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Correlation of Tumor Necrosis Factor Receptor-1 (TNFR1) with the Degree of Nephropathy in Diabetic Type 2 Patients

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ABSTRACT

Background: *Diabetes Mellitus (DM) is chronic metabolic disorder described by defects in action or secretion of insulin or both lead to hyperglycemia, the chronic diabetes hyperglycemia is related with dysfunction, failure and long-term damage of different organs. Type II diabetes mellitus (TIIDM) is a highly prevalent disease with a hereditary basis and the intervention of environmental risk factors, particularly bad lifestyle practices that lead to overweight and obesity. Diabetes mellitus is one of the world's most serious public health issues. Diabetic patients have a high morbidity and mortality rate as a result of the development of various diabetic complications, including nephropathy, vasculopathy, cardiomyopathy, retinopathy, and neuropathy.*

Diabetic nephropathy is a complication of diabetes that affects approximately 40% of diabetic patients. Diabetic nephropathy, a primary cause of end-stage renal disease (ESRD), affects 30–40% of patients who require maintenance dialysis, putting an additional burden on healthcare systems.

The present study was mainly aimed to the correlation TNF-receptor 1 , in serum as markers for primary detection of degree DN in a sample of Iraqi patients having type two diabetes mellitus (T2DM). Between August 2023 and January 2024, a grand total of 120 patients with type II DM were investigated. patients were selected from the Center of Diabetes and Endocrinology in Al-Sader Teaching Hospital in Najaf city were enrolled in this study. The patients were divided into three groups based on their albumin-to-creatinine ratio (ACR): normoalbuminuria, microalbuminuria, and macroalbuminuria. All participants underwent clinical evaluation along with a range of tests such as blood pressure, weight and height measurements, blood tests fasting blood sugar (FBS), glycated hemoglobin (HbA1c), serum urea and creatinine in addition to albumin and creatinine in urine. TNFR1 were measured by ELISA technique. The prevalence of microalbuminuria and macroalbuminuria was 63.29% and 11.10% respectively in the group of patients in this research. This implies that diabetic nephropathy is present in about 74.39% of the diabetic populations in this research.

Conclusion: *Based on the result of this study a significantly high concentrations of TNF receptor 1 were discovered in diabetic patients with macroalbuminuria and microalbuminuria compared to diabetic groups with normoalbuminurin. TNFR receptor 1 was found No correlating with the age,gender urine creatinine and HbA1c.*

Keywords: *TNFR1, T2DM, Nephropathy, Albuminuria.*

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INTRODUCTION

Diabetic mellitus (DM): is a chronic metabolic disorder characterized by immpairment in the action,or both resulting in elevated blood sugar levels (hyperglycemia). This chronic hyperglycemia associated with diabetes is linked to dysfunction , failure and long-term damage to various organs [1] In 2020,the classification of diabetes mellitus still consists of two main types, namely type 1 and type II.Howerer, each of these types includes afew rare variations [2].Type two dibetes mellitus (T2DM), formerly known as noninsulin dependent diabetes mellitus (NIDDM) or adult onset [3].Type 2 diabetes mellitus (T2DM) is a common ,long term metabolic disorder that manily effects adults,type 2 diabetes is defined by lack of production insulin and impaired insulin response,also known as insulin resistance [4].complication from diabetes mellitus are numerous. The main reason of these problem is persistently high blood sugar levels. Increased blood glucose levels result in damage to small blood vesssels known as "microvascular diasease" and large arteries , known as "macrovascular disease ". Diabetic complication happen due to vascular damage,leading to damage to tissues and organs,These complication include nephropathy,neuropathy,retinopathy.[5]

Diabetes nephropathy (DN) : is a renal disease characterized by microangiopathy, which can lead to proyinuria, hypertension, and gradual decline in kidney function. Chronic hyperglycemia in diabetic patients causes an elevation in the glycation of basement membranes in the nephrons, resulting in impaired filtration function [6]. DN is a complication of both type 1 and type 2 diabetes mellitus ,It is caused by microvascular alterations and can result in kidney faliure and cardiovascular disease [7]. An increase in protein excretion in the urine is the traditional defintion of(DN),Also known as microalbuminuria , the early stage is marked by small rise in albumin levels in the urine. Proteinuria or macroalbuminuria is a sign of a more advanced disease,later cases are known as overt(DN).[8]

Microalbuminuria is when you pee 30 to 299 mg of albumin per 24 hours, and macroalbumin is when you pee more than 300 mg of albumin per 24hours[9]. diabetic nephrppaty is diagnosed when the amount of albumin in the urine exceeds 30 mg in a 24-hour period,or when the estimated glomerular filtration rate falls below 60mL/min per 1.73[10]. Albuminuria is a defining characteristic of diabetic nephropathy [11]

Tumor necrosis factor "TNF" is primarily synthesized by monocytes, although renal cells (including endothelial,epitheial,mesangial, and tubular cell) also contribute to its production, albeit to a lesser degree[12]. TNF can bind separate receptor : TNF receptor 1 (TNFR1) , also referred to as p55, Transmembrane TNF attaches to and stimulates the TNFR1, while soluble TNF can attach to receptor but effectively stimulates TNFR1 [13].

TNFR1 is expressed on almost all types ubquitously [14]. TNFR1 is primarly found in glomerular and tubular endothelial cell within the kidneys [15]. TNFR1 is linked to end-stage renal disease (ESRD) [16].

MATERIAL AND METHODS

One hunderd twenty T2DM patients including (86 females and 34 males) attended the Center of Diabetes and Endocrinology in Al-Sader Teaching Hospital in Najaf.

The patients were split into three groups in relation to the albumin-creatinine ratio (ACR): Group 1 including type two diabetic patients with normoalbuminuria patients (NA), Group 2 including type two diabetic patients with microalbuminuria (MA), Group 3 including type two diabetic patients with macroalbumiburia (CN clinical nephropathy).

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The inclusion criteria include:

T2DM patients diagnosed with diabetes on the criteria for determining plasma glucose levels are based on both, fasting plasma glucose and the plasma glucose levels tolerance test or glycosylated hemoglobin test [17]. Both genders were included

Exclusion criteria involve:

Type 1 DM, Hypertension, and Traumaor acute illness.

TNFR1 assessment:

Enzyme-linked immunosorbent Assay (ELISA) (sunlong, China) was used to evaluate. the blood levels of TNFR1 in people with diabetic patient type two were evaluated using the sandwich immunodetection method.

Statistical Analysis:

All information from both study groups was calm and examined using the Statistical Package for the Social Sciences (SPSS)s

RESULTS

This study showed significant differences in values for HbA1c, serum creatinine, serum urea, urine albumin, and urinary ACR between the patient groups (P< 0.05), also showed no significant difference in the mean values for BMI, age, FBS, urine creatinine, serum albumin and e GFR between the patients groups (P> 0.05).**Table 1**. The mean was highest in normoalbuminuria, followed by microalbuminuria and lastly macroalbuminuria. **Table 2.** A receiver operating characteristic (ROC) analysis was conducted to evaluate the diagnosis value of TNFR1 and if it is more sensitive or specific than ACR, and eGFR, and which of them is more sensitive or unique to diabetic nephropathy diagnosis.

Table (3) reflects a correlation between TNFR1 and eGFR output data for ROC curves. A cutoff value of TNFR1(12.84), eGFR (103), Nephropathy was predicted by a serum level of TNFR1 with 60.9% sensitivity, 51.4% specificity, and 0.587 accuracy. Aurine level of albumin with 85.1% sensitivity, 82.6% specificity, and 0.894 accuracy. Aurine level of creatinine with 59.5% sensitivity, 50% specificity, and 0.490 accuracy **Table (4-5).** A serum level was of uria 55.4% sensitivity, 54.3% specificity, and 0.561 accuracy. The level of serum creatinine was 56.8% sensitivity, 50% specificity, and 0.554 accuracy, **Table(4-5).** person correlation analyses have revealed that no relationships between TNFR1, eGFR, and ACR variables were studied in diabetic patients with nephropathy.

Table -1 Baseline characteristics of the patients.

Characteristics	ACR ratio			P- value
	Normoalbuminuria N=46	Microalbuminuria N=63	Macroalbuminuria N=11	
Age, (year) Mean± S.D	54.33± 10.760	56.06± 11.153	51.36± 8.606	0.365
Body mass index (kg/m2)² Mean± S.D	29.75± 5.322	30.63± 5.080	34.06± 8.092	0.069
FBS (mg/dl) Mean± S.D	320.65± 100.082	318.27± 83.748	358.36± 111.946	0.413
HbA1c median (IQR)	10.00 (1.60)	10.00 (2.60)	11.00 (1.30)	**0.012***
U. Albumin (mg/L) median (IQR)	6.50 (22.00)	84.00 (58.00)	200.00 (4.00)	**<0.001****
U. Creatinine (mg/dl) median (IQR)	44.00 (55.25)	48.00 (54.00)	57.00 (15.00)	0.602

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S. Creatinine (mg/dl) Mean± S.D	0.81± 0.365	0.82± 0.349	1.37± 0.469	**<0.001****
S. Urea(mg/dl) median (IQR)	31.00 (14.25)	31.00 (12.00)	43.00 (5.00)	**0.002****
e GFR Mean± S.D	111.93± 61.218	118.86± 56.703	99.09± 37.155	0.535
Urinary ACR Mean± S.D	17.71± 7.97	85.53± 60.54	376.82± 43.19	**<0.001****

***: highly significant difference, S.D.: Std. Deviation, N: number, IQR: Interquartile Range. The mean serum TNFR1 was no significantly different among all study groups (p> 0.05),*

Table 2. A receiver operating characteristic (ROC) analysis of TNF1.

Characteristics	ACR ratio			P-value
	Normoalbuminuria N=46	Microalbuminuria N=63	Macroalbuminuria N=11	
TNF 1 (pg/ml) Mean± S.D	32.11±34.152	25.53±28.847	21.39±12.609	0.409

***: Highly Significant difference, S.D.: Std. Deviation.*

Table 3. Cutoff Points and Validity of The Studied Parameters in Diabetic Patients.

Characteristic	eGFR	TNF1
AUC	0.527	0 .587
SE	0.056	0.054
Sig.	0.616	0.111
95% Confidence Interval	0.418-0.636	0.482-0.692
Optimal Cut-Point Value	103	12.84
Sensitivity (%)	58.1%	60.9%
Specificity (%)	45.7%	51.4%
PPV (%)	63.23%	43.75%
NPV (%)	40.38%	67.85%
Diagnostic effectiveness (accuracy)	53.33%	55
Youden's index	0.04	0.12

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Table 4 Correlations of TNF1, eGFR, and ACR Ratio in type II Diabetic Patients.

Parameter	Statistics	TNF 1(pg/ml)	eGFR
TNF 1(pg/ml)	*R*	-	0.173
	P. value	-	0.029*
eGFR	*R*	0.173	-
	P. value	0.029*	-
Urinary ACR	*R*	-0.129	-0.084
	P. value	0.08	0.180
R: Pearson's correlation coefficient, *: Correlation is significant at the 0.05 level (1-tailed), **: Correlation is significant at the 0.01 level (1-tailed).			

DISCUSSION

Diabetic kidney disease is the primary microvascular complication of diabetes mellitus (DM) and the main reason why people get end-stage kidney disease worldwide [17]. The current study showed that the BMI was not significant among the study group the mean BMI higher in macroalbuminuria followed by microalbuminuria and lastly normoalbuminuria group, something that has been discussed in previous studies [18][19]. Age was not significant between study groups, the result was similar to the findings reported by [20][21], The present study has shown that age is not significantly correlated with the degree of DN. This present research indicates a mean high level of HbA1c macroalbuminuria followed by microalbuminuria and then by normoalbuminuria group (P=0.012) comparable findings are consistent with other research, suggesting that hyperglycemic is the driving force for DN development [22][23].

Blood urea levels increase in conjunction with albuminuria, greater levels were recorded in macroalbuminuria followed by microalbuminuria and normoalbuminuria(p=0.002), Similar results have been noted [24][25]. High blood urea indicates kidney function abnormality, Abnormal urea is a symptom of nephropathy, There is a need for early detection of nephropathy [26].

The serum creatinine significant change in mean among the patient's group(p=0.001) Macroalbuminuria was the greatest mean followed by microalbuminuria and, finally, normoalbuminuria. The study results were similar to those of the studies[27][28], Increased creatinine in blood indicates nephron abnormality[29]. The result of the present study reports the mean TNFR1 in normoalbuminuria, microalbuminuria, and macroalbuminuria were 32.11,25.53 and 21.39 respectively.

The result of current study is not significant with diabetic nephropathy the reason may be due to small sample size, genetics, the difference in the duration of the disease, age, and sensitivity of the measurement and working methods. The result of the current study disagreed with another study that showed serum concentration of TNFR1 with research in Japan [30].

CONCLUSIONS

1-The majority of patients with type II diabetes in AL-Najaf City have either microalbuminuria or normoalbuminuria

2-There is no significant correlation between the duration of diabetes and the occurrence of diabetic nephropathy. Additionally, there is no significant correlation between age, gender, BMI, and the occurrence of diabetic nephropathy.

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3-There is a significant association (strong correlation) between diabetic nephropathy and HbA1c, serum urea, and serum creatinine, eGFR. However, there is a weak correlation between fasting blood sugar and diabetic nephropathy.

REFERENCES

1- Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., ... & IDF Diabetes Atlas Committee. (2019). Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. *Diabetes research and clinical practice*, *157*: 107843.

2- Hoogwerf, B. J. (2020). Type of diabetes mellitus: Does it matter to the clinician?. *Cleveland Clinic journal of medicine*, 87(2): 100-108.

3- Gilor, C., Niessen, S. J. M., Furrow, E., and DiBartola, S. P. (2016). What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. *Journal of veterinary internal medicine*, *30*(4), 927-940.

4- American Diabetes Association. (2018). Standards of medical care in diabetes abridged for primary care providers. *Clinical diabetes: a publication of the American Diabetes As-sociation*, *36*(1), 14.

5- Patel, D. M., Bose, M., and Cooper, M. E. (2020). Glucose and Blood Pressure-Dependent Pathways–The Progression of Diabetic Kidney Disease. *International journal of molecular sciences*, 21(6):2218.

6- Pavkov ME, Collins AJ, Coresh J, Nelson RG. (2018). Kidney disease in diabetes. In: Diabetes in America, 3rd edition. Cowie CC, Casagrande SS, Menke A, Cissell MA, Eberhardt MS, Meigs JB, et al, editors. Bethesda: National Institutes of Health

7- Khalil, H. (2017). Diabetes microvascular complications-A clinical update. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews*, 11: 133-139.

8- Zhang, Ji., Liu, J. and Qin, X. (2018) ‗Advances in early biomarkers of diabetic nephropathy', Revista da Associação Médica Brasileira, 64(1):85–92

9- Gnudi L, Coward RJ, Long DA. (2016); Diabetic Nephropathy: Perspective on Novel Molecular Mechanisms. Trends in Endocrinology and Metabolism; 27(11):820-830 .

10- Hu, Y., Li, Q., Min, R., Deng, Y., Xu, Y., and Gao, L. (2021). The association between serum uric acid and diabetic complications in patients with type 2 diabetes mellitus by gender: a cross-sectional study. *PeerJ*, 9: 1-22.

11- Yu, Z. L., Wong, C. S., Lai, Y. T., Chou, W. H., Faridah, I. N., Kao, C. C., ... and Chang, W. C. (2020). Gender differences in genetic associations of RAB38 with urinary protein-to-creatinine ratio (UPCR) levels in diabetic nephropathy patients. *Journal of personalized medicine*, 10(4): 184.

12- Donate-Correa, J., Luis-Rodríguez, D., Martín-Núñez, E., Tagua, V. G., Hernández-Carballo, C., Ferri, C., Rodríguez-Rodríguez, A. E., Mora-Fernández, C., & Navarro-González, J. F. (2020). Inflammatory targets in diabetic nephropathy. *Journal of Clinical Medicine*, *9*(2). https://doi.org/10.3390/jcm9020458

13- M. Grell, E. Douni, H. Wajant, M. Lohden, M. Clauss, B. Maxeiner, et al.,

 Copyright © The Author(s)

The transmembrane form of tumor-necrosis-factor is the prime activating ligand of the 80 kDa tumor-necrosis-factor receptor, Cell 83 (1995) 793–802.

14- Cabal-Hierro, L.; Lazo, P.S. Signal transduction by tumor necrosis factor receptors. Cell Signal. 2012, 24,1297–1305. [CrossRef] [PubMed]

15- Al-Lamki, R.S.; Mayadas, T.N. TNF receptors: Signaling pathways and contribution to renal dysfunction. Kidney Int. 2015, 87, 281–296. [CrossRef] [PubMed]

16- Lee JE, Gohda T, Walker WH, Skupien J, Smiles AM, Holak RR, Jeong J, McDonnell KP, Krolewski AS, Niewczas MA. Risk of ESRD and all cause mortality in type 2 diabetes according to circulating levels of FGF-23 and TNFR1. PLoS One. 2013;8(3):e58007.

17- Singh, D. K., Winocour, P. and Farrington, K. (2010) 'Oxidative stress in early diabetic nephropathy: fueling the fire', *Nature Reviews Endocrinology*. Nature Publishing Group, a division of Macmillan Publishers Limited. All Rights Reserved., 7, p. 176.

18- Ibrahim A,Arogundade FA,Sanusi AA, Ikem R,Akintomide AO,Akinsola.AA. Which factors actually influence the development and progression of overt nephropathy in Nigerian diabetics ? Cent Afr Jaed. 2009;55:28.

19- ViswanathanV,Tilak p, S kumpatla S. Risk factors associated with the development of overt nephropathy in type 2 diabetes patients : a 12 years observational study . Indian J Med Res. 2012;136:46-53

20- Shahwan, M. J., Gacem, S. A., and Zaidi, S. K. (2019). Prevalence of Diabetic Nephropathy and associated risk factors among type 2 diabetes mellitus patients in Ramallah, Palestine. Diabetes and Metabolic Syndrome: *Clinical Research and Reviews*, 13(2): 1491–1496.

21- Thakur, S. K., Dhakal, S. P., Parajuli, S., Sah, A. K., Nepal, S. P., and Paudel, B. D. (2019). Microalbuminuria and Its Risk Factors in Type II Diabetic Patients. *Journal of Nepal Health Research Council*, 17(1): 61–65.

22- Choi, D. W., Jeon, J., Lee, S. A., Han, K. T., Park, E. C., & Jang, S. I. (2018). Association between smoking behavior patterns and glycated hemoglobin levels in a general population. *International journal of environmental research and public health*, *15*(10): 2260

23- Ghazanfari, Z. *et al.* (2010) 'A Comparison of HbA1c and Fasting Blood Sugar Tests in General Population.', *International journal of preventive medicine*, 1(3), pp. 187–194.

24- Al-Refai, A. A. *et al.* (2014) 'Urinary Neutrophil Gelatinase Associated Lipocalin as a Marker of Tubular Damage in Type 2 Diabetic Patients with and without Albuminuria', *Journal of Nephrology*, 04(01), pp. 37–46. doi: 10.4236/ojneph.2014.41006.

25- Shoukry, A., Bdeer, S. E.-A. and El-Sokkary, R. H. (2015) 'Urinary monocyte chemoattractant protein-1 and vitamin D-binding protein as biomarkers for early detection of diabetic nephropathy in type 2 diabetes mellitus.', *Molecular and Cellular Biochemistry*. Springer US, 408(1–2), pp. 25–35. doi: 10.1007/s11010-015-2479-y.

26- Sirivole, M. R. and Sadhvimani Eturi (2017) ‗A study on blood urea and serum creatinine in diabetes mellitus

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from Sangareddy District, Telangana ‘, International Journal of Medical and Health Research, 3(12):132–136

27- Zhang, D., Ye, S., and Pan, T. (2019). The role of serum and urinary biomarkers in the diagnosis of early diabetic nephropathy in patients with type 2 diabetes. *PeerJ*, 2019(6): 1–14.

28- Hamza, A. H., Al-Bishri, W. M., Damiati, L. A., and Ahmed, H. H. (2017). Mesenchymal stem cells: A future experimental exploration for recession of diabetic nephropathy. *Renal Failure*, 39(1): 67–76.

29- Harita, N. *et al.* (2009) ‘Lower serum creatinine is a new risk factor of type 2 diabetes: the Kansai healthcare study’, *Diabetes care*. Am Diabetes Assoc, 32(3), pp. 424–426.

30- Carlsson, A. C., Östgren, C. J., Nystrom, F. H., Länne, T., Jennersjö, P., Larsson, A., & Arnlöv, J. (2016). Association of soluble tumor necrosis factor receptors 1 and 2 with nephropathy, cardiovascular events, and total mortality in type 2 diabetes. *Cardiovascular Diabetology*, *15*(1). https://doi.org/10.1186/s12933-016-0359-8.

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