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Thrombosis in Hemodialysis Patients; Their Association with Tissue Factor and Tissue Factor Pathway Inhibitor

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Abstract

Background: Thrombotic complications are common in patients undergoing maintenance hemodialysis.

The aim of the study: to measure tissue factor (TF) and tissue factor pathway inhibitor (TFPI) levels in hemodialysis patients and to elucidate their role with thrombotic episodes.

Methods: 61 patients on hemodialysis as well as 19 healthy persons were included. The patients were reclassified into high and low groups according to the 90th and 10th percentile of controls of both TF and TFPI respectively to predict if higher than the 90th percentile of TF or lower than 10th percentile of TFPI were associated with thrombotic complications or not. All participants subjected to complete hemogram, measurement of TF and TFPI by enzyme linked immunosorbent assay.

Results: TF and TFPI were significantly higher in patients than control group ($p<0.001$and <0.05 respectively). Six patients showed at least one thrombotic episode (9.8%). TF was significantly increased ($p<0.001$) between the groups of patients who experienced or not thrombotic episodes. TFPI showed no significant differences in patients with or without thrombosis.TF was significantly associated with thrombosis when using multiple regression analysis, whereas TFPI was not. Patients above the 90th percentile of TF were significantly correlated with thrombosis (r=0. 4). Whereas, Patients below the 10th percentile of TFPI were not.

Conclusion: TF and TFPI increase in hemodialysis patients. TF is higher in hemodialysis patients with thrombosis whereas TFPI is not. TF above the 90th percentile is significantly correlated with thrombosis. TFPI below the 10th percentile is not. TF could be a contributor to thrombosis in hemodialysis patients.

Keywords: Hemodialysis; Tissue factor; Tissue factor pathway inhibitor; Thrombosis

Introduction

Thrombotic events in end-stage renal disease, particularly in hemodialysis patients, are common. The two-year death rate of end-stage renal disease, dialysis patients who sustain an acute myocardial infarction is 73 percent [1]. These are not limited to the consequences of accelerated atherogenesis; thrombosis of vascular access grafts, pulmonary emboli, and deep-venous thrombosis are seen as well. The mechanisms contributing to increased risk of thrombosis point to the nexus of inflammation and coagulation [2].

Tissue Factor (TF) a transmembrane glycoprotein normally anchored to vascular cells is the primary cellular initiator of the extrinsic pathway of coagulation [3]. TF activates clot formation by forming a complex with factor VIIa (TF/FVIIa), thus activating factor X. TF is expressed in blood leukocytes obtained from end-stage renal disease patients, and hemodialysis transiently enhances its expression. The presence of soluble TF in human circulation and its participation in the formation of *ex-vivo* thrombi has been demonstrated [4].

The main inhibitor of the TF pathway is called tissue factor pathway inhibitor (TFPI) [5]. TFPI is a single-chain polypeptide, which is synthesized mainly by endothelial cells and exists on the endothelium and in plasma in a free form and lipoprotein-associated forms [6]. It occurs in two forms TFPI-1 and TFPI-2. TFPI-1 is the main inhibitor of the TF pathway; TFPI-2 is a strong inhibitor of trypsin, plasmin, plasma kallikrein, and FXIa amidolytic activity [7-10]. TFPI inhibits directly factor Xa. While Xa is inhibited, the Xa-TFPI complex can subsequently also inhibit the TF/FVIIa complex, preventing the clot formation [5].

The aim of this study was to measure tissue factor and tissue factor pathway inhibitor in hemodialysis patients and to elucidate their role with thrombotic episodes in these patients.

Subjects and Methods

Subjects

The analytical methods of this study were carried out in the laboratory of the Hematology and Immunology Department, Faculty of Medicine, Umm Al-Qura University in accordance with the

approved guidelines. This study was carried out from January 2011 to September 2011; it included 61 patients with chronic renal failure as well as 19 healthy subjects as a control group. The Patients were attended to King Abdulaziz Hospital, Makkah, Saudi Arabia. The description and classification of all subjects are summarized in Table 1. Thirty-two patients (52.4%) were on top of hypertension, 27 patients (44.3%) on top of diabetes mellitus, of the previous patients 12 had both diabetes and hypertension. All patients were taken low molecular weight heparin during dialysis. The duration of hemodialysis ranged from 2-25 years with a mean year of 7.7 ± 6.5.

	Patients		Control	
	No. (61)	%	No. (19)	%
Sex				
Males	30	49.2	7	36.8
Females	31	50.8	12	63.2
Hypertension	32	52.4	-	-
Diabetes mellitus	27	44.3	-	-
Thrombosis	6	9.8	-	-
Combined cases	12	19.7	-	-
Died	2	3.3	-	-
Age/years mean ± SD	48 ± 14.4	-	45.7 ± 10.9	P>0.05
Duration of dialysis/ years Mean ± SD	7.7 ± 6.5	-	-	-
Range	2-25	-	-	-

Table 1: Clinical data of patients and control group.

Reclassifications of the patients into high and low groups were done to predict if patients above the 90th percentile of TF or patients below the 10th percentile of TFPI were associated with thrombotic complications or not and also to detect any other associations. The high TF group was defined as TF above the 90th percentile among the controls as reported earlier [11]. Low TFPI group was defined as TFPI below the 10th percentile among the controls as reported earlier [12]. Type of access: all of our patients had fistula.

Erythropoietin use: none of our patients have taken erythropoietin as the protocol to give erythropoietin when the hemoglobin level is below 9 g/dl.

Exclusion criteria: all patients with a history of thrombosis or a family history with thrombosis or any predisposing factors to thrombosis such as use of oral contraceptive pills or steroids or obesity or any patients with polycythemia were excluded from the study.

Sample collection

4 ml of blood was collected from patients and controls under complete aseptic conditions. The samples of patients were taken before dialysis and before taking heparin. 2 ml of blood was dispensed into a tube containing EDTA as anticoagulant substances for performing complete blood count at the time of collection. The remaining of EDTA samples were centrifuged for 15 minutes at 2-8°C, and then the plasma was separated and kept on -80°C until use for measurement of soluble tissue factor and tissue factor pathway inhibitor. The others 2 ml of blood were collected in heparin tubes for the determination of biochemical markers.

Methods

All patients and control group were subjected to the followings:

- A full clinical history.
- Complete hemogram analysis using Sysmex XT 2000i, (Sysmex Corporation of America, Long Grove, Illinois, USA) including red blood cells count, hemoglobin, packed cell volume, mean corpuscular hemoglobin, mean cell volume, mean corpuscular hemoglobin concentration, red cell distribution, white blood cells count and platelets.
- Measurement of soluble tissue factor by Enzyme Linked Immuno Sorbent Assay (ELISA) (Uscn Life Science, Inc. Wuhan, Cat.No.E90524Hu.). The CV % of intra assay precision was <10%. The CV% of inter assay precision was <12%. The minimum detectable dose of this kit was <0.17 ng/mL.
- Detection of soluble tissue factor pathway inhibitor by Enzyme Linked Immuno Sorbent Assay (ELISA) (Uscn Life Science Inc. Wuhan, Cat.No.E90394Hu.). The CV % of intra assay precision was <10%. The CV% of inter assay precision was <12%. The minimum detectable dose of this kit was less than 33 pg/mL.
- Determination of serum glucose, urea, creatinine, calcium, phosphorous, sodium, potassium, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin, albumin, cholesterol, triglycerides, high density lipoprotein and low density lipoprotein on Dimension RxL max integrated chemistry system (Dade Behring, USA).

Ethical declaration

The faculty of medicine, Umm AlQura University ethics committee has approved the protocol of this study, which registered and approved by the national committee of ethical approval Saudi Arabia HAPO-02-K-012. All participants gave informed consent according to the declaration of Helsinki.

Statistical analysis

The Statistical analysis of this study was done using STATISTICA BASIC program version 5 and SPSS version 20. All quantitative data are described in the form of mean ± SD, median and range. Comparison between the groups was performed by using student t test and Mann-Whitney U test according to the distributions of the results. In addition, if there were a small number of patients in any group the Mann-Whitney U test was used. The Chi-Square test was used when comparing qualitative data in different group studied. Moreover, Spearman correlation was used. Multiple regression analysis was used to detect if there was any associations between TF or TFPI and all the parameters studied. The sensitivity and specificity of TF and TFPI was done. A P>0.05 was considered statistically not significant while a p<0.05 and p<0.001 were considered significant and highly significant respectively.

Results

This study included 61 patients with chronic renal failure as well as 19 healthy subjects serving as a control group. The patients were 30 men and 31 women with male to female ratio of 1:1.03. Their mean

age was (48.0 ± 14.4) years. They had been on hemodialysis treatment for mean period of (7.5 ± 6.4) years. The control group was 7 men and 12 women with male to female ratio of 1:1.7. Their mean age was (45.7 10.9) years. During the period of the study, six of our patients developed thrombosis (9.8%), 5 developed thrombosis in the fistula and one developed deep venous thrombosis. Two patients died (3.3%) Table 1. The routine laboratory investigations between patients and control are not shown.

A highly significant increase of TF and significant increase of TFPI was found when the patients compared to the control group (P<0.001 and P<0.05 respectively) Table 2. No significant differences were found between males and females with regard to the concentration of both TF and TFPI in patients and control group Figure 1.

In this study, the patients who had developed thrombosis had higher significant values of TF, serum creatinine and potassium than those without thrombosis (p<0.05). No other significant differences were detected for all the remaining parameters including tissue factor pathway inhibitor, complete blood count and the biochemical tests (p>0.05) Table 3.

The TF was introduced as a dependent variable in the multiple regression analysis test with co-variables of age, sex, thrombosis, duration of dialysis, platelet count and history of diabetes mellitus or hypertension. TF was significantly associated with thrombosis (multiple R0.34, squared multiple R0.155, F10.89, p=0.0017). The same was done with TFPI and no significant association was obtained (multiple R0.19, squared multiple R0.03, F0.2, p=0. 8).

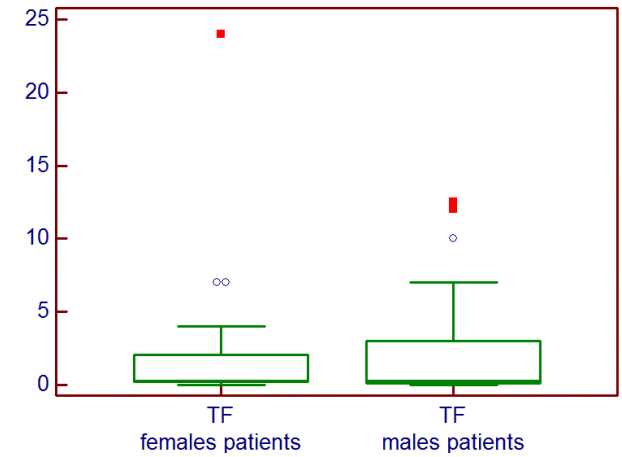

Figure 1: Tissue Factor concentrations in males and female patients.

Parameters studied	Patients group			Control group				P and significances
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Z or t value	
TF ng/mL	2.0 ± 4.1	0.3	0.0-24.0	0.26 ± 0.6	0.1	0.0-3.0	z=-3.1	0.001 HS
TFPI ng/mL	46.7 ± 19.6	49	2–75	34.89 ± 13.5	35	2.5-60	t=2.4	0.017 S
TF: Tissue Factor; TFPI: Tissue Factor Pathway Inhibitor; HS: Highly Significant; S: Significant								

Table 2: Comparison between patients and control group concerning TF and TFPI.

Parameters Studied	Patient with thrombosis (N=6) Mean ± SD	Patient without thrombosis (N=55) Mean ± SD	P and significances*
TF ng/mL	6.85 ± 9.16	1.48 ± 2.81	0.002 S
Creatinine mg/dL	11.57 ± 4.15	8.76 ± 3.11	0.04 S
Potassium mmol/L	5.1 ± 0.89	4.43 ± 0.63	0.02 S
TFPI ng/ml	47.8 ± 19.5	46.6 ± 19.8	0.89 NS
The significant values are shown only with exception of TFPI; NS: Not Significant; S: Significant			
*Mann-Whitney U test was used			

Table 3: Comparison between patients with and without thrombosis.

In the high group of TF (above the 90th percentile of controls), significant decrease of red blood cells counts, hemoglobin concentration and hematocrit were found (median ≥ 0.39) when compared to the low group (P<0.05). No Significant differences were found with regard to age, duration of the disease, white blood cell counts, platelet counts, serum creatinine, TFPI, cholesterol and triglycerides (P>0.05) Table 4. In addition, no significant differences were found with regard to history of diabetes mellitus, hypertension and thrombosis (p>0.05) using chi square test. Four out of six patients with thrombosis were in the high group (above 90th percentile) and the remaining two patients in the low group, but with an absence of significance. Moreover, significant positive correlations of TF with serum creatinine (r=0. 5) and thrombosis (r=0. 4) were detected in the high group of TF (P<0.05). On the other hand, no significant correlations were detected in the low group of TF (p>0.05).

In the low group of TFPI (below the 10th percentile of controls, median ≤13.5 ng/ml)), no significant differences were found with regard to age, duration of the disease, white blood cell counts, platelet counts, serum creatinine, TF, red blood cell counts, hemoglobin concentration, hematocrit, cholesterol and triglycerides (P>0.05) Table 5. In addition, no significant differences were found with regard to history of diabetes, hypertension and thrombosis (p>0.05) using chi square test. On the other hand, no significant correlations were detected in both the groups of TFPI (p>0.05). The sensitivity of TF was 73.8% and the specificity was 63.2%. The area under the curve was 0.738, the cut off was 0.19 ng/ml and the confidence interval was from 0.621 to 0.854. The sensitivity of TFPI was 72.1% and the specificity

was 68.4%. The area under the curve was 0.712, the cut off was 35.5 ng/ml and the confidence interval was from 0.597 to 0.827.

Parameters studied	Mean ± SD High group (N=27) (>0.39)*	Mean±SD Low group (N=34) (≤0.39)*	P and significances
Age/years	47.9 ± 13.9	48.02 ± 15.07	0.97 NS
Duration/years	6.89 ± 6.2	8.35 ± 6.7	0.39 NS
WBC count × 10^9/l	6.5 ± 2.4	6.3 ± 1.9	0.79 NS
RBC × 10^{12}/l	4.01 ± 0.50	4.3 ± 0.7	0.04 S
Hb g/dL	11.4 ± 1.6	12.3 ± 1.8	0.04 S
Hct %	34.8 ± 4.2	38.1 ± 5.5	0.01 S
Platelets count × 10^9/l	241.8 ± 141.5	236.4 ± 100.9	0.8 NS
Creatinine mg/dL	8.6 ± 2.6	9.3 ± 3.7	0.4 NS
TFPI ng/ml	46.5 ±19.9	46.8 ± 19.7	0.9 NS
Cholesterol mg/dl	133.4 ± 19.6	144.31 ± 35.7	0.4 NS
Triglycerides mg/dl	92.8 ± 32.0	111.6 ± 65.9	0.4 NS

*cut off ; WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; Hct: Hematocrite; TFPI: Tissue Factor Pathway Inhibitor; NS: Not Significant; S: Significant

Table 4: The comparison between the high and the low group of TF using 90th percentile of controls as a cutoff value.

Parameters studied	Mean ± SD High group (N=55) (≥13.5)*	Mean ± SD Low group (N=6) (<13.5)*	P and significances
Age/years	47.73±11.33	48.29 ± 17.66	0.881 NS
Duration/years	8.3 ± 6.8	7 ± 6.0	0.10 NS
WBC × 10^9/l	7.04 ± 2.31	5.7 ± 1.84	0. 16 NS
RBC × 10^{12}/l	4.16 ± 0.43	4.24 ± 0.84	0.656 NS
Hb g/dL	11.71 ± 1.22	12.23 ± 2.36	0.277 NS
Hct %	36.26 ± 3.62	37.16 ± 6.68	0.508 NS
Platelet counts × 10^9/l	239.79 ± 124.53	237.71 ± 115.77	0.946 NS
Creatinine mg/dL	9.61 ± 2.98	8.35 ± 3.57	0.137 NS
TF ng/ml	2.16 ± 3.66	1.83 ± 4.60	0.758 NS
Cholesterol mg/dl	138.0 ± 19.2	142.2 ± 38.2	0.206 NS
Triglycerides mg/dl	87.7 ± 23.7	119.6 ± 71.2	0.507 NS

*cut off ; WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; Hct: Hematocrite; TF: Tissue Factor; NS: Not Significant

Table 5: The comparison between the high and low group of TFPI using 10^{th} percentile of controls as a cutoff value

Discussion

Cardiovascular disease is the leading cause of death in end-stage renal failure patients undergoing maintenance Hemodialysis (HD), with higher mortality risk as compared with the general population [13]. This excess of cardiovascular risk and accelerated atherosclerosis is due to an increased prevalence of traditional risk factors, and a number of hemodynamic and metabolic factors characteristic of chronic kidney disease and HD treatment [14]. Among them, abnormal haemostasis appears to contribute to the cardiovascular complications in this population [15,16]. A major role in determining thrombogenicity of human atherosclerotic lesions has been ascribed to the tissue factor (TF) -dependent pathway of blood coagulation. In the present study, TF levels were significantly higher in hemodialysis patients when compared to the control group ($p<0.01$). This finding is in agreement with the results reported by other investigators who demonstrated that TF levels were higher in HD patients than in healthy volunteers [17-19]. There are several possible mechanisms to explain the association of HD and higher levels of TF. A direct effect of decreased renal clearance may explain an increase in levels of smaller molecular weight hemostatic markers such as soluble TF, as these may be filtered at the glomerulus. Soluble TF has a MW of 29 kDa [20]. In our study, the significant positive correlation of tissue factor with serum creatinine may confirm this suggestion. In contrast, other authors reported that electrolyte or acid-base abnormalities in HD patients may alter activities of enzymes involved in coagulation and generate a thrombotic milieu and soluble TF would have to be tested in animal studies to be filtered at the glomerulus or not [21]. The TFPI was significantly increased in our HD patients in comparison to healthy subjects ($p<0.05$). This is in accordance with previous studies [15,22,23]. The elevated levels of TFPI in our HD patients may be a compensatory mechanism for the elevation of TF but absence of a significant correlation between TF and TFPI denote that there are other factors contributing to its elevation. The continuous endothelial injury from frequent fistula paracentesis, the presence of temporary or permanent central venous catheters and the use of grafts are possible causes of higher values of TFPI as it is considered as a marker of endothelial injury [23].

In our work, it was found that patients presenting thrombotic complications had significantly elevated TF plasma levels when compared to hemodialysis patients who did not present any thrombotic complications ($p<0.01$). Moreover, TF was significantly associated with thrombosis in our work using multiple regression analysis. Therefore, our findings provide evidence that plasma TF levels are linked to the incidence of thrombosis. These results are consistent with other observations [15,23]. Chronic renal insufficiency is associated with an activation of the tissue factor pathway of coagulation, which culminates in dialyzed patients with end stage renal disease. This activation is associated with indirect signs of activation/injury of endothelial cells, of monocytes, and of platelets. All of these cells participate in thrombus formation with different mechanisms [24,25]. On the other hand, TFPI levels were similar between patients who had thrombotic complications and those without thrombotic complications ($p>0.05$) and both groups had high values of TFPI. These data are concordant to available published one [23]. The TFPI inhibits directly factor Xa and indirectly its complex TF/FVIIa, preventing the clot formation. Despite the concomitant increase in total TFPI concentrations, TF and factor VIIa generations are sufficient to be associated with the enhanced fibrin formation in some patients and this may explain why not all patients had thrombosis. In addition, the activation of TF, in combination with

other independent risk factors, as hypertension, diabetes, age, smoking, HD duration and type of heparin used, seem to contribute to the appearance of thrombotic events [26].

In our work, Patients above the 90th percentile of TF were significantly correlated with thrombosis and creatinine and were more anemic than patients below the 10th percentile. Moreover, 4/6 of patients with thrombosis were in the high group (above 90th percentile) and the remaining two patients in the low group, but with an absence of significance. This again confirms the association of TF with thrombosis in our HD patients. Also, provide the poor general condition of these patients as denoted by the higher creatinine and the lower hemoglobin. Moreover, this finding suggests that patients in the high group of TF are more liable to develop complications, especially thrombosis than the lower one. In our study, Patients below the 10th percentile of TFPI were not significantly correlated or associated with thrombosis. No previous results or reports were found to confirm our results with regard to 90th and 10th percentile of both TF and TFPI respectively in our HD patients.

Conclusion and Recommendations

Tissue factor and tissue factor pathway inhibitor increase in hemodialysis patients. TF is higher in hemodialysis patients with thrombosis whereas TFPI is not differing in these patients. TF above the 90th percentile is significantly correlated with thrombosis. TFPI below the 10th percentile is not. TF could be a contributor to thrombosis in hemodialysis patients.

Further studies need to be done to gain better insight into the extent of the relationship between TF; TFPI and the thrombotic incidence in hemodialysis patients and to predict the cutoff value that can denote the incidence of thrombosis.

Limitation of the Study

Only six of our patients developed thrombosis, 5 in the fistula itself and one had deep venous thrombosis. The short time of follow up to the patients this was 9 months only.

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Author Contributions

AZ: Design of the study, clinical selection, performance of laboratory investigations, statistical analysis, preparing tables and figures, writing and revising of the main manuscript text.

TAMA, HA, MS, SH, NB and ST: performance of the laboratory investigations, preparing tables and figures and revising of the main manuscript text.

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