Original Article

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Soluble Vascular Cell Adhesion Molecule-1 as an Atherogenic Biomarker in Coronary Artery Disease: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: Coronary atherosclerosis is a condition that affects the arteries supplying the heart. The soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) belongs to the immunoglobulin superfamily, and its expression is increased in vascular endothelial cells in atherosclerosis.

Aim: To estimate serum sVCAM-1 in atherosclerotic Coronary Artery Disease (CAD) patients with varying severity and to look for its association with the Atherogenic Index (AI).

Materials and Methods: This hospital-based cross-sectional study was carried out in the Department of Biochemistry at NEIGRIHMS, a tertiary care Institute in the northeastern part, Shillong India, for a period of one year (2019) with 68 angiographically confirmed newly diagnosed CAD patients and were divided into three groups as Single Vessel Disease (SVD), Double Vessel Disease (DVD) and Triple Vessel Disease (TVD). The following biochemical tests were performed on fasting serum samples: Glucose, lipid profiles {Total cholesterol, High Density Lipid (HDL)-C, Low Density Lipid (LDL)-C, Triglycerides (TG)}, Interleukin-6(IL-6), and sVCAM-1. The Chi-square test was used to assess the significance of the association of risk factors such as hypertension, smoking, and diabetes in the participants. One-way Analysis of Variance (ANOVA) was conducted to identify significant differences in the levels of the estimated parameters among the participant groups.

Results: The average age of presentation for the study participants was 61±10.8 years. The study involved 68 recently diagnosed patients with confirmed CAD, of whom 59 (87%) were males and 9 (13%) were females. Among the total patients, 44 (65%) were smokers, 45 (66%) had hypertension, and 29 (43%) were diabetic. The Chi-square test revealed a significant association between smoking (p-value=0.015) and hypertension (p-value=0.008) with CAD, but no association was found with diabetic status. The level of serum sVCAM-1 was found to increase with the number of vessels involved. Significant differences were observed in the levels of serum cholesterol and LDL-C among the groups (TVD>DVD>SVD). The bivariate Pearson's correlation test between Antherogenic Index (AI) and sVCAM-1 showed a statistically significant positive correlation (r=0.33, p-value=0.0059).

Conclusion: Serum sVCAM-1 levels may be used for the follow-up study of patients with CAD, which could be more economical and convenient compared to {Total cholesterol, High Density Lipid (HDL)-C, Low Density Lipid (LDL)-C, Triglycerides (TG)} angiography.

Keywords: Atherogenic index, Atherosclerosis, Cardiovascular disease, Immunoglobulin

INTRODUCTION

Coronary Artery Disease (CAD) is an atherosclerotic condition characterised by inflammation and the buildup of plaque within the coronary arteries, which supply oxygen-rich blood to the heart muscle. This buildup, known as atherosclerosis, narrows the arteries and restricts blood flow to the heart [1]. It is noteworthy that cardiovascular disease is the primary cause of death in both developed and developing nations [1]. In India, there has been a significant rise in CAD cases over the past decade, particularly in urban areas compared to rural regions. The mortality rates due to CAD, when adjusted for age, are notably high, with 349 per 100,000 in men and 265 per 100,000 in women [2]. These rates are two to three times higher than those observed in the United States [3].

The CAD typically arises from the narrowing and subsequent blockage of arteries due to atheromatous deposits. Atherosclerosis, the underlying process, predominantly affects medium and large-sized arteries, characterised by irregular thickening of the artery wall that eventually leads to narrowing of the arterial passage. The earliest observable sign of atherosclerosis is the fatty streak, followed by the development of fibrous plaque, which is a characteristic feature of established atherosclerosis [4].

Researchers have found that atherosclerosis may start early in life, and surprisingly, even maternal hypercholesterolemia during pregnancy can be associated with the formation of fatty streaks in the human foetus [5,6]. Atherosclerosis is the primary risk factor for cardiovascular diseases, characterised by low-grade chronic inflammation along with lipid accumulation in the blood vessels and subsequent plaque formation. The disease appears firstly in the aorta (during foetal life), then in coronary arteries in the second decade of life, and finally in cerebral arteries during the third decade [7]. Researchers have now concluded that the inflammatory cascade leads to the development of atherothrombosis in large part [8].

The soluble Vascular Cell Adhesion Molecule-1 (sVCAM-1) belongs to the immunoglobulin superfamily and is expressed in vascular endothelial cells. As demonstrated by Li H et al., the expression of soluble sVCAM-1 on endothelial surfaces is an early and necessary step in the pathogenesis of atherosclerosis [9]. Its expression increases the recruitment of monocytes and T-cells to sites of endothelial injury. sVCAM-1 has been related to the extent of atherosclerosis, established angiographically in multiple vascular beds in patients with peripheral arterial disease [10-12]. In different studies, soluble Cell Adhesion Molecules (sCAMs) have been found to be positively related to common carotid Intima-Media Thickness (IMT) [13,14].

Additionally, sVCAM-1 has been linked to the pathogenesis of atherosclerosis. De Caterina R et al., and another study conducted by Mu W et al., showed that sVCAM-1 levels were directly associated with carotid IMT and played an important role in the development as well as the prognosis of atherosclerosis [15,16]. In a study by Wu TT et al., on Nigerian women, AI was found to be a strong predictor of CAD [17]. Most of the research conducted has focused on animal

models, and in studies involving humans, the focus has mainly been on tissues such as the heart and aorta [9,13]. Although there are some studies that have looked at measuring sVCAM-1 levels in blood serum or plasma, the amount of available data, especially concerning the Indian population, is quite limited [14-16].

With this perspective in mind, the present study was carried out to estimate the serum levels of sVCAM-1 in CAD and to look for any existing association between the laboratory parameters and the angiographic diagnosis of CAD.

MATERIALS AND METHODS

It was a hospital-based cross-sectional study carried out for one year in 2019 in the Department of Biochemistry at NEIGRIHMS, a tertiary care Institute in the northeastern part Shillong, India. Ethical clearance was obtained from the Institute's Ethics Committee (IEC approval no. NEIGR/IEC2015/0041), and informed written consent was obtained from all the subjects selected for the study.

Inclusion criteria: The study enrolled patients presenting to the Department of Cardiology who were diagnosed with CAD consecutively for the first six months of the study. All patients suspected to have CAD underwent clinical evaluation, echocardiography, followed by catheter angiography in the Department of Cardiology. Confirmed, newly diagnosed patients with CAD were included in the study.

Exclusion criteria: Patients with medical renal disease, any form of arteritis, on hypolipidemic drugs including statins, pregnant women, known primary hyperparathyroidism, or having any malignancy that may affect the progression of the disease were excluded from the study.

Sample size: Total of 68 patients who attended the Cardiology Department within that time period and met the inclusion criteria were included in the study.

Study Procedure

Demographic profiles such as age and gender were recorded for all the subjects, followed by the following investigations: medical history, details of the present illness, past illnesses, family history, physical examination, and routine laboratory tests were carried out to establish a clinical diagnosis. Data regarding smoking status, hypertension, and diabetes mellitus were also collected.

Depending on the number of vessels involved, the patients were divided into three groups: Patients were classified as Single Vessel Disease (SVD) if only one blood vessel had significant stenosis, Double Vessel Disease (DVD) if two vessels were involved, and Triple Vessel Disease (TVD) if three vessels were involved. SVD, DVD, and TVD are designated as groups I, II, and III, respectively. The term SVD refers to the presence of atleast a ≥70% stenosis of one major coronary artery (left anterior descending, left circumflex, or right coronary arteries) or one of their respective major branches (diagonal, obtuse marginal, posterior descending, or posterior left ventricular arteries) [18].

Ankle Brachial Index is an important predictor of atherosclerosis and cardiovascular disease. It was calculated among the participants using the following formula: log10 (TG/HDL-C) [18]. It can be classified as low-risk for values between 0.3 to 0.1, medium-risk for values between 0.1 to 0.24, and high-risk for values greater than 0.24 [19].

Venous blood samples of 5 ml were collected from each patient and centrifuged for 15 minutes at 3000 rpm at room temperature to obtain the serum. The following biochemical tests were performed on the fasting serum sample: Glucose, lipid profiles (Total cholesterol, HDL-C, LDL-C, TG), IL-6, and sVCAM-1.

Estimation of fasting serum glucose and lipid profiles was done by the photometric method in a fully automated chemistry analyser: Beckman Coulter AU2700. IL-6 estimation was performed by the chemiluminescence method in an automated immunoassay machine: DXI 300. Estimation of sVCAM-1 was done in an automated Enzyme linked Immunosorbent Assay (ELISA) processor (Transasia).

STATISTICAL ANALYSIS

A database was prepared for all the subjects, and statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) software (version 20.0, Chicago, US) for Windows. The values of the biochemical parameters estimated for the participants are expressed as Mean±SD units. The Chi-square test was performed to assess the significance of the association of risk factors such as hypertension, smoking, and diabetes. One-way ANOVA was conducted to identify significant differences in the levels of the estimated parameters among the groups of participants. The Post-hoc Games Howell Test (GHT) was carried out for pairwise comparisons to determine significant differences. The Pearson's correlation (r) test was utilised to explore any associations among the various parameters within the groups.

RESULTS

The study included 68 newly diagnosed angiographically confirmed patients suffering from CAD, out of which 59 (87%) were men and 9 (13%) were women. The average age of presentation for the study participants was 61±10.8 years. Among the total patients, 44 (65%) were smokers, 45 (66%) had hypertension, and 29 (43%) were diabetic. The Chi-square test indicated a significant association between smoking (p-value=0.015) and hypertension (p-value=0.008) with CAD, but no association was found with diabetic status [Table/Fig-1].

The different parameters estimated in these groups, with values represented in mean±SD units has been presented in [Table/Fig-2]. One-way ANOVA was conducted to assess the equality of means among the groups, revealing a significant difference (F=45.02, p=<0.001) among the groups for serum sVCAM-1 levels. Levene's test indicated significance at a p-value of 0.001. Consequently, the post-hoc Games-Howell test was performed, showing significant differences between group I and II (p-value=0.001), group I and III (p-value=0.001), and group II and III (p-value=0.0056) at the 0.05 level. ANOVA for serum cholesterol showed a significant difference (F=6.062, p-value=0.004) at the 0.05 level, with Levene's

Parameters	Group-I SVD	Group-II DVD	Group-III TVD	ANOVA	
				F-value	p-value
sVCAM-1 (ng/mL)	32.42±18.78	74.14±49.58	168.82±57.49	45.02	<0.001*
IL6 (5.3-7.5 pg/mL)	15.12±18.44	45.74±70.04	36.84±50.54	1.51	0.228
Total cholesterol (150-200 mg/dL)	161.27±67.57	163.67±57.54	226.38±89.05	6.06	0.004*
TG (mg/dL)	134.54 ±67.06	131.62 ±68.44	174.37±70.68	2.98	0.058
HDL-c (mg/dL)	39.27±12.13	34 ±9.21	38.63±11.73	1.20	0.306
LDL-c (mg/dL)	95.23±66.01	93.87 ±54.57	166.06±97.75	7.11	0.002*
RBS (mg/dL)	147.86±48.17	138.53±54.23	147.59±66.83	0.321	0.638
Atherogenic Index (AI)	0.51	0.55	0.68	4.3	0.017*

[Table/Fig-1]: Demographic profile of the study groups.

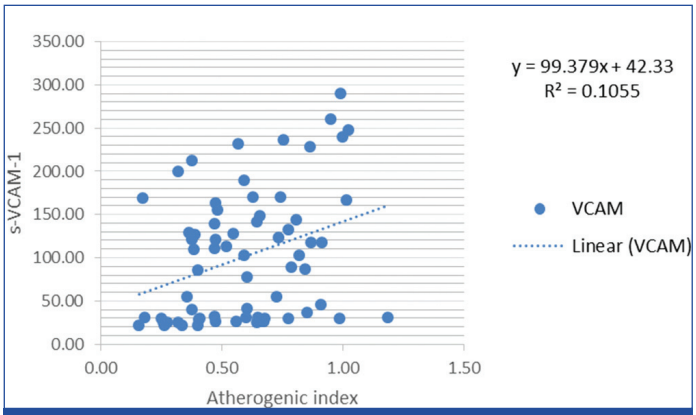
test indicating significance (p-value=0.008) for serum cholesterol. Post-hoc GHT revealed significant differences between group I and II (p-value=0.032) and group II and III (p-value=0.01). ANOVA for serum LDL was significantly different (F=7.11, p-value=0.002) among the groups at the 0.05 level, with Levene's test showing significance (p-value=0.008). Post-hoc GHT indicated a significant difference between group I and II (p-value=0.024) and group II and III (p-value=0.006).

Parameters	SVD	DVD	TVD
Number of participants	15	26	27
Gender	M=11, F=4	M=23, F=3	M=25, F=2
Age (mean±SD) (years)	60.2±10.5	65.4±11.2	56.4±11.5
Hypertensive	5	18	22
Diabetics	6	11	12
Smoking history	5	16	22

[Table/Fig-2]: The different studied parameters expressed in Mean±SD, and one-way ANOVA analysis.
*Statistically significant p-value; †Dynamic range of sVCAM-1 varied from 13.64 to 225.49 pg/mL

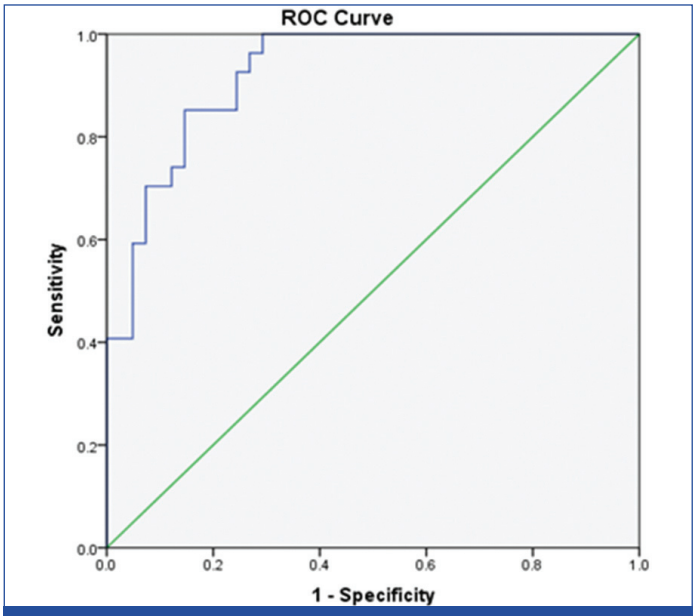
The mean values of all three groups of participants were in the high-risk category, i.e., above 0.24. A significant difference in AI among the three groups of CVD patients was found (F=4.3, p-value=0.017).

A bivariate Pearson's correlation test was conducted to explore the association between AI and sVCAM-1, revealing a statistically significant positive correlation (r=0.33, p-value=0.004) [Table/Fig-3].



[Table/Fig-3]: Pearson's correlation between Atherogenic index (AI) and sVCAM-1 in CAD patients.

In Receiver Operating Characteristic (ROC) analysis [Table/Fig-4a,b], it was found that the recommended cut-off value of sVCAM-1 >92.45 ng/mL showed a maximum area under the curve of 92.3%, which is



[Table/Fig-4a]: ROC curve showing cut-off for s-VCAM-1.

Area	Std. Error	Asymptomatic (significance)	Asymptomatic 95% confidence interval	
			Lower bound	Upper bound
0.923	0.030	0.0001	0.864	0.983

[Table/Fig-4b]: Area under the curve (Test result variables: sVCAM-1).
a: Under the non parametric assumption; b: Null hypothesis: true area=0.5

significant at p<0.0001 level. The sensitivity was around 92.6% and specificity around 73.2%. The upper bound and lower bound levels were 0.983 and 0.864, respectively, at a 95% confidence interval.

DISCUSSION

In current study, the estimation of serum sVCAM-1 has revealed a significant difference in its serum level among the classified groups, showing a trend of increasing sVCAM-1 levels with an increase in the number of vessels involved. Specifically, a higher mean concentration of sVCAM-1 in TVD compared to DVD and Single Vessel Disease (SVD) has been observed (TVD>DVD>SVD). This suggests that sVCAM-1 can be considered an indicator of the severity of CAD based on the number of vessels involved. In a study by Mu W et al., they explored the correlation between the severity of atherosclerosis and sVCAM-1 expression in aortic tissue, finding a positive correlation (r=0.532) [16]. In a recent study done by Chetan IM et al, found that an association between VCAM-1 and high CVR suggesting the existence of endothelial dysfunction and atherosclerosis [20].

Zeitler H et al., also discovered significantly elevated sVCAM-1 levels in patients with coronary heart disease and acute myocardial infarction [21]. Atherosclerosis is an inflammatory condition triggered by inflammatory cytokines secreted by immune cells or defective vascular cells. Under normal conditions, the vascular endothelium prevents thrombosis and clot formation through the secretion of various anticoagulants and antiplatelet mechanisms. However, endothelial cell dysfunction, loss of apical polarity, increased permeability, transition to mesenchymal-like cells, and apoptosis promote atherosclerosis development [22].

Numerous studies have demonstrated that preinflammatory and inflammatory cytokine activation leads to the expression of Vascular Cell Adhesion Molecule-1(VCAM-1) in endothelial cells [23,24]. VCAM-1 plays a role in the pathogenesis of atherosclerosis by promoting the migration of leukocytes towards the endothelial surface and increasing smooth muscle cell proliferation. When VCAM-1 molecules expressed on the surface of endothelial cells are shed into the blood, they form soluble proteins (sVCAM-1). Detecting and estimating sVCAM-1 in the blood serves as an indirect indicator of VCAM-1 expression levels and is relatively easier to perform [25]. Theiss HD et al., demonstrated that VCAM-1 mRNA levels were increased in patients with ischemic cardiomyopathy [26].

In a study conducted by Hackman A et al., it was observed that the level of sVCAM-1 in the blood was directly proportional to higher levels of triglycerides [27]. Saidi H et al., found in their study that elevated sVCAM-1 levels in atherosclerotic patients were associated with the activation and damage of endothelial cells [28]. Another study by Steinberg D and Witztum JL revealed the close association between dyslipidemia and atherosclerosis [29]. The results indicated significant differences in the serum levels of TC, LDL-C were significantly different among the groups, while serum High-Density Lipoprotein cholesterol (HDL-c) and Apolipoprotein-AI (Apo-AI) levels were significantly decreased compared to reference values.

In present study, a significant difference in the Atherogenic Index (AI) level among the classified groups was also observed, with a trend of increasing AI levels corresponding to the number of coronary vessels involved, i.e., Single Vessel Disease (SVD) < DVD < TVD.

Limitation(s)

No follow-up study was conducted to examine serum sVCAM-1 levels in CAD patients; only the baseline level was measured. Serial

measurements would have better accounted for fluctuations in its levels over time.

CONCLUSION(S)

To conclude, serum sVCAM-1 levels have been found to be significant in differentiating patients with CAD according to severity. This laboratory parameter is relatively cost-effective and convenient compared to imaging techniques such as CT or MR angiography. It offers a non invasive means of monitoring disease activity over time, which could lead to more efficient patient management and allocation of resources. sVCAM-1 has also been found to significantly correlate with AI, indicating an association between the development of CAD and AI. However, further research is needed to validate the utility of sVCAM-1 as a biomarker for CAD follow-up. Longitudinal studies involving large patient populations would be necessary to establish its reliability and predictive value over time.

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