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Role of Apolipoprotein C-III (Apo C-III) in the Pathogenesis of Coronary Artery Disease: A Case-Control study

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ABSTRACT
Apolipoprotein C-III (Apo C-III) is increasingly identified as a significant regulator of the metabolism of triglyceride-rich lipoproteins (TRLs) and may provide new ways for evaluating hypertriglyceridemia. Higher Apo C-III levels are associated with a higher risk of coronary artery disease. We aimed to evaluate the relationship between serum Apolipoprotein C-III concentration and risk factors of coronary artery disease in CAD patients. This case-control study was carried out in the Department of Cardiology, SRM Medical College Hospital and Research Centre, Kattankulathur. A total of 32 patients with confirmed CAD and 32 age and sex-matched apparently healthy controls were enrolled for this study. Biochemical parameters were measured in fasting blood samples. Apolipoprotein C-III levels were estimated by ELISA (Fine Test Kit) and Lipid Profile parameters were measured using Beckman coulter Auto Analyzer. The P value <0.05 was considered statistically significant. The mean levels of Apolipoprotein C-III, total cholesterol, triglycerides, LDL-Cholesterol (low-density lipoprotein cholesterol) were significantly elevated and HDL-Cholesterol (high-density lipoprotein cholesterol) were significantly lower in CAD patients. Apolipoprotein C-III had a positive correlation with fasting plasma glucose, LDL-C, TyG Index, LDL-C/HDL-C and a negative correlation with TC, TG, HDL Cholesterol, VLDL cholesterol, SdLDL cholesterol, non-HDL Cholesterol, RLP Cholesterol and Total Cholesterol/HDL Cholesterol among CAD patients. The odds of developing CAD in those with Apolipoprotein C-III ≥350.06 ng/ml was 23.4 times (95% CI:6.36-86.14). In Conclusion, elevated levels of Apolipoprotein C-III play a significant role in the CAD progression and are related to coronary artery disease risk factors.
Keywords: Apolipoprotein C-III, Coronary artery disease, Hypertriglyceridemia, Low-density lipoprotein, Risk factor

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INTRODUCTION

Cardiovascular disease is now a primary global cause of disability and premature death despite encouraging advances in understanding atherothrombosis prevention, diagnosis and treatment [1]. The proportion of deaths from cardiovascular disease is higher than other non-communicable diseases (diabetes, cancer, stroke)(2). Apo C-III is a key regulator of circulating triglyceride-rich lipoproteins (TRLs) [3]. It was discovered by Brown et al. in 1969 [4]. Apo C-III is the most prevalent member of the apolipoprotein C family and is produced mainly by the liver and intestine. Triglyceride metabolism is strongly associated with Apo C-III, which is a key regulator for non-fasting and fasting triglycerides [5]. It is found primarily in triglyceride-rich lipoproteins (TRLs) such as chylomicrons and VLDL-Cholesterol (very low-density lipoprotein cholesterol) and also in HDL-Cholesterol (high-density lipoprotein cholesterol) and low-density lipoprotein cholesterol particles to a smaller degree. When discovered, Apo C-III was established as a lipoprotein lipase (LPL) inhibitor and a primary regulator for plasma

triglyceride-rich lipoproteins (TRLs) levels [6]. Apo C-III levels were proportional to the plasma levels of triglycerides and also linked to hypertriglyceridemia severity [7]. Increased plasma levels of apolipoprotein C-III and its build-up in TRLs have been causally associated with hypertriglyceridemia in persons with metabolic syndrome (8). It is a significant lipolysis regulator since it inhibits lipoprotein lipase, which helps to hydrolyze the triglycerides-rich lipoproteins [9]. A high level of Apo C-III inhibits hepatic lipase activity and prevents the liver's lipoprotein receptors from intake of TRLs remnants.

An increasing number of research shows that Apo C-III is a multifunctional protein which regulates not only TRLs metabolism but also endothelial function. Its capacity to cause endothelial dysfunction associates with hyperlipidemia and also enhances inflammatory reactions that leads to atherosclerotic development, thus raising the risk of coronary atherosclerosis [10]. Apolipoprotein C-III can interact with the endothelial-bound lipoprotein lipases and decreases their function. It can interact more closely with endothelial cells, which inhibit phosphorylation by insulin-dependent IRS-1 (Insulin receptor substrate-1) and eNOS (endothelial nitric oxide) production. Endothelial impairment increases the proinflammatory reaction to cytokines [11]. This association between apolipoprotein C-III and endothelium also enhances the vascular cell adhesion molecule-1, that can increase leukocyte mobilization to produce atheroma. It can also improve its activities on monocytes by increasing its adherence to endothelium with β1-integrins [12]. Apo C-III also reduces the anti-inflammatory activity of HDL-C(13). Thus, Apolipoprotein C-III targeting may be an effective new therapeutic method for decreasing the risk of CHD in dyslipidemia patients [10]. At present literature, regarding Apo C-III estimation among the Indian population is not widely available. Therefore, in this study Apolipoprotein C-III levels in patients with coronary artery disease (CAD) were compared to those in healthy controls, and the relationship between conventional cardiac risk factors and Apolipoprotein C-III in coronary artery disease development was also examined.

MATERIAL AND METHODS

This case-control study was performed from Dec 2020 to Mar 2021 in the department of cardiology at SRM Medical College Hospital and Research Centre, Kattankulathur, Kancheepuram, Tamil Nadu, India. The study consisted of 64 participants, out of whom 32 were patients with angiographically proven CAD in the age group of 30-70 years of both genders. CAD was defined as angiographically proven coronary disease with >50% stenosis of at least one major epicardial coronary artery. Age and sex-matched 32 apparently healthy volunteers attending the master health check-up program formed the control group. Patients suffering from renal disease, hepatic disease, endocrine disorders and pregnant women were considered as exclusion factors.

All the participants were given detailed information about the study and informed written consent was acquired from them. The demographic details, relevant history and anthropometric measurements like height, weight and BMI were recorded. Under aseptic precautions, after 8 to 10 hours of overnight fasting, 5ml of venous blood sample was drawn into sodium citrate and plain vacutainers. Plasma glucose was measured by Hexokinase method, Triglycerides (TGL) by Glycerol Peroxidase, total cholesterol (TC) by Cholesterol Oxidase, LDL-C and HDL-C by Direct method using Beckman Coulter Auto analyzer (AU 480). VLDL-C was calculated by the Friedwald formula, non-HDL-C (mg/dl) is calculated as TC – HDL-C, RLP-C was calculated using the formula TC- (HDL-C + LDL-C), SdLDL-C (mg/dl) was calculated as 0.580 (non-HDL-C) + 0.407 (direct LDL-C) – 0.719 (calculated LDL-C) – 12.05, TyG index was calculated as ln[fasting triglycerides (mg/dl) × fasting glucose (mg/dl)/2]. About 0.5 ml of serum was stored at -20˚ C for the quantification for Apo C-III was done by (Fine test kit) ELISA method.

The study protocol was approved by the Institutional Ethics Committee(ECN: 1866(A)IEC/2019) and informed written consent was taken from all the participants.

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package for Scientific Studies (SPSS) version 25. The results were represented as mean ± standard deviation (SD). Independent student's t-test was used to compare the mean ± SD levels of various parameters between two groups and one-way ANOVA was used to compare the difference in more than two groups. Pearson's correlation equation was used to determine the relationship between various variables. ROC curve was utilized to determine the cut-off value. Bivariate logistic regression was performed for to evaluate the Odds ratio to assess the risk of developing CAD. It was considered statistically significant at P value <0.05.

RESULTS

The study included 64 participants (54 males and 10 females). Among the 32 patients with CAD, 27 (84.4%) were males and 5 (15.6%) were females. The mean age of the CAD group was found to be 51±7.6 years (range 30-70 years). The mean BMI was 25.5 ± 2.8 kg/m^2. Among them 9.4% were obese, 56% were

diabetic, 34.3% were smokers, 34.3% were hypertensive and 37.5% had hypercholesterolemia. The control group consisted of 27 males (84.4%) and 5 females (15.6%) with a mean age of 47±14 years. The BMI of the control group was 24.8 ± 2.86, which was closer to the patients with CAD.

In terms of the number of vessels involved, among the 32 cases with CAD, SVD (single-vessel disease) was most prevalent 16(50%), followed by DVD (double vessel disease) 13(40.6%) and TVD (triple vessel disease) 3(9.4%). In the study population, the CAD was more prevalent in the male subjects compared to females with a ratio of 5:1 illustrated in (Table 1).

Table 1. Sex distribution in cases and controls.

Group	Sex	
	Female	Male
Case	5 (15.6%)	27 (84.4%)
Control	5 (15.6%)	27 (84.4%)

To study the effect of age on CAD, we divided the case and control subjects into four groups from (30-40), (41-50), (51-60), (61-70). We found that a higher proportion of CAD patients were between the age group of 51-60 years (Table 2).

Table 2. Age group distribution in Cases and controls.

Age Groups (Years)	Groups			
	Case		Control	
	No.	%	No.	%
30-40	3	9.3	13	40.6
41-50	11	34.3	4	12.5
51-60	16	50	8	25
61-70	2	6.25	7	21.8

The mean levels of Apolipoprotein C-III, fasting plasma glucose (FPG), total cholesterol (TC), triglyceride (TG) and low-density lipoprotein cholesterol (LDL-C) were significantly increased in the CAD group compared to controls (Table 3).

Table 3. Comparison of study parameters between Control and CAD group.

Parameter	CAD group, N=32 Mean±SD	Control group, N=32 Mean±SD	p value
Age (years)	51±7.6	47±14	0.1605
BMI (kg/m²)	25.5±2.82	24.8±2.86	0.3280
ApolipoproteinC-III (ng/ml)	434.41±90.68	313.48±34.30	<0.0001***
FPG (mg/dL)	169±64.2	105±9.08	<0.0001***
TC (mg/dL)	179±48.9	158±22.9	0.0315*
TGL (mg/dL)	178±87.9	87.8±33.2	<0.0001***
HDL-C (mg/dL)	40±9.9	45±7.8	0.0284*
LDL-C (mg/dL)	126±36.2	106±20.4	0.0084**
VLDL-C (mg/dL)	35.6±17.6	17.56±6.649	<0.0001***
SdLDL-C (mg/dL)	45.4±17.4	28.16±8.62	<0.0001***
non-HDL-C (mg/dL)	140±43.1	113±22.1	0.0025**
RLP-C (mg/dl)	17±15	7.9±4.6	0.0017**
TyG INDEX	9.45±0.63	8.36±0.41	<0.0001***
TC/HDL-C	4.61±1	3.6±0.7	<0.0001***
LDL-C/HDL-C	3.28±0.93	2.4±0.6	<0.0001***

Data were expressed as Mean ± Standard Deviation, BMI: body mass index, FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very-low-density lipoprotein cholesterol; RLP-C: remnant lipoprotein cholesterol. The significance was determined by independent student 't' test using SPSS 25 version. The values are statistically significant based on the 'P' value.

Significant: *P-value < 0.05, **P-value < 0.01, ***P-value <0.001.

Not Significant: P-value > 0.05.

Receiver Operating Characteristic (ROC) curve was created to evaluate the cardiometabolic risk of Apolipoprotein C-III. An Apolipoprotein C-III cut-off value of ≥350.06 ng/ml is shown to be predictive of CAD with 81% sensitivity and 85% specificity (Figure 1). The area under the curve (AUC) was moderately high (AUC = 0.910, 95% CI = 0.838–0.983, p = <0.0001) indicative of high sensitivity and specificity to predict the correlation of Apolipoprotein C-III with CAD.

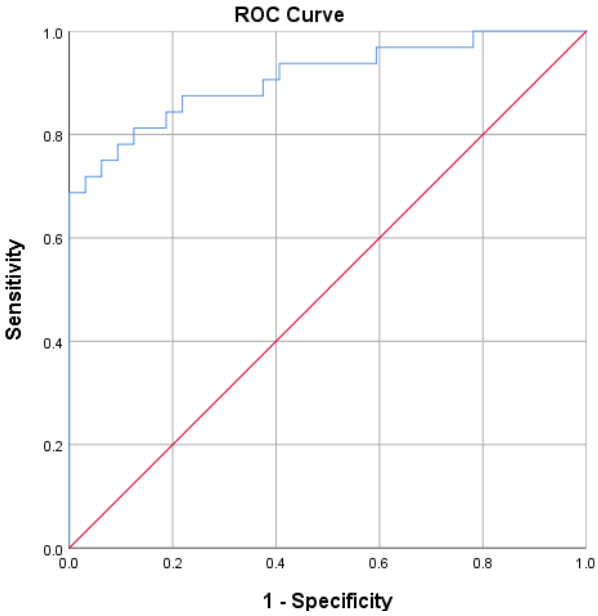

Figure 1. ROC curve computed in SPSS software 25 for the optimal cut-off level of Apolipoprotein C-IIIwith CAD. The cut-off determines by the area near the highest sensitivity and specificity area.

In our study, Apolipoprotein C-III had a non-significant positive correlation with fasting plasma glucose, LDL-C, TyG Index, LDL-C/HDL-C and negative correlation with TC, TG, HDL-C, VLDL-C, SdLDL-C, non-HDL-C, RLP-C and TC/HDL-C among CAD patients. The values are summarized in (Table 4).

Table 4 Pearson's correlation coefficient between Apolipoprotein C-III with other laboratory parameters in patients with CAD.

Parameters	CAD group, N=32	
	r value	p value
FPG (mg/dL)	0.288[a]	0.110
TC (mg/dL)	-0.053[b]	0.772
TGL (mg/dL)	-0.168[b]	0.359
HDL-C (mg/dL)	-0.004[b]	0.984
LDL-C (mg/dL)	0.101[a]	0.584
VLDL-C (mg/dL)	-0.168[b]	0.359
SdLDL-C (mg/dL)	-0.016[b]	0.930
non-HDL-C (mg/dL)	-0.060[b]	0.746
RLP-C (mg/dL)	-0.213[b]	0.242
TyG Index	0.040[a]	0.828
TC/HDL-C	-0.110[b]	0.549
LDL/HDL-C	0.088[a]	0.632

FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very-low-density lipoprotein cholesterol; RLP-C: remnant lipoprotein cholesterol. The significance was determined by independent student 't' test using SPSS 25 version. The values are statistically significant based on the 'P' value.

[a]Positive Correlation, [b]Negative Correlation.

Significant: *P-value < 0.05, **P-value < 0.01, ***P-value <0.001.

Not Significant: P-value > 0.05.

All patients having CAD were stratified into three groups in terms of the number of vessels involved. The incidence was found to be 50% (16) single vessel disease (SVD), 41% (13) double vessel disease (DVD) and 9% (3) triple vessel disease (TVD). One-way ANOVA was carried out to compare the relationship between the three groups of CAD patients were illustrated in (Table 5).

Table 5. Comparison of study parameters between SVD, DVD and TVD in CAD group.

Parameter	Single vessel disease, N=16 Mean±SD	Double vessel disease, N=13 Mean±SD	Triple vessel disease, N=3 Mean±SD	F value	p value
Clinical factors					
Age, years	49±8.9	54±5.7	52±3.1	1.681	0.204
BMI (kg/m²)	26±3.21	25.2±2.64	24.4±0.25	0.515	0.603
Apolipoprotein C-III (ng/ml)	409.33±70.86	454.57±108.16	480.79±93.28	1.356	0.274
FPG(mg/dL)	165±77.3	166±50.5	208±35.6	0.588	0.562
TC (mg/dL)	198±48.4	155±39.7	185±58.3	3.147	0.058
TGL (mg/dL)	196±96.6	153±80.2	193±63.8	0.922	0.409
HDL-C (mg/dL)	41±9.1	37±9.7	44±16	0.809	0.455
LDL-C (mg/dL)	138±36.1	106±31.1	144±22.8	3.795	0.034*
VLDL-C (mg/dL)	39.2±19.3	30.5±16	38.7±12.8	0.922	0.409
SdLDL-C	50.6±18.7	36.8±14.4	54.6±1.01	3.118	0.059
non-HDL-C (mg/dL)	157±44.3	118±33.7	141±42.2	3.393	0.047*
RLP-C	19±16	12±12	32±17	2.534	0.097
TyG INDEX	9.49±0.68	9.3±0.58	9.86±0.47	1.034	0.368
TC/HDL-C	4.95±1.16	4.26±0.75	4.28±0.28	2.013	0.152
LDL/HDL-C	3.49±0.95	2.94±0.68	3.62±1.62	1.514	0.237

FPG: fasting plasma glucose; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; VLDL-C: very-low-density lipoprotein cholesterol; RLP-C: remnant lipoprotein cholesterol. The significance was determined by independent student 't' test using SPSS 25 version. The values are statistically significant based on the 'P' value.
Significant: *P-value < 0.05, **P-value < 0.01, ***P-value <0.001.
Not Significant: P-value > 0.05.

DISCUSSION

As a major regulator for the metabolism of triglyceride-rich lipoproteins(TRLs) in human subjects, Apolipoprotein CIII is widely recognized to mediate its effects through lipoprotein lipase non-dependent and lipoprotein lipase-based mechanisms [14]. Several studies have indicated that Apo C-III is an independent predictor of coronary artery disease. Olivieri *et al*. [15] and Scheffer *et al*. [16] showed an association between increased Apo C-III levels and risk of coronary artery disease. Hypertriglyceridemia has been linked to elevated levels of Apo C-III, which inhibits lipoprotein lipase-mediated hydrolysis of TRL and hepatic absorption mediated by apo-E [17].

Inconsistent with Badran et al.(19), Ahmed Hussein et al.(20) and Christus *et al*.[21] the current study also found higher rates of SVD among CAD. In this study, about two-thirds of the patients with CAD had SVD (16, 50%), followed by DVD (13, 41%) and TVD (3, 9%). The most common vessel involved was LAD (left anterior descending) (19), followed by RCA(right circumflex artery) [11], LCA (left circumflex artery) (5), ramus (2) and left main coronary (1). In another study from South India, most of the patients (57.14%) had SVD, which was seen on CAG, followed by normal coronaries (22.45%); DVD accounted for 16.3% and multivessel disease accounted for 4% [18].

Many studies have established that cardiovascular disease is more common among male subjects and the underlying cause has been clearly known(22). In our study population among the 32 patients with CAD, 27 (84.4%) were males and 5 (15.6%) were females. Based on our study, CAD is more common in men (84.4% versus 15.6%).Similar findings were observed by Leening MJ et al. in his follow-up study of up to 20 years, in which 2888 participants developed cardiovascular disease of which males were more likely than females to develop coronary heart disease as their first event [23]. In addition, the results of the Wegner's study [24] shows that women develop CAD and the first acute myocardial infarction several years later than men. Likewise, Abbasi et al.(25) studied the gender differences in the risk of coronary artery disease (CAD) in Iran. They stated that of the 44,820 patients examined, 37,358 had coronary artery disease which is more common among men (25,363) than in women (11,995).

In our study out of 32 patients, 3(9.4%) belonged to the age of 30-40 years, 11(34.3%) to those aged 41 to 50 years, 16(50%) to those aged 51 to 60 years and 2(6.3%) to those aged 61 to 70 years. Therefore, the higher proportion of CAD patients (16/32) were between the age group of 51 - 60 years which shows the occurrence of CAD in the relatively elder age group. Indians experience their first myocardial infarction at a median age of 53 years, nearly 10 years younger than their peers in developed nations(26). The American Heart Association (AHA) reports that the incidence of CAD in American men and women is

about 40% between the age of 40–59 years and about 75% between the age of 60–79 years and about 86% in those above the age of 80 [27].

Our findings reflect previous studies on the relation between Apo CIII and CAD risk(16). In the present study, the mean level of Apo C-III was significantly greater in CAD patients compared to healthy controls (434.41±90.68 ng/ml vs. 313.48±34.30 ng/ml). Similar findings were observed by Capelleveen *et al*.[14] in their "EPIC-Norfolk Prospective Population Study" on analysis of plasma Apolipoprotein C-III levels and risk of CAD.

The prospective study performed by Scheffer et al.(16)on 2244 participants who had participated in the "Hoorn study" concluded that the increased levels of Apo C-III were found to be a significant and independent risk factor of cardiovascular metabolic risk. Apo C-III was found to be positively correlated with fasting plasma glucose, LDL-C, TyG Index, LDL-C/HDL-C and negatively correlated with TC, TGL, HDL-C, VLDL-C, SdLDL-C, non-HDL-C, RLP-C and TC/HDL-C among CAD patients. Meanwhile, findings by Capelleveen *et al*. [14] and Scheffer *et al.*[16] observed that Apo C-III had a positive correlation with fasting plasma glucose, total cholesterol, triglycerides and LDL-Cholesterol (low-density lipoprotein cholesterol), as well as a negative correlation with HDL-Cholesterol (high-density lipoprotein cholesterol).

In this study, the optimal cut-off values obtained by the analysis were Apo C-III (350.6, AUC-0.910, CI-0.838-0.983 P = <0.0001). The ANOVA demonstrated the association between angiographic findings in the CAD group and the risk factors of CAD. It shows that there was no association between the disease severity and the Apo C-III levels, whereas LDL-C and non-HDL-C had a significant positive relationship between the three groups of CAD.

The logistic regression test showed that an increase in levels of Apo C-III plays a significant role in the development of risk factors in coronary artery disease (OR = 23.4, 95% CI: 6.36-86.14 P = <0.0001), which is similar to the findings of Scheffer *et al*. [16]. As the Apo C-III levels become lower due to the administration of statins, the lipid-lowering drugs may have affected our findings(28). However, the risk ratios in this analysislikely underestimate the high chance of Apo C-III risk.

Wang et al.(29) in their study showed that exercise lasting 8 weeks resulted in a considerable reduction in Apo C-III and triglyceride concentrations relative to baseline. Zheng *et al*.[30] in their findings showed that statin therapy, successfully reduces the Apo C-III induced endothelial cell activation. Statins are found to directly decrease endothelial adhesion caused by Apo C-III and show new vascular protection in patients with high plasma Apo C-III levels [30]. The results of Nessim *et al*.[31] reported that niacin therapy has also established a reduction in Apo C-III circulatory levels. The randomized study by Gaudet *et al*. [32] among hypertriglyceridemia patients showed that low levels of triglyceride were seen when administered with ISIS 304801, a second-generation antisense inhibitor for the synthesis of Apo C-III. The plasma levels of Apo C-III were decreased by 71% to 90% and the triglyceride levels by 56% to 86% after 13 weeks of study drug administration. Christie reported that a single dose of RNAi therapy demonstrated an effective and reliable decrease in serum Apo C-III and triglyceride levels up to 16 weeks in healthy volunteers [33].

The main limitation of the study is the relatively small sample size (32 cases and 32 controls in this study) and lesser females (10 females and 54 males). This study needs to be performed on a larger sample size to validate these findings and in addition to the conventionally used ones, advanced lipid parameters can also be used as CAD markers.

CONCLUSION

The present study observation found that among the study participants, Apolipoprotein C-III levels were significantly higher in CAD patients and strongly correlated with established independent risk factors of CVD. Serum lipids, lipoprotein levels and lipid ratios were also significantly elevated among the patients with CAD. Thus, the evaluation of Apolipoprotein C-III is a significant independent predictable marker of cardiovascular disease along with serum lipids and lipoprotein levels.

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CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

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