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Original Research Article

An association of plasma cyclophilin A with severity of coronary artery disease

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ABSTRACT

Background: Plasma cyclophilin A (CyPA), an emerging biomarker of cardiovascular disease, is likely to play a crucial role in all stages of atherosclerosis. Very few studies have been conducted on the association of plasma CyPA with coronary artery disease (CAD) in India. The aim of the present study was to determine an association between plasma CyPA levels and CAD severity.
Methods: The present cross-sectional observational study was conducted on 100 patients aged ≥18 years who presented with symptoms suggestive of CAD. The presence or absence of cardiovascular risk factors such as gender, hypertension, diabetes mellitus, dyslipidaemia, family H/O CAD, smoking, etc. were noted. Coronary angiography was performed on each patient. Quantitative estimation of plasma CypA levels and high-sensitivity C-reactive protein (hs-CRP) was done.
Results: The mean serum CypA (66.6 Vs 44.9 ng/ml) and hs-CRP (29.8 Vs 21.4 mg/l) were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD. There was a statistically significant positive correlation (r=0.251) between CypA levels and hs-CRP (p value=0.012). The mean low-density lipoprotein cholesterol (181 Vs 160.8 mg/dL) and mean triglycerides (179 Vs 168 mg/dl) were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD. There was no statistically significant difference between the type of CAD and mean total cholesterol and high-density lipoprotein cholesterol.
Conclusions: CypA levels were increased in obstructive CAD patients. High CypA serum levels could be a novel biomarker in CAD patients associated with severe CAD.

Keywords: Association, Coronary artery disease, Cyclophilin A

INTRODUCTION

Coronary artery disease (CAD) is a major risk factor for myocardial ischemia and a leading cause of mortality in developed countries. The prevalence of CAD risks in Indians is 11% for non-diabetic patients and 21.4% for diabetic patients. CAD is a lifelong process resulting from the interaction of many risk factors like unhealthy and sedentary lifestyles, behavioural traits, environmental influences and genetic predisposition.[1,2] Atherosclerosis is the anatomical substrate of most cardiovascular diseases as it is a response by the vessel wall to chronic multifactorial injury finally leading to the formation of fibrous plaques or atheroma. Diagnosing cardiac disease is more challenging as ECG and biomarkers like creatine kinase-MB, troponins, etc. can be confusing in the early stages of the disease.[3] Other biomarkers used to estimate cardiovascular damage like lactate dehydrogenase and high-sensitivity C-reactive protein (hs-CRP) lack specificity and are found to be raised in several non-cardiac conditions.

These biomarkers do not correlate with the anatomical severity.[4] Plasma Cyclophilin A (CyPA) an emerging biomarker of cardiovascular disease, is likely to play a crucial role in all the stages of atherosclerosis. A critical

step in the progression of atherosclerosis is the development of an oxidizing environment because of the activation of macrophages that have become loaded with oxidized low-density lipoprotein (LDL) and other lipids.

These macrophages produce abundant reactive oxygen species (ROS) and secrete several growth factors that contribute to the progression of atherosclerosis.[5] It has been widely recognized that oxidative stress, generated by excessive ROS, promotes CAD.[6] Moreover, ROS induce the secretion of CyPA from vascular smooth muscle cells (VSMC).[7,8] The extracellular CyPA induces extracellular adhesion molecule expression and promotes VSMC proliferation and migration.[9]

Several risk factors, such as hypertension, diabetes mellitus (DM), smoking and ageing induce the generation of ROS and promote the secretion of CyPA. Circulating CyPA augments ROS production synergistically.[10] Therefore, secreted plasma CyPA, acting as a pro-inflammatory cytokine, synergistically augments ROS production, contributing to the onset of atherosclerosis and its progression.[11] Several issues need to be considered regarding the role of CyPA as a biomarker.

First, CyPA may be used with other biomarkers to predict and treat acute coronary syndrome (ACS) before myocardial damage occurs.[12] Secondly, several basic science studies have demonstrated an association between CyPA and ROS which are causative for CAD, but the research is lacking.[13] Very few studies are conducted on the association of plasma CyPA and CAD in India. Therefore, the present study was conducted to determine an association between levels of plasma CyPA and severity of the CAD.

METHODS

This cross-sectional observational study was conducted between January 2022 and September 2022 in Poona hospital and research centre, a tertiary care hospital in Pune, India. After approval from the institutional ethics committee (Letter#RECH/ECBHR/2020-21/434), written informed consent was obtained from all the patients. One hundred patients aged ≥18 years of either sex who presented to the internal medicine department with symptoms suggestive of CAD were included.

Patients with known ischaemic heart disease who had undergone angioplasty in the past, patients undergoing catheterization for other reasons like valvular heart disease, congenital heart disease, cardiomyopathy, etc., patients with known chronic inflammatory diseases, rheumatoid arthritis, malignancy, sepsis, viral infections, asthma, neuro-degeneration and those on dialysis were excluded.

After selection, a complete history was obtained either from the patients or relatives. A socio-economical background of the family, initial symptoms and clinical examination was conducted. The findings were noted in the pre-tested study proforma. The presence or absence of the following cardiovascular risk factors were assessed in each subject.

Male gender, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg or being on antihypertensive medication), hyperlipidaemia (total serum cholesterol (TC) >220 mg/dl or taking lipid-lowering medication), DM, family history of CAD (having first or second-degree relatives with cardiovascular disease- male <55 years and female <65 years), postmenopausal state and smoking (current and past smokers with regular smoking duration more than 1 year).[14]

Hypertension was defined according to Eighth Joint National Committee (JNC)-8 criteria as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥ 90 mm Hg or patient on antihypertensive medication irrespective of blood pressure.[15] The blood pressure was measured with a mercury sphygmomanometer in a sitting position after about 5-10 minutes of rest according to standard guidelines. Dyslipidaemia was defined as per the national cholesterol education program, adult treatment panel III (NCEP ATP III) criteria.

The subjects were classified as dyslipidaemia when presented with one or more of the following: plasma TC≥6.22 mmol/l (240 mg/dl), LDL cholesterol ≥4.14 mmol/l (160 mg/dl) or high-density lipoprotein (HDL) cholesterol <1.03 mmol/l (40 mg/dl). The venous blood samples collected from subjects were centrifuged, the plasma was separated and used for further analysis.[16]

DM was defined as per the diagnostic criteria by the World Health Organization (WHO) in 2000 AD as below, with or without other cardiovascular risk factors (e.g., smoking, hyperlipidaemia, etc.).[17] Patient's complaints of symptoms suggestive of DM (polyuria, polydipsia, weight loss) with one of the following: 1. Fasting plasma glucose 7.0 mmol/l (126 mg/dl), 2. Random plasma glucose (or 2 hours after an ideal oral glucose tolerance test) 11.1 mmol/l (200 mg/dl) (in asymptomatic patients two samples were required to confirm the DM).

Coronary angiography was performed with a Shimadzu Bransistalexa system, Japan and routine projections were obtained for the definition of coronary anatomy. The films were analysed by interventional cardiologist who was unaware of the clinical data and plasma CypA levels. The patients were divided into three groups according to the presence and severity of atherosclerotic lesions.[18]

Group 1: normal coronaries - coronary stenosis <20% or luminal irregularities. Group 2: non-obstructive coronaries- 20%-50% left main coronary artery, 20%-70% any other epicardial artery. Group 3: obstructive coronaries- >50% left main coronary artery, >70% any other epicardial coronary artery.

Quantitative estimation of plasma CypA levels was done before coronary angiography using Cyclophilin A ELISA kit (the kit was sandwich enzyme immunoassay-Cloud Clone Corp Technology, USA). The hs-CRP estimation was measured by Nephelometry. The primary objective was to find an association between levels of plasma CyPA and the severity of the CAD, whereas the secondary objective was to determine a correlation between CypA levels and hs-CRP.

Statistical analysis

Data collected was entered in Excel 2019 and analysis of data was done using Statistical Package for Social Sciences (SPSS) for Windows, Version 22, IBM Corporation, USA. The data on categorical variables are shown as n (% of cases) and the data on continuous variables are presented as mean and standard deviation (SD). Comparison of the distribution of categorical and continuous variables was done using the Chi-Square or Fisher's exact test and unpaired students t-test respectively. Pearson's correlation was used to find the correlation between CypA and hs-CRP. A p value<0.05 was considered statistically significant.

RESULTS

Table 1 depicts the demographic and clinical profile of the study participants. Non-obstructive and obstructive CAD were observed in 56 (56.0%) and 44 (44.0%) patients, respectively. The mean serum CypA levels of the study population were 54.4 ng/ml, with an SD of 16.2 ng/ml. The mean hc-CRP of the study population was 25.1 mg/l, with an SD of 8.9 mg/l. There was no statistically significant difference between the type of CAD and comorbidities such as hypertension, DM and dyslipidaemia (Table 2). The percentage of male patients and patients who had H/O smoking cigarettes was significantly higher in obstructive CAD as compared to non-obstructive CAD. There was no statistically significant difference between the type of CAD and alcohol consumption and post-menopausal state (Table 3).

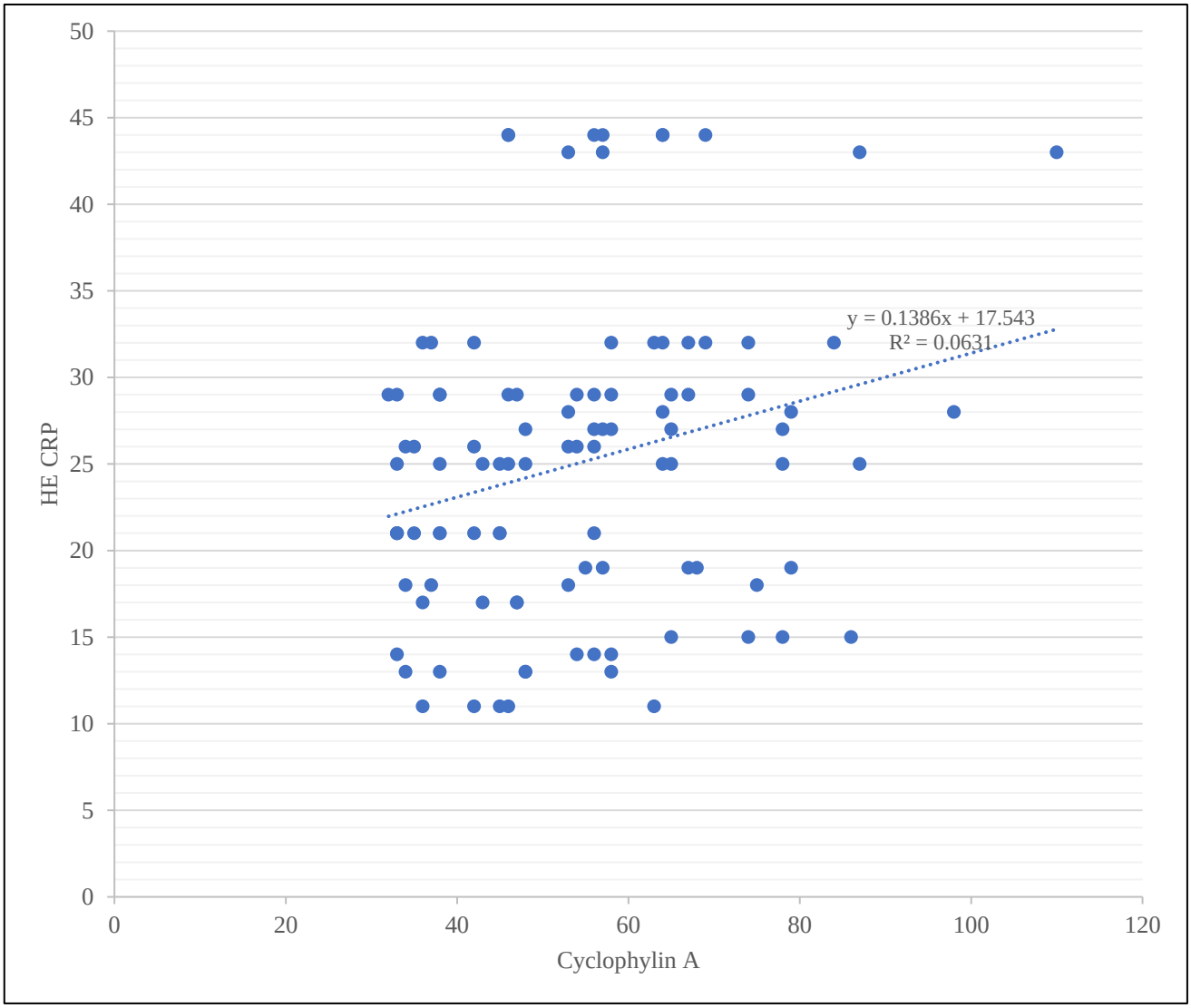

Figure 1: Correlation of Cyclophilin A levels and high sensitivity C-reactive protein.

The mean LDL cholesterol and the mean triglycerides (TG) were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD. There was no statistically significant difference between the type of CAD and the mean TC and the mean HDL cholesterol (Table 4). The mean serum CypA and hc-CRP were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD (Table 5). There was a statistically significant positive correlation (r=0251) between CypA levels and hs-CRP (p value=0.012) (Figure 1).

Table 1: Demographic and clinical profile.

Variables	N (%)
Age group (in years)	
31-40	8 (8.0)
41-50	39 (39.0)
51-60	36 (36.0)
>60	17 (17.0)
Gender	
Males	66 (66.00)
Females	34 (34.0)
Clinical features	
Chest pain	90 (90.0)
Breathlessness	64 (64.0)
Pedal oedema	65 (65.0)
Chronic cough	54 (54.0)
Co-morbidities	
Hypertension	57 (57.0)
Diabetes mellitus	60 (60.0)
Dyslipidaemia	62 (62.0)
Other risk factors	
H/O Cigarette Smoking	63 (63.0)
Post-Menopausal state (n=34)	6 (17.6)
Family H/O CAD	23 (23.0)

CAD-Coronary artery disease

Table 2: Distribution of study participants according to CAD and co-morbidities.

Comorbidities		CAD		P value
		Non-obstructive N (%)	Obstructive N (%)	
Hypertension	Absent	25 (44.6)	18 (40.9)	0.708
	Present	31 (55.4)	26 (59.1)	
Diabetes mellitus	Absent	25 (44.6)	15 (34.1)	0.285
	Present	31 (55.4)	29 (65.9)	
Dyslipidaemia	Absent	24 (42.9)	14 (31.8)	0.250
	Present	32 (57.1)	30 (68.2)	

Chi-square test was used, CAD-coronary artery disease.

Table 3: Distribution of study participants according to CAD and risk factors.

Risk factors		CAD		P value
		Non-obstructive N (%)	Obstructive N (%)	
Gender				
Males		30 (53.6)	36 (81.8)	0.003*
Females		26 (46.4)	8 (18.2)	
H/O cigarette smoking	Absent	27 (48.2)	10 (22.7)	0.009 *
	Present	29 (51.8)	34 (77.3)	
Alcohol consumption	Absent	20 (35.7)	21 (47.7)	0.220*
	Present	36 (64.3)	23 (52.3)	
Post-menopausal state (n=34)	Absent	20 (77.0)	8 (100.0)	0.428**
	Present	6 (23.0)	0 (0.0)	

*Chi-square test was used, **Fisher's exact test was used, CAD-coronary artery disease.

Table 4: Distribution of study participants according to CAD and lipid profile.

Lipid profile	CAD		P value
	Non obstructive	Obstructive	
Mean total cholesterol (mg/dl) ±SD	253±49.5	263.8±61.8	0.334
LDL cholesterol (mg/dl) ±SD	160.8±12.7	181±31.7	0.0001
HDL cholesterol (mg/dl) ±SD	42.2±7.1	43.9±6.9	0.251
TG (mg/dl) ±SD	168±14.0	179±20.9	0.002

Unpaired t-test was used, CAD-Coronary artery disease, LDL-Low density lipoprotein, HDL-High density lipoprotein, TG-Triglycerides, SD-Standard deviation.

Table 5: Distribution of study participants according to CAD and mean Cyclophilin A levels and high sensitivity CRP.

Variables	CAD		P value
	Non-obstructive	Obstructive	
Mean cyclophilin A levels±SD (ng/ml)	44.9±10.2	66.6±12.3	0.0001
Mean high sensitivity CRP±SD (mg/l)	21.4±6.7	29.8±9.3	0.0001

Unpaired t-test was used, CAD-Coronary artery disease, CRP-C-reactive protein, SD-Standard deviation.

DISCUSSION

This observational study was conducted to find an association of plasma CypA with the severity of CAD in the tertiary care hospital. In the present study, the percentage of male patients who had obstructive CAD (81.8 %) was significantly higher (p-value=0.003) than the patients of non-obstructive CAD (53.6%). Alfonso et al, reported that the percentage of male patients was significantly (p value =0.001) higher in the CAD group (87.5%) as compared to the control group (50.0%).[19] In the present study, the percentage of patients who had H/O smoking cigarettes was significantly higher (p value=0.009) in obstructive CAD (77.3%) as compared to non-obstructive CAD (51.8%). Alfonso et al, reported that H/O smoking was 37.5% and 2.3% in patients with CAD and controls respectively (p value <0.001).[19]

In the present study, there was no statistically significant difference between the type of CAD and comorbidities such as hypertension, DM and dyslipidaemia. Alfonso et al, reported that the prevalence of hypertension (47.5% vs 6.8%, p value <0.001), DM (17.5% Vs 2.3%, p value <0.05) and dyslipidaemia (67.5% Vs 13.6%, p value <0.001) was significantly higher in CAD patients as compared to the controls.[19]

In the present study, the mean LDL cholesterol and the mean TG were significantly higher in patients with obstructive CAD patients as compared to non-obstructive CAD patients. There was no statistically significant difference between the type of CAD and the mean TC and the mean HDL cholesterol. Contrary to the present study, Alfonso et al, observed that the mean TC (mg/dl) was significantly lower (p value 0.004) in CAD patients (177.05±6.74) as compared to the controls (202.57±1.54), whereas the mean HDL cholesterol (mg/dl) was significantly higher (p value <0.001) in controls (58.00±2.55) as compared to CAD patients (36.53±1.29) and the mean TG (mg/dl) was significantly higher (p value <0.001) in CAD patients (164.00±11.31) as compared to the controls (106.89±6.84).[19] The study further stated that the mean LDL cholesterol (mg/dl) was comparable (p value =0.071) between CAD patients (108.00±5.54) and the controls (122.03±3.90).

Manawsami et al, reported that the mean TC (mg/dl) was comparable (p value=0.78) between CAD patients (152±6.5) and the controls (163±7.9), whereas the mean HDL cholesterol (mg/dl) was significantly higher (p value <0.001) in controls (38±2.1) as compared to CAD patients (32±1.0) and the mean TG (mg/dl) was comparable (p value <0.077) between CAD patients (161±18) and the controls (138±15).[20] The study further stated that the mean LDL cholesterol (mg/dl) was significantly higher (p value =0.003) in CAD patients (88±4.9) as compared to the controls (61±8.6).

In the present study, the mean CypA (ng/ml) levels were 66.6±12.3 and 44.9±10.2 in patients with obstructive and non-obstructive CAD respectively (p value=0.0001). Manawsini et al, reported the mean CypA (ng/ml) levels were 27±1.0 and 38±1.6 in controls and CAD patients respectively (p value <0.001).[20] Yan et al, reported that the median serum concentrations of CyPA were significantly higher in patients with angina pectoris (12.1 (3.5–21.2) ng/ml) and acute myocardial infarction 13.9 (4.7–26.4) ng/ml as compared with those obtained from control (2.2 (0.8–3.2) ng/ml) and stable angina group (2.6 (0.9–3.9) ng/ml.[21] Alfonso et al, reported that the mean CypA (ng/ml) levels were 2.44±0.46 and 7.80±1.30 in controls and CAD patients respectively (p value <0.001).[19] Ebrahim et al, reported that the mean CyPA (ng/ml) was 6.92 in controls, whereas the median CyPA (ng/ml) levels were 32.90 and 30.00 in patients with stable CAD with type 2 DM and stable CAD respectively (p value<0.001).[22] Bayon et al, reported that the mean CyPA (ng/ml) levels were 2.53±0.53, 5.52±0.759 and 7.80±1.30 in controls, chronic CAD and acute CAD respectively (p value

<0.001).[23] Satoh et al, stated that the plasma CyPA levels were significantly higher in patients with significant coronary stenosis as compared to those without it (p value <0.001).[24]

In the present study, the mean serum hs-CRP (mg/l) was significantly higher (p-value=0.0001) in patients with obstructive CAD (29.8±9.3) as compared to non-obstructive CAD patients (21.4±6.7). Alfonso et al, reported that the mean CRP (mg/dl) levels were 0.49±0.14 and 43.45±15.10 in controls and CAD patients respectively (p value <0.001).[19] Manawsini et al, reported the mean hs-CRP (mg/l) levels 5.1±1.5 and 18±3.1 in controls and CAD patients respectively (p value <0.001).[20]

In the present study, there was a statistically significant positive correlation (r=0.251) between CyPA levels and hs-CRP (p value=0.012). Alfonso et al, reported a statistically significant positive correlation (r=0.409) between CyPA levels and CRP (p value <0.05).[19] Manaswini N et al, also reported a statistically significant positive correlation (r=0.36) between CyPA levels and hs-CRP (p value <0.001).[20] Yan et al, reported a statistically significant positive correlation (r=490) between CyPA levels and hs-CRP (p value =0.0001) in patients with acute coronary syndrome.[21]

CyPA might be thought of as a molecule that contributes to inflammation and atherosclerosis when it is discussed in the context of atherosclerosis. CyPA was expressed to a significant degree in the locations of unstable atherosclerotic plaques, particularly those that were connected with macrophages and foam cells. CypA was involved in the development of atherosclerosis, as well as oxidative stress, the production of nitric oxide and most likely the control of blood pressure. At every stage of the disease, inflammation plays a critical part in the progression of atherosclerosis. It has been shown that CRP, which acts as an indication for inflammatory processes, might serve as a risk biomarker for ACS. Patients who suffer from cardiovascular disease have a bad prognosis when they have elevated blood levels of CRP.

It had been previously reported how CypA and CRP correlate with one another, as well as the function that both play in determining the likelihood of developing CAD or serving as indicators of a proinflammatory condition in DM individuals. The formation of vascular intracellular ROS, which had been well acknowledged to be involved in the aetiology of cardiovascular disease, might be responsible for the considerable rise of the circulating CyPA levels that were detected in sera of stable CAD patients with and without type 2 DM.[19] Satoh et al, concluded that the plasma CyPA level is a novel biomarker of CAD.[24] A control group without CAD was not included in the study. An association between the number of coronary vessels involved and CyPA was not studied. A receiver operative characteristic curve to find the cut-off value of CyPA was not done. The sensitivity and specificity of CyPA to detect the severity of CAD was not calculated. The number of subjects involved in this study is relatively small, however, it is representative of the number a single-centre study, there are likely selection biases and limitations of the generalizability of the findings and for that, multi-centre studies with larger sample sizes are needed to substantiate the results of the present work.

CONCLUSION

The mean serum CypA (66.6 Vs 44.9 ng/ml) and hs-CRP (29.8 Vs 21.4 ng/ml) were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD. There was a statistically significant positive correlation (r=0251) between CypA levels and hs-CRP (p-value=0.012). The mean LDL cholesterol (181 Vs 160.8 mg/dl) and mean TG (179 Vs 168 mg/dl) were significantly higher in patients with obstructive CAD as compared to non-obstructive CAD. There was no statistically significant difference between the type of CAD and mean TC and HDL cholesterol.

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