Al-Rafidain J Med Sci. 2023;5(Suppl 1):S8-13.
DOI: https://doi.org/10.54133/ajms.v5i1S.273

AJMS

Online ISSN (2789-3219)

Research Article

Estimation of Tenascin-C Levels in Iraqi Patients with Diabetic Nephropathy

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Received: 30 August 2023; Revised: 29 September 2023; Accepted: 11 October 2023

Abstract

Background: Diabetic nephropathy (DN) is a highly malignant chronic microvascular complication of diabetes that is the principal cause of end-stage renal disease (ESRD). ***Objective***: The purpose of this study is to ascertain the correlation between diabetic nephropathy and Tenascin-C (TNC), in addition to quantifying TNC levels at different phases of this pathogenesis. ***Methods***: Thirty healthy subjects and ninety T2DM patients participated in this cross-sectional study. Patients were divided into three groups according to the albumin-creatinine ratio (ACR): normal albuminuria, microalbuminuria, and macroalbuminuria. By employing an ELISA reagent, the serum TNC concentration was ascertained. ***Results***: Significant disparities were observed in the concentrations of TNC and FBG, TC, TGs, HDL, LDL, and VLDL between individuals with diabetic nephropathy and those who were in good health. There were also substantial differences between the levels of TNC and kidney function in patients with various disease stages. Furthermore, a noteworthy positive correlation was identified between TNC and blood concentrations of ACR, urea, and creatinine. ***Conclusions***: Based on the available evidence, it can be deduced that TNC may serve as the most precise predictor of diabetic nephropathy and may be associated with its progression.

Keywords: Diabetic nephropathy, Extracellular matrix, Tenascin-C, Type 2 diabetes.

تقدير مستويات تيناسين سي لدى المرضى العراقيين المصابين باعتلال الكلية السكري

الخلاصة

الخلفية: اعتلال الكلية السكري (DN) هو أحد المضاعفات الوعائية الدقيقة المزمنة الخبيثة للغاية لمرض السكري والتي تعد السبب الرئيسي لعجز الكلى في المرحلة النهائية. **الهدف**: الغرض من هذه الدراسة هو التأكد من العلاقة بين اعتلال الكلية السكري ومستوى تينياسين سي (TNC)، بالإضافة إلى تحديد مستوياته في مراحل مختلفة من هذا المرض. **الطرق**: شارك ثلاثون شخصا سليما وتسعين مريضا بالنوع الثاني من السكري (T2DM) في هذه الدراسة المقطعية. تم تقسيم المرضى إلى ثلاث مجموعات وفقا لنسبة الألبومين والكرياتينين :(ACR) بيلة الألبومين الطبيعية، بيلة الألبومين الدقيقة، وبيلة الألبومين الكبيرة. من خلال استخدام كاشفELISA ، تم التأكد من تركيز TNC في المصل. **النتائج**: لوحظت تفاوتات كبيرة في تركيزات TNC و FBG و TC و TGsو HDL و LDL و VLDL بين الأفراد المصابين باعتلال الكلية السكري وأولئك الذين كانوا بصحة جيدة. كانت هناك أيضا اختلافات جوهرية بين مستويات TNC ووظائف الكلى في المرضى الذين يعانون من مراحل مرضية مختلفة. علاوة على ذلك، تم تحديد علاقة إيجابية جديرة بالملاحظة بين TNC وتركيزات الدم من ACR واليوريا والكرياتينين. **الاستنتاجات**: بناء على الأدلة المتاحة، يمكن استنتاج أن TNC قد يكون بمثابة المؤشر الأكثر دقة لاعتلال الكلية السكري وقد يرتبط بتطوره.

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Article citation: Shaban A, Abbas SA, Abed BA. Estimation of tenascin-C levels in Iraqi patients with diabetic nephropathy. *Al-Rafidain J Med Sci*. 2023;5(Suppl 1):S8-13. doi: https://doi.org/10.54133/ajms.v5i1S.273

INTRODUCTION

Diabetes is estimated to affect 9.3% (463 million people) in 2019, 10.2% (578 million) in 2030, and 10.9% (700 million) in 2045, according to projections [1]. Because type 2 diabetes mellitus (T2DM) significantly increases the global diabetes burden [2,3], this is especially concerning. An increase in diabetes prevalence will result in more chronic and acute illnesses in the general population, which will have a significant impact on quality of life, demand for healthcare services, and monetary expenditures. Diabetes-related macrovascular consequences, such as coronary heart disease [4, stroke, and peripheral vascular disease [5,] as well as microvascular problems, such as end-stage renal disease (ESRD) [6]. The annual growth rate of diabetes-related chronic kidney disease (CKD) is expected to rise as well, particularly in low- and middle-income countries [7]. Diabetes-related retinopathy and neuropathy [8, as well as lower-extremity amputations] are mostly to blame for the burden. Malignancies, age-related outcomes (such as dementia), infections, and liver disease are now being recognized as causally linked disorders [9]. Reduced endothelial cell fenestration, microalbuminuria, macroalbuminuria, glomerular thickening, interstitial fibrosis, and the development of nodular glomerulosclerosis are all symptoms of DN. The role of the renin-angiotensin-aldosterone system, hereditary variables, and inflammation in the development of DN is also important [10]. DN is frequently characterized clinically by a progressive increase in urine albumin excretion, a steady rise in blood pressure, and an increased risk of cardiovascular disease [11]. Tenascin-C (TNC), an extracellular matrix glycoprotein that modulates cell adhesion to fibronectin, is thought to be anti-adhesive [12]. Tenascin-C, Tenascin-R, Tenascin-W (TN-W, also known as Tenascin-N), and Tenascin-X (TN-X) are further members of the tenascin family, each with its own expression pattern [13]. TNC is essentially never expressed in the bulk of well-grown organs, but it is significantly enhanced at multiple sites of pathological circumstances, such as tissue injury and inflammation. TNC, according to the information now available, aids in the progression of diabetes patients' inflammation and atherosclerosis [14]. Tenascin-C is an ECM component, and models of diabetes and insulin resistance have shown that the ECM remodels [15,16]. This protein has been detected in higher concentrations in the retinas of persons with diabetes and chronic renal disease [17,18]. The goal of this study is to analyze the level of TNC in the various stages of diabetic nephropathy and see if it can be used as a diagnostic biomarker.

METHODS

Study design and patient selection

Ninety patients, 30 with T2DM and 60 with DN, between the ages of 30 and 60, who visited the national center for diabetes treatment and research, Mustansiriyah University are included in this study. The patients were divided into three main groups based on the albumin-creatinine ratio (ACR): 30 diabetes patients with an ACR of 30 mg/g (normoalbuminuria group), 30 patients with an ACR ranging from 30 to 300 mg/g (microalbuminuria group), and 30 patients with an ACR > 300 mg/g (macroalbuminuria group). This study included 30 healthy volunteers (aged 30 to 60) who served as controls. Subjects that met the exclusion criteria included T1DM, were pregnant, and had hepatic or ESRD.

Blood and urine sample collection

The morning following an eight-hour fast, urine and blood samples were collected. Urine samples were examined right away. The serum from blood samples was separated by centrifuging at 1500 rpm for 15 minutes, and it was then stored at -20°C for analysis.

Outcome measurements

Tenascin-C concentration was measured using an ELISA kit from Cloud-Clone Corp., United States. Fasting blood glucose (FBG), urea, and creatinine levels were assessed using an enzymatic method. Albumin and creatinine concentrations were calculated using the collected urine samples. The microalbumin level was measured using urine test strips; the test is based on "protein error". Based on a reaction between creatinine and 3,5-dinitrobenzoic acid in an alkaline medium, creatinine can be measured in urine. By dividing the microalbumin level by the urine's creatinine level, the albumin/creatinine ratio (ACR) was determined.

Statistical analysis

The data were evaluated using IBM SPSS for Windows, Version 21.0. A one-way analysis of variance (ANOVA) was used to assess whether the mean changes among the four distinct studied groups are statistically significant. The Pearson correlation analysis was used to determine the correlation coefficient (r) value. Additionally, ROC curve analysis was used in this study to assess each marker's ability to identify illnesses. Significant differences were considered at $p<0.05$.

RESULTS

The baseline characteristics of the T2DM patients (n=90) and controls (n=30) are displayed in Table 1 as mean±SD. Between the patient group and the healthy controls, there were no differences in age or gender

(p=0.537). Between the three patient groups, there is a highly significant difference in the disease duration values (p=0.000). Between patient groups and control groups, FBS values likewise demonstrated a highly significant difference (p=0.000).

Table 1: Baseline characteristics of the studied groups.

Parameters	Control (n=30)	Patient groups			p-value
		DM with normoalbuminuria (n=30)	DM with microalbuminuria (n=30)	DM with macroalbuminuria (n=30)	
Age (year)	52.10±8.65[a]	54.73 ±6.30[a]	53.4±6.91[a]	53.67±5.54[a]	0.537
Disease duration (year)	-------	4.20±1.21[a]	8.83±2.85[b]	12.80±0.96[c]	0.000
BMI (Kg/m^2)	23.34±2.59[a]	29.84±6.99[b]	28.53±4.29[b]	29.99±4.56[b]	0.000
FBG (mg/dl)	105.32±8.76[a]	181.20±79.11[b]	191.63±79.13[b]	219.20±103.21[b]	0.000
B. U. (mg/dl)	16.89±3.25[a]	18.53±3.01[a]	41.63±9.07[b]	70.33±14.35[c]	0.000
S. Cr. (mg/dl)	0.65±0.12[a]	0.81±0.19[a]	1.52±0.14[b]	2.16±0.57[c]	0.000
ACR (mg/g)	-----	16.37±3.46[a]	116.65±45.70[b]	681.04±217.78[c]	0.000

Values are presented as mean±SD. ACR: albumin creatinine ratio; S.Cr: serum creatinine; B.U: blood urea; BMI: body mass index; Significant variants between two groups are denoted by different superscripts (a,b,c) at p<0.05.

In comparison to patients with normoalbuminuria and the control group, the patient groups with microalbuminuria and macroalbuminuria show higher significant differences (p=0.000) in creatinine and urea levels. The ACR values in the three patient groups demonstrate a highly significant difference (p=0.000) among them. Between the control and patient groups, the lipid profile showed a substantially different difference (Table 2). Tenascin-C mean±standard deviation (SD) values for the examined groups are displayed in Table 3.

Table 2: Lipid profile of the studied groups.

Parameters	Control (n=30)	Patient groups			p-value
		DM with normoalbuminuria (n=30)	DM with microalbuminuria (n=30)	DM with macroalbuminuria (n=30)	
TC (mg/dl)	129.97±16.69[a]	172.73±26.39[b]	179.77±31.52[b]	188.43±26.10[b]	0.000
TGs (mg/dl)	100.96±20.09[a]	171.90±24.50[a,b]	177.43±22.42[a,b]	191.87±32.26[b]	0.000
VLDL-C (mg/dl)	21.79±5.34[a]	38.27±4.81[b]	40.90±7.39[b]	41.20±11.09[b]	0.000
HDL-C (mg/dl)	55.86±4.77[a]	40.17±7.96[b]	39.77±6.12[b]	36.23±6.97[b]	0.000
LDL-C (mg/dl)	56.46±7.03[a]	90.90±38.11[b]	92.57±40.26[b]	106.50±36.35[b]	0.000

Values are presented as mean±SD. HDL: high density lipoprotein; LDL: low density lipoprotein; TC: total cholesterol; TG: triglyceride; VLDL: very low density lipoprotein. Significant variants are denoted by different superscripts (a,b) at p<0.05.

There are substantial differences across patient groups, as well as a high level of significance between the patient groups and the control groups (p=0.000). The relationship between TNC and clinical and biochemical factors was then examined.

Table 3: The TNC levels of the studied groups.

Parameters	Control (n=30)	Patient groups			p-value
		DM with normoalbuminuria (n=30)	DM with microalbuminuria (n=30)	DM with macroalbuminuria (n=30)	
TNC (pg/ml)	66.54±11.18[a]	259.55±35.64[b]	881.65±122[c]	1606.99±249.27[d]	0.000

Values are presented as mean±SD. Significant variants between two groups are denoted by different superscripts (a,b,c) at p<0.05; Tenascin-C: TNC.

Table 4, we found a positive correlation between kidney function and TNC (creatinine in normoalbuminuria, micro-, and macroalbuminuria groups r=0.474, p=0.008, r=0.442, p=0.015 and r=0.379, p=0.039 and urea in normoalbuminuria, micro-, and macroalbuminuria groups r=0.518, p=0.003, r=0.433, p=0.017 and r=0.547, p=0.002), respectively. Tenascin-C levels and ACR have a parallel positive connection of r=0.397, p=0.030, and r=0.387, p=0.034 in the normoalbuminuria and macroalbuminuria groups, respectively. In comparison to healthy people, the results of the ROC analysis show that TNC had a great capacity to predict nephropathy in the diabetic group, which included patients with normoalbuminuria, microalbuminuria, and macroalbuminuria.

Table 4: Correlation of TNC (pg/ml) levels with studied parameters

Parameters	DM with normoalbuminuria		DM with microalbuminuria		DM with macroalbuminuria	
	r	*p*	*r*	*p*	*r*	*p*
Age (years)	-0.058	0.759	-0.093	0.623	-0.209	0.268
BMI (Kg/m^2)	0.149	0.431	0.131	0.491	0.015	0.937
Duration of disease (years)	-0.155	0.413	-0.036	0.850	0.241	0.200
FBG (mg/dl)	-0.054	0.778	-0.008	0.965	0.024	0.901
BU (mg/dl)	0.518	0.003	0.433	0.017	0.547	0.002
SC (mg/dl)	0.474	0.008	0.442	0.015	0.379	0.039
TC (mg/dl)	-0.136	0.474	-0.130	0.493	-0.060	0.753
TGs (mg/dl)	0.080	0.674	-0.055	0.773	0.110	0.563
HDL (mg/dl)	0.017	0.928	0.066	0.727	0.108	0.571
LDL (mg/dl)	-0.217	0.248	-0.153	0.421	-0.061	0.749
VLDL (mg/dl)	-0.013	0.946	-0.188	0.320	-0.097	0.611
ACR (mg/g)	0.397	0.030	0.274	0.142	0.387*	0.034

This outcome was attained as a consequence of investigations that took into account the test's sensitivity and specificity parameters as well as the area under the curve (Figure 1). The value of (AUC= 1.000 and p<0.001) in the normoalbuminuria group indicates that TNC has the capacity to predict DN in individuals who are free of illness, and the p value is 0.001, with higher sensitivity at 100% and specificity at 100%. We demonstrated that the TNC has a high ability to distinguish between groups with microalbuminuria and healthy groups with higher sensitivity at 100% and specificity at 100% through the value of (AUC= 1.000 and p<0.001) in the microalbuminuria group. As a result, TNC has a good ability to discriminate between macroalbuminuria and healthy groups, with better sensitivity at 100% and specificity at 100%. We also exhibited the same values of normoalbuminuria and microalbuminuria in the macroalbuminuria group (AUC= 1.000 and p<0.001).

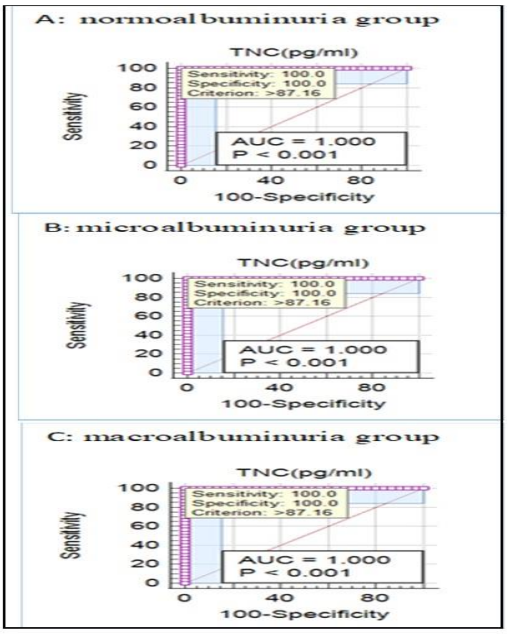

Figure 1: The results of a ROC analysis of the TNC level of patient groups compared to healthy groups (A–C).

DISCUSSION

Diabetic nephropathy (DN) is a medical condition marked by glomerulosclerosis that can happen to both type 1 and type 2 diabetics. It causes severe proteinuria, abnormally high blood pressure (BP), and secondary renal function impairment. Proteinuria is the primary clinical symptom of DN and a separate risk factor for the disease's development [19]. This study found that the patient groups' blood urea and serum creatinine levels increase over the course of diabetes. An important predictor of clinical diabetic nephropathy is the length of diabetes. In addition, individuals with microalbuminuria who have had diabetes for a long period could perhaps experience a more severe glomerulopathy before their illness can be clinically diagnosed as microalbuminuria. The length of the patient's illness had a big impact on how severe the glomerulopathy was [20]. Patients with DM frequently have dyslipidemia, which raises the risk of cardiovascular disease (CVD) and mortality [21]. Abnormal HDL, LDL, TG, and TC concentrations are its defining characteristics [22]. Because crucial lipid metabolism enzymes and pathways are impacted by insulin resistance or malfunction, lipid problems in diabetes mellitus are prevalent [23]. Due to the linkages between the metabolism of carbohydrates and lipids, a number of factors can affect blood lipid levels in people with diabetes. Consequently, any imbalance in the metabolism of carbohydrates leads to a disturbance of lipid metabolism [24]. People with diabetic kidney disease had higher plasma concentrations of VLDL-C, LDL-C, total cholesterol, and triglycerides but lower levels of HDL-C [25]. This is in line with the findings we made, according to which the level of lipid profile is higher in macroalbuminuria groups than in microalbuminuria groups, which is more than normal albuminuria, with the exception of HDL-C, which is the reverse. Recently, dyslipidemia has been identified as a major risk factor for the development of DN and is thought to frequently occur in diabetes patients. This is in line with the findings we made, according to which the level of lipid profile is higher in macroalbuminuria groups than in microalbuminuria groups, which is more

than normal, with the exception of HDL-C, which is the reverse. [26]. When exposed to pathological stresses, the extracellular glycoprotein Tenascin-C (TNC) is known to influence the fibrosis and inflammatory response in different organs [27]. Diabetes and other chronic inflammatory illnesses are linked to TNC. Additionally, ECM remodeling brought on by inflammation speeds up the evolution of T2DM [15]. A crucial stage of ECM remodeling is TNC overexpression [28]. TNC is mostly expressed by NG2+PDGFR+ cells around the damaged tubules, and STAT3 is a signaling pathway at least partially mediating the profibrotic impact of TNC [29]. Tenascin-C is hence involved in the etiology of diabetes and its accompanying consequences. Li *et al*.'s [14] findings supported the notion that TNC is an important biomarker for predicting the prevalence and severity of cardiovascular illnesses in people with type 2 diabetes. Tenascin-C levels have been observed in the study published by Liabeuf *et al.* in 2011 [30]. to rise with increasing (CKD) stage in patients without heart failure and to correlate with outcomes in such a situation, this is in line with the findings we made, which showed that the levels of TNC in the groups with macroalbuminuria were greater than those with microalbuminuria, which in turn were higher than the groups with normoalbuminuria. Strong evidence was obtained in the study by Xie *et al.* (2022) [29] showing that kidney fibrosis is significantly influenced by the non-structural matrix protein TNC, which has numerous functional domains. It might work Interstitial fibrosis and the development of kidney damage may both be treated by targeting the TNC pathway as a possible therapeutic target.

Conclusion

In diabetic nephropathy, the serum level of TNC was significantly increased when compared to healthy controls and well correlated with creatinine, urea, and ACR. TNC can be considered a biomarker for the possibility of developing diabetic nephropathy.

ACKNOWLEDGMENT

The authors thank the Department of Chemistry, College of Science and National Diabetes Center, Mustansiriyah University for support.

Conflict of interests

No conflict of interest was declared by the authors

Funding source

The authors did not receive any source of fund.

Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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