

The Relation between the Level of Serum Tumor Necrosis Factor – Alpha and Hemodialysis Adequacy in Diabetic and Non Diabetic Patients on Maintenance Hemodialysis

Abstract

Background: Hemodialysis is still the most common renal replacement therapy (RRT) modality in end stage renal disease patients (ESRD), the first problem to be faced when choosing hemodialysis for patients with ESRD is the vascular access, dialysis delivery should be adequate not only to improve quality of life but also to prolong survival, quality of life adjusted for life expectancy defined kt/v of 1.3 as the optimal cost-effective dialysis, An ideal access delivers a flow rate to the dialyzer adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (eg, infection, stenosis, thrombosis, aneurysm, and limb ischemia). Of available accesses, the surgically created fistula comes closest to fulfilling these criteria, working fistula must have all the following characteristics; blood flow adequate to support dialysis which usually equates to blood flow greater than 600 ml/min, a diameter greater than 0.6 cm, with a location accessible for cannulation and a depth of approximately 0.6 cm (ideally between 0.5 and 1cm) from the skin surface. In hemodialysis patients with an arteriovenous fistula (AVF), access failure is primarily due to fistula stenosis, which predisposes to thrombosis and subsequent access loss. The risk for access failure differs individually, Fistula stenosis is histologically characterized by endothelial cell injury and intimal hyperplasia induced by factors like TNF- α , which could induce proliferation of vascular smooth muscles leading to subsequent intimal hyperplasia. Resulting in fistula stenosis and subsequent access failure. TNF-alpha influences the risk for hemodialysis access failure in diabetic ESRD patients there is advanced calcified atherosclerosis which leads to frequently inadequate arterial inflow and eventually also to venous run-off problems. So ESRD patients with diabetes have worse access survival rates and hemodialysis adequacy.

Methods: The study was conducted to 60 ESRD patients divided to group I (30 Diabetic ESRD patients on HD) and group II (30 Non - diabetic ESRD patients on HD). We estimate serum TNF-alpha in all patients. Assess AVF by Doppler U/S and estimate hemodialysis adequacy by using single pool Kt/v .

Results: We found that serum TNF-alpha level is significantly elevated in diabetic group, Kt/v is significantly decreased in diabetic group, AVF vein diameter was statistically significantly decreased in diabetic group, we also found that TNF-alpha was statically positively significant with duration of dialysis, FBG and lastly we found that TNF-alpha may affect hemodialysis adequacy adversely particularly in diabetic ESRD patients on HD.

Conclusion: TNF-alpha is significantly elevated in diabetic ESRD patients on HD, vein diameter was significantly decreased in diabetic ESRD patients on HD. TNF-alpha is significantly positive correlated with duration of dialysis and duration of arteriovenous fistula so TNF -alpha may affect hemodialysis adequacy adversely particularly in diabetic patients on HD.

Keywords: ESRD; Hemodialysis; Arteriovenous fistula; TNF-alpha; Hemodialysis adequacy; Diabetics

Research Article

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Abbreviations: RRT: Renal Replacement Therapy; ESRD: End Stage Renal Disease; NKF: National kidney Foundation; TCC: Tunneled Cuffed Catheter; KDOQI: Kidney Disease Outcomes Quality Initiative; AV: Arteriovenous; CKD: Chronic Kidney Disease; SLE: Systemic Lupus Erythromatosis; AVF: Arteriovenous Fistula; TG: Triglycerides; LDF: Low Density Lipoprotein; HDL: High Density Lipoprotein; ALT: Alanine Amino Transferase; AST: Amino Transferase

Introduction

Hemodialysis is still the most common renal replacement therapy (RRT) modality in end stage renal disease patients (ESRD). The first problem to be faced when choosing hemodialysis for patients with ESRD is the vascular access, In diabetic ESRD patients there is advanced calcified atherosclerosis which leads to frequently inadequate arterial inflow and eventually also to venous run-off problems. So ESRD patients with diabetes have worse access survival rates and hemodialysis adequacy [1]. Dialysis delivery should be adequate not only to improve quality of life but also to prolong survival [2]. The aim of dialysis is thus, to decrease morbidity, increase quality of life and prolong life span [2]. To achieve this dialysis must be performed effectively [3]. Inadequate dose of dialysis increases duration of hospitalization and the overall cost of care [4]. One method of assessing dialysis adequacy is calculation of kt/v . This index reflects the efficiency of dialysis and correlates with mortality and morbidity rate of patients. Quality of life adjusted for life expectancy defined kt/v of 1.3 as the optimal cost-effective dialysis dose [4].

Vascular access is vital to delivering adequate hemodialysis therapy. The type of vascular access used in HD patients is recognized to have a significant influence on survival. The use of a tunneled cuffed catheter (TCC) is associated with a substantially greater risk of sepsis, hospitalization and mortality compared to the use of AVF [5-8]. An ideal access delivers a flow rate to the dialyzer adequate for the dialysis prescription, has a long use-life, and has a low rate of complications (eg, infection, stenosis, thrombosis, aneurysm, and limb ischemia). Of available accesses, the surgically created fistula comes closest to fulfilling these criteria [9,10]. The National kidney Foundation (NKF) issued the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for Vascular Access in an effort to improve patient survival and quality of life, reduce morbidity, and increase efficiency of care [9].

Two primary goals were originally put forth in vascular access guidelines:

- a. Increase the placement of native fistulae.
- b. Detect access dysfunction before access thrombosis [9].

In general, a working fistula must have all the following characteristics; blood flow adequate to support dialysis which usually equates to blood flow greater than 600 ml/min, a diameter greater than 0.6 cm, with a location accessible for cannulation and a depth of approximately 0.6 cm (ideally between 0.5 and 1cm) from the skin surface [9]. Access stenosis or thrombosis is a costly threat to patency in association with significant morbidity to the patient. Native fistula patency is significantly better than synthetic grafts and should be considered as the first method in maintaining long-term vascular access patency [11,12].

Studies investigating the pathophysiology of vascular access stenosis which predisposes to thrombosis suggest that the endothelial repair response to injury in the face of excess growth promoters, inflammation and oxidative stress leads to luminal hyperplastic intimal growth. In the presence of prothrombotic environment in the renal patient, vascular thrombosis can occur. The typical lesion of access thrombosis is new intimal vascular smooth muscle cell proliferation in the anastomotic draining vein, this can occur in response to endothelial injury due to repeated vein cannulation. Approximately 50-70% of lesions are within 3-5 cm of the vein anastomosis [13].

In hemodialysis patients with an arteriovenous (AV) fistula, access failure is primarily due to fistula stenosis, which predisposes to thrombosis and subsequent access loss. TNF-alpha influences the risk for hemodialysis access failure. The risk for access failure differs individually, Fistula stenosis is histologically characterized by endothelial cell injury and intimal hyperplasia induced by factors like TNF- α , which could induce proliferation of vascular smooth muscles leading to subsequent intimal hyperplasia. Resulting in fistula stenosis and subsequent access failure [14]. Vascular access dysfunction is a well-known cause for a reduction in delivered dialysis, although the prevalence of this problem as a cause for a fall in Kt/v is not known, Inadequate vascular access flow rate due to stenosis leads to mixing of blood from the venous side of the dialysis circuit into the arterial inflow line. This reduces the concentration gradient and reduces net removal for dialyzable solutes [15].

Aim of the study

The aim of this work is to study the relation between serum tumor necrosis factor-alpha and hemodialysis adequacy in diabetic and non-diabetic ESRD patients on maintenance hemodialysis by early detection of AVF dysfunction.

Methods & Subjects

The study will be conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and informed consent will be obtained from each patient. The study was carried out in Dialysis units in Armed Forces Hospital & Police Hospital, Alexandria on 60 elderly ESRD patients on HD & 15 healthy elderly as a control.

Our subjects were divided into 3 main groups with 4 subgroups:

- A. Group I: 30 diabetic ESRD patients on HD
- B. Group II: 30 non-diabetic ESRD patients on HD
- C. Group III: 15 healthy controls.

Exclusion criteria

- a) Patients with less than 3 months duration of the native arteriovenous fistula.
- b) Patients with hypotension, systemic infection within one month before entry in the study or on warfarin therapy.
- c) Known chronic inflammatory disease other than chronic kidney disease (CKD) as systemic lupus erythromatosis (SLE) and vasculitis.

d) Smoking.

All patients will be subjected to the following

- I. Full history talking
- II. Routine investigations: Complete blood picture, Triglycerides (TG), total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL), Fasting blood glucose level, serum alanine amino transferase (ALT), serum aspartate amino transferase (AST), prothrombin time and activity, total proteins, serum albumin, Serum Calcium, serum phosphate.
- III. TNF-alpha level measurement with enzyme linked immunosorbent assay (ELISA) technique.
- IV. Doppler US study of the native AVF.
- V. Hemodialysis adequacy. (Kt/v).

Results

Our subjects were divided into 3 main groups with 4 subgroups:

Group I: 30 diabetic ESRD patients on HD divided to 2 subgroups:

- 1) Group Ia: 15 diabetic ESRD patients on HD with functioning AVF between 3 months and 6 months.
- 2) Group Ib: 15 diabetic ESRD patients on HD with functioning AVF more than one year.

Group II: 30 non-diabetic ESRD patients on HD divided to 2 subgroups:

- I. Group IIa: 15 non- diabetic ESRD patients on HD with functioning AVF between 3 months and 6 months.
- II. Group IIb: 15 non-diabetics ESRD patients on HD with functioning AVF more than one year (Table 1).

Table 1: Comparison between Group I & Group II according to U/S Doppler A.V fistula.

U/S Doppler A.V Fistula	Diabetic (n = 30)		Non diabetic (n = 30)		Test of Sig.	p
	No.	%	No.	%		
Central venous system stenosis	9	30.0	6	20.0	□□□□□□□□□□	0.120
Thrombosis	1	3.3	5	16.7	□□□□□□□□□□	^{FE} p = 0.195
Aneurysm	3	10.0	4	13.3	□□□□□□□□□□	^{FE} p = 1.000
Volume						
Min. – Max	350.0 – 1400.0		500.0 – 1400.0		Z = 1.739	0.082
Mean±SD	708.33±272.63		825.0 – 276.91			
Median	600.0		775.0			
Vein diameter						
Min. – Max	0.40 - 0.80		0.40 – 0.90		t = 2.695*	0.009*
Mean±SD	0.61±0.11		0.69±0.11			
Median	0.60		0.70			
Osteum						
Min. – Max	0.50 – 0.90		0.50 – 1.0		t = 1.330	0.189
Mean ± SD	0.77 ± 0.11		0.72 ± 0.14			
Median	0.80		0.70			

ann Whitney test

t: Student t-test

MC: Monte Carlo test

Z: Z for M

*: Statistically significant at p ≤ 0.05

a) Vein diameter was statistical significant between 2 groups being higher in group II as compared to group I.

Group III: 15 healthy controls.

- a) In group I, the Kt/v ranged from 0.87 to 1.34 with a median of 1.07.
- b) In group II, the Kt/v ranged from 0.89 to 1.41 with a median of 1.20.
- c) Kt/v was statistical significant between 2 groups being higher in group II as compared to group I (Table 2).
- ii. In group II, the serum TNF alpha ranged from 26.80 – 66.90 with a mean of 40.28±8.52
- iii. In group III (Healthy Control), the serum TNF alpha ranged from 21.20 – 66.60with a mean of 30.94±13.13
- iv. Serum TNF alpha was statistical significant between 3 groups being higher in group I as compared to group II as compared to group III (Healthy control) (Table 3 & 4).

Serum TNF alpha:

- i. In group I, the serum TNF alpha ranged from 29.80 to 74.20 with a mean of 51.89±10.86

Table 2: Comparison between Group I & Group II according to Kt/v.

	Diabetic (n = 30)	Non Diabetic (n = 30)	t	P
Kt/v				
Min. – Max	0.87 – 1.34	0.89 – 1.41	2.110*	0.039*
Mean±SD	1.09±0.13	1.17±0.14		
Median	1.07	1.20		

t: Student t-test

*: Statistically significant at p ≤ 0.05

Table 3: Comparison between the three studied groups according to TNF alpha.

	Diabetic (n = 30)	Non diabetic (n = 30)	Control (n = 15)	KW χ^2	P
TNF alpha					
Min. – Max	29.80 - 74.20	26.80 – 66.90	21.20 – 66.60	30.194*	<0.001*
Mean±SD	51.89±10.86	40.28±8.52	30.94±13.13		
Median	53.35	39.40	27.40		
Sig .bet .Grps	p ₁ <0.001*, p ₂ <0.001*, p ₃ <0.001*				

KW χ^2 : Chi square for Kruskal Wallis test

Sig. bet. grps was done using Mann Whitney test

p1: p value for comparing between diabetic and non diabetic

p2: p value for comparing between diabetic and control

p3: p value for comparing between non diabetic and control

*: Statistically significant at p ≤ 0.05

Table 4: Correlation between TNF alpha with different studied parameters for each group and total patients.

	TNF alpha					
	Diabetic		Non Diabetic		Total Patients	
	r _s	P	r _s	p	r _s	p
Age (years)	-0.127	0.504	-0.086	0.652	0.003	0.979
Duration of A.V fistula (years)	0.625*	<0.001	0.371*	0.045	0.125	0.342
Duration of dialysis (months)	0.790*	<0.001	0.312	0.093	0.504*	<0.001
U/S doppler AVF						
Volume	0.042	0.825	0.155	0.412	-0.072	0.587
Vein	-0.145	0.443	-0.031	0.869	-0.244	0.060
Osteum	-0.139	0.463	0.001	0.996	0.023	0.864
Kt V	-0.017	0.928	0.239	0.203	-0.084	0.552
Serum Creatinine	0.011	0.953	-0.169	0.372	-0.077	0.558
BUN	0.178	0.348	-0.061	0.750	0.004	0.976
FBS	0.379*	0.039	-0.101	0.594	0.505*	<0.001
Hg	-0.148	0.436	0.063	0.743	0.060	0.647
Plt	-0.306	0.100	0.160	0.398	-0.150	0.254
WBCs	-0.027	0.887	-0.146	0.442	-0.029	0.825
Cholesterol	0.077	0.687	-0.032	0.866	0.376*	0.003
TGA	-0.146	0.442	0.001	0.994	-0.077	0.557
LDL	-0.171	0.366	-0.116	0.542	0.012	0.929
HDL	0.145	0.446	0.070	0.715	0.229	0.078
SGOT	0.071	0.707	0.029	0.879	-0.005	0.973
SGPT	0.110	0.365	-0.161	0.395	-0.063	0.634
Total Protein	0.212	0.260	-0.066	0.728	-0.013	0.921
Alb.	-0.387*	0.034	-0.312	0.094	-0.316*	0.014
Prothrombin Time	-0.214	0.256	-0.147	0.438	-0.108	0.412
Prothrombin activity (%)	0.123	0.518	-0.256	0.173	-0.008	0.949
Ca	0.434*	0.017	0.159	0.403	0.216	0.098
Ph	0.114	0.459	-0.107	0.575	0.022	0.867

rs: Spearman coefficient

*: Statistically significant at p ≤ 0.05

Discussion

The present study was conducted on sixty individuals: thirty of them were diabetic End stage renal disease (ESRD) patients (group I) and thirty of them were non-diabetic End stage renal disease patients (group II) of matched age and sex. The main etiology of ESRD observed in our study was diabetic kidney disease (43%) or hypertensive nephropathy (35%) which is supported by what observed by Robert N & Allan J Collins [16] who found that (43.8%) of their patients had ESRD secondary to diabetic nephropathy and (26.8%) due to hypertensive nephropathy. An increase in the level of serum (TNF- α) in the diabetic group was observed in the present study in comparison to non-diabetic group and to healthy controls. In agreement with our results Lechleitner M et al. [17] found that TNF-alpha plasma levels are increased in type 1 diabetes mellitus and reveal a significant association with metabolic long-term control parameters, HbA1c.

Also Swaroop JJ et al. [18] suggest the possible role of TNF- α in the pathogenesis of type-2 diabetes mellitus and the importance of reducing obesity to prevent elevated levels of the cytokine and related complications.

Also Hu FB et al. [19] support the role of inflammation in the pathogenesis of type 2 diabetes. Elevated CRP levels are a strong independent predictor of type 2 diabetes and may mediate associations of TNF-alpha and IL-6 with type 2 diabetes. It was observed in this study that there was statistical significant higher incidence of history of arteriovenous fistula failure in diabetic patients in comparing with non-diabetic patients. Other studies supported our finding like Renan Nunes da Cruz et al. [20] and they found that diabetic patients had shorter mean duration of AVF patency and lower rate of access survival (Figure 1).

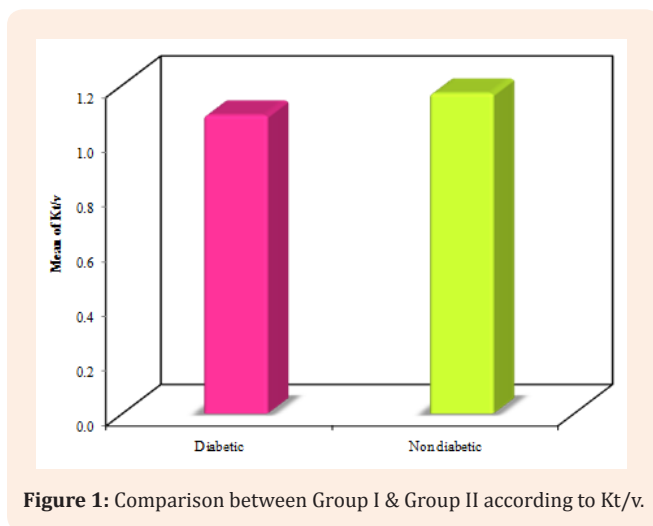


Figure 1: Comparison between Group I & Group II according to Kt/v.

Huijbregts HJT et al. [21] found that hemodialysis patients with diabetes can be expected to have reduced primary functional native AVF patency rates with high failure rate. According to AVF vein diameter in this study it was observed that the vein diameter (arterialized) was statistical significant decreased in diabetic ESRD group in compared to the non-diabetic ESRD group, In agreement with our results Conte MS et al. [22] found that diabetes was a significant, negative predictor of venous remodeling over the 24-week study (P = .02). The model-predicted change in lumen diameter from 2 to 24 weeks was -0.7 mm in diabetic patients (n

= 11) and +2.4 mm in non-diabetic patients (n = 15), a difference of 3.1 mm. A significant decrease in the Kt/v in diabetic ESRD group in compared to non-diabetic ESRD group depending on high incidence of arteriovenous fistula stenosis in diabetic group, in agreement with our findings Robbin ML et al. [23] revealed that patients with diabetes were significantly less likely to have a well-functioning AVF than patients without diabetes which is important for adequate hemodialysis.

It was observed in our study that hemodialysis adequacy (kt/v) of the non-diabetic group with AVF duration 3-6 months (Group IIa) was statistically significantly higher in comparing with the other 3 groups. This is supported by Anees M et al. [24] who found that non-diabetic patients had a better quality of life (QOL) as compared to diabetic patients plus that duration of dialysis had a reverse correlation with the overall QOL. It was observed in the present study that the level of TNF alpha is significantly positively correlated with duration of dialysis in total patients, consistent with our findings Kir HM et al. [25] support that TNF-alpha was increased for all patients with chronic renal failure (CRF), both hemodialysis and peritoneal dialysis. It was observed in the present study that the level of TNF alpha is significantly positively correlated with duration of arteriovenous fistula in both diabetic & non-diabetic group, consistent with our finding Chang CJ et al. [26] demonstrated that the thrombosed arteriovenous fistula was characterized by marked inflammation.

It was observed in our study that there is TNF alpha is positively correlated with fasting blood glucose. Consistent with our finding Niti Agarwal et al. [27], suggests TNF-alpha rising with elevated fasting blood glucose. It was observed in our study that there is TNF-alpha is consistent negatively correlated with albumin. Consistent with our finding Undurti N Das et al. [28] found that Tumor necrosis factor alpha induces hypoalbuminemia and polyunsaturated fatty acid deficiency. It was observed in our study that TNF alpha is positively correlated with calcium consistent with our finding. Harry L Uy et al. [29] demonstrate that TNF-alpha enhances PTHrP-mediated hypercalcemia.

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