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The Role of Hemostatic Factors in Atherosclerosis in Patients with Chronic Renal Disease

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Abstract

Introduction: Atherosclerotic cardiovascular disease remains the leading cause of increased morbidity and mortality observed in chronic kidney disease (CKD) patients. Endothelial dysfunction (ED) is thought to be a key initial event in the development of atherosclerosis. The aim of this study was to evaluate the potential role of hemostatic factors in atherosclerosis, thrombosis and cardiovascular complications in patients suffering from chronic renal disease.

Methods: The study was conducted on 50 renal patients divided into two groups of equal size. Group 1 consisted of 25 patients with end-stage renal disease (ESRD) on regular hemodialysis. Group 2 consisted of 25 chronic renal disease patients on conservative treatment. Twenty age- and sex-matched healthy subjects were included in the study to serve as a control group. Thrombomodulin (TM), von Willebrand factor (vWF), tissue plasminogen activator (t-PA), plasminogen activator inhibitor (PAI-1) and hsCRP were assessed. High-resolution B-mode ultrasonography of both the common and internal carotid arteries to measure carotid intima media thickness (CIMT) was performed on all subjects.

Results: There were highly significant increases in hsCRP, TM, vWF, tPA and PAI-1 in both patient groups compared to the control group ($P<0.01$ for all except for TM between group 2 and 3 $P<0.05$) with significant increase in group 1 compared to group 2 ($P<0.01$). In addition, there was a highly significant increase in CIMT in both patient groups compared to the control group ($P<0.01$) with a significant increase in group 1 compared to group 2 ($P<0.05$). The study revealed significant positive correlation of hemostatic factors (TM, vWf, PAI-1 & t-PA) with creatinine, urea, hsCRP & CIMT.

Conclusion: CKD patients have increased risk of atherosclerosis as measured by CIMT, which is used as a surrogate marker of early atherosclerosis and has been shown to be a strong predictor of future myocardial infarction and stroke. They have high levels of TM, vWF, tPA, PAI-1 that correlate with kidney function, hsCRP and CIMT. Therefore, these abnormalities in hemostasis may account for the increased risk of atherothrombosis in these patients. The elevated hsCRP levels and their correlation to hemostatic factors and CIMT might provide an important clue to link a systemic marker of inflammation to atherosclerosis. Further research is required to better understand the procoagulant state in patients with CKD.

Keywords: Chronic kidney disease (CKD), hemodialysis (HD), atherosclerosis, carotid intima media thickness (CIMT), TM, vWf, t-PA, PAI-1

1. Introduction

Atherosclerotic cardiovascular disease (CVD) remains the leading cause of increased morbidity and mortality observed in chronic kidney disease (CKD) patients (1). Endothelial cells form a natural barrier between circulating blood and the surrounding tissue. Along with this barrier function, the cells generate several anti-thrombotic factors that prevent hemostasis in the circulation. When damaged, endothelial cells lose their anti-thrombotic capacity and

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this can cause an increase in the risk of CVD or other disease complications (2). Endothelial dysfunction (ED) is thought to be the initial event in a process of atherosclerosis, and it has been suggested that ED precedes the development of atheroma in renal failure (1, 2). Clinical studies on the relationship between platelet and endothelial cell activation and CVD outcome require specific biomarkers for both cells (3). Acute or chronic endothelial cell activation can be estimated by measuring the concentrations of vWF, which is a large multimeric protein required for capturing platelets in fast-flowing blood. While examining endothelial function in chronic renal failure (CRF), previous studies have indicated a significant reduction in endothelium dependent dilation and the increase in concentrations of several endothelium-derived proteins, including endothelin-1, thrombomodulin (TM) and vWF (3-5). TM is a cell surface-expressed transmembrane glycoprotein receptor that is originally identified on vascular endothelium. It is an important molecule in the human natural anticoagulation system. Soluble TM (sTM) is released from injured endothelial cells into the circulation, where it binds thrombin and inhibits it from forming fibrin and activating platelets. Recent evidence has revealed that TM has several effects on cellular proliferation, adhesion and inflammation that are important steps in the development of atherosclerosis (6). Plasminogen is an inactive proenzyme that can be converted to the active enzyme plasmin, which degrades fibrin into soluble fibrin degradation products by two physiological plasminogen activators (PA): the tissue type PA (t-PA) and the urokinase type PA (u-PA). Both generate plasmin locally. Plasminogen activator inhibitor -1(PAI-1) is the main inhibitor of these plasminogen activators. By binding to plasminogen activators, it causes their inactivation and thus suppresses fibrinolytic activity (7). Carotid intima media thickness (CIMT) is increasingly used as a surrogate marker of early atherosclerosis, and it has been shown to be a strong predictor of future myocardial infarction and stroke (8). It could be measured easily, safely, reliably, and inexpensively with B-mode ultrasound, and when CIMT is measured at different extracranial carotid sites, the predictive value of this measurement increases (9). CIMT was found to increase in patients with impaired renal function (10). The general objective of this research was to determine the potential role of hemostatic factors in atherosclerosis, thrombosis and cardiovascular complications in patients suffering from chronic kidney disease (CKD). The specific objectives were 1) to determine the difference in the levels of hemostatic factors between the studied groups, and 2) to determine the association between hemostatic factors and CIMT (surrogate marker of early atherosclerosis), kidney disease severity and markers of inflammation (hsCRP).

2. Material and Methods

2.1. Study population

The study was conducted on 50 patients admitted to the Nephrology Department and Dialysis unit of Theodor Bilharz Research Institute (TBRI) in Giza, Egypt. The study was carried out in 2014-2015. The patients were divided into two groups. Group 1 included 25 ESRD patients on regular hemodialysis (HD) treatment (3 sessions weekly, 4 hours each for a period of more than 3 months). Group 2 included 25 CRD patients on conservative treatment. Twenty age- and sex-matched healthy subjects selected from medical and paramedical staff were included in the study to serve as a control group (group 3). Exclusion criteria included acute infection caused by blood transfusion in the previous month, chronic viral infections (e.g., hepatitis B, hepatitis C, human immunodeficiency virus), active immunological disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, vasculitis), use of anti-inflammatory medication, antibiotics or antifungal treatments at the time of the study, previous transplants, or history of malignancy. The Ethical Committee of TBRI approved the study, and it was conducted in accordance with the Helsinki Declaration (1975). All participants gave written informed consent.

2.2. Blood collection

Blood samples were obtained under completely aseptic conditions from all patients and controls. EDTA blood for complete hemogram used automated hemogram (ACT Differential, Beckman, France). Sera for liver and kidney function tests, cholesterol, triglycerides, serum calcium and phosphorus were used (Hitachi 736, Hitachi, Japan).

2.3. Special investigations

The followings laboratory techniques and materials were employed in this research:

1) High-sensitivity CRP (hsCRP) was assayed by ELISA technique using hsCRP kit (Bio Vendor, France)
2) Plasma TM level was assayed by ELISA technique using Asserachrom TM kit (Diagnostica Stago, France)
3) Plasma vWF antigen level was assayed by ELISA technique using an Asserachrom vWF kit (Diagnostica Stago, France)
4) Plasma level of t-PA antigen was assayed by ELISA technique using ZYMUTEST t-PA antigen kit (Hyphen BioMed, France)

5) Plasma level of PAI-1 antigen was assayed by ELISA technique using ZYMUTEST PAI-1 antigen kit (Hyphen BioMed, France)
6) High-resolution B-mode ultrasonography of both the common and internal carotid arteries was performed by a member of the study team using an ultrasound machine (Toshiba Memo 30 scanner) equipped with a 7.5 mHz high-resolution transducer

Patients were examined in the supine position with the head tilted backwards. After the carotid arteries were located by transverse scans, the probe was rotated to 90° to achieve and record a longitudinal image of the common carotid arteries. At the posterior wall of the common carotid artery the maximum CIMT was measured, which was 2cm before the bifurcation, and this has been the distance between the first and second echogenic lines of the anterior and posterior arterial walls. The image was concentrated on the posterior wall of the common carotid artery, and gain settings were employed to improve the image quality. Vertical to the arterial wall, measurement was performed for accurate measurement of CIMT. Three CIMT measurements were selected and the average measurement was employed. In a blind manner for the clinical and laboratory data for cases and control subjects, a member of the study team obtained all of the CIMT measurement sonograms.

2.4. Statistical Analysis

Statistical analysis was performed using SPSS version 17. Data were expressed as the mean ± standard deviation (SD) for numerical variables. $P \leqslant 0.05$ was considered to be statistically significant, and $P < 0.01$ was considered to be highly statistically significant. To evaluate correlations among the variables, the Spearman Rank correlation coefficient was used, and a 0.95 confidence interval was quoted.

3. Results

The demographic data of HD, renal impairment patients and the control group revealed mean ages 49.64 ± 12.23, 54.76 ± 11.88, 54.27 ± 11.66 years, respectively. There were 16 males (64%) and 9 females (36%) in group 1, 15 males (60%) and 10 females (40%) in group 2, and 12 males (60%) and 8 females (40%) in the control group. Duration of HD was 60.80± 46.51 months in group 1. There was a significant increase in systolic blood pressure in the renal impairment group compared to the control (table1). The laboratory data showed significant decreases in cholesterol, Ca, albumin, Hb and platelets in both patient groups compared to the controls, with significant decreases in Ca in group 1 compared to those in group 2. Also, there were significant increases in Ph, creatinine and urea in both patient groups compared to the control group, with a significant increase in creatinine in group 1 compared to group 2 (table 2).

There were highly significant increases in hsCRP, TM, vWF, t-PA and PAI-1 in both patient groups compared to the control group, with a significant increase in group 1 compared to group 2 (table 3). There was a highly significant increase in CIMT in both patient groups compared to the control group, with a significant increase in group 1 compared to group 2 (table 4). The hemostatic factors (TM, vWf, PAI-1 and t-PA) showed significant positive correlations with creatinine, urea, hsCRP & CIMT in addition to significant negative correlations with Ca, Hb and platelets (table 5). Regarding CIMT, it showed positive correlations with DBP, DOD, creatinine, urea & hsCRP (table 6).

Table 1. Demographic data of patient groups and the control group

Variables		Group 1		Group 2		Group 3		P value		
		Mean	SD	Mean	SD	Mean	SD	1 & 3	2 & 3	1 & 2
Age (Years)		49.64	12.23	54.76	11.88	54.27	11.66	NS	NS	NS
Sex	Male	16 (64%)		15 (60%)		12 (60%)				
	Female	9 (36%)		10 (40%)		8 (40%)				
DOD (Month)		60.80	46.51							
SBP (mmHg)		114.08	39.66	127.00	14.14	119.00	8.06	NS	<0.05	NS
DBP (mmHg)		82.00	11.18	78.00	7.64	78.67	4.42	NS	NS	NS

DOD: Duration of Dialysis; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Table 2. Laboratory parameters of patient groups and the control group

Variables	Group 1		Group 2		Group 3		P value		
	Mean	SD	Mean	SD	Mean	SD	1 & 3	2 & 3	1 & 2
Creatinine (mg/dl)	9.12	2.94	3.88	1.51	1.17	0.14	<0.01	<0.01	<0.01
Urea (mg/dl)	153.64	38.99	130.64	48.37	30.93	4.70	<0.01	<0.1	NS
Cholesterol (mg/dl)	164.64	38.35	163.56	37.68	187.13	13.18	<0.01	<0.01	NS
TG (mg/dl)	176.48	121.39	144.56	54.21	150.80	15.25	NS	NS	NS
HDL (mg/dl)	50.48	25.20	54.36	21.46	53.13	16.34	NS	NS	NS
LDL (mg/dl)	100.08	21.82	89.60	32.17	103.84	26.66	NS	NS	NS
Ca (mg/dl)	7.80	0.88	8.60	0.53	9.49	0.72	<0.01	<0.01	<0.01
Ph (mg/dl)	5.54	1.52	4.86	0.86	3.39	0.75	<0.01	<0.01	NS
Alb (mg/dl)	3.36	0.62	3.18	0.45	4.02	0.38	<0.01	<0.01	NS
Hb (gm/dl)	10.36	1.79	9.74	1.75	11.87	1.45	<0.01	<0.01	NS
TLC	7.64	1.84	7.49	2.00	7.43	0.93	NS	NS	NS
Platelet	217.48	49.72	237.32	57.38	317.33	91.81	<.01	<.01	NS
hsCRP	7.33	2.90	4.97	1.01	2.12	0.71	<.01	<.01	<.01

TG: triglycerides; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; Ca: calcium; Ph: phosphorus; Alb: albumin; Hb: hemoglobin; TLC: total leucocytic count; hsCRP: high sensitivity C reactive protein.

Table 3. Specific laboratory parameters of the patient groups and the control group

Variables	Group 1		Group 2		Group 3		P value		
	Mean	SD	Mean	SD	Mean	SD	1 & 3	2 & 3	1 & 2
TM (pg/dl)	805.61	463.42	531.10	187.41	417.95	99.63	<0.01	<0.05	<0.01
vWF (%)	131.88	10.67	89.97	5.59	52.98	4.49	<0.01	<0.01	<0.01
t-PA (ng/ml)	1.55	0.19	0.59	0.05	0.24	0.02	<0.01	<0.01	<0.01
PAI -1 (ng/ml)	24.28	4.01	13.51	1.75	6.29	0.92	<0.01	<0.01	<0.01

Table 4. CIMT of the patients group and the control group

Variables	Group 1		Group 2		Group 3		P value		
	Mean	SD	Mean	SD	Mean	SD	1&3	2&3	1&2
CIMT (cm)	1.07	0.15	0.96	0.14	0.43	0.14	<.01	<.01	<.05

CIMT: carotid intima media thickness.

Table 5. Correlation between hemostatic factors and other parameters

Variable	Index	Creat	Urea	hsCRP	CIMT
TM	r	0.346	0.250	0.283	0.288
	P value	0.005	0.045	0.022	0.020
Vwf	r	0.823	0.708	0.698	0.777
	P value	0.000	0.000	0.000	0.000
t-PA	r	0.790	0.599	0.677	0.684
	P value	0.000	0.000	0.000	0.000
PAI-1	r	0.769	0.600	0.710	0.709
	P value	0.000	0.000	0.000	0.000

Creat: creatinine; hsCRP: high sensitivity C reactive protein; CIMT: carotid intima media thickness

Table 6. Correlation between CIMT and other parameters

	Index	DBP	DOD	Creat	Urea	hsCRP
CIMT	r	0.316	0.423	0.580	0.772	0.581
	P Value	0.010	0.035	0.000	0.000	0.000

DBP: Diastolic Blood Pressure; DOD: Duration of Dialysis; Creat: creatinine; hsCRP: high sensitivity C reactive protein

4. Discussion

The pathogenesis of cardiovascular damage in CRF patients is far more complex than in the general population. Several studies have demonstrated that even mild renal impairment carries an increased risk for cardiovascular death, and therefore CRF has been referred to as a vasculopathic state (11). TM and vWF are traditional markers of ED, which leads to atherosclerosis and subsequent arterial thrombosis. t-PA and PAI -1 are key elements regulating fibrinolysis, which when deficient predisposes to fibrin deposition on the vessel wall and eventually atherosclerosis (12). In the present study there was a highly significant increase in vWF in both diseased groups (HD group and non-HD CKD group) compared to the control group, with a highly significant increase in the HD group compared to the non-HD CKD group that showed a highly significant correlation with CIMT. In agreement with our results, previous studies have shown a positive association between levels of vWF and risk of coronary heart disease and stroke. In ischemic stroke, a particular association of vWF levels with etiologic subtypes, such as large artery atherosclerosis and cardioembolic stroke, was found. Despite the fact that prospective studies have identified vWF levels as a predictor of ischemic stroke, the mechanism by which increased vWF levels are related to stroke is still unclear. ED is the first phase in the development of atherosclerotic plaques. Because endothelial activation is related to atherosclerosis and an association of vWF with ischemic stroke has been found, atherosclerosis may be a determinant of vWF levels (13).

Regarding plasma level of t-PA and PAI-1, there was a highly significant increase of both markers in HD group and in the non-HD CKD group compared to the control group. In addition, a highly significant increase in both parameters in the HD group compared to the non-HD CKD group was found. Both t-PA and PAI-1 positively correlated with serum creatinine. The positive linear correlation between t-PA and PAI-1 was previously detected by Kopeć and his colleagues (14). Also, Gray et al. and Bono found a linear relationship between t-PA and PAI-1 plasma concentrations in patients with ischemic heart disease and diabetes respectively, and they concluded that high t-PA and higher PAI-1 antigen concentrations are associated with low t-PA activity (15, 16).

In our study, there was a highly significant correlation between both t-PA and PAI-1 and CIMT. The significantly increased t-PA and PAI-1 in our study is consistent with a procoagulant state associated with uremia. Similar findings have been reported by Segarra et al., who found significant statistical association between levels of both PAI-1 and t-PA and major vascular risk factors in HD patients. This suggests that the elevation of these molecules is caused by ED, which puts HD patients at risk of developing atherosclerosis (17).

Regarding TM, it was significantly increased in the HD and the non-HD CKD groups compared to the control group, and it was positively correlated with serum creatinine. In agreement with our study, Bao et al. found that the levels of sTMin all patients with CKD were significantly higher than those of healthy controls and were correlated with serum creatinine; they concluded that sTM may play a critical role in the development of CKD as a biomarker of endothelial cell damage, anticoagulation and anti-inflammation (18). Dubin et al. found that even small decrements in effective glomerular filtration rate (eGFR) are associated with significantly higher levels of sTM. These results suggest that dysregulation of hemostasis could play an important pathologic role in CKD (19). Also, Xin et al. found that TM level was significantly higher in CKD patients as compared to healthy controls with higher levels in HD patients as compared to non-HD patients, and they attributed these findings to inflammation and ED (20). In our study, TM level was positively correlated with CIMT. This is in agreement with the studies of Xin et al. and Olivot et al. (20, 21). In contrast to our study, Dosa et al. found that patients with high TM plasma level had less severe carotid artery stenosis than those with low TM plasma level (22). Decreased renal clearance in patients with renal disease may explain the increased levels of smaller molecular weight hemostatic markers such as TM, as it would be filtered by the glomerulus. But it seems unlikely that other higher molecular weight molecules such as vWF are elevated as a direct result of decreased renal clearance. It is possible that elevation of these markers relates to processes initiated by smaller molecules (23). Electrolyte- or acid-base abnormalities and inflammation associated

with low eGFR may alter activities of enzymes involved in coagulation (19). Atherosclerosis in renal disease is associated with markers of impaired fibrinolysis. Deficient fibrinolysis may predispose to fibrin deposition and contribute to occlusive thrombus formation on fissured plaque, provoking atherothrombosis (12).

We found a highly significant increase in CIMT in the HD group and the non-HD CKD group compared to the control group, with a significant increase in CIMT in the HD group compared to the non-HD CKD group. In our study the CIMT was positively correlated with TM, vWf, PAI-1, t-PA, DBP, DOD, creatinine, urea and hsCRP. So, CIMT was correlated with the markers of ED, the inflammatory marker (hsCRP) and the parameters of CKD severity. In agreement with our study, El-Banawy et al. and Park et al. found that the mean CIMT was significantly higher in HD patients than in the control group. These findings are frequently attributed to the process of accelerated atherosclerosis commonly observed in ESRD patients (24, 25). Also, Xin et al. found that the atherosclerotic plaques incidence and CIMT increased significantly in CKD patients compared to healthy volunteers, and they attributed this finding to the process of inflammation and ED (20).

5. Conclusions

Patients with CKD have an increased risk of atherosclerosis as measured by CIMT, which is used as a surrogate marker of early atherosclerosis and was shown to be a strong predictor of future myocardial infarction and stroke. CKD patients have high levels of TM, vWF, t-PA, PAI-1 that is correlated with hsCRP and CIMT. So, these abnormalities in hemostasis may account for the increased risk of atherothrombosis in these patients. The elevated hsCRP levels and their correlation to hemostatic factors and CIMT might provide an important clue in linking a systemic marker of inflammation to atherosclerosis. To understand the procoagulant state better in patients with CKD, further research is required to explore the role it plays in increasing cardiovascular morbidity and mortality in this patient population, along with identifying potential therapeutic interventions that could be translated into optimized cardiovascular and potentially renal consequences in these patients.

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Conflict of Interest:

There is no conflict of interest to be declared.

Authors' contributions:

All authors contributed to this project and article equally. All authors read and approved the final manuscript.

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