RESEARCH PAPER

Serum and urinary TGF-β1 in diabetic nephropathy patients

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Abstract

Background: Diabetes mellitus is a chronic metabolic illness that causes hyperglycaemia. This hyperglycaemia may be the consequence of a malfunction in insulin synthesis, insulin action, or both. DM can raise the risk for the development of microvascular as well as macrovascular problems. An increase in oxidative stress and inflammation are two of the hallmarks of diabetes, which is recognized as a disorder in and of itself. TGF-beta is a member of the TGF-beta subfamily, which is a part of the TGF-beta superfamily.

Methods: The current research comprised a total of 130 individuals, all were placed into three primary groups; 50 diabetic patients without nephropathy, 50 diabetic patients with nephropathy, and 30 persons in good health who were the same age and gender as the patients being studied,50 urine sample has been taken from participants to measure the concentrations of the parameters, the standard procedures and techniques were used.

Results: The results of the present study revealed that the mean value of serum TGF β1 was significantly higher in diabetic patients without nephropathy and diabetic patients with nephropathy (40.19 ± 3.56ng⁄ml), (51.21 ± 5.20ng⁄ml) respectively as compared to controls (24.80 ± 3.51 ng⁄ml) with a high significant difference (P <0.01). The level of TGF β1 showed a positive correlation in the study population with fasting blood sugar (r = 0.273, P = 0.006).

***Conclusion*:** The main finding of the present study is that there was a significant difference ($p < 0.05$) between serum TGF-β1 in diabetic patients with nephropathy, diabetic patients without nephropathy and controls.

Keywords: type 2 Diabetes mellitus, nephropathy, TGF-β1, Cystatin-C.

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Introduction

The prevalence of diabetes mellitus type 2, which now exceeds 9% globally, is estimated to impact around 463 million people and is one of the top 10 main causes of mortality.[1,2] In Basrah (Iraq), the total prevalence of diabetes in adults is 19.7 per cent. Of this number, 8.7 percent had previously obtained a diagnosis, while 11 percent were found via screening. [3]As a result, several researches have been carried out in Basrah to investigate diabetes from various aspects.[4,5] This condition has been rising at an exponential rate. Therefore, one of the primary concerns of public health researchers and clinical health professionals[6] is the development of methods to postpone the beginning of type 2 diabetes mellitus and early treatment techniques to halt its progression. It has been shown that inflammation has a significant role in the development and progression of type 2 diabetes (T2DM), including an increase in the levels of

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inflammatory biomarkers; hence, the treatment of T2DM should focus on lowering inflammation.[7,8] Diabetes mellitus is a chronic metabolic illness that causes hyperglycemia. This hyperglycaemia may be the consequence of a malfunction in insulin synthesis, insulin action, or both. Diabetes mellitus can raise the risk for the development of microvascular as well as macrovascular problems. An increase in oxidative stress and inflammation are two of the hallmarks of diabetes, which is recognized as a disorder in and of itself. TGF-beta is a member of the TGF-beta subfamily, which is a part of the TGF-beta superfamily. [9-11] A wide variety of biological processes are controlled by the TGF-beta subfamily, which is engaged in their regulation, such as the development of cells and differentiation, adhesion, proliferation, tissue repair, morphogenesis, and apoptosis.[10,11] These are only some of the functions. Only TGF-beta isoforms 1-3 are expressed in mammals,[12] even though there have been five different TGF-beta isoforms discovered in vertebrates belonging to this subfamily. The TGF- beta 1 isoform that is prominent in the kidney is the one that causes responses to be triggered by many signalling pathways. These pathways include SMAD, protein mitogen-activated kinases, extracellular regulatory kinase, p38, and Jun kinase[13] which are examples of proteins that play a role in signal transduction . Through three mechanisms, renal fibrosis has been firmly linked to TGF- beta1 activity in the setting of kidney disease:

1. A pro-fibrotic phenotype is brought about in the kidneys as a result of an increase in the production of extracellular matrix (ECM) as well as epithelial-mesenchymal transition (EMT).
2. Increased type I and IV collagen, fibronectin, and laminin synthesis.
3. The matrix breakdown may be reduced by increasing the expression of matrix metallo-protease inhibitors [14,15,20]

Method

This case-control study was conducted at Al-Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC) in Basrah governorate between November 2022 to May 2023. The study included 100 patients (50 males and 50 females) with T2DM, and 30 control healthy subjects (15 males and 15 females). Patient selection was carried out based on predefined inclusion and exclusion criteria. A total of 100 patients with T2DM, with an age range between (75<-30) years, were diagnosed for one year or above. Patients received different treatments such as insulin and/or OAHD. A group of 30 healthy subjects (no history of diabetes mellitus and appears to be in a good health state), attended the Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC). To achieve compatibility between patients and this group, the control group matched patients in age and sex.

Inclusion Criteria:

- Type 2 diabetic patient

Exclusion Criteria:

An individual having the following criteria was excluded based on patient's history:

- chronic liver disorders, cardiac diseases, and coronary artery diseases (CAD).
- Malignancy.
- Autoimmune disorders.

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- Individuals with chronic renal conditions, as well as those with acute or chronic inflammatory disorders, including patients who are on anti-inflammatory medicines, nonsteroidal anti-inflammatory drugs (NSAIDs), or other treatments that have the potential to impact renal function.

Sample collection:

After overnight fasting (> 8 hours), blood samples were obtained from diabetic patients and the non-diabetic (control group) by venipuncture using a disposable butterfly in the sitting position. (5 to 6 ml) of blood were obtained from each subject and divided into two parts:

A. The rest of the blood was placed in disposable vacutainer blood collection tubes without anticoagulant and was left for 30 minutes at room temperature, followed by centrifugation for 5 minutes at 3000 rpm to collect serum. Then separated serum was stored in new disposable plastic tubes parts of which were used for estimation of glucose, creatinine, and other parts stored in the freezer for subsequent analysis of TGF-β1 and Cystatin-C levels.

B. part of 2 ml from each drawn sample was dispensed in a tube containing (EDTA) to be used in the measurement of HbA1c levels.

C. Urine samples :Ten ml of urine was collected from each patient with T2DM and healthy subjects, for determination of Albumin.

The statistical analysis

The data were represented as means with the standard deviation. The statistical studies were conducted with SPSS, version 26, developed by IBM in the United States. A significance level of $P < 0.05$ was deemed to be statistically significant.

Results

The mean and standard deviation of FBS, HbA1c, Creatinine, Albuminuria, Cystatin C, serum TGF-b1 and level of urine TGF-b1 for both cases and controls were demonstrated in the (Table-1). The study showed that the mean of FBS in cases (DM and DN) was highly significant (211.10 ± 68.70) and (244 ± 92.27) respectively, compared to controls (98.23 ± 11.42 mg/dl) ($P < 0.01$). Additionally, the mean values of HbA1c were highly significant in cases (DM and DN) (8.78 ± 2.22) and (8.87±1.76) respectively, compared to controls (4.91 ± 0.58 %) ($P < 0.01$). The mean values of Creatinine and Cystatin-C were higher in diabetic patients with nephropathy (3.54 ± 2.44 and 90.55 ± 8.06 ng/ml) compared to controls (0.68 ± 0.11 and 43.05 ± 8.92 mg⁄dl) with high significant differences ($P < 0.01$). The mean values of Albuminuria were higher in diabetic patients with nephropathy (160.78 ± 171.63 ug/mg) compared to controls (6.7 ± 2.56 ug/mg) having a statistically significant difference ($P < 0.05$). The study found that the mean value of serum TGF-β1 in diabetic patients without nephropathy and diabetic patients with nephropathy (40.19 ± 3.56ng⁄ml), (51.21 ± 5.20ng⁄ ml) respectively as compared to controls (24.80 ± 3.51 ng⁄ml) with a high significant difference ($P < 0.01$). The study

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found that the mean value of urine TGF-β1 in diabetic patients without nephropathy and diabetic patients with nephropathy (was 29.26 ± 4.69ng⁄ml), (51.68 ± 2.49 ng⁄ml) respectively as compared to controls (10.35 ± 4.88 ng⁄ml) with a high significant difference (P < 0.01

Table 1. The research sample was distributed based on the biochemical characteristics

Parameters	Controls N=30 Mean ± SD	Cases N=100	P-value* (Between groups)	
		DM Mean ± SD	DN Mean ± SD	
Gender	Male	15(11.5%)	50(38.5%)	-
	Female	15(11.5%)	50(38.5%)	-
FBS (mg⁄dl)	98.23±11.42	211.10±68.70	244±92.27	< 0.01
HbA1c (%)	4.91±0.58	8.78±2.22	8.87±1.76	< 0.01
Creatinine (mg⁄dl)	0.68 ± 0.11	0.81±0.25	3.54±2.44	< 0.01
Cystatin-C (ng⁄ml)	43.05 ±8.92	77.02±4.41	90.55±8.06	<0.01
TGF β1	24.8 ± 3.51	40.19±3.56	51.21±5.20	<0.01
TGF β1 urine	10.35 ±4.88	29.26±4.69	51.68±2.49	<0.01
Albuminuria	6.7 ± 2.56	14.08±6.53	160.78±171.63	<0.05

The Pearson correlation analysis of the biochemical parameters with Cystatin-C, albuminuria, serum TGF-β1 and levels of urine TGF-β1 were presented in (Table-2). The study revealed that serum TGF-β1 correlates positively and significantly with creatinine, albuminuria, cystatin-C and urine TGF-β1, the study showed no correlation of serum TGF-β1 with HbA1c. This study shows that there is no significant correlation between cystatin-C with FBS and HbA1c.

Table 2. Pearson Correlation of the biochemical parameters with Cystatin-C, albuminuria, TGF-β1 and urine TGF-β1 levels in the study population:

Correlations					
		Cystatin-C	Albuminuria	TGF-B1	TGF-B1 URINE
FBS	Correlation Coefficient	0.163	0.234*	0.273**	0.291
	P-value	0.105	0.019	0.006	0.069
A1C	Correlation Coefficient	0.017	0.147	0.064	0.042
	P-value	0.869	0.143	0.527	0.799
CREA	Correlation Coefficient	0.541**	0.638**	0.546**	0.611**
	P-value	0.006	0.009	0.004	0.003
Cystatin C	Correlation Coefficient	1	0.487**	0.597**	0.698**
	P-value		0.003	0.005	0.005
Albuminuria	Correlation Coefficient	0.487**	1	0.515**	0.625**
	P-value	0.003		0.004	0.001
TGF B1	Correlation Coefficient	0.597**	0.515**	1	0.913**

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Receiver-operating characteristic (ROC) curve analysis for Cystatin-C, albuminuria, serum TGF-β1 and level of urine TGF-β1 in the study population were presented in (Table-3). The study found that the sensitivity and specificity of TGF-β1 level were higher than the sensitivity and specificity of Cystatin-C (92.0, 94.0% and 88.0, 86.0%) respectively, and the best cut-off values for TGF-β1 and Cystatin-C were (44.45 and 82.35 ng/ml) respectively, while the area under the curve for TGF-β1 and Cystatin-C (0.983 and 0.970 respectively). Regarding the sensitivity and specificity of urine TGF-β1 and albuminuria, there were no differences (98.0,99.0% and 98.0, 99.0%) respectively, and the best cut-off value for urine TGF-β1 and albuminuria were (46.60 ng/ml and 49.00 ug/mg) respectively, while the area under the curve for urine TGF-β1 and albuminuria (0.990 and 0.990) respectively.

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Table 3. Receiver-operating characteristic (ROC) curve analysis for the biochemical parameters Cystatin-C, albuminuria, TGF-β1 and urine TGF-β1 levels in the study population:

Variables	The area under the ROC curve (AUC)	Best cut-off	Sensitivity (%)	Specificity (%)
Cystatin-C	0.981	82.35	88.0	86.0
Serum TGF-β1	0.983	44.45	92.0	94.0
Urine TGF-β1	0.990	47.05	93.0	90.0

The Spearman's correlation analysis of the study variables with Cystatin-C, albuminuria, serum TGF-β1 and level of urine TGF-β1 was demonstrated in the (Table-4). The study found that serum TGF-β1 correlates positively and significantly with BMI, while for urine TGF-β1, the study revealed that urine TGF-β1 correlates negatively but not significantly with disease duration. Regarding Cystatin-C, the study showed a positive correlation and significance between Cystatin-C with BMI.

Table 4. Correlations of the serum TGF-β1 levels with biochemical and clinical characteristics.

Variables	r - Value	P – Value
Age (year)	0.179	0.264
BMI (kg/m^2)	0.202	0.044
Duration of DM	0.045	0.654
FBG (mg ⁄ dL)	0.273	0.006
HbA1c (%)	0.064	0.527
Cystatin-C	0.597	0.005
Creatinine	0.546	0.004

The Spearman's correlation analysis of the study variables with Cystatin-C, albuminuria, serum TGF-β1 and level of urine TGF-β1 was demonstrated in the (Table-3). The study found that serum TGF-β1 correlates positively and significantly with BMI, while for urine TGF-β1, the study revealed that urine TGF-β1 correlates negatively but not significantly with disease duration. Regarding Cystatin-C, the study showed a positive correlation and significance between Cystatin-C with BMI.

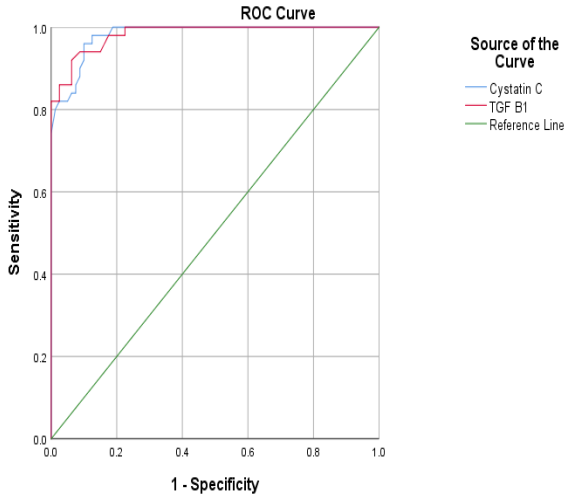

Fig 1. ROC between TGF b1 and Cystatin c

Discussion

The most prevalent kind of diabetes, type 2 diabetes mellitus, is a complex chronic metabolic illness with rising worldwide incidence. Just over 95% of DM patients globally have T2DM. [5] This research aimed to assess TGF β1 as a biochemical marker for diabetic nephropathy in type II diabetic individuals. the study tries to correlate serum and urinary TGF β1 with another biochemical marker in diabetic nephropathy (creatinine, cystatin-C, albuminuria, blood glucose, HbA1c). This study population have a mean value of 8.83 ± 1.99 for HbA1c% which is comparably lower than HbA1c 9.31% ± 2.77% Agarwal et al.[6] Although more than

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61% of the patients in the present study had poor glycaemic control and only 18%, and 21% of them achieved good and fair glycaemic control respectively. Concerning the level of serum TGF β1, the mean value of this marker is high in diabetic patients with nephropathy compared with control. this finding is consistent with Yehia M et al.[7] who discovered a relationship between serum TGF β1 and diabetic nephropathy. In addition, when comparing diabetic patients with nephropathy to diabetic patients without nephropathy, the level of serum TGF β1 and the mean value of this marker are both shown to be increased in diabetic patients with nephropathy. Yaqiu et al.[8] concluded that the serum concentration of TGF β1 began to increase in the early stages of diabetic nephropathy and that as diabetic nephropathy progressed, the serum level of TGF β1 increased significantly. These results were supported by Yaqiu et al.[8], who stated that their findings demonstrated that the serum concentration of TGF β1 began to increase in the early stages of diabetic nephropathy. According to the findings of the current research, diabetic individuals who also have nephropathy have cystatin C levels that are considerably higher than those of diabetic patients who do not have nephropathy (90.558.06 vs. 77.024.41ng/ml). Similar results were revealed by Jeon YL et al[9]. They stated that the higher level of cystatin C is most likely due to the that the level of cystatin C was strongly correlated with diabetic nephropathy. Jeon YL et al[9] found significantly higher levels of cystatin C in diabetic patients than in controls. It was hypothesized that the tubular phase, which occurs before the glomerular manifestation, was the likely cause of this increase. This evidence implies that the cystatin C levels in serum are associated with subclinical tubular impairment and that they might be an early detectable measure of renal involvement before the emergence of albuminuria. The study revealed that serum TGF-β1 correlates positively and significantly with creatinine, albuminuria, cystatin-C and urine TGF-β1. This study showed that there is no significant correlation between cystatin-C with FBS, these findings were consistent with those obtained by Yehia M. Shaker et al.[7] (ROC) curve analysis for TGF-β1, Cystatin-C and albuminuria in the study population. The study found that the sensitivity and specificity of TGF-β1 level were higher than the sensitivity and specificity of Cystatin-C (92.0, 94.0% and 88.0, 86.0%) respectively. Regarding the fact that there was no difference between the sensitivity and specificity of urine TGF-1 and albuminuria (98.0, 99.0 percent and 98.0, 99.0 percent respectively), these findings were corroborated by Yehia M et al.[7] Moreover, this study found that there was a significant and positive correlation between the serum TGF β1 and urine TGF β1 with serum creatinine levels, which in coherence with Yehia M et al.[7] In addition, patients with long-term diabetes (5 years) had higher levels of TGF β1 than those newly diagnosed; however, this difference is not statistically significant ($p > 0.05$), which could be explained by the fact that the level of TGF β1 increases as the duration of the participant's cases increases.[21] Although the present study revealed a non-significant difference in the level of TGF β1 concerning diabetic treatment ($p > 0.05$), as well as the TGF β1 levels, were higher in patients who used OAHD therapy

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(46.72 ± 7.18) and lower in patients who were kept on dietary (40.55 ± 4.63). These findings were consistent with those obtained by Yehia M. Shaker et al.[7] Having observed a substantial connection between TGF β1levels and blood glucose, they concluded that alterations in TGF β1 levels may be related to nephropathy. Regarding HbA1c, the research observed no association between HbA1c and TGF β1 in the study group (r = 0.064, p = 0.527). These findings were consistent with those of Yehia M. Shaker et al[7]. The present investigation revealed a substantial positive connection between serum TGF-1 and creatinine, albuminuria, cystatin-C, and urine TGF-1 (r = 0.546, p = 0.004), (r = 0.515, p = 0.004)), (r = 0.597, p = 0.005)), and (r = 0.913, p = 0.002), respectively. an increased level of serum TGF-β1in type 2 diabetic patients may be associated with nephropathy. These results, which were congruent with those of Hefini, et al[22], showed that there were significant positive relationships between the concentration of TGF-1 in urine and albuminuria in those who had type II diabetes. TGF-1 may play an essential role in the evolution of glomerular disease by influencing the inflammatory response via glomerulosclerosis, as the results of several studies have shown. (Coimbra et al.,[23].; Border et al.,[24]., Yamamoto et al.,[25].; Bertoluci et al).[6] The current study found that serum and urinary TGF-β1 is a more accurate and reliable test for diabetic nephropathy than cystatin-C. This finding is supported by compatible studies that have investigated the role of TGF-β1 in diabetic nephropathy. A study conducted in 2017 found that serum TGF-β1 levels were significantly increased in patients with type 2 diabetes mellitus (T2DM) and diabetic nephropathy (DN) and could be used as a diagnostic marker for diabetic nephropathy, Qiao, Y. C. et al.[27] Another study conducted in 2021 found that anti-TGF-β1 antibody therapy in patients with diabetic nephropathy could be a promising treatment option, Voelker, J. et al.[28] Overall, the literature suggests that TGF-β1 is a reliable biomarker for diabetic nephropathy and has potential diagnostic and therapeutic applications.

Conclusion, and Recommendation: the result of the current study demonstrated that the mean value of the serum concentration of serum TGF-β1and urine TGF-β1 was significantly higher in patients with nephropathy than in apparently healthy controls. These results also revealed that the serum level of serum TGF-β1was significantly higher in poorly controlled diabetic patients. The study found that there was a significant positive association between the levels of serum TGF-β1with the disease duration, The study found that there was a significant positive association between the levels of serum TGF-β1with urine TGF-β1. future investigations are required to take into consideration the clinical potential of TGF -β1 as a marker in T2DM.

Limitations: We were aware that moderate sample size, and strict inclusion criteria, may limit the results of this study.

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Conflict of interest: The authors of this research have confirmed that there are no competing interests that might influence the publication of this work.

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المصل و TGF-β1 البولي في مرضى اعتلال الكلية السكري

الخلفية: داء السكري هو مرض استقلابي مزمن يسبب ارتفاع السكر في الدم. قد يكون ارتفاع السكر في الدم هذا نتيجة لخلل في تخليق الأنسولين أو عمل الأنسولين أو كليهما. يمكن أن يزيد DM من خطر تطور مشاكل الأوعية الدموية الدقيقة وكذلك الأوعية الدموية الكبيرة. زيادة الإجهاد التأكسدي والالتهاب هما من السمات المميزة لمرض السكري، والذي يعرف بأنه اضطراب في حد ذاته TGF-beta .هو عضو في عائلة-TGF ، والتي تعد جزءا من betaالفرعية.

الأساليب: شمل البحث الحالي ما مجموعه ١٣٠ فردا، تم وضعهم جميعا في ثلاث مجموعات أساسية. ٥٠ مريضا بالسكري بدون اعتلال الكلية ، و ٥٠ مريضا بالسكري يعانون من اعتلال الكلية، و ٣٠ شخصا يتمتعون بصحة جيدة وكانوا من نفس عمر وجنس المرضى الذين تتم دراستهم،٥٠ تم أخذ عينة بول من المشاركين لقياس تركيزات المعلمات ، وتم استخدام الإجراءات والتقنيات القياسية.

النتائج: كشفت نتائج الدراسة الحالية أن متوسط قيمة TGF β1 في المصل كان أعلى معنويا في مرضى السكري دون اعتلال الكلية ومرضى السكري الذين يعانون من اعتلال الكلية(٤٠،١٩ ± ٣,٥٦ نانوغرام / مل)،(٥١،٢١±٥،٢٠ نانوغرام/ مل) على التوالي مقارنة بالشواهد (٢٤,٨٠ ± ٣,٥١ نانوغرام// مل) مع فرق معنوي مرتفع (P <0.01). أظهر مستوى TGF β1 وجود علاقة إيجابية في مجتمع الدراسة مع سكر الدم الصائم (r = 0.273، P = 0.006).

الاستنتاج: النتيجة الرئيسية للدراسة الحالية هي أن هناك فرقا كبيرا (p < 0.05) بين مصل TGF-β1 في مرضى السكري المصابين باعتلال الكلية ومرضى السكري الذين لا يعانون من اعتلال الكلية والضوابط.

الكلمات المفتاحية: داء السكري من النوع ٢، اعتلال الكلية، TGF-β1، Cystatin-C

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