International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2013): 6.14 | Impact Factor (2013): 4.438

Influence of Soluble Endothelial Protein C Receptor (sEPCR) on Hypercoagulable State of Haemodialysis Patients

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Abstract: ***Thrombotic events are common in end-stage renal disease patients. Several thrombosis favoring haematologic alterations have been demonstrated in these patients. This study sought correlation between plasma levels of soluble endothelial protein C receptor (sEPCR) and thrombotic events in Haemodialysis (HD) patients and other possible thrombotic risk factors. 50 HD patients and 30 healthy controls were included. The patients were divided into two groups according to presence of thrombosis in the last 6 months: group 1(n=25) (without history of thrombosis) and group 2 (n=25) (with history of thrombosis). Plasma level of sEPCR was assessed by sandwich enzyme-linked immunosorbent assay (ELISA). Mean sEPCR level was significantly higher in HD patients than in controls. Group 2 patients had significantly higher mean sEPCR compared with group 1 patients. Upon performing ROC curve analysis a cutoff point >200 ng/ml for sEPCR was able to discriminate between the two patients' groups with 90.3% prognostic accuracy. In addition, upon classifying the patients into tertiles according to plasma sEPCR levels, the percentage of thromboses development was significantly increasing with increasing levels of sEPCR. Our findings demonstrate an association of sEPCR level in HD and thromboses development and suggest it as candidate marker for the hypercoagulable state in these patients.***

Keywords: sEPCR, thrombosis, hypercoagulation, haemodialysis

1. Introduction

Chronic kidney disease (CKD) is a growing health problem in developing countries in addition to being an established risk factor for thrombosis [1]. It is widely believed that not only CKD but also the haemodialysis (HD) process by itself activates platelets, coagulation and fibrinolysis. Indeed, end stage renal disease (ESRD) is labeled a hypercoagulable state [2].

The protein C (PC) pathway plays a major role in inhibiting blood coagulation. PC is activated on the surface of vascular endothelial cells by the thrombin–thrombomodulin (TM) complex. The endothelial PC receptor (EPCR), a receptor which binds circulating PC and presents it to the thrombin–TM complex, enhances PC activation by ≈8-fold in vitro [3] and by ≈20-fold in vivo [4]. Activated PC (APC), in conjunction with its cofactor protein S, degrades coagulation cofactors Va and VIIIa, thereby attenuating thrombin generation [5]. EPCR also circulates as a soluble form (sEPCR) which results from either cleavage of the EPCR molecule near the transmembrane domain by the action of metalloproteases, which are stimulated by thrombin and by some inflammatory mediators (e.g., TNFα, IL-1β)[6] thus, decreasing cell surface expression of EPCR and increasing plasma levels of its soluble form[7]. Another source for sEPCR has been shown to be derived from alternative splicing of A3 haplotype mRNA transcripts and direct secretion of a truncated sEPCR form that lacks the transmembrane and intra cellular domains. Such shedding or alternative splicing of membrane EPCR would be expected to have a negative impact on endothelial integrity, and on the delicate balance of coagulation and inflammation [8].

sEPCR binds with similar affinity to protein C and activated protein C, and this molecule inhibits activated protein C [9] and thereby may impact thrombotic diseases [10].Therefore, a higher level of sEPCR has been hypothesized to increase the risk of thrombosis [11]. Accordingly, this study was done to examine whether plasma levels of sEPCR, representative of a dysregulated protein C pathway, are correlated with thrombotic events in HD patients and other possible thrombotic risk factors.

2. Patients and Methods

Fifty adult patients undergoing HD were recruited from Haemodialysis Unit, Internal Medicine Department of Ain Shams University Hospitals with the following inclusion criteria: age ≥ 18 years and having been on intermittent HD for at least 12 months. Patients with a known clotting disorder, diabetes mellitus, amyloidosis, vasculitis, malignancy or smokers were excluded. An informed consent was obtained from all patients. Two groups of patients were identified: **Group 1:** included twenty five patients who had no history of thrombosis. **Group 2:** included twenty five patients who had history of thrombosis within last six months during disease course.

Two patients complained of myocardial infarction (MI) (diagnosed by laboratory investigations), two patients had Ischemic stroke (diagnosed by radiological investigations) and 21 patients developed arteriovenous fistula (AVF) thrombosis. The Failure of the vascular access in less than 1 month after construction was considered surgical failure and was not included as a thrombotic event. An AVF thrombosis was diagnosed by insufficient fistula blood flow for HD treatment, and then it was confirmed radiologically)

In addition, all patients were further classified into tertiles according to plasma sEPCR levels: lowest (< 25% sEPCR level), intermediate (25%–75% sEPCR level), and highest (> 75% sEPCR). The tertiles were compared for thromboses percentages. Thirty age-matched healthy subjects were taken as control group. ***All patients were subjected to the following:*** Full history taking laying stress on demographic features, dialysis duration, drug history and thrombotic events. Laboratory investigations including: Complete blood count (CBC) using Coulter LH 750 (Beckman), serum levels of creatinine, urea, uric acid, albumin, calcium, phosphorus and parathyroid hormone (PTH). Enzyme-linked immunosorbent assay (ELISA) for soluble endothelial protein C receptor (sEPCR) level was performed on serum samples collected from both controls and patients groups using (Asserachrom sEPCR kit, Diagnostica Stago, Asnieres, France). The study was conducted in accordance with the stipulations of the local ethical and scientific committees of Ain shams University and the procedures respected the ethical standards in Helsinki declaration of 1964.

3. Statistical Analyses

Statistical analyses were conducted with SPSS software (Statistical Package for the Social Sciences, Version 20.0, SPSS Inc. Chicago, Ill., USA). Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between two groups with qualitative data were done by using ***Chi-square test***. The comparison between two independent groups with quantitative data and parametric distribution was done by using ***Independent t-test***. The comparison between more than two groups with parametric distribution was done by using ***One Way Analysis of Variance (ANOVA).*** Median and IQR of the sEPCR were used to define the sEPCR tertiles. Pearson correlation coefficient was used to assess the relation between two studied parameters in the same group. The receiver operating characteristic curve (ROC) was used to assess the best cut off point with the sensitivity and specificity. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: $p > 0.05$: Non significant, $p < 0.05$: Significant and $p < 0.01$: Highly significant.

4. Results

Mean sEPCR levels were significantly higher in HD patients than they were in healthy controls (232.75 ± 110.60) ng/ml (range 60-450 ng/ml) vs (18.87 ± 10.31) ng/ml (range 0.7-32 ng/ml), p=0.000) (Figure 1). Distributions of age and sex were similar between patients and healthy controls (age 38.2 ± 7.27 vs. 43.27 ± 12.95 years; male sex 60% vs. 46%; p= 0.644 and 0.23 respectively). Groups 1 and 2 were similar with regard to possible risk factors for thromboses (demographic features, dialysis duration, body mass index and laboratory parameters such as whole blood count and serum levels of creatinine, urea, uric acid, albumin, calcium and phosphorus). However, patients in group 2 had significantly higher PTH level than group 1(Table 1).

sEPCR levels were significantly higher in patients in group 2 compared with patients in group 1 (318.40 ± 73.86 vs. 150.38 ± 69.54 ng/ml, p = 0.000) (Figure.1).The percentage of thromboses development was significantly increasing with increasing levels of sEPCR as evidenced by classifying patients into 3 tertiles according plasma sEPCR levels. The low sEPCR tertile included sEPCR levels ≤110 ng/ml (13 patients), the high sEPCR tertile was ≥ 310ng/ml (12 patients) and the median tertile included 25 patients. The percentage of thromboses development was significantly higher in the high sEPCR tertile [all the 12 patients had history of thrombosis (100.0%)] compared with the other two groups [7.69% in the low quartile (1\13 patients had history of thrombosis) and 48.0% in the intermediate quartile (12/25 patients had history of thrombosis); p =0.000] (Figure 2).

Using ROC curve analysis, to obtain the best cut- off value for sEPCR level to differentiate between patients with thrombotic and non thrombotic manifestations. The best diagnostic cut-off for sEPCR was 200 ng/ml (Figure 3).

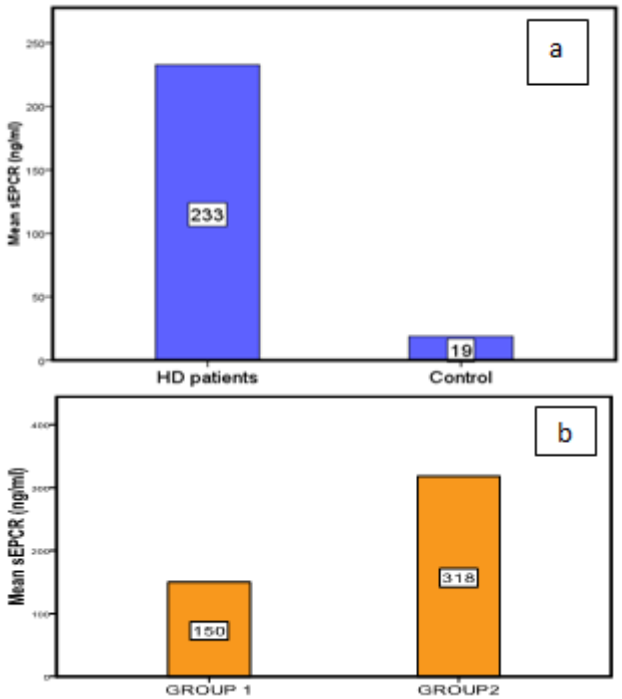


Figure 1: (a) Plasma sEPCR levels of HD patients and healthy controls (p = 0.000) **(b)** Plasma sEPCR levels in group 1 (without history of thrombosis) and group 2 (with history of thrombosis) (p = 0.000)

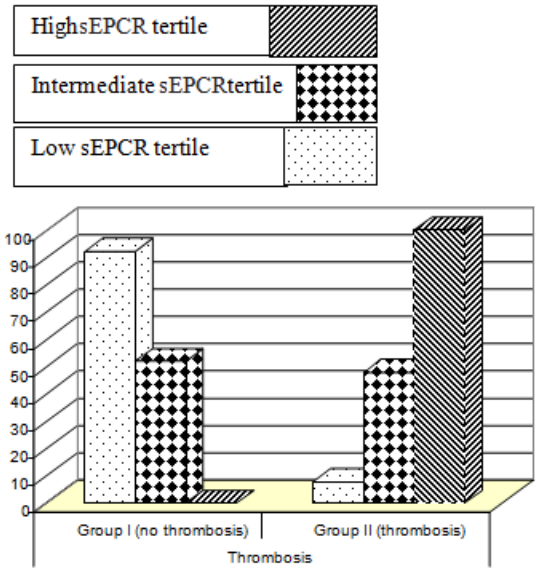
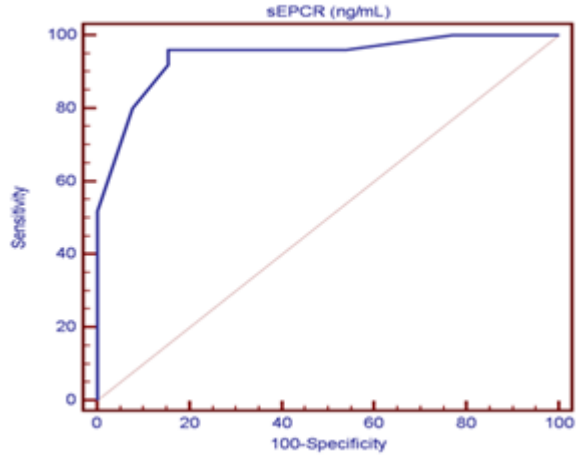


Figure 2: Comparison between three sEPCR tertiles and percentages of thrombosis occurrence. The percentage of thromboses development was significantly higher in the highest sEPCR quartile [all the 12 patients had history of thrombosis (100.0%)] compared with the other two groups [7.69% in the lowest quartile (1\13 patients had history of thrombosis) and 48.0% in the intermediate quartile (12/25 patients had history of thrombosis); p =0.000]



Cut off point	AUC	Sensitivity	Specificity	+PV	- PV	Accuracy
>200 ng/ml	0.943	96.00	84.62	85.7	95.7	90.31

AUC: Area under the curve, +PV: Positive predictive value, -PV: Negative predictive value

Figure 3.ROC curve analysis showing the prognostic performance of sEPCR to differentiate between HD patients as regards thrombotic manifestations. The best cut-off for sEPCR was 200 ng/ml.

Table 1: Laboratory data of the two patients' groups showing that Groups 1 and 2 were similar with regard to possible risk factors for thrombosis except for the PTH which was statistically significant higher in group 2 (HD patients with thrombosis history)

Laboratory data		Group1		Group 2		Test of significance	
		Mean	SD	Mean	SD	t	p-value
CBC parameters							
Hb (g/dL)		10.49	1.73	10.48	2.75	0.019	0.985
RBC (10^6/mL)		3.89	0.78	3.74	1.10	0.575	0.568
WBC's (10^3/mL)		6.21	2.18	6.76	2.52	0.832	0.410
Plat (10^3/mL)		207.27	75.65	199.4	63.11	0.403	0.689
Hct (%)		32.88	5.75	31.31	9.18	0.733	0.467
MCV (fL)		82.03	13.67	85.36	10.51	0.971	0.336
MCH (pg)		31.30	11.28	28.11	4.35	1.322	0.192
MCHC (g/dL)		32.65	1.36	32.34	2.54	0.533	0.597
Kidney parameters							
Urea (mg/dL)		166.96	41.30	175.96	40.23	0.788	0.435
Creatinine (mg/dL)		7.03	2.18	7.54	2.30	0.819	0.416
Uric acid (mg/dL)		4.79	1.06	4.47	1.02	1.084	0.284
Others							
Ca (mg/dL)		7.76	1.42	10.48	12.42	1.109	0.273
Ph (mg/dL)		4.98	1.28	5.14	1.49	0.430	0.669
PTH (pg/mL)		279.68	182.1	432.65	328.1	2.069	0.044*
Demographic data		**Group1**		**Group 2**		**Chi-square test**	
		Mean	**SD**	**Mean**	**SD**	**X^2**	**p-value**
Age (yrs)		38.96	12.86	37.76	11.65	0.346	0.731
BMI (kg/m^2)		21.35	3.62	22.5	2.99	0.320	0.751
Dialysis duration(yrs)		6.77	4.17	8.16	3.66	1.264	0.212
Sex	**Female N (%)**	17(68.0%)		10(40.0%)		2.899	0.088
	Male N (%)	8 (32%)		15(60%)			

BMI: Body Mass Index N: Number, SD: Standard deviation CBC: Complete blood count, Hb: Hemoglobin, RBCs: Red blood cells, WBCs: White blood cells, Plat: Platelets, Hct: Hematocrite, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, Ca: Calcium, Ph: Phosphorus, PTH: Parathyroid hormone. * Significant p< 0.05; ** highly significant p< 0.01

5. Discussion

Vascular complications represent 20-25% of all hospitalized patients on hemodialysis. The spectrum of thromboembolic events in ESRD patients is wide, the most frequent thrombotic event being arteriovenous (AV) access thrombosis [12].Changes in the haemostatic system may play a major role in the pathogenesis of cardiovascular complications and vascular thrombosis; during haemodialysis, platelets, coagulation and fibrinolytic systems could be importantly affected due to several known factors (e.g. alterations in vessel wall integrity and platelet function, reduced blood flow in the native arteriovenous fistula, velocity of procedure, type of membrane, artificial vascular access, circuit composition, and the type of anticoagulation)[13], [14].

Thus, it is essential to investigate haemostatic alterations in patients on haemodialysis so that adequate regimes for anticoagulant therapy could be implemented. The aim of the present study was to explore the level of sEPCR in haemodialysis patients, to correlate its level with other parameters that are possible risk factors for thrombotic events (i.e., demographic features, dialysis duration, body mass index, and various laboratory parameters such as whole blood count and serum levels of albumin, calcium, phosphorus, uric acid, creatinine, urea, parathyroid hormone (PTH) and correlate its level with the thrombotic events.

The study was carried on 50 HD patients, divided into 2 groups; group 1 with no history of thrombosis and group 2 with history of thrombosis within the previous 6 months. Patients with increased tendency toward thrombotic events (diabetic patients, malignancy patients, smokers, autoimmune disorders patients and patients with known clotting disorders) and patients on anti coagulant therapy were excluded.

Our results showed statistically higher significant serum level of sEPCR in both groups of HD patients compared to the healthy control group in addition to a statistically higher significant serum level of sEPCR among group 2 (with thrombosis) patients compared to group1(without thrombosis)patients. Indeed ***Bilgic et al., (2007)*** [15] demonstrated a relationship between plasma sEPCR levels and development of AVF thrombosis in HD patients.

Likewise, numerous studies investigated the correlation of sEPCR to thrombosis in various disorders. ***Ulu et al., (2007)*** [16] reported that sEPCR level was higher in a group of a stroke patients compared to a control group and those patients with high sEPCR level were found to have the A3 haplotype of the EPCR gene and thus concluded that sEPCR level is higher than normal in those with the A3 haplotype and that this might be associated with a tendency to develop thrombosis. Also, many studies reported the association of A3 haplotype with increased plasma level of sEPCR and proposed it as a candidate risk factor for thrombosis [17], [18], [19], [20]. Also, ***Gumus et al., (2006)*** [21] observed that the sEPCR level was statistically significantly higher in patients with central venous occlusion compared to control group. Similarly ***Ducros et al., (2012)*** [22] correlated the leukemia-associated hypercoagulability to high sEPCR plasma level and recommended its measurement in routine work up for these patients. Also, ***Elgammal et al., (2012***) [23] found a higher level of sEPCR in β thalassemia patients in relation to controls and suggested that sEPCR could be implicated in the haemostatic derangements and endothelial dysfunction in β thalassemia patients. In addition ***Stearns-Kurosawa et al., (2002)*** [24] previous study demonstrated a relationship between plasma sEPCR levels and thrombin generation in healthy subjects and in patients undergoing anticoagulant therapy and thus suggested that sEPCR levels may be a marker for a hypercoagulable state.

Conversely, in a prospective study published by ***Kallel et al., (2012***) [6] who investigated the relationship between sEPCR and the risk of cardiovascular events (CVE), although they found sEPCR level was elevated in association with classical cardiovascular risk factors but there was no significant relation to long term incidence of CVE. However, they attributed these discrepancies to differences in study design (retrospective vs prospective) and differences in patients' ages. ***Yamagishi et al., (2009)*** [11] documented that there was no overall association between sEPCR and venous thromboembolism risk (VTE) in the Longitudinal Investigation of Thromboembolism Etiology (LITE) pooled data from the Cardiovascular Health Study (CHS) and also suggested that sEPCR levels might reflect damage to venous endothelium at or after a VTE event and this might explain why sEPCR was not associated with VTE overall in their study compared to other studies. Also ***Atalay et al., (2013)*** [25] found no statistically significant difference in sEPCR level between essential thrombocytosis (ET) and polycythemia vera (PV) patients with and without thrombosis. Likewise ***Javanmard et al. (2013)*** [26] found the plasma sEPCR level wasn`t different between cerebral venous and sinus thrombosis (CVST) patients and the control group and documented no significant quantitative association between the risk of CVST and level of sEPCR. These discrepancies confirm and highlight the need for further larger study group on different patient conditions, ages and longer follow up time to be able to measure sEPCR before and after a thrombotic event.

Other possible risk factors for thrombosis were studied and compared between the 2 patients groups, there was no statistically significant difference between the 2 patients groups as regards hematological and biochemical profile. However, a statistically significant difference was found as regards PTH level.

Regarding PTH, there were several studies suggesting the involvement of PTH directly or through the calcium/phosphorus levels, in the development of atherosclerotic lesions in patients with end-stage renal disease (ESRD) and failure of AVF. In our study, we found, a statistically significant increase in serum PTH among group 2 (with thrombosis) compared to group 1(without thrombosis). This was previously reported by ***Grandaliano et al. (2003)*** [12] who found that patients with at least one episode of AVF dysfunction had mean

PTH plasma concentration significantly higher than the ones with no AVF dysfunction and they suggested that there was a potential association between PTH plasma levels and the incidence of AVF failure. In contrast, ***Bilgic et al. (2007)*** [15] found no relationship between PTH level and the development of AVF thrombosis.

In our study, a cut-off point of 200 ng/ml for sEPCR was able to differentiate between HD patients with and without thrombosis with prognostic accuracy of 90.3%. Likewise, ***Ducros et al. (2012)*** [22] proposed the same cut off and documented that the thrombotic risk in patients increased when level of sEPCR was higher than 200 ng/ml, suggesting that sEPCR released from endothelial cells of HD patients could serve as a 'trap' for PC preventing its binding to EPCR on the surface of endothelial cells and favoring a hypercoagulable state.

We classified the 50 HD patients into 3 tertiles according to sEPCR level. Low tertile included patients with sEPCR less than 25th quartile, median tertile included patients with sEPCR between 25th and 75th quartile and high tertile included patients with sEPCR above 75th quartile. We found that the rate of thrombosis development was significantly higher in the high sEPCR tertile group compared to the other two tertiles. So, the incidence of thrombosis increased with increasing sEPCR levels. These results are in agreement with those of ***Bilgic et al. (2007)*** [15] ***and Ducros et al. (2012)*** [22] who revealed that detection of plasma sEPCR levels provides a powerful insight into thrombotic risk assessment.

In conclusion, our findings demonstrate that high sEPCR level in HD patients is a marker for a hypercoagulable state. Quantification of plasma sEPCR level would allow clinicians to discriminate between patients at imminent risk of thromboembolism and those who are not and thereby adopt the required care. Also, the determination of plasma sEPCR provides us not only a powerful tool for the assessment of thrombotic risk factor in patients but also arms us for taking preventive measures in time. Testing in larger populations, normal individuals and serial measurements are warranted for confirmation of such an association which would be a first step toward identification and subsequent validation of a novel biomarker of vasculopathy and hypercoagulability.

6. Acknowledgment

AbdelgaffarAA, Ismail MM, Farweez BA and Elmasry RF contributed to the design of this study. Farweez BA and Elmasry RF contributed to data acquisition. Farweez BA and Elmasry RF participated to the statistical analysis of data under the supervision of AbdelgaffarAA, Ismail MM. Farweez BA wrote the manuscript. All authors read and approved final manuscript.

7. Disclosure

The authors state that they have no conflict of interest.

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