Original Article

The Relation between the Level of Serum Transforming Growth Factor Beta and Hemodialysis Adequacy in Diabetic and Non Diabetic Patients on Maintenance Hemodialysis.

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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 intimal hyperplasia, which is induced by growth factors, among which transforming growth factor β1 (TGF-β1) is of major importance. TGF-β1 influences the risk for hemodialysis access failure. By inducing synthesis of extracellular matrix proteins, overproduction of TGF-β1 may accelerate the development of intimal hyperplasia, resulting in fistula stenosis and subsequent 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 TGF-beta 1 in all patients. Assess AVF by Doppler U/S and estimate hemodialysis adequacy by using single pool Kt/v **Results:** we found that serum TGF-beta 1 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 TGF beta 1 was statically positively significant with duration of dialysis, FBG and cholesterol level, lastly we found that TGF-beta is significantly correlated with Kt/v and may affect hemodialysis adequacy adversely particularly in diabetic ESRD patients on HD **Conclusion:** TGF-beta is significantly elevated in diabetic ESRD patients on HD, negatively correlated with AVF vein diameter and significantly correlated with Kt/v and may affect hemodialysis adequacy adversely particularly in diabetic patients on HD.

Keywords: ESRD, Hemodialysis, arteriovenous fistula, TGF-beta 1, Hemodialysis adequacy, diabetics.

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:

- Increase the placement of native fistulae.
- 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 accessiblefor 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. The risk for access failure differs individually, an observation that is independent from vascular anatomy in a significant number of patients. Fistula stenosis is histologically characterized by intimal hyperplasia, which is induced by growth factors, among which transforming growth factor β1 (TGF-β1) is of major importance.[14,15]

TGF-β1 influences the risk for hemodialysis access failure. By inducing synthesis of extracellular matrix proteins, overproduction of TGF-β1 may accelerate the development of intimal hyperplasia, resulting in fistula stenosis and subsequent access failure. [15]

A haphazard hyperplastic smooth muscle response of the intima with angiogenesis occurring in both intima and adventitia is associated with the presence of macrophages and cytokines, including transforming growth factor beta1 (TGF- β1), basic fibroblast growth factor (bFGF), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF).[15]

The pathologic features of HD vascular access stenosis are composed of intimal hyperplasia, VSMC proliferation in the media with subsequent migration to intima, and excessive accumulation of extracellular matrix, which are mediated by several growth factors among which TGF-β and PDGF are of major importance. (16)

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. (17)

Aim of the Study:

The aim of this work is to study the relation between serum transforming growth factor beta 1 (TGF-β 1) 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:

Group I : 30 diabetic ESRD patients on HD

Group II: 30 non-diabetic ESRD patients on HD

Group III: 15 healthy controls.

Exclusion criteria:

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

All patients will be subjected to the following:

- Full history talking
- Routine investigations: Complete blood picture, Triglycerides (TG), total cholesterol, low density lipoprotein (LDL) and high density lipoprotein (HDL), Fasting blood glucose level, serum alanine aminotransferase (ALT), serum aspartate aminotransferase (AST), prothrombin time and activity, total proteins, serum albumin), Serum Calcium, serum phosphate.
- TGF- β1 level measurement with enzyme linked immunosorbent assay (ELISA) technique.
- Doppler US study of the native AVF.
- 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:

Group Ia: 15 diabetic ESRD patients on HD with functioning AVF between 3 months and 6 months.

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:

Group IIa: 15 non- diabetic ESRD patients on HD with functioning AVF between 3 months and 6 months.

Group IIb: 15 non-diabetics ESRD patients on HD with functioning AVF more than one year.

Group III: 15 healthy controls.

Serum TGF beta: Table (I)

- In group I, the serum TGF beta ranged from 7985.5 pg/ml to 39222.5 pg/ml with a mean of 23450.6 ± 8265.5 pg /ml.
- In group II, the serum TGF beta ranged from 6676.3 pg/ml to 30088.7 pg/ml with a mean of 15785.3 ± 7200.6 pg/ml..
- In group III (Healthy Control), the serum TGF beta ranged from 4790.4 pg/ml to 230896 pg/ml with a mean of 8813.2 ± 5757.3pg/ml.
- Serum TGF beta was statistical significant between 3 groups being higher in group I as compared to group II as compared to group III (Healthy control)

Ultra Sound Doppler study of arterio venous fistula: Table (II)

1- Central venous system stenosis:

- In group I, there were 9 patients with central venous system stenosis (30%)
- In group II, there were 6 patients with central venous system stenosis (20%).
- No significant statistical difference was observed between the two groups regarding the Central venous system stenosis.

2- Venous Thrombosis:

- In group I, there was 1 patient with venous thrombosis (3.3%)
- In group II, there were 5 patients with venous thrombosis (16.7%).
- No significant statistical difference was observed between the two groups regarding the venous thrombosis.

3- Aneurysmal dilatation:

- In group I, there were 3 patients with aneurysmal dilatation (10%)
- In group II, there were 4 patients with aneurysmal dilatation (13.3%).
- No significant statistical difference was observed between the two groups regarding the aneurysmal dilatation.

4- Volume:

- In group I, the volume ranged from 350 ml to 1400 ml with a mean of 708.33 ± 272.63
- In group II, the volume ranged from 500 ml to 1400 ml with a mean of 825.0 – 276.91
- No significant statistical difference was observed between the two groups regarding the AVF volume.

5- Vein diameter:

- In group I, the vein diameter ranged from 0.4 cm to 0.8 cm with a mean of 0.61 ± 0.11
- In group II, the vein diameter ranged from 0.4 cm to 0.9 cm with a mean of 0.69 ± 0.11
- Vein diameter was statistical significant between 2 groups being higher in group II as compared to group I.

6- Osteum diameter:

- In group I, the osteum diameter ranged from 0.5 cm to 0.9 cm with a mean of 0.77 ± 0.11
- In group II, the osteum diameter ranged from 0.5 cm to 1 cm with a mean of 0.72 ± 0.14
- No significant statistical difference was observed between the two groups regarding theOsteum diameter.

Ultra Sound Doppler study of arterio venous fistula: Table (VI)

1- Central venous system stenosis:

- In group Ia, there were 4 patients with central venous system stenosis (26.7%)
- In group Ib, there were 5 patients with central venous system stenosis (33.3%).
- In group IIa there were 4 patients with central venous system stenosis (26.7%)
- Group IIb there were 4 patients with central venous system stenosis (26.7%)
- No significant statistical difference was observed between the four groups regarding the central venous system stenosis.

2- Venous Thrombosis:

- In group Ia, there was 0 patient with venous thrombosis (0%)
- In group Ib, there were 1 patients with venous thrombosis (6.7%).
- In group IIa there were 1 patients with venous thrombosis (6.7%)
- In Group IIb there were 4 patients with venous thrombosis (26.7%)
- No significant statistical difference was observed between the four groups regarding the venous thrombosis.

3- Aneurysmal dilatation:

- In group Ia, there was 1 patient with aneurysmal dilatation (6.7%)
- In group Ib, there were 2 patients with aneurysmal dilatation (13.4%).
- In group IIa there were 0 patients with aneurysmal dilatation (0%)

- In group IIb there were 4 patients with aneurysmal dilatation (26.7%)
- No significant statistical difference was observed between the four groups regarding the aneurysmal dilatation.

4- Volume:

- In group Ia, the volume ranged from 350 ml to 1300 ml with a mean of 753.33 ± 286.90
- In group Ib, the volume ranged from 400 ml to 1400 ml with a mean of 663.33 ± 259.44
- In group IIa, the volume ranged from 500 ml to 1300 ml with a mean of 823.33 ± 235.94
- In group IIb, the volume ranged from 500 ml to 1400 ml with a mean of 826.67 ± 321.20
- No significant statistical difference was observed between the four groups regarding the volume.

5- Vein diameter:

- In group Ia, the vein diameter ranged from 0.4 cm to 0.8 cm with a mean of 0.63 ± 0.11
- In group Ib, the vein diameter ranged from 0.4 cm to 0.8 cm with a mean of 0.59 ± 0.11
- In group IIa, the vein diameter ranged from 0.4 cm to 0.9 cm with a mean of 0.70 ± 0.14
- In group IIb, the vein diameter ranged from 0.5 cm to 0.9 cm with a mean of 0.69 ± 0.08
- No significant statistical difference was observed between the four groups regarding the vein diameter.

6- Osteum diameter:

- In group Ia, the osteum diameter ranged from 0.5 cm to 0.9 cm with a mean of 0.77 ± 0.12
- In group Ib, the osteum diameter ranged from 0.6 cm to 0.9 cm with a mean of 0.76 ± 0.11
- In group IIa, the osteum diameter ranged from 0.5 cm to 0.9 cm with a mean of 0.70 ± 0.12
- In group IIb, the osteum diameter ranged from 0.5 cm to 1 cm with a mean of 0.74 ± 0.15
- No significant statistical difference was observed between the four groups regarding the Osteum diameter.

Kt/v: Table (V)

- In group I, the Kt/v ranged from 0.87 to 1.34 with a median of 1.07.
- In group II, the Kt/v ranged from 0.89 to 1.41 with a median of 1.20.
- Kt/v was statistical significant between 2 groups being higher in group II as compared to group

Kt/v: Table (VI)

- In group Ia, the Kt/v ranged from 0.87 – 1.30 with a mean of 1.11 ± 0.13.
- In group Ib, the Kt/v ranged from 0.89 – 1.34 with a mean of 1.07 ± 0.13.
- In group IIa, the Kt/v ranged from 0.97 – 1.41 with a mean of 1.22 ± 0.14.
- In group IIb, the Kt/v ranged from 0.89 – 1.32 with a mean of 1.11 ± .13.
- Kt/v was statistically significant between 4 groups being higher in group (IIa) as compared to the other 3 groups.

Table (I): Comparison between Group I & Group II & Group III according to TGF beta

	Diabetic (n = 30)	Non diabetic (n = 30)	Control (n = 15)	$^{KW}\chi^2$	p
TGF beta					
Min. – Max	7985.50 - 39222.50	6676.3 - 30088.7	4790.4 - 23089.6	30.509*	<0.001*
Mean ± SD	23450.6 ± 8265.5	15785.3 ± 7200.6	8813.2 ± 5757.3		
Median	24504.90	14073.35	6887.40		
Sig .bet .Grps	$p_1 = 0.001^*$, $p_2 < 0.001^*$, $p_3 < 0.001^*$				

$^{KW}\chi^2$: Chi square for Kruskal Wallis test

Sig. bet. grps was done using Mann Whitney test

p_1: p value for comparing between diabetic and non diabetic

p_2: p value for comparing between diabetic and control

p_3: p value for comparing between non diabetic and control

***:** Statistically significant at $p \leq 0.05$

(Table II): Comparison between the four Subgroups (Ia, Ib, IIa, IIb) & Control group III according to TGF beta

- In group Ia, the serum TGF beta ranged from 7985.5 pg/ml to 33084.3 pg/ml with a mean of 19624.0 ± 6394.1 pg /ml.
- In group Ib, the serum TGF beta ranged from 8139.5 pg/ml to 39222.5 pg/ml with a mean of 27277.2 ± 8321.9 pg/ml.
- In group IIa the serum TGF beta ranged from 6676.3 pg/ml to 30088.7 pg/ml with a mean of 12327.9 ± 7355.9pg/ml.
- Group IIb the serum TGF beta ranged from 8795.3 pg/ml to 29442.4 pg/ml with a mean of 19242.6 ± 5261.2 pg/ml.
- In group III (Healthy Control), the serum TGF beta ranged from 4790.4 pg/ml to 230896 pg/ml with a mean of 8813.2 ± 5757.3pg/ml.
- Serum TGF beta was statistical significant between 5 groups being higher in group Ib as compared to group Ia as compared to group IIb as compared to group IIa as compared to group III (Healthy control)

(Table II): Comparison between Group I & Group II according to U/S Doppler AVF

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	$\chi^2 = 3.455$	0.120
Thrombosis	1	3.3	5	16.7	$\chi^2 = 2.963$	^{FE}p =0.195
Aneurysm	3	10.0	4	13.3	$\chi^2 = 0.162$	^{FE}p = 1.000
Volume						
Min. – Max	350.0 – 1400.0		500.0 – 1400.0			
Mean ± SD	708.33 ± 272.63		825.0 – 276.91		Z = 1.739	0.082
Median	600.0		775.0			
Vein diameter						
Min. – Max	0.40 - 0.80		0.40 – 0.90			
Mean ± SD	0.61 ± 0.11		0.69 ± 0.11		t =2.695*	0.009*
Median	0.60		0.70			
Osteum						
Min. – Max	0.50 – 0.90		0.50 – 1.0			
Mean ± SD	0.77 ± 0.11		0.72 ± 0.14		t = 1.330	0.189
Median	0.80		0.70			

χ^2: Chi square test

MC: Monte Carlo test

Z: Z for Mann Whitney test

t: Student t-test

*: Statistically significant at p ≤ 0.05

(Table III): Comparison between the four Subgroups (Ia, Ib, IIa, IIb) according to U/S Doppler A.V fistula

	Diabetic (Group I)				Non Diabetic (Group II)				Test of sig.	P
	A.V.F 3 – 6 months (n = 15) (Group Ia)		A.V.F >1 year (n = 15) (Group Ib)		A.V.F 3 – 6 months (n = 15) (Group IIa)		A.V.F >1 year (n = 15) (Group IIb)			
	No.	%	No.	%	No.	%	No.	%		
Central venous system stenosis	4	26.7	5	33.3	4	26.7	2	13.3	$\chi^2 = 6.128$	0.116
Thrombosis	0	0	1	6.7	1	6.7	4	26.7	$\chi^2 = 6.667$	0.142
Aneurysm	1	6.7	2	13.3	0	0.0	4	26.7	$\chi^2 = 4.948$	0.185
Volume										
Min. – Max	350.0 – 1300.0		400.0 – 1400.0		500.0 – 1300.0		500.0 – 1400.0			
Mean ± SD	753.33 ± 286.90		663.33 ± 259.44		823.33 ± 235.94		826.67 ± 321.20		$^{KW}\chi^2 = 4.281$	0.233
Median	700.0		600.0		800.0		700.0			
Vein diameter										
Min. – Max	0.40 – 0.80		0.40 – 0.80		0.40 – 0.90		0.50 - .080			
Mean ± SD	0.63 ± 0.11		0.59 ± 0.11		0.70 ± 0.14		0.69 ± 0.08		F= 2.708	0.054
Median	0.60		0.60		0.70		0.70			
Osteum										
Min. – Max	0.50 – 0.90		0.60 – 0.90		0.50 – 0.90		0.50 – 1.0			
Mean ± SD	0.77 ± 0.12		0.76 ± 0.11		0.70 ± 0.12		0.74 ± 0.15		F = 0.883	0.456
Median	0.80		0.80		0.70		0.80			

χ^2: Chi square test

F: F test (ANOVA)

$^{KW}\chi^2$: Chi square for Kruskal Wallis test

(Table IV): 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		
Mean ± SD	1.09 ± 0.13	1.17 ± 0.14	2.110*	0.039*
Median	1.07	1.20		

t: Student t-test

*: Statistically significant at $p \leq 0.05$

(Table V): Comparison between the four Subgroups (Ia, Ib, IIa, IIb)according to Kt/v

	Diabetic (Group I)		**Non Diabetic (Group II)**		**F**	**P**
	A.V.F 3 – 6 months (n = 15) (Group Ia)	**A.V.F >1 year (n = 15) (Group Ib)**	**A.V.F 3 – 6 months (n = 15) (Group IIa)**	**A.V.F >1 year (n = 15) (Group IIb)**		
Kt/v						
Min. – Max	0.87 – 1.30	0.89 – 1.34	0.97 – 1.41	0.89 – 1.32		
Mean ± SD	1.11 ± 0.13	1.07 ± 0.13	1.22 ± 0.14	1.11 ± .13	3.594	0.019*
Median	1.12	1.05	1.24	1.10		
p_1	0.815		0.113			
p_2			0.123	0.836		

F: F test (ANOVA)

Sig. bet. grps was done using Post Hoc test (Tukey) test

p_1: p value for comparing between A.V.F 3 – 6 months and >1year in each diabetic and non-diabetic group

p_2: p value for comparing between diabetic and non-diabetic in each A.V.F 3 – 6 months and >1 year

* : Statistically significant at p ≤ 0.05

Table (VI): Correlation between TGF Beta with different studied parameters for each group and total patients

	TGF Beta					
	Diabetic (Group I)		**Non Diabetic (Group II)**		**Total patients**	
	r_s	**P**	**r_s**	**P**	**r_s**	**p**
Duration of dialysis (months)	0.456*	0.009	0.420*	0.015*	0.556*	<0.001*
U/S doppler AVF						
Volume	-0.230	0.113	-0.309	0.097	-0.295	0.216
Vein diameter	-0.479*	0.007	-0.202	0.283	-0.481*	<0.001
Osteum	-0.217	0.250	-0.288	0.225	-0.129	0.325
Kt V	-0.385*	0.035	-0.453*	0.012	-0.509*	<0.001*
FBS	0.362*	0.050	0.155	0.415	0.531*	<0.001
Cholesterol	0.501*	0.005	0.017	0.930	0.570*	<0.001

r_s: Spearman coefficient *: Statistically significant at p ≤ 0.05

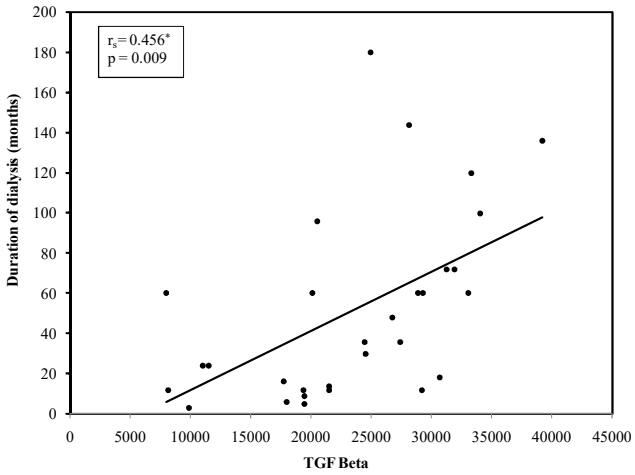

Figure (1): Correlation between TGF Beta with Duration of dialysis (months) for Diabetic group (Group I)

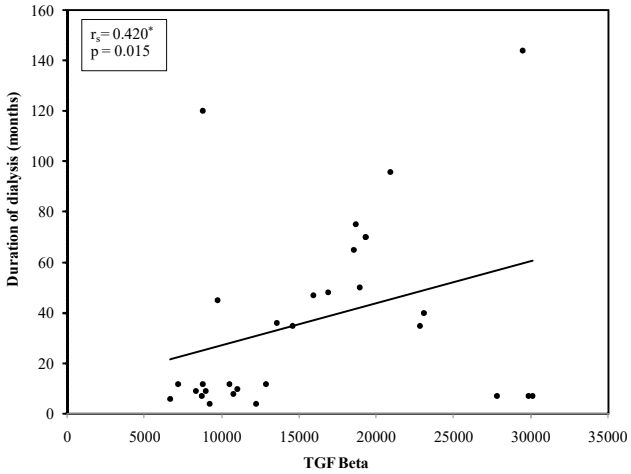

Figure (2): Correlation between TGF Beta with Duration of dialysis (months) for Non Diabetic group (Group II)

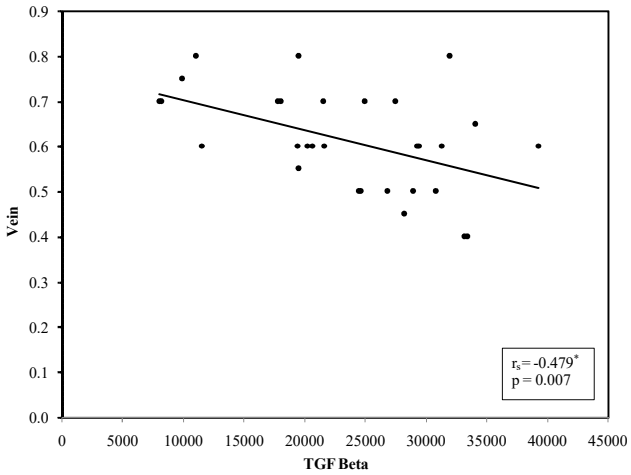

Figure (3): Correlation between TGF Beta with Vein diameter for Diabetic group (Group I)

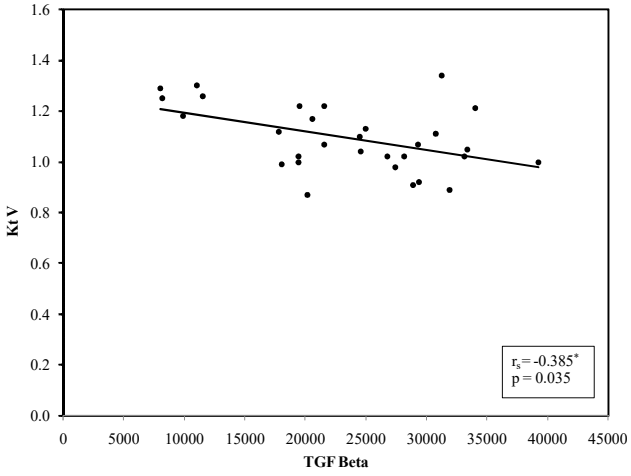

Figure (4): Correlation between TGF Beta with Kt/V for Diabetic group (Group I)

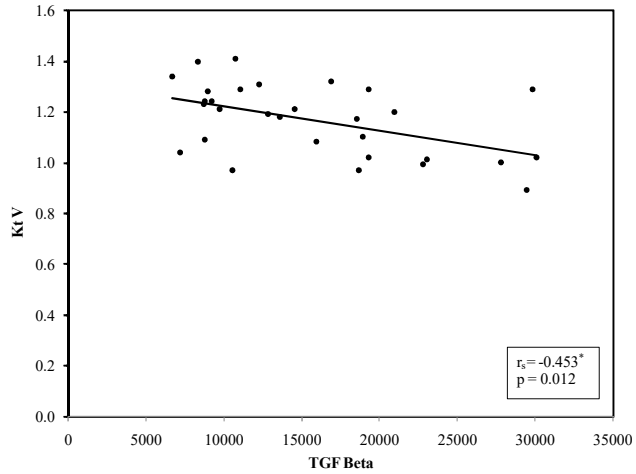

Figure (5): Correlation between TGF Beta with Kt/V for Non Diabetic group (Group II)

Discussion:

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 et al [18] who found that (43.8%) of their patients had ESRD secondary to diabetic nephropathy and (26.8%) due to hypertensive nephropathy.

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 [19] and they found that diabetic patients had shorter mean duration of AVF patency and lower rate of access survival.

Huijbregts HJTet al[20] found that hemodialysis patients with diabetes can be expected to have reduced primary functional native AVF patency rates with high failure rate.

An increase in the level of serum (TGF-β) 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 Ahmed KYet al [21] found higher circulating serum levels of TGF beta 1 in patients with diabetes type 1 and type 2 and in those with diabetic nephropathy than the non-diabetics

Ibrahim.S et al [22]strongly support the hypothesis that hyperglycemia may trigger the activation of TGF beta 1 which lead to increase the serum level of TGF beta 1 in type 2 diabetic patients than healthy control.

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[23] 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 [24] 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.

An increase in the level of serum (TGF-β) in the diabetic patients with AFV more than 1 year (Group Ib) was observed in the present study in comparison to other groups. Weiss MF et al [25] who found that oxidative hyperactivity in the uremic status usually leads

to an increased amount of circulating and tissue inflammatory molecules, Interaction with dialysis membranes have also been reported as an important cause leading to oxidative stress, resulting in an increased expression of endothelin-1, which has been associated with intimal hyperplasia and smooth muscle cell vasoconstriction. TGF-β and PDGF have also been implicated in intimal hyperplasia but seem to be clustered at the venous end of the failed AV access.

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[26] 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 TGF beta is significantly positively correlated with duration of dialysis in both diabetic & non-diabetic group, consistent with our findingsLin CC et al[27] strongly support that Interaction with dialysis membranes have also been reported as an important cause leading to oxidative stress leads to an increased amount of circulating and tissue inflammatory molecules such as TGF beta & PDGF have also been implicated in intimal hyperplasia of the AVF

It was observed in the present study that the level of TGF beta is significantly negatively correlated with vein diameter of AVF in diabetic group. Consistent with our findings Stracke S et al [28] found that there is a venous neointimal thickening of the arteriovenous fistulas represents a local inflammatory process and appears to be associated with increased expression of TGF-beta1 and IGF-I., TGF-beta1 may be an important trigger of ECM production and deposition.

It was observed in the present study that the level of TGF-beta is significantly negatively correlated with Kt/v in both diabetic & non-diabetic group.

It was observed in the present study that the level of TGF-beta is significantly positively correlated with fasting blood glucose in diabetic group. Consistent with our findings Garud MS et al[29] demonstrated that in diabetic nephropathy hyperglycemia cause increase in the expression of TGF- β1 genes, TGF- β 1 proteins and their receptors. Increased blood glucose level also activates the TGF- β via activation of glucose transporters (GLUT) which lead to increase level of serum TGF beta 1.

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