehfeld J. Chromogranin A in cardiovascular endocrinology. Acta Physiol. 2021 ;231, e13615.
20. Yu Z, Gong Y, Cui L, Hu Y, Zhou Q, Chen Z, Yu Y, Chen Y, Xu P, Zhang X, Guo C, Shi Y. High throughput transcriptome and pathogenesis analysis of clinical psoriasis. J Dermatol Sci. 2020; 98(2): 109-118.
21. Ebert A, König J, Frommer L, Schuppan D, Kahaly GJ. Chromogranin serves as novel biomarker of endocrine and gastric autoimmunity. The Journal of Clinical Endocrinology & Metabolism. 2020;105(8): 2606-2615.
22. Ioannidis M, Mahata S, van den Bogaart G. The immunomodulatory functions of chromogranin A-derived peptide pancreastatin. Peptides. 2022;158: 170893.
23. Kamil KA, Darweesh MF. Soluble CD8 and CD25 along with anti-tTG autoantibody as non-invasive prognostic factor in celiac patients. Egypt J Immunol.2025; 32(2):17-26. doi: 10.55133/eji.320202.
24. Herold Z, Herold M, Nagy P, Patocs A, Doleschall M, Somogyi A. Serum chromogranin A level continuously rises with the progression of type 1 diabetes, and indicates the presence of both enterochromaffin-like cell hyperplasia and autoimmune gastritis. Journal of Diabetes Investigation. 2020; 11(4): 865-873.
25. Assmann T, Recamonde-Mendoza M, De Souza BM, Crispim D. MicroRNA expression profiles and type 1 diabetes mellitus: systematic review and bioinformatic analysis. Endocr Connect. 2017 Nov;6(8):773-790.
26. Liu Y, Ma J, Yu F, Ping H, Zhang W, Li L, Xu, Li Y. Decreased serum microRNA-21, microRNA-25, microRNA-146a, and microRNA-181a in autoimmune diabetes: potential biomarkers for diagnosis and possible involvement in pathogenesis." International journal of endocrinology. 2019; (1): 8406438.
27. Ghorbani S, Talebi F, Chan W, Masoumi F, Vojgani M, Power C and Noorbakhsh F. MicroRNA-181 variants regulate T cell phenotype in the context of autoimmune neuroinflammation. Frontiers in immunology. 2017; 8: 758.
28. Mousa M, Ali A J, and Ben Romdhane W M. The Major role of TNF-α and miR-203 in the immune Response of Diabetic Foot Ulcer. E.J. of Medical Microbiology. 2025;34(1). DOI 10.21608/ejmm.2024.338511.1379
29. Scherm M, Daniel C. miRNA-mediated immune regulation in islet autoimmunity and type 1 diabetes. Frontiers in endocrinology. 2020; 11: 606322.
30. Santos A, Ferreira L, da Silva A, Alves L, Damasceno J, Kulikowski L, Cunha-Neto E, da Silva MER. Progression of Type 1 Diabetes: Circulating MicroRNA Expression Profiles Changes from Preclinical to Overt Disease. J Immunol Res. 2022:2734490.
31. Zhang L, Wu H, Zhao M, Lu Q. Identifying the differentially expressed microRNAs in autoimmunity: a systemic review and meta-analysis. Autoimmunity. 2020;53(3):122–136.