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ORIGINAL ARTICLE

Association of sP-selectin levels and demographic variables with Coronary Artery Disease

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ABSTRACT

Background: Coronary Artery Diseases (CAD) are among the major causes of global morbidity, mortality and disability. P-selectin, being an adhesion molecule, is found in platelet granules and endothelial cells and plays a vital role in inter-platelet aggregation as well as migration of leukocytes into the vascular wall

Objective: The objective of present study was to determine the level of sP Selectin in patients with CAD and compare it with healthy controls in Pakistani population. Moreover, association of CAD with p-selectin levels and other demographic variables were to BE assessed. Correlation of p-selectin levels and gender was also to be assessed.

Materials and Methods: It is a cross sectional, analytical study including 60 CAD patients and 60 controls (with ages between 40-60 years, both genders). sP Selectin levels were determined by ELISA.

Results: Mean P Selectin serum level in patients was 414.27±216.48 ng/ml with control group mean P Selectin level of 510.88±257.26 ng/ml. Mean P Selectin serum level in males was 438.215 ± 201.54 ng/ml with control group mean P Selectin level of 499.119 ± 290.02 ng/ml.

Conclusions: sP Selection levels are higher in control group with a significant difference which can be due to use of antiplatelet drugs. CAD was positively associated with BMI, positive family history, smoking history and history of hypertension. Females had significantly higher p-selectin levels than males. More studies are needed with bigger sample size in our population

Key Words: Coronary Artery Disease (CAD)**,** sP Selectin

INTRODUCTION

Coronary artery disease (CAD) is distinguished by the presence of atherosclerosis within the epicardial coronary arteries. Progressive narrowing of the coronary artery lumen by atherosclerotic plaques impairs ante grade flow to the myocardium.

On average, in the US, one person succumbs to cardiovascular disease (CVD) every 36 seconds. According to 2018 data, daily CVD fatalities reach around 2,380. Out of total deaths due to CVD, 42% were the result of coronary heart disease[(1)]. The burden of CVD is borne predominantly by middle-income countries, with approximated incidence rates 30 percent greater than high-income nations. This is seen in the roughly fourfold increase in disability-adjusted life years owing to CVD afflicting middle-income nations compared to affluent, high-income countries[(2)]. An expected increase from 9 million just in the year 1990 up to 19 million, only after 20 years, in 2010, the number of deaths from CAD was expected to rise in emergent nations (India, Sub-Saharan Africa, China, the Far East and Latin America)[(3)].

Pakistan is included in these developing regions that is just as burdened by this CVD rise as other nations of the world, yet little documentation exists on this issue. Pakistani people belonging to the South Asian population have the highest known rate of CAD[(4)]. CVDs are a severe problem for both men and women, affecting 17.5 percent of the population analyzed. Females are more likely than males to get diseases at a young age (5). CAD therefore, has become a major health problem of this country[(6)].

sP Selectin: One of the earliest inflammatory steps leading to atherogenesis is the slowing, tethering, and subsequent attachment of circulating leukocytes to the vascular endothelium. In atherosclerosis, an alteration in thrombocytes and endothelial cells occurs[(7)]. Endothelial damage or activation causes the release of specific substances and alterations to the endothelium membrane, which comes into direct contact with platelets and leukocytes. Many adhesion molecules, such as intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), and the selectin family of molecules (P-selectin, L-selectin, and E-selectin), have been discovered as a result of this concept. They all have important roles in initiating leukocyte migration within the vessel wall.[(8)]**.**

P-selectin, being one of the cell adhesion molecules of interest, since it is expressed by both platelets and endothelial cells under specific conditions, plays a function in initial leukocyte "rolling," and the soluble form could be used as a predictor of unfavourable cardiovascular events[(9)]. P-selectin showing strong expression in the endothelium overlying atherosclerotic deposits and fatty streaks, reduced fatty streak formation in P-selectin–deficient mice, and inhibition of monocyte rolling and attachment across endothelium by anti-P-selectin antibodies all point to P-role selectin's in atherogenesis[(10)]. Normal endothelium and inactive fibrous plaques do not express P-selectin. P-selectin is a well-known prognostic indicator for CVD[(11)] .

Within 2 minutes of inflammatory mediator stimulation, P-selectin is expressed at the surface of endothelial cells, peaks after 10 minutes, and goes to baseline in 3 hours. Cytokines like IL-1 and TNF-, as well as thrombin, lipopolysaccharide, and oxygen radicals, cause further P-selectin production within 2 hours. P-selectin is also increased by adenosine or epinephrine.

P-selectin is important for platelet clumping and aggregation. On the surface of an active platelet, there are around 10,000 P-selectin particles. P-selectin is in charge of activating the endothelium and establishing a positive feedback loop. These molecules are also found in plasma, implying their release, loss, or cleavage from plasma membrane due to the illness process[(12)].

In both humans and animals, the role of PSGL-1 as well as P-selectin in leukocyte rolling and platelet-leukocyte interactions, on endothelium has been demonstrated[(13)]. The PSGL-1 gene has a lot of variability and is linked to the likelihood of developing cerebrovascular disease, according to preliminary genetics[(14)].

Diabetes, hypertension, atrial fibrillation, congestive heart failure, acute coronary syndromes and stroke all benefit from P-selectin. Diabetes, smoking, hypertension, and hypercholesterolemia all cause an elevation in soluble P-selectin levels. Acute MI onset is aided by soluble P selectin[(15)].

The aim of the present study was to find out a link between sP-selectin in patients of CAD and to compare the levels of sP-selectin in healthy subjects and CAD patients. Association of CAD and demographic variables were also assessed. Moreover, association of P-selectin with gender was also investigated.

MATERIALS AND METHODS

This correlational study was done at University of Health Sciences in collaboration with Punjab Institute of Cardiology and Gulab Devi Chest Hospital, Lahore for sample collection. The study included 120 patients (both males and females) of CAD, within 41-60 years of age. Controls included 120 healthy individuals, matched for gender and age, with no previous history of CAD. Samples were also matched for BMI (60 patients and 60 controls with BMI <25, 60 patients and 60 controls with BMI >25). Patients having more than 70% stenosis in any one vessel were included while those having diabetes mellitus, any acute infection and renal or liver diseases were excluded from the study.

Patients and controls were notified about the goal of the study and after taking their written consent, 5 ml of venous blood sample was drawn after 10 hour fast. Serum was separated and aliqouts were stored at -80°C till further use.

Demographic features of the patients and control were recorded in a self designed proforma. Age, gender, BMI, smoking history, history of hypertension and family history of CAD was documented.

Measurement of P-selectin levels: Bender MedSystems human sP-selectin ELISA kit (Catalouge Number BMS219/3, Vienna, Austria, Europe) was used for sP-selectin estimation.

Statistical Analysis: All data was statistically analyzed utilizing SPSS® (Statistical Package for Social Sciences), software version 25 for windows). Categorical variables were assessed by using Chi-square test, while quantitative variables were analyzed by t-test. A p-value of less than 0.05 was taken as significant. Regression analysis was applied to get the correlation between the disease and multiple variables. All the results were analyzed on the same pattern between males and females included in the study.

RESULTS

This study included total 240 subjects (male and female), out of whom 120 were angiographically confirmed patients of CAD. 120 controls, age and sex matched, with no previous history of MI or angina pectoris were also a part of the study.

Clinical and demographic variables of patients and controls are demonstrated in Table 1. These results indicate that the patients have a higher value of BMI. We found a significant difference in the family history of CAD among patients and controls with more patients having positive family history of the disease. Smoking history is also significantly associated the patients with CAD. There is a significant difference in the history of hypertension among patients and controls depicting 85% of the patients suffering from hypertension.

Serum p-selectin levels of patients ranged from 96.68 to 1045.13 ng/ml with a mean value of 414.271 ± 216.48 ng/ml. P-selectin level of controls ranged from 147.54-1287.54 with a mean value of 510.882 ± 257.26 ng/ml.

Comparison and association between P-selectin levels among patients and controls is depicted in Table 2 and Fig 1.

Table 1: Demographic and Clinical features of Patients and Controls

Feature	Patients	Control	Statistics	OR (95% CI)
	Mean ± SD			
Age	51.233 ± 6.65	49.25 ± 6.26	t = 2.376 (p=0.018)	
BMI	28.372 ± 5.17	26.88 ± 3.89	t = 2.509 (p=0.013)	
	N (%)			
Positive Family History	68 (56.7%)	52 (43.3%)	4.267 (p=0.039)	1.710 (1.026-2.850)
Positive Smoking History	50 (41.7%)	24 (20%)	13.207 (p=<0.001)	0.350 (0.197-0.623)
Presence of hypertension	102 (85%)	34 (28.3%)	χ^2 = 78.462 (p=<0.001)	0.070 (0.037-0.132)
Gender				
Male	72 (60%)	72 (60%)		
Female	48 (40%)	48 (40%)		
Angiographic findings				
Single vessel disease	52 (43.3%)	-		
Double vessel disease	38 (31.7%)	-		
Triple vessel disease	30 (25 %)	-		

OR= Odds Ratio; CI= Confidence interval; SD= Standard deviation; N= number of subjects

Table 2. Comparison of mean serum p-selectin levels among patients and controls

	Patients	Control	t	p-value
Mean serum p-selectin levels	414.271 ± 216.48	510.882 ± 257.26	-3.148	(p=0.002)

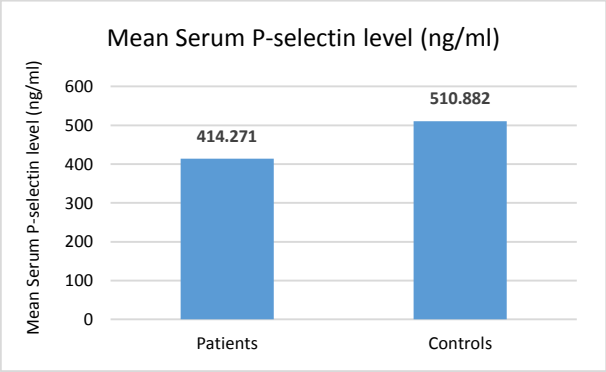

Fig 1. Comparison of mean sP-selectin level of patient and control groups

Regression analysis confirms the association between p-selectin levels, hypertension, smoking history and CAD. Family history of the disease and BMI did not show a significant association as shown in Table 3.

Table 3: Logistic regression analysis of variables among patients and controls

Variables	B	Odds Ratio	95% CI	p-value
BMI	0.021	1.022	0.948-1.101	0.578
Positive family history	0.258	1.295	0.681-2.463	0.431
Smoking History	-1.294	0.274	0.132-0.571	0.001
History of hypertension	-2.784	0.062	0.029-0.130	<0.001
P-selectin levels	0.001	1.001	1.000-1.003	0.046

CI= Confidence interval; p = probability value

Comparison and association of demographic and clinical variables of the disease among males and females is demonstrated in Table 4. Males had a lower BMI as compared to controls. There was no significant difference in the family history of the disease among males and females. Males were significantly involved in smoking habit while only a few females had smoking history. There was a significant difference in the history of hypertension among males and females.

Serum p-selectin levels of males ranged from 96.68 to 899.06 ng/ml with a mean value of 438.215 ± 201.54 ng/ml. P-selectin level of females ranged from 116.16-1287.54 with a mean value of 499.119 ± 290.02 ng/ml. Comparison and association between p-selectin levels among males and females is depicted in Table 5 and Fig 2.

Table 4: Demographic and Clinical features of males and females

Feature	Males	Females	Statistics	OR (95% CI)
	Mean ± SD			
Age	50.486 ± 6.57	49.87 ± 6.47	t = -0.712 (p=0.479)	
BMI	27.011 ± 4.09	28.56 ± 5.21	t = 2.569 (p=0.011)	
	N (%)			
Positive Family History	64 (56.7%)	56 (43.3%)	4.444 (p=0.035)	0.571 (0.339-0.963)
Positive Smoking History	68 (41.7%)	06 (20%)	45.340 (p=<0.001)	13.421 (5.581-32.643)
Presence of hypertension	72 (85%)	64 (28.3%)	χ^2 = 6.516 (p= 0.011)	0.500 (0.293-0.854)
Angiographic findings				
Single vessel disease	36 (43.3%)	16		
Double vessel disease	20 (31.7%)	18		
Triple vessel disease	16 (25 %)	14		

OR= Odds Ratio; CI= Confidence interval; SD= Standard deviation; N= number of subjects

Table 5. Comparison of mean serum p-selectin levels among patients and controls

	Males	Females	t	p-value
Mean serum P-selectin levels	438.215 ± 201.54	499.119 ± 290.020	1.920	(p=0.056)

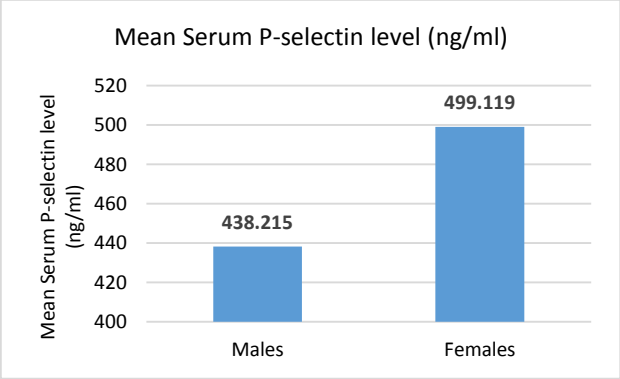

Fig 2. Comparison of mean sP-selectin level of males and females

Regression analysis confirms the association of smoking history, history of hypertension and p-selectin levels with gender as shown in Table 6. The association of P-selectin with gender which was non-significant by chi square test was significantly associated with female gender by regression analysis.

Table 6: Logistic regression analysis of variables among males and females

Variables	β	Odds Ratio	95% CI	p-value
BMI	-0.051	0.950	0.885-1.019	0.154
Positive family history	-0.532	0.587	0.315-1.094	0.094
Smoking History	2.874	17.701	6.859-45.683	<0.001
History of hypertension	-1.182	0.307	0.153-0.614	0.001
P-selectin levels	-0.002	0.998	0.997-1.000	0.008

CI= Confidence interval; p = probability value

DISSCUSSION

CAD is emerging as a major cause of disability, morbidity and mortality in most of the South Asian nations including Pakistan. The Asian continent has a larger CVD burden than American and European nations, with the major burden falling on economically deprived communities, mostly in the South Asian region (16). The total number of deaths due to CVD in Pakistan during the year 2019 were 408486[17].

In our study we analyzed the risk factors of CAD. We found that BMI and hypertension were significantly high in the patients vs. controls. Similarly, Liaquat and Javed in 2018 also reported higher BMI as well as both systolic and diastolic blood pressure in patients group as compared to controls[4].

In a review article hypertension and smoking was declared as a major risk factor for Pakistani population[18]. In our study, smoking was significantly associated with CAD. We have considered that both males and females have the equal risk to develop CAD, which is supported by the a previous study[19]. However, in another research in 2008, women were found to have more electrocardiographic signs of ischemia than men[20]. It is also identified that young men are at a risk of premature CAD subjected to the presence of risk factors[21].

Elevated levels sP-selectin are independent risk factors for CVD. In Pakistan, sP-selectin have not been studied in detail and no cut off values of these variables are available for our population. In this study we have estimated and compared the levels of P-selectin in patients suffering from CAD and also in subjects with no history of CAD.

We have included patients having CAD diagnosed on the basis of angiography. Patients having ≥70% stenosis in any one vessel were included in the study. Also Norman in 2010[22] and Hameed in 2017[23] included angiographically confirmed CAD patients for their investigations.

sP-selectin is one of the study's main variables. In comparison to controls, the mean blood sP-selectin level in patients was considerably lower. Patients' decreased levels could be attributable to antiplatelet and lipid-lowering medications they're taking. Clopidogrel inhibits P-selectin expression ex vivo in healthy controls, but aspirin inhibits P-selectin expression in patients with CVD, according to a 2009 study by Fox[24]. In another study it was reported that soluble p-selectin levels are lower in CAD patients on acetylsalicylic acid[25]. It is reported in another investigation that patients who respond to clopidrogel exhibit less than 50% aggregation of platelets[26].

Conversely, P-selectin expression was positively linked with CAD[27]. In a multiethnic investigation it was found that P-selectin was positively associated with high adiposity, diabetes and heart diseases[28]. In a similar study it was reported that p-selectin is a risk factor for atherosclerosis but is not associated with the severity of the disease[15]. But in a Chinese study it has been reported that p-selectin levels are higher in patients with CVD and is also associated with the severity of the disease[29]. A recent study revealed that P-selectin is associated with CAD[30]. So, due to its role in platelet aggregation, soluble p-selectin has been considered as a novel marker for CVD[31],[32].

We also divided our subjects according to gender and BMI of males were lower as compared to females and most of the males were hypertensive. This contrasted with the results of a study which reported that males have higher BMI as compared to females and found no difference in blood pressure of males and females[4].

There was a significant difference in the mean serum sP-selectin levels of males as compared to females with females having a higher value than males. In a study by Hajilooi there was non-significant difference in sP-selectin levels of males and females but males had a higher value[33]**.** In apparently healthy women who later developed CVD, baseline sP-selectin levels were higher than in those who did not[34]. In a multiethnic investigation,

mean p-selectin levels were found to be significantly higher in males[28].

The fact that our sample size is limited means that causal inferences cannot be formed, which is one of the study's potential drawbacks. We've taken CAD patients with a stenosis of 70% or more in any one artery. Controls with less than 70% stenosis are nevertheless susceptible to atherosclerosis. Instead of plasma, we used serum and sP-selectin levels correlated well in serum and plasma so similar results are likely to be obtained irrespective of which sample is used. As platelets are activated during clotting, it is likely that sP-selectin shedding from platelet surface accounts for increase in serum level. Use of antiplatelet and lipid lowering drugs by patients may have affected the results of sP-selectin**.** Soluble platelet release factors like sP-selectin can be used as biomarkers for CVD[35]. P-selectin expression on platelets, a measure of platelet activation, is increased in young patients with angiographically confirmed CAD[27].

CONCLUSIONS

Following conclusions can be drawn from the study:

- Mean serum sP-selectin level was less in patients as compared to controls.
- A significant difference was found in the mean sP-selectin levels of both genders.
- Increased BMI, positive family history, smoking history and presence of hypertension are significant risk factors for CAD.

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