Original Article

Association of E-selectin with hematological, hormonal levels and plasma proteins in children with end stage renal disease

Rokhsareh Meamar[1,2], Mohammad Shafiei[3], Amin Abedini[3], Mohammad Reza Aghaye Ghazvini[4,5], Peyman Roomizadeh[3], Shahram Taheri[5], Alaleh Gheissari[5]

[1]Isfahan Neurosciences Research Center, [3]Isfahan Kidney Diseases Research Center, [4]Isfahan Center of Health Research, Isfahan University of Medical Sciences, [2]Department of Medical Sciences, Najafabad Branch, Islamic Azad University, Isfahan, [5]National Institute of Health Research, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Background: Hypercoagulable state is a common serious problem in patients with end-stage renal disease (ESRD). ESRD patients are in a condition of chronic inflammation. An increased level of E-selectin, "a key adhesion molecule that regulates leukocyte bindings to endothelium at damaged sites," accompanies the higher risk of inflammation in ESRD patients. We aimed to investigate the possible correlation among E-selectin as an adhesion molecule, coagulation factors, and inflammatory factors in children with ESRD.

Materials and Methods: Thirty-five child patients with ESRD who had been on regular dialysis treatment were registered in our study. Nighteen sex- and age-matched healthy volunteers were used as the control group. Laboratory tests were requested for the evaluation of hematological and biochemical parameters, and parathyroid hormone (PTH), and for coagulation state; fibrinogen, protein C, and protein S were measured. The enzyme-linked immunosorbent assay (ELISA) (Biomerica, CA, and IDS, UK). for serum E-selectin assay was provided by R and D Systems (Abingdon, UK).

Results: Hemoglubolin (Hb), blood urea nitrogen (BUN), creatinine, calcium, PTH, triglyceride (TG) concentrations in serum as well as E-selectin showed significant difference between the two study groups, as indeed was expected. Serum E-selectin was significantly higher (P value = 0.033) in dialysis patients than in healthy subjects. E-selectin was positively correlated only with phosphorus in ESRD children (r = 0.398, P = 0.018). No association was found for other parameters.

Conclusion: Although in our study circulating E-selectin concentration "as an inflammatory maker" is independently positively associated with limited blood markers, for better evaluation, well-designed cohort studies should be examined in ESRD children.

Key Words: E-selectin, hematological and hormonal levels, plasma proteins, renal disease

Address for correspondence:
Dr. Alaleh Gheissari, Department of Pediatric Nephrology, Isfahan Kidney Diseases Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: alaleh.gheissari@gmail.com

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INTRODUCTION

Hypercoagulable state is a common serious problem in patients with end-stage renal disease (ESRD). ESRD patients are in a state of chronic inflammation. Inflammation in conjunction with hypercoagulability increases mortality and CV morbidity in dialysis patients.[1,2] Various factors have been investigated

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as the possible causes of inflammation. Among these factors, pro-inflammatory cytokines, adhesion molecules, homocysteine, and parathyroid hormone-related protein (PTHrP) have been widely discussed.[3-6] Since adhesion of leukocytes to the impaired endothelium plays a crucial role in the inflammatory process, focusing on different adhesion molecules conveys new evidence. E-selectin, a member of the selectin family is a key adhesion molecule that regulates leukocyte bindings to endothelium at damaged sites.[7,8] An increased level of E-selectin accompanies the higher risk of inflammation in ESRD patients.[7] In spite of the bulk of studies considering the levels of adhesion molecules in ESRD adults, data on ESRD children is scarce. Therefore, we aimed to investigate the possible correlation among E-selectin as a key adhesion molecule, proteins C and S as markers of anticoagulation state, fibrinogen as a coagulation factor, homocysteine as an independent factor of thrombosis, and parathyroid hormone (PTH) as a known inflammatory factor in ESRD children.

MATERIALS AND METHODS

Thirty-five child patients with ESRD (13 male and 22 female) who had been on regular dialysis treatment (on hemodialysis [HD] and on peritoneal dialysis [PD]) for at least 6 months were registered in our study. Nineteen sex- and age-matched healthy volunteers were used as the control group. A fasting blood sampling was performed between 8.00 and 10.00 am.

The following laboratory tests were requested for the evaluation of hematological and biochemical parameters: complete blood count (CBC), hemoglobulin (Hb) (g/dl), blood urea nitrogen (BUN) (mg/dl), creatinine (mg/dl), triglyceride (TG) (mg/dl), cholesterol (mg/dl), low density lipoprotein (LDL) (mg/dl), and high density lipoprotein (HDL) (mg/dl). Serum biochemicals were measured with Hitach 902 (Boehringer Mannheim, Germany) autoanalyzer using commercial kits. Hematological parameters were determined by using the Sysmex K1000 (TOA Medical Electronics, Japan). PTH (normal range: 10-65 IU/l) were analyzed by ELISA (Biomerica, CA, and IDS, UK). Other laboratory data from peripheral blood including calcium (mg/dl) and phosphorus (mg/dl) were assessed by spectrophotometric methods Hitach 902 (Boehringer Mannheim, Germany) autoanalyzer). Fibrinogen (mg/dl), Protein C(%) and Protein S (%) were measured by coagulation based assays using Mahsa-yaran (Iran) and Hyphen Biomed (France) products. Serum homocystein(μmol/L) levels were enzymatically determined by using a commercial kit from Axis-shield diagnostics (UK). The ELISA kit for serum E-selectin (ng/ml) assay was provided by R and D Systems (Abingdon, UK).

Statistical analysis

Standard statistical methods (mean ± SD) were utilized to summarize parametric values, and *t*-test and D'Agostino's K^2 test were performed to compare the control group with the case group of children with ESRD. Statistical analysis was conducted by using the SPSS version 18 (IBM, USA). The Pearson correlation analysis was used to examine the correlations between plasma E-selectin and the values of the other parameters.

RESULTS

The mean values for age in the case and control groups were 13.37 ± 4.7 years and 11.14 ± 3.93 years, respectively, $P > 0.05$. Demographic data of the case group are demonstrated in Table 1. Table 2 shows different variables in patients with ESRD and in the control group. Hb, BUN, creatinine, calcium, PTH, and TG concentrations in serum as well as E-selectin behaved significantly differently in the two study groups, as indeed was expected. Serum E-selectin was significantly higher ($P = 0.033$) in dialysis patients than in healthy subjects. The correlation analysis for E-selectin and relevant parameters is included in Table 3. According to this table E-selectin was positively correlated only with phosphorus in ESRD patients. No association was found for the other parameters.

DISCUSSION

In the present study, we evaluated the levels of leukocyte adhesion molecules (E-selectin) and its correlation with some inflammatory and thrombosis factors in ESRD children. To the best of our knowledge, it is the first study that compares such markers in this age group.

In addition to the traditional risk factors of CV morbidity in a normal population, such as hypertension and dyslipidemia, ESRD patients have a higher incidence of thrombosis due to disease-specific risk

Table 1: Demographic data of case group

Demographic data	Minimum	Maximum	Mean	SD
Age	3.0	20.0	13.3714	4.70973
Height (cm)	80.00	167.00	136.3571	21.82469
Weight (kg)	10.00	58.00	36.0000	14.95287
BMI (kg/m^2)	12.05	28.67	18.4108	4.26550
SBP (mmHg)	60.00	160.00	118.3333	23.88573
DBP (mmHg)	40.00	120.00	78.6296	20.29713

BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure

Table 2: Biometric, biochemical, and hormonal levels in patients with ESRD and controls group

Variables	Patients	Controls	*P*	95% CI	
				Upper	Lower
SBP (mmHg)	128.86±18.93	98.94±19.76	0.000	18.65159	41.16795
DBP (mmHg)	91.45±10.66	55±9.42	0.000	30.77162	42.14267
E-selectin (ng/ml)	6.09±2.18	4.81±1.96	0.033	0.11071	2.46253
Hb (g/dl)	9.79±1.61	12.6±0.99484	0.000	−3.65034	−2.03346
Cholesterol (mg/dl)	179.23±49.25	160.82±26.17	0.118	−4.93618	41.75696
TG (mg/dl)	162.69±135.81	66.72±0.10	0.000	47.75717	144.15971
BUN (mg/dl)	57.94±16.29	12.26±2.13	0.000	−2.03346	51.35306
Creatinine (mg/dl)	6.23±2.20	0.63±0.18	0.000	4.83596	6.35893
Calcium (mg/dl)	8.50±1.31	9.33±0.05	0.001	−1.29098	−0.37569
Phosphorus (mg/dl)	5.89±1.50	6.16±0.55	0.528	−1.30701	0.75654
PTH (IU/l)	363.83±253.08	33.32±29.07	0.000	241.9918	419.0050

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, Hb: Hemoglubolin, TG: Triglyceride, PTH: Parathyroid hormone, CI: Confidence interval, ESRD: End-stage renal disease

Table 3: Correlation between plasma E-selectin and relevant parameters in 39 patients with ESRD

Variables	E-selectin	
	Pearson *r*	*P*
BMI (kg/m^2)	−0.311	0.069
SBP (mmHg)	−0.191	0.272
DBP (mmHg)	−0.165	0.345
Hb (mg/dl)	0.141	0.419
Cholesterol (mg/dl)	0.069	0.695
LDL (mg/dl)	−0.143	0.412
HDL (mg/dl)	0.153	0.379
TG (mg/dl)	0.010	0.953
BUN (mg/dl)	−0.010	0.954
Creatinine (mg/dl)	0.089	0.610
Calcium (mg/dl)	0.077	0.661
Phosphorus (mg/dl)	0.398	0.018
PTH (IU/l)	−0.315	0.065
Hemocysteine (μmol/L)	−0.061	0.730
Protein C (%)	0.109	0.532
Protein S (%)	−0.215	0.215
Albumin (g/dL)	0.040	0.820
Fibrinogen (mg/dL)	−0.049	0.781

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, Hb: Hemoglubolin, TG: Triglyceride, PTH: Parathyroid hormone, CI: Confidence interval, ESRD: End-stage renal disease, BMI: Body mass index

factors. Among these causes the following factors: hyperparathyroidism (HPT), hyperphosphatemia, anemia, and homocysteinemia have been given more attention.[9] In addition, it has been shown that endothelial dysfunction and inflammation are linked to renal function impairment[10] as well as acting as one of the first hallmarks in the pathogenesis of atherosclerosis.[11]

Adhesion molecules such as E-selectin, P-selectin, and L-selectin provoke leukocyte adhesion and advance a series of events to arterial injury. For a variety of proatherogenic conditions such as type 2 diabetes[12] and salt-sensitive hypertension,[13] increased levels of E-selectin have been described; this is compatible with our observation of a significant elevation of E-selectin in children with ESRD. Actually, high E-selectin in these conditions is currently explained as a marker of endothelium injury.[14] E-selectin, after stimulation by cytokines, is expressed provisionally on endothelial cells only upon damage,[15] therefore, it is reasonable that an elevated E-selectin level in the urine may serve as an early indicator for kidney damage.[16] Indeed, E-selectin was presented as a risk factor in ESRD[6] as the Leu554Phe polymorphism of the E-selectin gene is related with the severity of carotid atherosclerosis in ESRD patients leading to susceptibility to the damaging effects of inflammation on the arterial wall.[17] As regards this marker acting as a risk factor for ESRD, a relationship between E-selectin and different risk factors in ESRD seems logical. The positive correlation between E-selectin and BMI, blood pressure and TG in cases without a past medical history of cardiovascular disease (CVD), diabetes, or stroke has been presented,[18] but E-selectin had a positive association only with serum phosphorus in our reports.

Hyperphosphatemia is a predictable event of progressive chronic renal failure or after renal transplantation and in the majority of ESRD patients on dialysis.[19,20] Hyperphosphatemia is one of the main risk factors for the progression of secondary HPT, and this condition is correlated with the enhancement of CV morbidity and mortality in ESRD patients.[21] The endothelium was recognized as a target for PTH, and HPT is associated with subclinical inflammation and endothelial dysfunction.[22] In HPT patients, the vasoactivity of endothelium was altered, and such modification may increase the risk of CVDs.[22] Regarding the fact that 97% of patients in our study had HPT; we conclude that HPT can be act as one of the reason for increment of E-selectin.

Another commonly used marker for kidney injury is serum creatinine, and it has been suggested that there is an inverse association between inflammatory molecules and creatinine clearance.[23] Previous studies have also presented that a reduced glomerular filtration rate was accompanied with an increased CV mortality and morbidity.[24] In patients with predialysis renal failure, reduction in endothelium vasodilatation has been shown. The association between creatinine clearance and some biochemical markers of endothelial dysfunction such as sVCAM-1 has been presented,[10] but in our study we did not find any correlation between creatinine and E-selectin; our small sample size could explain this difference.

In summary, the circulating E-selectin concentration is independently positively associated only with serum phosphorus in Iranian children with ESRD, but for better evaluation, well-designed cohort studies should be performed for this population.

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