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The Diagnostic Value of Tumor Necrosis Factor α Receptor 2 as a Marker of Renal Dysfunction

Fatin A. hameed[(1)]

Israa H. Saadoon[(2)]

Ali M. Al Ameri [(3)]

(1) Microbiology, College of Medicine, University of Kerbala.
Iraq

(2) Medical Microbiology, College of Medicine, University of Tikrit.
Iraq

(3) Medical Microbiology, College of Medicine, University of Kerbala.
Iraq

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ABSTRACT

Background: Chronic kidney disease (CKD) is increasingly recognized as global health problem. There is evidence that CKD can be detected using simple laboratory tests, and that treatment can prevent or delay complications of decreased kidney function, slow the progression of kidney disease and reduce the risk of cardiovascular disease (CVD).

Aim: The present study was conducted to evaluate the role of tumor necrosis factor α receptor 2 (TNFR2) as a biomarker for detection of renal dysfunction.

Materials and Methods: The study was carried out for the period from February to June 2019 and included 180 patients (their ages were between 19 and 85 years old) and were divided into 60 patients with renal impairment, 60 hemodialysis patients, and 60 patients with normal renal function (as a control group). Each group included patients with hypertension, patients with diabetes mellitus, and hypertensive- diabetic patients. The patients were attended to Center of Kidney Disease and Transplantation, Dialysis Unit of Baghdad Teaching Hospital – Medical City , Dialysis Unit of Tikrit Teaching Hospital and private laboratory in Samarra City.

Urine sample was collected from each patient for bacteriological study and detection the level of TNFR2.

Results: The present study revealed that only 18% of samples had positive bacterial growth. The most common isolated bacteria were E.coli. The mean of TNFR2 was higher in patients with renal impairment and positive urine culture than those with negative culture. However, the difference was statistically significant. The difference in the mean of TNFR2 between hemodialysis patients with positive urine culture and those with negative culture was statistically non- significant. The mean of TNFR2 in the patients with positive urine culture was higher than those with negative culture. The difference was statistically non- significant. The difference in the mean of TNFR2 between hypertensive patients with normal renal function (control) and hypertensive- hemodialysis was statistically significant.

Conclusion: Level of urine TNFR2 can be used as a marker for early detection of renal dysfunction.

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*Corresponding author E mail : faten_a@gmail.com

Introduction

Chronic kidney disease represents a worldwide major public concern and its prevalence continues to rise (1). The most widespread reasons of CKD are diabetes and hypertension (2, 3).

Hypertension is considered to be a low-grade inflammatory condition characterized by the presence of different proinflammatory cytokines. Tumor necrosis factor-α (TNF-α) is a component of the proinflammatory cytokines that is associated with salt-sensitive hypertension (SSH) and related renal injury. Many last studies have submitted guide that TNF-α exerts a direct renal action by regulating hemodynamic and excretory function in the kidney(4, 5). Tumor necrosis factor-α has been involved in inflammatory renal tissue injury induced by hypertensive kidney diseases (6, 7).

About 20% of the 400 million individuals with diabetes mellitus have diabetic nephropathy (8). Diabetic kidney disease is a major cause of morbidity and mortality in diabetes. Diabetic kidney disease is the single most common cause of ESRD in many parts of the world including Europe, Japan, and the USA, and patients with diabetes account for 25% to 45% of all patients enrolled in ESRD programs (9).

Several studies including studies in type 1 and type 2 diabetes have find circulating tumor necrosis factor (TNF) receptors to be linked with renal outcome, although the underlying biology remains to be established (10, 11, 12). A previous study reported that levels of TNF-α clearly increased in patients with UTI (13)

Materials and Methods

The study was carried out for the period from February to June 2019 and included 180 patients (their ages were between 19 and 85 years old) who attended to Center of Kidney Disease And Transplantation, Hemodialysis Unit of Baghdad Teaching Hospital – Medical City , Dialysis Unit of Tikrit Teaching Hospital and private laboratory in Samarra City.

Patients enrolled in this study included 3 groups. The first group included 60 patients with renal impairment who were divided into hypertensive patients, diabetic patients

and hypertensive- diabetic patients. The second group included 60 hemodialysis patients who were divided into hypertensive patients, diabetic patients and hypertensive- diabetic patients. The third group was the control and included 60 patients with normal kidney function who were divided into hypertensive patients, diabetic patients and hypertensive- diabetic patients.

A midstream urine (MSU) sample was collected (30 ml of urine) in sterile cap and transported to the laboratory within 30 minutes for bacteriological study and preparing urine to immunological study.

Urine culture was done for all of 180 patients who were included in this study. Urine samples were cultured by using sterile loop on solid media (Nutrient agar, Blood agar and MacConkey agar) with using streaking method. Then the plates incubated at 37Cº for 24-48 hours (14). Bacterial colonies were identified according to morphology, color and consistency on Nutrient and MaCconkey's agar medium and type of hemolysis on blood agar medium

Detection of TNF-R2 was done by using Human soluble tumor necrosis factor receptor 2 (TNF-R2) ELISA Kit from Shanghai Yehua Biological Technology Company.

Statistical analysis was done by using SPSS version 24, namely Man Whitney test and student t-test for two-mean comparison. Analysis of variance was used to compare more than two means. Finding of P value < 0.05 was regarded significant.

Results

The current research revealed that only 18% of samples had positive bacterial growth. The most common isolated bacteria were E.coli. The study revealed that the mean of TNFR2 was higher in patients with renal impairment and positive urine culture than those with negative culture. However, the difference was statistically significant.. Table 1.

Table 1: Comparison of TNFR2 in patients with renal impairment and positive urine culture and those with negative culture.

Patients with renal impairment		No.	TNFR2			*P value*
			Mean	S.D.	S. Error Mean	
Urine culture	Positive	13	2.8736308	.916327	.254143	0.004785
	Negative	47	1.958532	.920049	.134203	

The study showed that the difference in the mean of TNFR2 between hemodialysis patients with positive urine culture and those with negative culture was statistically non-significant.. Table 2.

Table 2: Comparison of TNFR2 between hemodialysis patients with positive urine culture and those with negative culture.

Hemodialysis patients		No.	TNFR2			*P value*
			Mean	S.D.	S. Error Mean	
Urine culture	Positive	15	1.617733333	0.708383	0.1829	0.789851
	Negative	42	1.676404762	0.768472164	0.118577829	

The present research revealed that the difference in the mean of TNFR2 between the control group (patients with normal renal function) with positive urine culture and those with negative culture was statistically non- significant.. Table 3.

Table 3: Comparison of TNFR2 between the control group with positive urine culture and those with negative culture.

Control group		No.	TNFR2			*P value*
			Mean	S.D.	S. Error Mean	
Urine culture	Positive	4	1.48075	0.370970237	0.185485118	0.413658
	Negative	56	1.666089	0.703886568	0.094060799	

The current work revealed that in the mean of TNFR2 in the patients with positive urine culture was higher than those with negative culture. The difference was statistically non- significant.. Table 4.

Table 4: Comparison of TNFR2 between the patients with positive urine culture and those with negative culture.

Patients		No.	TNFR2			*P value*
			Mean	S.D.	S. Error Mean	
Urine culture	NEGATIVE	145	1.919862	0.831495203	0.071563713	0.169238
	POSITIVE	32	2.18525	0.999214724	0.176637877	

The current work revealed that the difference in the mean of TNFR2 between hypertensive patients with normal renal function and those with renal impairment was statistically non-significant.. Table 5.

Table 5: Comparison of TNFR2 between hypertensive patients with normal renal function and those with renal impairment.

Hypertensive Patients	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Normal renal function	24	2.122292	0.739843901	0.151020004	0.845125
Renal impairment	24	2.168417	0.880565229	0.179744625	

The present study revealed that the difference in the mean of TNFR2 between hypertensive control and hypertensive- hemodialysis was statistically significant.. Table 6.

Table 6: Comparison of TNFR2 between hypertensive control and hypertensive- hemodialysis.

Hypertensive Patients	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Normal renal function	24	2.122292	0.739843901	0.151020004	0.011612
Hemodialysis	24	1.645458	0.482210308	0.098430767	

The difference in the mean of TNFR2 between diabetic control and diabetic renal impairment patients was statistically non- significant.. Table 7.

Table 7: Comparison of TNFR2 between diabetic control and diabetic renal impairment patients.

Diabetic Patients	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Normal renal function	18	1.858389	0.609873867	0.143748649	0.491854
Renal impairment	12	1.680583	0.726057656	0.209594792	

The difference in the mean of TNFR2 between diabetic control and diabetic hemodialysis patients was statistically non- significant.. Table 8.

Table 8: Comparison of TNFR2 between diabetic control and diabetic hemodialysis patients.

Diabetic Patients	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Normal renal function	18	1.858389	0.60987387	0.14374865	0.054919
Hemodialysis	11	1.438909	0.500016491	0.150760644	

The difference in the mean of TNFR2 between the control group and renal impairment patients was statistically non- significant.. Table 9.

Table 9: Comparison of TNFR2 between the control group and renal impairment patients.

Group	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Control	60	2.06983	.773957	.099917	0.590
Renal impairment patients	60	2.15738	.987995	.127550	

The difference in the mean of TNFR2 between the control group and hemodialysis patients was statistically significant.. Table 10.

Table 10: Comparison of TNFR2 between the control group and hemodialysis patients.

Group	No.	TNFR2			*P value*
		Mean	S.D.	S. Error Mean	
Control	60	2.06983	0.773957257	0.099917452	0.004379
Hemodialysis patients	57	1.660965	0.747327046	0.098985885	

Discussion

The present study demonstrated that the commonest organism isolated from the urine was *E.coli*. This result was similar to that obtained by other researchers (15, 16).

Phagocytes, such as neutrophils and macrophages, play an essential role in the innate cellular immune response against bacterial infections. Neutrophils are particularly important; they clear bacteria by phagocytosis or kill them by secreting toxic compounds (17). The defense against UTI depends on neutrophils (18). However, macrophages produce proinflammatory cytokines, such as tumor necrosis factor (TNF), during bacterial infections (19).

Results of the current investigation revealed that there was significant relation between level of TNFR2 and positive urine culture in patients with renal impairment but the relation was not significant in those with hemodialysis and those with normal renal function (the control group).

Niewczas *et al* (20) revealed that high levels of circulating TNFR1 or TNFR2 (levels of both highly correlated)predicted ESRD in T2D during 8–12 years of follow-up. The strong association of TNFRs with the risk of ESRD was replicated in Later studies (21, 22). Engel and colleagues (23) showed that TNF is increased in the bladder during UTI .

In contrast, Olszyna and coworkers (24) reported that concentrations of TNF in

serum and urine were below the limit of detection in the vast majority of controls and pyelonephritic patients, and no significant differences between these two groups were found. They showed that only TNF receptors had higher concentrations in urine of pyelonephritic patients. Kim and colleagues(25) showed the same results, too.

The present study revealed that the difference between the level of TNFR2 in hypertensive patients with normal renal function and those with renal impairment was statistically non- significant, while the difference was significant when the comparison was with hypertensive patients with hemodialysis.

Hypertension is chronic inflammatory states so an elevated concentration of inflammatory cytokines can be expected including TNF(26).

The present study revealed that the difference between the level of TNFR2 in diabetic patients with normal renal function (control group) and diabetic renal impairment patients was statistically non- significant. Also, the difference between the level of TNFR2 in the control group and hemodialysis patients was statistically non- significant.

Diabetic kidney disease (DKD) is one of the most common diabetic complications, as well as the leading cause of chronic kidney disease and end-stage renal disease around the world (27). Islam *et al* (28) concluded that there was a strong correlation of serum, but not urine of TNFR1/2 concentrations with current eGFR. Griffin *et al* (29) concluded that there was a strong association between serum TNFR-1 and -2 and eGFR in patients with diabetic kidney disease but the correlation between urine TNFR-1 and -2 with eGFR was less closely.

References

1- Liabeuf S, Okazaki H, Desjardins L, *et al*. Vascular calcification in chronic kidney disease: are biomarkers useful for probing the pathobiology and the health risks of this process in the clinical scenario?. Nephrology Dialysis Transplantation 2013;29(7):1275-1284.

2- Izet MP. Public health aspects of nephrology, dialysis and kidney transplantation in Bosnia and Herzegovina. Materia Socio-medica 2015;27(2):68.

3- Ghonemy TA, Farag SE, Soliman SA, El-Okely A, El-Hendy Y. Epidemiology and risk factors of chronic kidney disease in the El-Sharkia Governorate, Egypt. Saudi Journal of Kidney Diseases and Transplantation 2016; 27(1): 111.

4- Majid DS, Prieto MC, Castillo A. Tumor necrosis factor-alpha receptors (type 1 & type 2) are differentially expressed in renal tissues during chronic dietary intake of high salt and angiotensin ii treatment. Hypertension 2015;66(Sup pl 1): AP247.

5- Mehaffey E, Majid DS. Tumor necrosis factor-α, kidney function, and hypertension. American Journal of Physiology-Renal Physiology 2017; 313(4): F1005-F1008.

6- Majid, DS. Tumor necrosis factor-α and kidney function: experimental findings in mice. In: Advances in TNF Family Research .Springer, New York, NY;2011: 471-480.

7- Castillo A, Islam MT, Prieto MC, Majid DS. Tumor necrosis factor-α receptor type 1, not type 2, mediates its

acute responses in the kidney. American Journal of Physiology- Renal Physiology 2012; 302(12): F1650-F1657.

9- Afkarian M, Zelnick LR, Hall YN, *et al*. Clinical manifestations of kidney disease among US adults with diabetes, 1988-2014. JAMA 2016; 316(6): 602-610.

10- Niewczas MA, Gohda T, Skupien, J, *et al*. Circulating TNF receptors 1 and 2 predict ESRD in type 2 diabetes. Journal of the American Society of Nephrology 2012; 23(3):507-515.

11- Gohda T, Niewczas MA, Ficociello LH, *et al*. Circulating TNF receptors 1 and 2 predict stage 3 CKD in type 1 diabetes. Journal of the American Society of Nephrology 2012; 23(3): 516-524.

12- Forsblom C, Moran J, Harjutsalo V, *et al*. Added value of soluble tumor necrosis factor-α receptor 1 as a biomarker of ESRD risk in patients with type 1 diabetes. Diabetes Care 2014; 37(8): 2334-2342.

13- Al-Khafaf DM. Study of some microbial and Immunological parameter in patients with urinary tract infection in Al-Diwanyia city. Al-Qadisiah Medical Journal 2012; 8(13): 28-38.

14- Collee J, Fraser AG, Marmian BP, Simon SA. Mackie and McCarthey Practical Medical Microbiology. 4th ed. Churchill and Livingstone; 1996.

15- Vakili M, Khazaei Z, Ayatollahi J, *et al*. The pattern of antibiotic resistance of pathogens isolated from urine cultures of patients referred to Yazd Central Laboratory in 2012-2013. Biomedical Research and Therapy 2018; 5(5): 2271-2278.

16- Thass N, Kumar M, Kaur R. Prevalence and antibiogram of bacterial pathogens causing urinary tract infection in a tertiary care hospital. International Journal of Medical Science and Public Health 2019; 8(1): 53-58

8- McGrath K, Edi R. Diabetic Kidney Disease: Diagnosis, Treatment, and Prevention. American Family Physician 2019; 99(12).

17- Amulic B, Cazalet C, Hayes GL, Metzler KD, Zychlinsky A. Neutrophil function: from mechanisms to disease. Annual Review of Immunology 2012; 30:459-489.

18- Frendéus B, Godaly G, Hang L, Karpman D, Svanborg C. Interleukin-8 receptor deficiency confers susceptibility to acute pyelonephritis. The Journal of infectious diseases 2001; 183 (Supplement 1): S56- S60.

19- Mosser DM, Edwards JP. Exploring the full spectrum of macrophage activation. Nature Reviews Immunology 2008;8 (12): 958.

20- Niewczas MA, Ficociello LH, Johnson AC, *et al*. Serum concentrations of markers of TNFα and Fas-mediated pathways and renal function in nonproteinuric patients with type 1 diabetes. Clinical Journal of the American Society of Nephrology 2009;4(1):62-70.

21- Skupien J, Warram JH, Niewczas MA, *et al*. Synergism between circulating tumor necrosis factor receptor 2 and HbA1c in determining renal decline during 5–18 years of follow-up in patients with type 1 diabetes and proteinuria. Diabetes Care 2014; 37(9): 2601-2608.

22- Yamanouchi M, Skupien, J, Niewczas, MA, *et al*. Improved clinical trial enrollment criterion to identify patients with diabetes at risk of end-stage renal disease. Kidney International 2017; 92(1): 258-266.

23- Engel D, Dobrindt U, Tittel A, *et al*. Tumor necrosis factor alpha-and inducible nitric oxide synthase-producing dendritic cells are rapidly recruited to the bladder in urinary tract infection but are dispensable for bacterial clearance. Infection and Immunity 2006; 74(11): 6100-6107.

24- Olszyna DP, Prins JM, Buis B, van Deventer SJ, Speelman P, van der Poll T. Levels of inhibitors of tumor necrosis factor alpha and interleukin 1β in urine and sera of patients with urosepsis. Infection and Immunity 1998; 66(8): 3527-3534.
25- Kim KH, Hong YM, Kim GH. Urinary interleukin-1β levels in children with urinary tract infection. Journal of the Korean Pediatric Society 1997;40(7):981-990.
26- Ramseyer VD, Garvin JL. Tumor necrosis factor-α: regulation of renal function and blood pressure. American Journal of Physiology-Renal Physiology 2013; 304(10):.F1231-F1242.
27- Lin, CH, Chang YC, Chuang LM. Early detection of diabetic kidney disease: present limitations and future perspectives. World Journal of Diabetes 2016;7(14): 290.
28- Islam MN, Griffin T, Wallace E, O'Shea P, O'Brien T, Griffin M. Serum and urine soluble TNFR-1 and TNFR-2 differentially correlate with eGFR and albuminuria in diabetic kidney disease. Nephrology Dialysis Transplantation 2017; 32(Suppl_3): iii10-iii11.
29- Griffin TP, Islam MN, Wallace E, O'Shea PM, O'Brien T, Griffin MD. Clinical utility of serum and urine soluble TNFR-1 and TNFR-2 in diabetic kidney disease. Irish Journal of Medical Science 2017; 186 (S367-S367):236.