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RESEARCH ARTICLE

Inflammation and arterial stiffness in coronary artery disease

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ABSTRACT

Background: Coronary artery disease (CAD) has become endemic in recent times and has become a leading cause of death in India. Atherosclerosis and arterial stiffening are the major sequelae to CAD. Among many risk factors, high sensitive C-reactive protein (hsCRP) has been shown to be strongly associated with CAD and subsequent arterial stiffening. However, there is a paucity of literature of this association in Indian population. Therefore, the present study is aimed to assess the correlation between hsCRP and arterial stiffness in CAD. **Aim and Objectives:** The objectives of the study were (i) to asses hsCRP levels in CAD, (ii) to evaluate the arterial stiffness and lipid profile in CAD, and (iii) to correlate hsCRP and arterial stiffness in CAD. **Material and Methods:** It is a cross-sectional study of 50 angiographically proven CAD cases and 50 healthy control participants. hsCRP was measured by fluorescent immunoassay using Finecare kit. Pulse wave analysis of augmentation index (AIX) and subendocardial viability ratio (SEVR) was carried out using sphygmocor (EM3). Lipid profile parameters were measured by the enzymatic method. All the measured parameters were analyzed by student "*t*" test using SPSS version 22. **Results:** There is a significant difference in hsCRP levels ($P < 0.0001$), AIX ($P < 0.005$), SEVR ($P < 0.0001$), and high-density lipoprotein (HDL) ($P < 0.05$) in CAD cases when compared to controls. A positive correlation was observed between hsCRP and AIX and found a negative correlation between hsCRP and HDL. **Conclusion:** The present study concludes that there is a significant elevation of hsCRP in established cases of CAD in Indian population. hsCRP and arterial stiffness are strongly associated with CAD independent of hyperlipidemia.

KEY WORDS: Coronary Artery Disease; High Sensitive C-reactive Protein; Arterial Stiffness; Augmentation Index; Sub Endocardial Viability Ratio; Lipid Profile in Coronary Artery Disease

INTRODUCTION

Coronary artery diseases (CAD) have been leading cause of morbidity and mortality in India. Recent trends indicate that the disease has escalated to younger age groups also. It has a significant presence in males and females in both urban and rural population.[1] The prevalence of its associated risk factors has been found to exist increasingly in the population. With such a fast pace of increasing incidence, a number of epidemiological studies have been carried out in India to trace the prevalence of cardiovascular diseases (CVD) over time. Some of them have forecasted the future incidence and prevalence of CVD in India.[1] CAD are epidemic in India, 17% of total deaths in India are due to coronary heart disease.[2] CVD are leading cause of death in India. CVD deaths are mainly due to ischemic heart disease and stroke.[3] Atherosclerosis is a disorder caused by chronic inflammation which can impair vascular function with the interaction of white blood cells in walls of arteries. Arterial stiffness is associated with an increased risk of cardiovascular disorders[4,5] CAD is a consequence of arteriosclerosis and atherosclerosis.[6,7] The stiffness of the artery is reflected

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in wave reflection, pulse wave velocity (PWV) and augmentation index (AIX). Inflammation is a major cause for arterial stiffness and subsequently CAD. Increased levels of inflammatory markers such as C-reactive protein (CRP) and interleukin-6 have been associated with cardiovascular diseases which are implicated in its pathogenesis.[8]

The elasticity and distensibility of arteries during the cardiac cycle maintain constant blood pressure. The decrease in the elasticity of the aortic vessel wall increases the peripheral resistance (afterload) and the diastolic blood pressure (DBP) leading to hypertension. Hypertension is an established risk factor for CVDs.[9]

Atherosclerosis, inflammation, and endothelial injuries are some of the potential mechanisms linking arterial stiffness and plasma lipid. Patients with stiffer blood vessels and high central pulse pressures are associated with hypercholesterolemia.[10] According to some studies, it was found that lower low-density lipoproteins (LDL) were linked with higher mortality risk which is opposite to what was expected.[11-13] Some studies have reported that there is an association between inflammatory markers high sensitive CRP (hsCRP) and arterial stiffness.[14]

The independent pathogenesis for atherosclerosis, in contrast, vascular inflammation as reflected by elevated hsCRP which can cause abnormality in wall property as represented by abnormal stiffness and these mechanisms have been investigated as predictors for CAD.[15,16] Increased serum concentration of total cholesterol (TC), triglycerides (TGL), and LDL is known to be the risk factors of cardiovascular disease; whereas increased concentration of high-density lipoprotein (HDL)-cholesterol is cardioprotective.[17] Arterial stiffness is regarded as a modifiable risk factor because there is a reduction in arterial stiffness following lipid-lowering therapy; however, there is an inconsistent relationship between serum lipid profile and arterial stiffness. A significant association between dyslipidemia and AIX was not found. However, there is a paucity of literature of this association in Indian population. Therefore, the present study is aimed to assess the correlation between hsCRP and arterial stiffness in CAD.

MATERIALS AND METHODS

This cross-sectional case–control study is approved by the Institutional Ethical Committee. The study includes 50 angiographically proven CAD cases were recruited from Cardiology Department, Narayana Medical College and Hospital, Nellore, after obtaining clearance with informed written consent and 50 apparently healthy controls with no history of CAD were recruited from employees of Narayana Medical College and Hospitals selected as control subjects.

Subjects with type 2 diabetes mellitus (DM) and fever were excluded in the study. DM was excluded by estimation of fasting blood glucose as per the standard diabetic criteria.

The fasting blood samples were collected and serum separated by centrifugation from both cases and controls. Lipid profile TC, TGL, LDL, HDL, and Very LDL (VLDL) were estimated by an enzymatic method using Humastar fully automated analyzer. The Institutional Ethical Committee gave clearance to execute the study protocol (NMCH/IEC/22/2017).

Arterial Stiffness

In the same subjects, arterial stiffness was measured and recorded using SphygmoCor instrument. AIX and PWV were recorded in both cases and controls.

After an initial rest period of 10 min, average blood pressure of three readings was taken. PWV, AIX, and subendocardial viability ratio (SEVR) were derived using SphygmoCor device. The set up consists of a hand-held tonometer attached to a device and a laptop. High fidelity sequential pressure waveforms were obtained by placing the tonometer on the radial artery of the dominant wrist. The device then applies a transfer function to these peripheral measurements and central (aortic) pressure parameters, and degree of augmentation secondary to reflected wave from the periphery was estimated. This permits derivation of AIX and SEVR.[18]

Estimation of hsCRP

The Finecare hsCRP rapid quantitative test is based on fluorescence immunoassay technology. The Finecare hsCRP rapid quantitative test uses a sandwich immunodetection method when the sample is added to the sample well of the test cartridge. The florescence-labeled detector hsCRP antibody binds to a hsCRP antigen in a blood specimen. As the sample mixture migrates on the nitrocellulose matrix of test strip by capillary action, the complexes of detector antibody and hsCRP are captured to a hsCRP antibody that has been immobilized on the test strip. Thus, the more hsCRP antigen is in the blood specimen, the more complexes are accumulated on the test strip. Signal intensity of fluorescence of detector antibody reflects the amount of hsCRP captured and Finecare FIA Meter shows hsCRP concentrations in a blood specimen. The default results unit of Finecare hsCRP rapid quantitative test is displayed as XXX mg/L form Finecare FIA Meter. The working range and the detection limit of the hsCRP test system are 0.5–200 mg/L and 0.5 mg/L, respectively.

Statistics

AIX and SEVR were measured in both groups and statistically analyzed using SPSS version 22. Normality of data sets was tested using Kolmogorov–Smirnov test, and data sets were normally distributed. Students "*t*" test was performed to estimate the group difference. $P < 0.05$ was considered to be significant. Further, the association between hsCRP and AIX was analyzed with Pearson correlation test.

Table 1: Statistics of demographic, pulse wave analysis, and biochemical parameters

Parameter	Cases (n=50)	Controls (n=50)	P value
	Mean±SD	Mean±SD	
Age (years)	52±8.8	34±8.9	<0.005
SBP (mm of hg)	125±15.1	119±10.6	<0.005
DBP (mm of hg)	80±8.5	75±7.0	<0.005
HT (cm)	164±6.6	163±7.4	0.551
WT (kgs)	63±9.3	65±8.6	0.365
BMI (kg/m^2)	23±2.8	24±2.4	<0.05
AIX (%)	28±9.4	23±7.4	<0.005
SEVR	127±21.1	154±34	<0.0001
CHOL (mg/dl)	179±35.0	173±29.9	0.301
TGL (mg/dl)	153±49.1	139±47.9	0.157
LDL (mg/dl)	100±16.7	100±19.0	0.938
HDL (mg/dl)	40±7.0	43.3±8.1	<0.05
VLDL (mg/dl)	30±8.8	27±9.3	0.120
T.C/HDL	4.1±0.3	3.9±0.3	<0.05
HsCRP (mg/L)	6.3±4.9	0.9±0.3	<0.0001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, AIX: Augmentation index, SEVR: Subendocardial viability ratio, TC: Total cholesterol, TGL: Triglycerides, LDL: Low-density lipoproteins, HDL: high-density lipoproteins, VLDL: Very LDL, HsCRP: High sensitive C-reactive protein

RESULTS

According to our study, we found a significant difference in age, body mass index (BMI), systolic blood pressure (SBP), and DBP between the groups. In contrast to the expectations, there was no significant difference in lipid levels, i.e., TC, TGL, LDL, and VLDL. However, the HDL was significantly lower and the ratio of TC and HDL was significantly higher in CAD compared to the control group ($P < 0.05$). In addition, pulse wave measures such as AIX are significantly increased ($P < 0.005$) and SEVR was decreased ($P < 0.0001$) in CAD when compared to controls. Pearson correlations have revealed that there was significant relationship hsCRP and AIX which were in a positive relationship ($P \leq 0.010$, $r = 0.256$*) and found a negative correlation between hsCRP and HDL ($r = -0.09$) Table 1.

DISCUSSION

Our study findings can be summarized as follows; SBP and DBP in cases had a mean value of 125 and 80 mmHg, respectively, while in controls its found to be with a mean value of 119 and 75 mmHg. BMI was found to be within acceptable limits in both cases and controls. AIX was significantly higher among the cases when compared to controls with the mean value of 28% and 23%, respectively. SEVR was good enough among controls with a mean value of 154 while in cases it is compromised with a mean value of 127. Among the parameters of lipid profile, HDL alone has shown the statistically significant mean value of 40 mg/dl among cases, 43 mg/dl among controls, rest of the parameters in lipid profile were not significant enough to be considered. hsCRP, the predominant inflammatory circulation marker was significantly found among cases with a mean value of 6.3 mg/L, while among controls significantly low with a mean value of 0.9 mg/L.

The mean measured systolic blood pressure among the cases was 125 mm of hg (±15.1) and among controls it is found to be 119 mm of hg, reflecting the statistical significance with $P < 0.005$. Same is the case with DBP with $P < 0.005$ projecting the statistical significance. This finding is corroborative with the earlier study carried out.[15,19]

Arterial Stiffness and BMI

Mean BMI measured among the cases and controls are more or less well within the normal range, suggesting the insignificant role in causing atherosclerotic changes as presupposed.[19] Arterial stiffness is measured in terms of P.W.A which is measured as AIX and SEVR. P.W.A is carried out by AIX, which has shown with index mean value of 28 (±0.4) among the cases in contrast to controls with the mean value of 23 (±7.4) which forms the core finding of the study. This is also supplemented with SEVR. SEVR measured among cases is found to be with a mean value of 127 (±21.1) while among the controls it is found to be with a mean value of 154 (±34) which is very much significant statistically with $P < 0.0001$. Measured values with regard to SEVR are found to be inverse relation with AIX, suggesting higher the AIX, and lower the SEVR and vice versa.[4,16,20]

Lipid Profile and CAD

In the given study, contrary to the popular belief as far as lipid profile is concerned, TC and LDL, VLDL including TGL are found to be more or less the same among the cases and controls that make association between hypercholesterolemia and CAD questionable in the given scenario, though HDL values were statistically significant with relatively low levels among the cases when compared to controls. Previous studies carried out in this regard also shows not much of correlation between the levels of cholesterol and severity of the stiffness of the arteries measured among different subjects.[21,22]

Inflammation and Arterial Stiffness in CAD

The chronic inflammatory process is an essential element of atherosclerosis leading to CAD.[3] hsCRP, being a very sensitive indicator of the inflammatory process which is the major culprit predisposing to atherogenesis. Its measurement makes it an absolute parameter as it contributes to the stiffness of the blood vessel, which is measured in terms of AIX which also constitutes another most important index of the study. hsCRP measured among the cases and controls

were found a significant increase in cases when compared to controls. Which projecting the inflammatory process attributable to the stiffness of the blood vessel, which is also found to be very significant that is measured in terms of AIX. hsCRP values measured among the cases and controls have shown strong association with the CAD with $P < 0.0001$, i.e., statistically consistent. The previous studies carried out on these lines also suggested a positive correlation between hsCRP and arterial stiffness in the occurrence of CAD, as hsCRP alone constitutes a biomarker related to vascular wall biology found in circulation.[4,15,16,23]

Limitations

The study included only 50 patients from a single hospital, a larger study involving more patient groups from different hospitals could have been done to generalize our study results. However, it was not possible due to technical reasons. There was unequal gender distribution of subjects, which might have underpowered the results. In spite of small sample size the inflammatory circulating marker hsCRP, consequently, arterial stiffness was found to be high among the cases when compared to controls, though BMI and lipidemia were not showing much association with CAD in a given study.

CONCLUSION

This study reveals a strong association between arterial stiffness and the CAD. This finding is adequately supported by high hsCRP levels found in cases that mark the chronic inflammatory process, which is a major culprit for atherogenesis. Accordingly, AIX and hsCRP have shown unequivocal association with CAD.

Contrary to the popular belief the BMI and lipid profile measured among the two groups did not show much of variation, statistically insignificant, and turn out not be attributable factors for the pathogenesis of CAD. HDL levels were relatively significant apart from other parameters of lipid profile.

The study concludes that hsCRP is one of the biomarkers of chronic inflammation found in circulation and inflammation being the cause for atherogenesis compromising the elasticity of the blood vessel, hsCRP the marker of inflammation and AIX an index of the stiffness of artery consequent on atherosclerosis, stand out to be most reliable parameters for risk screening of CAD.

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