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Soluble P-Selectin Levels Are Associated with Cardiovascular Mortality and Sudden Cardiac Death in Male Dialysis Patients

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Key Words
Cardiovascular disease · Dialysis · End-stage renal disease · Inflammation · Sudden cardiac death · P-selectin

Abstract
Background/Aims: P-selectin is released by activated platelets and endothelium contributing to inflammation and thrombosis. We evaluated the association between soluble P-selectin and atherosclerotic cardiovascular disease (ASCVD) in dialysis patients. ***Methods:*** We measured soluble P-selectin in serum from 824 incident dialysis patients. Using Cox proportional hazards models, we modeled the association of P-selectin levels with ASCVD events, cardiovascular mortality and sudden cardiac death. ***Results:*** After adjustment for demographics, comorbidity and traditional cardiovascular risk factors, higher P-selectin levels were associated with increased risk of ASCVD and cardiovascular mortality among males (p = 0.02 and p = 0.01, respectively), but not females (p = 0.52 and p = 0.31, respectively; p interaction = 0.003), over a median of 38.2 months. Higher P-selectin was associated with a greater risk of sudden cardiac death among males (p = 0.05). The associations between increasing P-selectin and cardiovascular mortality as well as sudden cardiac death in males persisted after adjustment for C-reactive protein, interleukin-6, serum albumin and platelet count (p = 0.01 and p = 0.03, respectively). The risk for sudden cardiac death was more than 3 times greater for males in the highest tertile of soluble P-selectin compared with the lowest tertile after adjustment (HR: 3.19; 95% CI: 1.18 – 8.62; p = 0.02). ***Conclusion:*** P-selectin is associated with ASCVD, cardiovascular mortality and sudden cardiac death among male dialysis patients.

Introduction

The leading cause of death among patients with end-stage renal disease (ESRD) is cardiovascular disease (CVD), with rates that are 10 times greater than in the age-matched general population [1]. Sudden cardiac death, in particular, accounts for about 25% of deaths in dialysis patients [2]. A better understanding of the risk factors involved in the pathogenesis of CVD in dialysis patients is needed to improve poor outcomes.

P-selectin is a cellular adhesion molecule stored in the Weibel-Palade bodies of endothelial cells and in the alpha granules of platelets and expressed upon activation [3, 4]. Endothelial P-selectin binds to P-selectin glycoprotein li-

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gand 1 on leukocytes, promoting leukocyte rolling, a primary step in inflammation [5], whereas platelet P-selectin expression recruits prothrombotic microparticles into developing thrombi [6].

Soluble P-selectin levels are higher in patients with a lower glomerular filtration rate on dialysis [7, 8], suggesting they may contribute to the observed increase in CVD in patients with chronic kidney disease. In this study, we investigate whether levels of soluble P-selectin measured at dialysis initiation are associated with subsequent atherosclerotic cardiovascular disease (ASCVD) events, cardiovascular mortality and sudden cardiac death in prospective follow-up of patients with ESRD.

Subjects and Methods

The CHOICE (Choices for Healthy Outcomes in Caring for ESRD) study is a prospective cohort study which enrolled 1,041 adult dialysis patients between 1995 and 1998 from 81 US dialysis clinics associated with Dialysis Clinic, Inc. within a median of 45 days after initiation of dialysis (98% within 4.0 months), described previously [9]. Serum was available for the measurement of soluble P-selectin in 824 participants. The study was approved by the Institutional Review Board at Johns Hopkins University School of Medicine, and participants provided written informed consent.

Blood samples were collected prior to dialysis treatments according to CHOICE protocols, processed and immediately stored in –80°C freezers. Soluble P-selectin was measured on serum specimens which had not been previously thawed using enzyme-linked immunosorbent assay (R&D Systems Inc., Minneapolis, Minn., USA) with a manufacturer-reported coefficient of variation <10%. Routine laboratory measures (albumin, platelet count) were averaged from all values measured by the central laboratory in the first 3 months of dialysis. Serum cholesterol and inflammatory markers interleukin-6 and C-reactive protein were measured as previously described [10].

Comorbid conditions such as hypertension (blood pressure >140/90), diabetes mellitus, congestive heart failure and CVD (defined as any history of myocardial infarction, cardiac revascularization procedure, stroke, carotid endarterectomy, peripheral vascular disease or revascularization procedure, angina, or stress test positive for ischemia) were abstracted from charts. The Index of Co-Existent Disease (ICED) was calculated as a composite comorbidity score.

The first ASCVD event was defined as a composite of coronary heart disease (acute myocardial infarction, coronary artery bypass, coronary angioplasty or sudden cardiac death), cerebrovascular disease (ischemic stroke or carotid endarterectomy) or peripheral vascular disease (amputation, abdominal aortic aneurysm or lower extremity revascularization). ASCVD events were ascertained through December 31, 2004, using patient interviews, chart review and review of Medicare billing data. ASCVD hospitalizations and procedures were confirmed by adjudication as previously described [11, 12]. Fatal ASCVD was assessed by linking to the National Death Index for information on date and cause of death, with chart review to confirm cause of death when available. Sudden cardiac death was defined as an out-of-hospital death with the following codes: ICD-9 390–398, 402 or 404–429; and ICD-10, I00-I09, I11, I13 and I20–I51, as described previously [2]. Deaths were excluded from our sudden cardiac death definition if hyperkalemia, sepsis or malignancy was listed as a contributing cause of death, or if the death occurred in hospice.

Soluble P-selectin was analyzed as a log-transformed continuous variable and categorically by tertiles. Baseline characteristics were compared across tertiles using ANOVA (continuous variables) or Pearson's χ^2 test (categorical variables). We modeled the association between soluble P-selectin and time to ASCVD event, cardiovascular mortality and sudden cardiac death using Cox proportional hazards models with clustering by clinic. Survival time was defined as the time from enrollment in the study to the first ASCVD event, total cardiovascular death or sudden cardiac death with censoring at the time of non-cardiovascular death (n = 255), transplantation (n = 208) or end of follow-up (n = 106). The main model (model 1) was adjusted for demographic factors, dialysis modality (hemodialysis vs. peritoneal dialysis), comorbidity (including ICED, diabetes, prevalent CVD at dialysis initiation and congestive heart failure) and traditional cardiovascular risk factors, such as smoking and total cholesterol. Subsequent models adjust for other inflammatory markers (C-reactive protein, interleukin-6 and serum albumin; model 2) and platelet count (model 3). Interactions between soluble P-selectin tertiles and sex/race were tested in our final models. Analyses were performed using STATA Special Edition 10.0 (2008; College Station, Tex., USA) and a two-sided α of 0.05.

Results

Baseline characteristics of the study population stratified by tertiles of soluble P-selectin are shown in table 1. Mean age of the study population was 57.1 years (SD: 14.8) with similar distribution for males (mean age: 56.9; SD: 14.6) and females (mean age: 57.2; SD: 15.0). The overall study population was 30.8% black and 64.0% white, with 80.7% of the participants on hemodialysis versus 19.3% on peritoneal dialysis. CVD was common, with 42.5% of participants reporting a baseline history of CVD (35.1% among females, 49.1% among males). Increasing tertiles of soluble P-selectin were associated with younger age, white race and increased platelet count, white blood cell count, total cholesterol and C-reactive protein.

Within our study population, soluble P-selectin ranged between 20.0 and 364.7 ng/ml (median: 98.0). Soluble P-selectin was correlated with C-reactive protein (r = 0.09; p = 0.01), platelet count (r = 0.27; p < 0.01), white blood cell count (r = 0.25; p < 0.01) and age (r = –0.09; p = 0.01), but not with interleukin-6 (p = 0.6). Correlates of soluble P-selectin did not differ by sex (table 2). The distribution

Table 1. Baseline characteristics of the study population by tertile of soluble P-selectin

Characteristic	Tertile of P-selectin			p[a]
	lowest: 20.0–84.9 ng/ml	middle: 84.9–115.8 ng/ml	highest: 115.9–364.7 ng/ml	
n	275	275	274	–
Demographic				
Age (mean ± SD)	59.0 ± 15.3	55.9 ± 14.7	56.3 ± 14.2	0.03
Female, %	48.0	45.5	47.1	0.8
Black, %	38.2	28.0	26.3	0.01
Clinical				
Baseline HD, %	84.0	79.3	78.8	0.2
Body mass index (mean ± SD)	27.0 ± 6.6	27.1 ± 6.9	27.4 ± 7.1	0.8
Systolic blood pressure (mean ± SD)	149.5 ± 18.5	150.3 ± 19.2	151.2 ± 17.5	0.6
Smoking, %				
Never	46.7	35.7	38.9	
Former	39.1	49.6	43.4	0.06
Current	14.2	14.7	17.7	
Comorbidity, %				
Mild (ICED = 0/1)	32.9	32.0	36.1	
Moderate (ICED = 2)	39.1	40.4	32.9	0.4
Severe (ICED = 3)	28.1	27.6	31.0	
Prevalent CVD, %	37.6	42.6	47.5	0.07
Diabetic, %	52.9	55.3	59.5	0.3
Congestive heart failure, %	46.7	45.5	47.8	0.9
Laboratory				
Platelet count[b], $\times 10^3/\mu l$ (mean ± SD)	229 ± 73	249 ± 72	273 ± 81	<0.001
White blood cell count[b], $\times 10^3/\mu l$ (mean ± SD)	7.1 ± 2.4	7.6 ± 2.1	8.4 ± 2.4	0.02
Serum albumin, g/dl[b] (mean ± SD)	3.64 ± 0.36	3.63 ± 0.35	3.61 ± 0.39	0.6
Cholesterol, mg/dl (mean ± SD)	178.4 ± 46.2	191.1 ± 47.3	196.6 ± 54.7	<0.001
Median CRP, mg/dl (IQR)	0.31 (0.14, 0.57)	0.39 (0.18, 0.86)	0.39 (0.17, 1.10)	0.04
Median IL-6, pg/ml (IQR)	3.5 (2.4, 6.7)	4.1 (2.6, 7.1)	4.2 (2.6, 7.0)	0.4

Conversion factors for units: serum albumin in g/dl to g/l ×10; cholesterol in mg/dl to mmol/l ×0.02586. CRP = C-reactive protein; IL-6 = interleukin 6.

[a] p value by either ANOVA (continuous variables) or Pearson's χ^2 test (categorical variables).

[b] Mean value of the previous 3 months' measurements.

Table 2. Correlates of soluble P-selectin stratified by sex

Covariate	Males		Females	
	r	p value	r	p value
Age	–0.07	0.12	–0.10	0.05
Platelet count	0.31	<0.001	0.22	<0.001
White blood cell count	0.28	<0.001	0.22	<0.001
Serum albumin	–0.04	0.46	0.02	0.69
C-reactive protein	0.08	0.08	0.09	0.08
Interleukin-6	0.06	0.24	–0.03	0.52
Serum total cholesterol	0.17	<0.001	0.16	0.001
Body mass index	–0.01	0.91	0.05	0.40

of soluble P-selectin did not differ by sex (p = 0.5), dialysis modality (p = 0.4) or diabetes (p = 0.2). Soluble P-selectin levels were lower among blacks compared with whites (p = 0.01) and higher among those with previous CVD (p = 0.01).

Follow-up time to cardiovascular mortality or censoring in the cohort ranged from 3.4 to 111.3 months (median: 38.2). Four hundred forty-one participants (200 females and 241 males) had an ASCVD event and 255 participants (116 females and 139 males) died of cardiovascular causes during follow-up. There were a total of 119 sudden cardiac deaths (52 among females and 67 among males).

As the relative hazard for cardiovascular mortality with increasing levels of soluble P-selectin differed quali-

Table 3. Relative hazards for composite ASCVD and CVD death associated with P-selectin levels, by tertile of P-selectin and by $\log_e$P-selectin

			RH (95% CI), by tertile of P-selectin			RH (95% CI), per 0.1 log unit change in P-selectin
			lowest	middle	highest	
Males	Composite ASCVD	Crude	Ref.	1.34 (0.95–1.90)	1.30 (0.92–1.85)	1.03 (1.00–1.07)
		Model 1	Ref.	1.60 (1.09–2.36)*	1.61 (1.07–2.41)*	1.05 (1.01–1.09)*
		Model 2	Ref.	1.46 (0.98–2.19)	1.44 (0.94–2.21)	1.04 (1.00–1.08)
		Model 3	Ref.	1.25 (0.81–1.94)	1.39 (0.88–2.20)	1.03 (0.99–1.08)
	CVD Death	Crude	Ref.	1.41 (0.90–2.20)	1.30 (0.82–2.05)	1.04 (0.99–1.09)
		Model 1	Ref.	1.66 (0.98–2.80)	2.05 (1.18–3.59)*	1.09 (1.03–1.15)*
		Model 2	Ref.	1.62 (0.94–2.78)	1.78 (1.00–3.18)	1.07 (1.01–1.14)*
		Model 3	Ref.	1.54 (0.85–2.80)	1.92 (1.02–3.64)*	1.10 (1.02–1.17)*
Females	Composite ASCVD	Crude	Ref.	0.95 (0.65–1.38)	1.05 (0.72–1.52)	1.01 (0.97–1.06)
		Model 1	Ref.	0.70 (0.46–1.06)	0.79 (0.52–1.22)	0.98 (0.94–1.03)
		Model 2	Ref.	0.65 (0.42–1.00)	0.71 (0.46–1.10)	0.98 (0.93–1.02)
		Model 3	Ref.	0.63 (0.40–0.99)*	0.67 (0.42–1.06)	0.96 (0.91–1.01)
	CVD Death	Crude	Ref.	1.03 (0.65–1.65)	0.76 (0.46–1.27)	0.97 (0.91–1.03)
		Model 1	Ref.	0.97 (0.57–1.65)	0.70 (0.39–1.27)	0.97 (0.91–1.03)
		Model 2	Ref.	0.93 (0.55–1.59)	0.75 (0.41–1.39)	0.97 (0.92–1.03)
		Model 3	Ref.	0.92 (0.52–1.61)	0.66 (0.34–1.26)	0.97 (0.91–1.03)

Relative hazard (RH) in reference group is 1.0. Model 1: adjusted for age, sex, race, modality, smoking, comorbidity, diabetes, prevalent cardiovascular disease, history of congestive heart failure and cholesterol; model 2: adjusted for model 1, albumin, log(C-reactive protein), and log(interleukin-6); model 3: adjusted for model 2 and log(platelet count). All models were clustered by clinic. * $p < 0.05$.

tatively by sex (p interaction <0.01 in model 1; p interaction = 0.01 in model 3), all models were stratified by sex. To confirm that this interaction was not driven by premenopausal women in the cohort, a sensitivity analysis was performed excluding women less than 50 years of age. Results were similar; therefore, results using all women are presented here. There was not a statistically significant interaction between race and soluble P-selectin levels for composite ASCVD events or cardiovascular mortality (p = 0.22 and p = 0.13, respectively).

Table 3 presents the relative hazard of ASCVD events and cardiovascular mortality in sequentially adjusted models by sex. The relative hazard for the composite ASCVD endpoint among males in the main model (model 1) was 1.05 (95% CI: 1.01–1.09; p = 0.02) for each 0.1-log unit higher soluble P-selectin. This association attenuated after adjustment for other inflammatory markers and platelet count (HR: 1.03; 95% CI: 0.99–1.08; p = 0.2). The association with cardiovascular mortality among males was stronger with an estimated hazard ratio of 1.09 (95% CI: 1.03–1.15; p = 0.01) for each 0.1-log unit higher soluble P-selectin in the demographic and traditional cardiovascular risk factor adjusted model (model 1). This association was robust despite further adjustment for inflammatory markers (HR: 1.07; 95% CI: 1.01–1.14; p = 0.02), or additionally for platelet count (HR: 1.10; 95% CI: 1.02–1.17; p = 0.01). Among females, soluble P-selectin was not associated with either ASCVD events or cardiovascular mortality in any models.

Given the high burden of sudden cardiac death in dialysis patients and the observed association between soluble P-selectin and cardiovascular mortality among males, we evaluated the association between soluble P-selectin and sudden cardiac death in secondary analyses (table 4). In the demographic and traditional cardiovascular risk factor adjusted model, there was a 9% increased risk in sudden cardiac death for each 0.1-log unit higher soluble P-selectin (p = 0.05). This association was robust to further adjustment for other inflammatory markers and platelet count (HR: 1.12 for each 0.1-log unit higher soluble P-selectin; 95% CI: 1.01–1.25; p = 0.03). The highest tertile of soluble P-selectin had a greater than 3-fold increased risk of sudden cardiac death compared with the lowest tertile in the fully adjusted model (HR: 3.19; 95% CI: 1.18–8.62; p = 0.02).

Table 4. Relative hazards for sudden cardiac death associated with P-selectin levels, by tertile of P-selectin and by $\log_e$P-selectin

		RH (95% CI), by tertile of P-selectin			RH (95% CI), per 0.1 log unit change in P-selectin
		lowest	middle	highest	
Males	Crude	Ref.	1.27 (0.64–2.50)	1.66 (0.89–3.12)	1.05 (0.99–1.12)
	Model 1	Ref.	1.65 (0.73–3.72)	2.67 (1.19–6.01)	1.09 (1.00–1.18)*
	Model 2	Ref.	1.61 (0.70–3.69)	2.18 (0.94–5.07)	1.07 (0.98–1.17)
	Model 3	Ref.	1.85 (0.71–4.86)	3.19 (1.18–8.62)*	1.12 (1.01–1.25)*
Females	Crude	Ref.	1.07 (0.52–2.19)	0.79 (0.37–1.72)	0.97 (0.90–1.05)
	Model 1	Ref.	1.31 (0.58–2.97)	0.60 (0.21–1.69)	0.97 (0.88–1.06)
	Model 2	Ref.	1.15 (0.50–2.68)	0.52 (0.17–1.58)	0.96 (0.87–1.05)
	Model 3	Ref.	1.16 (0.47–2.84)	0.39 (0.12–1.26)	0.94 (0.85–1.04)

The relative hazard (RH) for reference group is 1.0. Model 1: adjusted for age, sex, race, modality, smoking, comorbidity, diabetes, prevalent cardiovascular disease, history of congestive heart failure and cholesterol; model 2: adjusted for model 1, albumin, log(C-reactive protein), and log(interleukin-6); model 3: adjusted for model 2 and log(platelet count). All models were clustered by clinic. p interaction by sex = 0.04 in model 1. * $p < 0.05$.

Discussion

In this study, we evaluated the association between soluble P-selectin levels at dialysis initiation and ASCVD. We found that baseline soluble P-selectin levels were associated with composite ASCVD, cardiovascular mortality and sudden cardiac death among males. The association with cardiovascular mortality and sudden cardiac death persisted despite adjustment for other inflammatory markers and platelet count.

P-selectin is involved in the early stages of atherogenesis by recruiting leukocytes into developing atherosclerotic plaques. In mouse models of atherosclerosis, P-selectin gene knockout slowed development of atherosclerotic lesions [13, 14], and overexpression led to increased plaque burden [15]. In humans, higher soluble P-selectin levels have been associated with greater atherosclerotic plaque burden [16, 17] and myocardial infarction [18]. In this study, we detected a marginal association between soluble P-selectin levels and aggregate ASCVD events among males after adjustment for demographics and cardiovascular risk factors, but the association did not persist after the adjustment for other inflammatory markers.

We detected a stronger, more robust association between soluble P-selectin and cardiovascular mortality and, particularly, sudden cardiac death among males. Autopsy studies in humans have demonstrated that intracoronary thrombosis and microemboli play a major role in the pathogenesis of sudden cardiac death [19]. Previous work in dogs has shown that thrombotic occlusion of coronary arteries has a greater propensity to induce malignant ventricular arrhythmias than mechanical occlusion of coronary arteries by balloon inflation [20]. This suggests that the process of thrombosis and platelet aggregation results in electrical instability in the heart independent of the amount of ischemic myocardium.

Previous human studies also support the hypothesis that greater expression of P-selectin is associated with unstable arrhythmias. Blood from humans with a prior history of ventricular fibrillation complicating myocardial infarction demonstrate greater expression of platelet P-selectin in response to challenge with lipopolysaccharide than their counterparts with myocardial infarction and without ventricular fibrillation [21].

Recently, genetic polymorphisms in the P-selectin gene (SELP) have been found to differ between patients with a history of ventricular fibrillation after myocardial infarction and those with uncomplicated myocardial infarction, again suggesting a pathogenic role of P-selectin in electrical destabilization of the myocardium after an ischemic injury [22].

Our findings of increased risk of cardiovascular mortality and, particularly, sudden cardiac death in patients with higher levels of soluble P-selectin are consistent with these prior reports and could indicate those at higher risk for sudden death. We also extend these findings by demonstrating that soluble P-selectin levels measured in a group at high risk for sudden cardiac death are associated with fatal disease over long-term follow-up.

Notably, in this study there was no association between soluble P-selectin and CVD in females. The distribution and correlates of soluble P-selectin by sex were similar and the number of cardiovascular events in males and females was also similar. Therefore, it is unlikely that differences in clinical characteristics by sex account for the observed heterogeneity. Although the exact mechanisms underlying this sex difference are not clear, a large volume of in vitro and in vivo work suggests that there are differences in endothelial function by sex. In particular, estrogen has been shown to increase factors which protect against endothelial activation, such as nitric oxide and endothelial-derived hyperpolarizing factor [23]. It is possible that increases in endothelial protective factors in females mitigate the effects of activated platelets making this pathway less important in the pathogenesis of fatal CVD. In our sensitivity analysis, we did not see differences when restricting our analysis to only older women; however, our sample size was limited making it difficult to explore this relationship and how it may be affected by age and other factors in women. The differences in risk associated with soluble P-selectin levels by gender should be confirmed in future studies.

Our study has several limitations. Membrane-bound P-selectin expression can be modified quickly in vivo and therefore a single measure of soluble P-selectin may not be a reliable indicator of overall exposure. Additionally, while some of the hypothesized effects of P-selectin in promoting early atherosclerotic plaque development may occur over time, other effects may be more acute in nature and could not be addressed with our study design.

Our study does, however, have many strengths. The CHOICE cohort is comprised only of incident dialysis patients. We have a prospective design with detailed ascertainment of baseline comorbidities and complete ascertainment of events for all participants over a clinically significant interval. We collected extensive covariate information on participants, including other inflammatory markers, allowing us to isolate the association of soluble P-selectin independent of these markers.

It has been previously shown that out-of-hospital sudden cardiac death makes up a significant proportion of the observed deaths in the CHOICE cohort, with a cumulative incidence of 20.4% after 8 years of follow-up [2]. The inflammatory markers interleukin-6 and C-reactive protein were both strongly associated with risk of sudden cardiac death in this cohort [2]. In this study, we demonstrate that soluble P-selectin is strongly associated with cardiovascular mortality and, in particular, sudden cardiac death independent of these established inflammatory markers. In aggregate, these results suggest the potential role of multiple inflammatory markers representing different components of the inflammatory cascade and thrombotic response, including cellular adhesion molecules, cytokines and generalized inflammatory markers as risk factors for sudden cardiac death and cardiovascular mortality.

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