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The Predictability of APO B, APO A, APO B/APO AI as Better Markers for CAD in South Indian Population

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Abstract: ***Aim:*** *To evaluate the association of non conventional risk factors for atherosclerosis ApoB, ApoAI and ApoAI/ApoB ratio in patients with and without CAD in comparison to conventional lipid parameters, hsCRP levels and Insulin resistance. Methods: A case-control study on 125 subjects each of 35-65 years of age, with and without CAD, confirmed by coronary angiogram was conducted and the levels of serum hsCRP, ApoB and ApoAI were estimated. Pearson's correlation was done to find the association of ApoB, ApoAI, and their ratio with other cardiovascular risk factors. Multivariate logistic regression analysis was used to estimate the effect of ApoB, ApoAI on CAD, controlling the other confounders. ROC analysis was done to calculate the sensitivity and specificity of ApoB, ApoAI and ApoAI/ApoB ratio for CAD. A value of P<0.05 was considered significant.* ***Results:*** *Apo A1 was significantly lower and the serum ApoB level was significantly higher in subjects with CAD, with and without DM than the control. The levels of conventional markers of CAD, like troponin t, CPK-MB and LDH were very highly significant with ApoB, ApoAI and ApoB/ApoAI ratio. Conclusion: Declined levels of ApoAI and elevated levels of ApoB among CAD subjects proved them to be efficient biomarkers for CAD.*

Keywords: apolipoproteins, CAD, biomarkers, lipids, diabetes mellitus

1. Introduction

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in both developed and developing countries [1]. The increase of CAD among Indians has been observed throughout the country, as well as among Indian immigrants in different parts of the world. CAD epidemic in India has entered into an epidemiological transition phase. It has been projected that mortality attributable to "circulatory system diseases" in India would rise by 103% in men and by 90% in women during the period 1985 to 2015.

Myocardial Infarction (MI) is a manifestation of CAD due to atherosclerotic plaque deposits undergoing dynamic changes. Pathogenesis actually involves interplay of dyslipidemia with oxidative damage and inflammation leading to atherosclerosis [2]. Lipids are involved in the pathogenesis of atherosclerosis, and hence lipid profile is a basic investigation done in cases of CAD. The lipoprotein transport system is central to the mechanism by which genes, diet and hormones interact to regulate the cholesterol and triglyceride plasma levels and their tissue distribution [3].

For over three decades it has been recognized that a high level of total cholesterol (TC), particularly low density lipoprotein cholesterol (LDL-C), is a major risk factor for developing MI but a considerable proportion of patients with MI have levels of LDLC and total cholesterol within the recommended range [4-6]. The other lipid parameters are also associated with elevated cardiovascular risk and it has been suggested that TC and LDL-C may not be the best discriminates for the presence of CAD.

Comprehensive Lipid tetrad index (CLTI) derived by the product of cholesterol, triglycerides and Lp(a) values divided by the HDL-C level may be the best estimate of the total burden of dyslipidaemia as it eliminates the need for various cut-off points and ratios involving the lipid subsets. A high index (>20,000) would indicate the presence of a highly atherogenic lipid profile. This index can serve as a better and novel risk factor for CAD and has been determined in few studies involving South Indian population [7].

Apolipoproteins (apo) AI and B are structural proteins for high density lipoproteins (HDL-C), and the very low density-low density lipoprotein spectrum (VLDL-LDL) respectively. Apo B containing lipoproteins carry lipid from liver and gut to the sites of utilization, while Apo AI containing particles mediate reverse cholesterol transport returning excess cholesterol from peripheral tissues to liver.

Apo AI mediates transferring cholesterol from cell surfaces to lipoprotein particles and activates the enzyme responsible for cholesterol esterification in the circulation, lecithin: cholesterol acyl transferase (LCAT). Cholesterol efflux from tissues occurs via receptors such as ABCA1 and ABCG1 [8, 9]. The sterol acquired by HDL-C is then trapped by LCAT-mediated formation of cholesteryl ester, and in the process the structure of the lipoprotein changes from discoidal to spherical as the lipid becomes sequestered in the hydrophobic interior. Cholesteryl ester in HDL-C is then either passed by the action of cholesteryl ester transfer protein (CETP) to Apo B containing lipoproteins (VLDL-C and LDL-C) and so finds its way back to the liver, or is removed directly from the HDL-C by receptors such as SR-B1 on hepatocytes [8].

The role of non-conventional lipid risk factors like Lp(a), Apo AI and Apo B -100 and other conventional lipid profile parameters in children and adolescents of premature CAD patients in India was evaluated in a study which explains the highest occurrence of premature CAD in this population [10]. In the last decade, mounting evidence also implicates apolipoprotein B and apolipoprotein A-I levels in the pathogenesis of CAD [11-13]. Indeed, several recent reports have raised the possibility that these measures might be superior to traditional lipid measures for CAD risk prediction based on the premise that Apo B levels better reflect the number of atherogenic lipoprotein particles in a given volume of plasma [14,15]. However, the published data are not entirely consistent because in some other studies Apo B and Apo AI did not perform better than traditional lipid measures for the purpose of risk prediction fuelling an intense debate. Though many researchers have studied ApoB/ApoA ratio and compared it with other lipid parameters, comparison with conventional lipid ratios have not been done for prediction of risk of CAD [16, 17]. Hence a study was conducted to evaluate the difference in various risk factors for atherosclerosis namely apoB, apoA1 and apoA1/ApoB ratio in comparison with LDL, HDL cholesterols, CLTI, hs-CRP levels and Insulin resistance in the study population with and without CAD.

2. Materials and Methods

The levels of serum hs-CRP, apoB and apoA1 were estimated in the study population, between the age group 35-65 years, admitted in the Cardiac Care Centre of a tertiary care teaching hospital. This investigation was carried out using a case control study. The subjects (n=125) with CAD confirmed by coronary angiogram were cases. The subjects (n=125) with absence of CAD confirmed by coronary angiogram comprised the control group.

Methods Adopted

Fasting venous blood samples (5ml) were collected from case and control, serum separated and assayed for hsCRP, Apo B, and Apo AI measurements. Serum concentrations of hsCRP were estimated using hsCRP latex DAIICHI kit (Daiichi Pure Chemicals Co. Ltd., Tokyo, Japan) by immuno-turbidimetric method using semi auto analyser (Star 21 plus, Rapid Diagnostics, USA). Serum concentrations of apolipoprotein AI were estimated using Daiichi kit (Daiichi pure co., chemicals, Japan) by immuno-turbidimetric method, using semi auto analyser (Star 21 plus, Rapid Diagnostics, USA). Serum concentrations of apolipoprotein B were estimated using Daiichi kit, Daiichi pure co., chemicals, Japan, by immuno-turbidimetric method using semi auto analyser (Star 21 plus, Rapid Diagnostics, USA). Insulin resistance was calculated using Homeostasis assessment (HOMA-IR) model using the formula: Fasting insulin (µIU/ml) x fasting glucose (mmol/litre) / 22.5. CLTI was derived by multiplying the three commonly measured lipids directly associated with CAD and dividing the product by HDL-C, which is inversely associated with CAD (total cholesterol×triglyceride×Lp(a)/HDL-C).

Statistical Methods

Descriptive statistics were used to summarize the clinical findings, risk factors, and coronary angiographic findings of patients. Student's t test, chi square test and analysis of variance test (ANOVA) were used to get the statistical significance. Pearson's correlation co-efficient analysis was done to find the associations of Apo B, Apo AI, and their ratio with other cardiovascular risk factors. The association between individual risk factor and outcome was estimated using univariate logistic regression. The multivariate logistic regression analysis was used to estimate the effect of Apo B, Apo AI on CAD, controlling the other confounders. ROC analysis was done to calculate the sensitivity and specificity of Apo B, Apo AI and Apo AI/Apo B ratio for CAD. As the distribution of Apo B, Apo AI were highly skewed, logarithmic transformation of Apo B, Apo AI were used for statistical analysis. A value of $P<0.05$ was taken as significant.

3. Results

In the current study, among 125 subjects diagnosed with CAD, 91 (73%) patients were males and 34 (27 %) were females. In angiographically proven control population 71 (57%) were females and 54 (43%) were males. Among cases 34 (27.2%), 35 (28%) and 56 (44.8%) had Single Vessel Disease, Double Vessel Disease and Triple Vessel Disease respectively. 73 (58.4%) subjects had type 2 DM with CAD and 52 (41.6%) had CAD without type 2 DM. Among the control subjects, 64 (51.2%) subjects had type 2 DM and 61 (48.8%) had no type 2 DM. In the total study population, 111(44.4%) subjects had positive family history of CAD while 139 (55.6%) subjects had no family history of CAD. Among the above study population 198 (79.2%) were non smokers. 37 (14.8%) were smokers and 15 (6%) were ex-smokers.

Table 1 shows characteristics of subjects with CAD and without CAD included in the case control study such as, age, body mass index (weight in kg / height in m^2), waist hip ratio and waist circumference, systolic blood pressure (mm Hg), diastolic blood pressure (mm Hg), glycated hemoglobin (%), total serum cholesterol (mg/dl), serum triglycerides (mg/dl), total serum cholesterol (mg/dl), serum triglycerides (mg/dl), LDL-C (mg/dl), HDL-C (mg/dl). We found that subjects with CAD when compared without CAD had higher systolic blood pressure (139 vs.128 mm Hg, $P < 0.01$), diastolic pressure (87 vs. 82 mm Hg, $P < 0.01$), fasting plasma glucose (144 vs. 127 mg/dl, $P < 0.05$) and glycated haemoglobin (7.0 vs. 6.5 %, $P < 0.05$). However, waist hip ratio (WHR) (94.4 vs. 93.2 cm, $P < 0.368$), LDL-C (109 vs. 107 mg/dl, $P= 0.550$) and HDL-C (40 vs. 41 mg/dl, $P= 0.213$) levels were not statistically significant between the subjects with CAD and without CAD.

Table 1: General characteristics of study subjects

*Variables**	*Subjects without CAD (n = 125)*	*Subjects with CAD (n = 125)*	*P value*
Age (years)	51 ± 8	55 ± 8	<0.01
BMI (kg/m^2)	26.5 ± 4.3	26.2 ± 4.0	0.333
Waist circumference (cm)	93.2 ± 11.4	94.4 ± 11.1	0.368
Systolic blood pressure (mm Hg)	128 ± 16	139 ±19	<0.01
Diastolic blood pressure (mm Hg)	82 ± 9	87 ± 9	<0.01
HOMA – IR	3.6 ±1.5	5.4 ± 1.7	<0.01
Fasting plasma glucose (mg/dl)	127 ± 51	144 ± 66	<0.05
Glycated haemoglobin (%)	6.5 ± 1.4	7.0 ±1.6	<0.05
Total serum cholesterol (mg/dl)	166 ± 42	172 ± 39	0.187
Serum triglycerides (mg/dl)	159 ± 86	185 ± 83	<0.01
LDL cholesterol (mg/dl)	107 ± 30	109 ± 30	0.550
HDL cholesterol (mg/dl)	41 ± 7	40 ± 7	0.213
hs-CRP (mg/dl)	0.44 ± 0.12	0.55 ± 0.13	<0.01

* Data is presented as mean± SD

The mean serum levels of Apo AI and Apo B among CAD and non-CAD subjects are reported in Figure 1. The mean serum Apo AI was significantly lower in subjects with CAD (141.06 ± 2.53 mg/dl; P<0.001) when compared to subjects without CAD (162.8 ± 3.37 mg/dl). However, serum Apo B was significantly higher in subjects with CAD (125.7 ± 1.51 mg/dl; P<0.001) compared to subjects without CAD (104.84 ± 1.49 mg/dl). The mean levels of Apo AI and Apo B in CAD and non-CAD patients with and without diabetes mellitus (DM) are reported in Figure 2. The subjects who had CAD with (144.31 ± 3.51 mg/dl) and without DM (136.50 ± 3.51 mg/dl) had significantly lower levels of Apo AI (P<0.05) than non-CAD subjects with (163.34 ± 4.90 mg/dl) and without DM (162.19 ± 4.63 mg/dl). The serum-Apo B level was significantly higher (P<0.05) among CAD subjects with (126.92 ± 1.91 mg/dl) and without DM (123.97 ± 2.44 mg/dl) compared to non-CAD subjects with (103.8 ± 1.99 mg/dl) and without DM (105.9 ± 2.24 mg/dl).

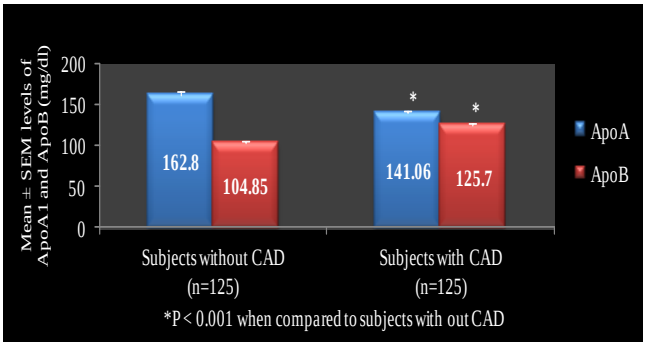


Figure 1: Apo AI and Apo B levels in relation to CAD

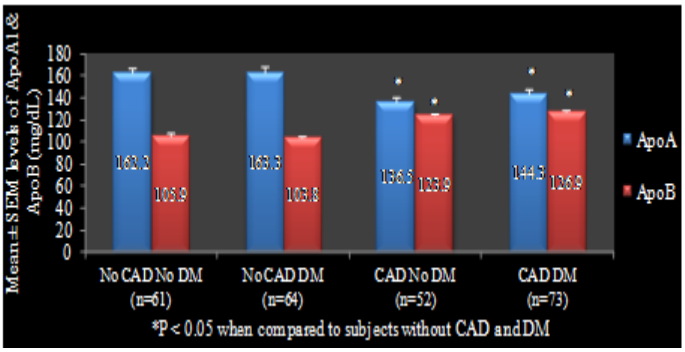


Figure 2: Apo AI and Apo B levels in relation to CAD and DM

Pearson's correlation analysis of Apo AI and Apo B and their ratio with cardiovascular risk factors revealed the following aspects. Apo B had significant correlation with systolic blood pressure (P<0.05), diastolic blood pressure (P<0.01); while Apo B/Apo AI was correlated with systolic blood pressure (P<0.05). Moreover, Apo B showed significant correlation with the biochemical parameters like FBS and HOMA- IR (P<0.05); with lipid profile namely serum TC, TG, LDL-C, HDL-C, non-HDL-C, CLTI and also hs-CRP levels (P<0.01); while Apo AI had significant correlation with HDL-C (P<0.01), FBS, serum TC and hsCRP (P<0.05). Moreover, Apo B/Apo AI was associated significantly with the biochemical parameters like FBS, HDL-C, LDL-C, CLTI and hsCRP (P<0.01). Cardiac markers were significantly associated (P<0.01) with Apo B, Apo AI and Apo B/Apo AI ratio; the same trend was observed with the Stenosis scores (Table 2).

Table 2: Pearson correlation analysis of Apo AI and Apo B and Apo B/Apo AI with cardiovascular risk factors

Risk Factors	*Apo B/Apo AI*		*Apo AI*		*Apo B*	
	r value	*P value*	*r value*	*P value*	*r value*	*P value*
Apo AI (mg/dl)	0.756**	< 0.001				
Apo B(mg/dl)	0.615**	< 0.001				
Age (Years)	0.148*	0.021	-0.069	0.280	0.102	0.109
Body mass index (kg/m^2)	-0.028	0.658	0.009	0.894	-0.059	0.356
Waist circumference	-0.016	0.806	0.053	0.408	0.025	0.699
Systolic blood pressure (mmHg)	0.128*	0.045	0.001	0.991	0.156*	0.014
Diastolic blood pressure (mmHg)	0.117	0.066	0.013	0.837	0.175**	0.006
HOMA IR	0.161*	0.012	-0.105	0.099	0.163*	0.010
Fasting Blood Sugar (mg/dl)	0.200**	0.002	-0.135*	0.034	0.137*	0.031
Glycated hemoglobin (%)	0.096	0.199	-0.016	0.834	0.110	0.140
Serum cholesterol (mg/dl)	0.104	0.106	0.131*	0.040	0.448**	< 0.001
HDL cholesterol (mg/dl)	-0.217**	0.001	0.405**	< 0.001	0.217**	0.001
LDL cholesterol (mg/dl)	0.219	0.001	0.102	0.109	0.594**	< 0.001
Non HDL cholesterol (mg/dl)	0.109	0.109	0.076	0.266	0.429**	< 0.001
TG : HDL	0.115	0.090	-0.109	0.108	0.090	0.182
Total Cholesterol : HDL	-0.013	0.845	-0.028	0.668	-0.038	0.551
Serum triglycerides (mg/dl)	0.111	0.083	-0.030	0.635	0.201	0.001
CLTI (mg/dl)^2	0.244**	< 0.001	-0.074	0.249	0.368**	< 0.001
hs-CRP (mg/dl)	0.253**	< 0.001	-0.148*	0.020	0.173**	0.006
Cardiac markers						
Troponin t levels (ng/dl)	0.380**	< 0.001	-0.182**	0.004	0.381**	< 0.001
CPK (u/l)	0.399**	< 0.001	-0.201**	0.001	0.407**	< 0.001
CPK-MB(u/l)	0.407**	< 0.001	-0.196**	0.002	0.411**	< 0.001
LDH (u/l)	0.289**	< 0.001	-0.160**	0.012	0.304**	< 0.001
Stenosis score	0.491**	< 0.001	-0.215**	0.001	0.539**	< 0.001

**Correlation is significant at 0.01 level
*Correlation is significant at 0.05 level

The association between serum apolipoproteins and angiographic severity of CAD is depicted in figure 3. A significant decreasing trend with Apo AI was observed in severity of CAD: No CAD (Mean ± SEM = 163.21± 3.41mg/dl) > SVD (Mean ± SEM = 143.2 ± 4.26 mg/dl) > DVD (Mean ± SEM = 141.18 ± 4.33 mg/dl) >TVD (Mean ± SEM = 138.58 ± 4.25 mg/dl). Meantime, a significant increasing trend with Apo B was observed in severity of CAD: NCAD (Mean ± SEM = 104.76 ± 1.49 mg/dl) < SVD (Mean ± SEM = 118 ± 2.18 mg/dl) < DVD (Mean ± SEM = 127.4 ± 3.34 mg/dl) <TVD (Mean ± SEM = 128.49 ± 2.23 mg/dl). In addition, family history (FH) is inherited in a dominant manner. In our analysis (Figure 4), the mean level of Apo AI was lower in FH-CAD (Mean ± SEM =150.52 ± 3.36 mg/dl) than in non-FH-CAD (Mean ± SEM=152.8 ± 2.94 mg/dl) while Apo B was higher in FH-CAD (Mean ± SEM=116.07±2.00 mg/dl) than in non-FH-CAD (Mean ± SEM =114.72±1.59 mg/dl). Even though there was no statistical significance, the elevated level of Apo B in subjects with FH-CAD and lower level of Apo AI in FH-CAD FH may probably play a role in the development of CAD. In the case of association of smoking and CAD, our study had shown that (Figure 5), the mean level of Apo AI is lower in smokers (Mean ± SEM=135.53±5.75 mg/dl) than in non-smokers (Mean ± SEM=154.94±2.40 mg/dl) and ex-smokers (Mean ± SEM=151.03±10.22 mg/dl). Meantime, the mean level of Apo B is higher in smokers (Mean ± SEM=117.16±2.97 mg/dl) than in non-smokers (Mean ± SEM=114.98±1.39mg/dl) and ex-smokers (Mean ± SEM= 115.07±6.65 mg/dl). These findings concluded that smoking and positive family histories of CAD are additional risk factors for CAD among individuals, who often have milder coronary artery stenosis.

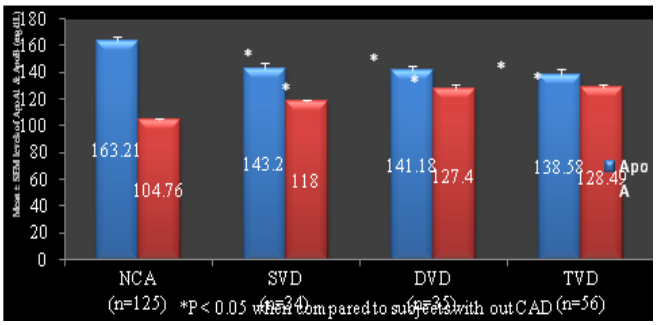


Figure 3: Apo AI and Apo B levels in relation to severity of CAD

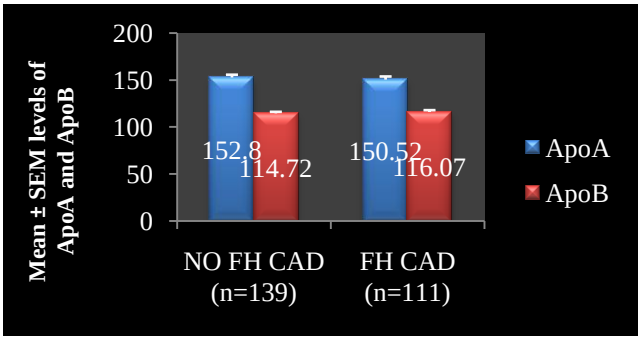


Figure 4: Apo AI and Apo B levels in relation to family history of CAD

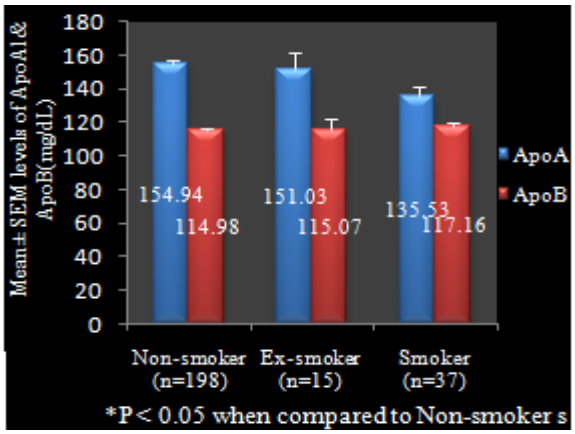


Figure 5: Apo AI and Apo B levels in relation to smoking

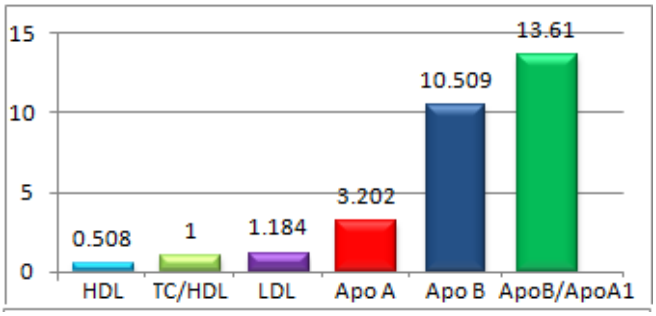


Figure 6: Odds ratio for Apo AI, Apo B, Apo B/Apo AI, HDL-C, LDL-C and TC/HDL-C (Dependent variable: CAD with 95% CI)

Multiple logistic regression analysis was performed using Apo AI and Apo B as the independent variables and the risk factors for CAD (Table 3). In model-1, the association of Apo B with elevated level of odds-ratio and confidence interval was highly significant (P<0.001) with the dependent variable of CAD. Moreover, the relation of Apo AI with low-level of odds-ratio and confidence interval was significantly correlated with the dependent variable of CAD. Consequently, after adjustment of age and gender in model-2, adjustment of insulin resistance in model-3, and even addition of FBS in model-4, the serum levels of Apo AI and Apo B were highly significant (P<0.001) with dependent variable CAD and thus proved as predictive markers for CAD.

Table 3: Multiple logistic regression analysis using CAD as dependent variable

Parameter	*Odds Ratio [OR]*	*95% Confidence Interval [CI]*	**P value**
Independent variable: Apo AI			
Model 1: Apo AI – Unadjusted	0.979	0.970 – 0.987	**<0.001**
Model 2: [Model 1 + adjusted for age and gender]	0.980	0.971 – 0.990	**< 0.001**
Model 3: [Model 2 + adjusted for insulin resistance]	0.982	0.972 – 0.992	**< 0.001**
Model 4: [Model 3 + FBS**]**	0.982	0.972 – 0.992	**< 0.001**
Independent variable: Apo B			
Model 1: Apo B – Unadjusted	1.077	1.056 – 1.099	**<0.001**
Model 2: [Model 1 + adjusted for age and gender]	1.080	1.056 – 1.104	**< 0.001**
Model 3: [Model 2 + adjusted for insulin resistance]	1.076	1.052 – 1.101	**< 0.001**
Model 4: [Model 3 + FBS**]**	1.076	1.052 – 1.100	**< 0.001**

In an attempt to find which among the lipid profile panel whether the conventional (LDL-C, HDL-C and TC/HDL-C) or the non-conventional (Apo B, apo A and Apo B/ Apo AI) parameters stand out to be better markers for CAD, the following interesting facts were revealed from the multiple logistic regression analysis: The odds ratio of non-conventional risk factors like Apo AI (OR: 3.202; 95% C.I.: 1.893-5.415; P<0.000), Apo B (OR: 10.509; 95% C.I.: 7.241-25.580; P<0.000) and Apo B/Apo AI ratio (OR: 13.610; 95% C.I.: 7.241-25.580; P<0.000) were comparatively higher than non-conventional risk factors like HDL-C (OR: 0.508; 95% C.I.: 0.299-0.862; P<0.012), LDL-C (OR: 1.184; 95% C.I.: 0.711-1.970; P<0.517) and TC/HDL-C (OR: 1.000; 95% C.I.: 0.999-1.000; P<0.527) respectively. In this case of prediction of better marker for CAD, Apo B was significantly higher than LDL-C, Apo AI was significantly higher than HDL-C and Apo B/Apo AI ratio was significantly higher than TC/HDL-C which demonstrates the higher potency of Apo B, Apo AI and Apo B/Apo AI in the prediction of CAD risk (Table 4 and Figure 6).

Table 4: Multiple logistic regression analysis for association of CAD with Apo AI, Apo B, Apo B/Apo AI, HDL-C, LDL-C and TC/HDL-C

HDL-C Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	0.508	0.299	0.862	0.270	0.012
Constant	2.676	-	-	0.201	< 0.001
LDL-C Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	1.184	0.711	1.970	0.260	0.517
Constant	1.451	-	-	0.182	0.041
Apo AI Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	3.202	1.893	5.415	0.268	< 0.001
Constant	0.743	-	-	0.183	0.104
Apo B Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	10.509	7.241	25.580	0.322	< 0.001
Constant	0.359	-	-	0.192	< 0.001
TC/HDL-C Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	1.000	0.999	1.000	0.001	0.527
Constant	1.026	-	-	0.128	0.843
Apo B/Apo AI Vs CAD					
CAD code	**95% C.I. for EXP(B)**			**Standard error**	**P value**
	Exp(B)	**Lower**	**Upper**		
CAD variables	13.610	7.241	25.580	0.322	< 0.001
Constant	0.359	-	-	0.192	< 0.001

F statistics showed (Table 5) overall high significance of Apo AI, Apo B and Apo B/Apo AI ratio in patients (P< 0.001). The overall variables (Apo AI, Apo B and Apo B/Apo AI ratio) exhibited an excellent explanation of the variation in the occurrence of CAD. Apo B/Apo AI ratio (F: 70.977) and Apo B (F: 46.271) had shown higher F value for occurrence of CAD which were highly significant (P<0.001) and proved itself as a potent predictor for CAD. Comparatively Apo AI (F: 12.230) had lower F value for occurrence of CAD, but was also highly significant (P<0.001) and also proved itself as an effective marker for CAD.

Table 5: Descriptive statistics for Apo AI, Apo B and Apo B/Apo AI

Apo AI	Sum of Squares	Mean	SD	SEM	F	P value
Between Groups	13462.482	13.9439	29.35914	2.83826	12.230	< 0.001
Within Groups	269686.206	28.8429	35.81714	3.02710	-	-
Apo B	Sum of Squares	Mean	Standard Deviation	Standard error	F	P value
Between Groups	44831.071	5.8300	15.72687	1.57269	46.271	< 0.001
Total	284143.141	22.2088	33.84876	2.14508	-	-
Apo B/Apo AI ratio	Sum of Squares	Mean	Standard Deviation	Standard error	F	P value
Between Groups	63691.548	8.4786	20.91210	1.76740	70.977	< 0.001
Within Groups	218953.851	40.9717	38.81175	3.76973	-	-

The Chi-Square test was performed to measure the value (presence or absence of normal and abnormal levels) of CAD risk factors among subjects (Table 6). The value of Apo B (59.999; P<0.001) and Apo B/Apo AI ratio (83.660; P<0.001) were higher than LDL-C (1.109; P<0.001) and the value of Apo AI (23.545; P<0.001) was higher than HDL-C (9.841; P<0.001) value which were highly significant for prediction of CAD among subjects. In this case, LDL-C had shown very lower Chi-Square value, likelihood ratio and linear-by-linear-association than Apo B and Apo B/Apo AI ratio. Also, the value of LDL-C and HDL-C were very inferior to minimum expected count. Hence, Apo B and Apo B/Apo AI ratio are the prospective predictors of CAD than all other risk factors, especially LDL-C.

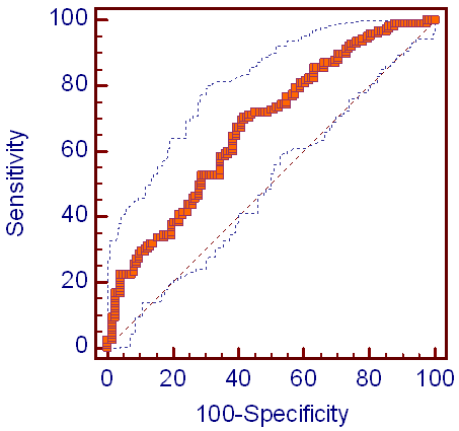
Table 6: Chi-Square Tests for association of CAD with Apo AI, Apo B and Apo B/Apo AI

Apo AI			
	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	23.545[a]	3	< 0.001
Likelihood Ratio	24.020	3	< 0.001
Linear-by-Linear Association	20.437	1	< 0.001
N of Valid Cases	250		
Apo B			
	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	59.999[b]	3	< 0.001
Likelihood Ratio	63.569	3	< 0.001
Linear-by-Linear Association	49.236	1	< 0.001
N of Valid Cases	250		
Apo B/Apo AI ratio			
	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	83.660[c]	3	< 0.001
Likelihood Ratio	90.306	3	< 0.001
Linear-by-Linear Association	75.582	1	< 0.001
N of Valid Cases	250		
LDL-C			
	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	1.109[d]	3	0.775
Likelihood Ratio	1.132	3	0.769
Linear-by-Linear Association	0.197	1	0.57
N of Valid Cases	250		
HDL-C			
	Value	**Df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	9.841[e]	3	0.020
Likelihood Ratio	9.608	3	0.022
Linear-by-Linear Association	5.072	1	0.024
N of Valid Cases	250		

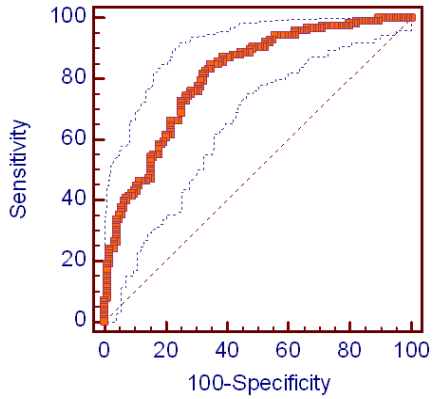
Notes:

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 14.71.
b. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 13.63
c. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 14.63
d. 0 cells (.0%) have expected count less than 5. The minimum expected count is 13.30
e. 0 cells (.0%) have expected count less than 5. The minimum expected count is 11.65

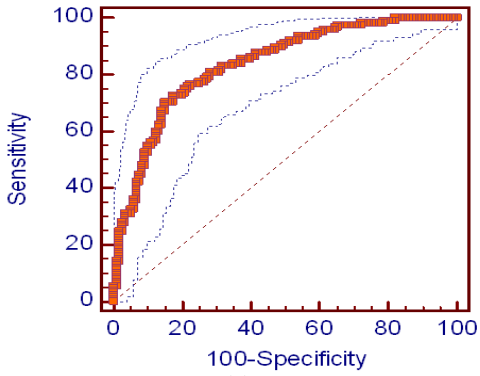
The receiver operating characteristic (ROC) curve of Apo AI, Apo B and Apo B/Apo AI ratio are represented in figure 7. The cut-off values for Apo B and Apo AI were determined as 109.3 and 150.2 mg/dl. The sensitivity value of Apo B and Apo B/Apo AI were maximally correlated with the area of true-positive than the areas of false-positive and false-negative in graph. Moreover, Apo AI was very moderately correlated with the area of true-positive than the areas of false-positive and false-negative. So the sensitivity score of Apo AI was negative, so the prediction of CAD prevalence was less (50.6%). But, the sensitivity score of Apo B (60.88%) was positive and the prediction of CAD prevalence also high (50.6%). In this case, our subjects had shown maximum sensitivity for Apo B (AUC: 0.809; 95% C.I: 0.755-0.856) which was highly significant (P<0.0001) with the prediction of CAD. Apo B/Apo AI ratio (AUC: 0.837; 95% C.I: 0.784-0.881) and Apo AI (AUC: 0.673; 95% C.I: 0.611-0.731) were also significant with P<0.0001, but the disease prevalence scores were less. Hence, the ROC curve concludes that, Apo B and the Apo B/Apo AI ratio are better markers than any other CAD predictors.



(a)



(b)



(c)

Figure 7: (a) the ROC curve of Apo AI. The ROC curve for the sample size of 250, disease prevalence – 50.6%, standard error – 0.0339, area under the ROC curve (AUC) – 0.673, 95% confidence interval – 0.611-0.731, Z-statistics – 5.106, and significance level p (<0.0001). (b) The ROC curve of Apo B. The ROC curve for the sample size of 250, disease prevalence – 60.82%, standard error – 0.0270, area under the ROC curve (AUC) – 0.809, 95% confidence interval – 0.755-0.856, Z-statistics – 11.477, and significance level p (<0.0001). (c) The ROC curve of Apo B/Apo AI ratio. The ROC curve for the sample size of 250, disease prevalence – 50.8%, standard error – 0.0253, area under the ROC curve (AUC) – 0.837, 95% confidence interval – 0.784-0.881, Z-statistics – 13.296, and significance level p was <0.0001.

4. Discussion

In a quest to find whether apolipoproteins AI and B stand out to be better markers than conventional lipids for CAD, angiographically verified case control study was pursued in a South Indian population. The odds ratio of non-conventional risk factors like Apo AI (OR: 3.202; P<0.001), Apo B (OR: 10.509; P<0.001) and Apo B/Apo AI ratio (OR: 13.610; P<0.001) were comparatively higher than non-conventional risk factors like HDL-C (OR: 0.508; P<0.012), LDL-C (OR: 1.184; P<0.517) and TC/HDL-C (OR: 1.000; P<0.527) respectively. It is very evident that from this study Apo B was significantly higher than LDL-C, Apo AI was significantly higher than HDL-C and Apo B/Apo AI ratio was significantly higher than TC/HDL-C which demonstrated the higher potency of Apo B, Apo AI and Apo B/Apo AI in the prediction of CAD risk. The Apo A I and Apo B remained the potent risk factors for CAD even after adjustment for age, gender, insulin resistance and FBS. The OR for prediction of CAD-incidence among study subjects was higher for Apo B. When adjusting for age, gender, insulin resistance and FBS, the contribution of the LDL-C and HDL-C lost their statistical significance. However, Apo B (OR=10.509; P<0.001) at any level of LDL-C, also especially in those having normal/low LDL-C levels and Apo AI (OR= 3.202; P<0.001) remained highly significant predictors for CAD. It was also found that the predictive value of the Apo B/Apo AI ratio was highly preserved.

This was one of the major objectives of this study to determine whether the Apo B is superior to conventional lipids, lipoproteins, and cholesterol ratios to predict risk of CAD. Moreover, we examined whether any lipids, lipoproteins, or cholesterol ratios add significant predictive information beyond that provided by the Apo B. Walldius, et al., found that the Apo B was the strongest of all risk factors including smoking, hypertension, abdominal obesity, diabetes, alcohol, psycho-social stress, vitamin intake, and exercise. In our study (ANNOVA, ROC curve) the single and strongest risk marker was the Apo B for CAD, which correlated with earlier [18-20]. Notably, the Apo B was also strongly predictive in those with normal lipid values. High Apo B group was apparently significantly associated with insulin resistance, inflammatory marker (hs CRP) and low HDL-C in spite of the lower levels of classical lipid risk factors - namely TC, LDL-C. Our findings are in agreement with the results from IRAS (insulin resistance atherosclerosis) study, in which Apo B was more closely associated with central adiposity, insulin resistance, thrombosis, and inflammation than LDL-C [21] and non-HDL-C [22].

Numerous trials have demonstrated that hypolipidemic therapies (primarily ustatins) directed at LDL-C lowering significantly reduce the risk of CAD disease. Nevertheless, even with adequate LDL-C lowering, many patients on statin therapy have significant residual CAD disease risk. One of the reasons of this residual risk may be that LDL-C is not the appropriate treatment target, especially in patients with obesity, metabolic syndrome, type 2 diabetes, in patients with cardiovascular disease, or generally in patients with the high cardio metabolic risk [22-25]. These patients usually have relatively low TC and LDL-C levels but increased number of small, dense LDL-C particles [26,27] and other atherogenic lipoproteins (VLDL-C, IDL-C), which are not reflected well by assessing LDL-C [28,29]. As all atherogenic lipoprotein particles each contain only one molecule of Apo B, the concentration of Apo B is a better marker of the total number of atherogenic particles in the blood. The predictive value of Apo B as the strongest single lipid associated risk factor has been shown in large observational studies [30, 31], in primary-prevention trials [32], and in secondary-prevention trials [33,34]. Thus, Apo B should be used for assessment of risk and evaluation of hypolipidemic therapy especially in subjects with cardio metabolic risk, because LDL-C may underestimate the risk in this population.

Furthermore, pathophysiological surrogate markers of atherosclerosis defined by coronary angiography and calcium scores of the coronary arteries, and by ultrasound techniques such as IMT of the carotid, endothelial and existence of femoral plaques all correlate strongly with a

high Apo B. In addition, a high Apo B also predicts risk of progression of carotid plaques. Importantly, previous researches explain that Apo B is associated with ischaemic and atherosclerotic diseases and their manifestations [35, 36]. All evidences indicate that the Apo B and Apo B/Apo AI ratio are specific for these conditions, and moreover the ratio is not a marker of risk for other diseases such as cancer, mental disorders, and accidents [20].

Global CAD cross-sectional case control studies [30,31,37] and Indian studies [38-40] are mimicking our South Indian analysis in evaluation of risk relationship for Apo B which was stronger than any other lipid, lipoproteins or lipid ratios. Furthermore, the Apo B adds predictive value on top of conventional risk factors including lipids and lipoproteins not only in all but also in most of the studies, where several conventional risk factors are measured. Although some studies have shown that Apo B, Apo AI and/or the Apo B/Apo AI ratio have similar, but not better predictive power than lipids and lipid ratios, to our knowledge, there is only one report from any event or any surrogate marker study that has shown that LDL-C, or any other lipid, lipoprotein or lipid ratio, is significantly better in explaining risk than the Apo B [41,42].

Based on the findings of the current study and prospective studies, especially the AMORIS [43] and the INTERHEART studies [44] suggesting that the risk of CAD disease is increasing almost linearly with increasing values of the Apo B, it seems logical to add Apo B as well as the Apo B/Apo AI ratio into clinical practice in order to simplify risk evaluation and to optimize lipid lowering therapy.

Based upon the novel conception it is now time to formulate a broader update of national and international guidelines to include Apo B, Apo AI and the Apo B/Apo AI ratio, to be acknowledged as primary risk variables of equal or even greater importance than LDL-C, HDL-C and TC/HDL-C ratio respectively. It is proposed that values indicating level of risk should be developed also taking the conventional risk factors into consideration as well as the prevalence and incidence of CAD diseases within varied geographic and socio-economic regions. The Apo B could be a simple, robust, accurate risk indicator of great value in health screening and during lipid-lowering therapy. Moreover there are also a number of user-friendly reasons for incorporating apolipoproteins into the clinical practice. As the analyses can also be made on non-fasted samples this is of added practical advantage for patients and physicians over the other methods assessing lipids and lipoproteins, which typically require fasting. Moreover, the results can be expressed as one number for the Apo B only, rather than by many values for LDL-C, HDL-C, TG, and lipid ratios. Furthermore, no sort is needed- just one number signifies whether one is on the risk scale.

Considering all new evidences of the advantages of using Apo B, apo AI and the Apo B/apo AI ratio as stronger tools for predicting CAD risk, we propose an unique shift to predict lipid-related CAD risk – the apolipoproteins paradigm in this South Indian population. However, it is evident that there exists a pedagogical impedance to modify patients, clinicians, and other healthcare stakeholder's perception to shift from cholesterol to apolipoproteins. In order to keep the common viewpoint of cholesterol being a foremost risk factor, instead of still lingering with the older paradigm: 'LDL-C–the lesser the better', we now recommend a new paradigm: 'apolipoproteins suggestive of the cholesterol balance – the lower the better'. This paradigm is probably more sensitive and specific, and indicates an enhanced approach to estimate CAD risk and to decide the target levels for therapy. Hence, in spite of the increased expenditure for assay and instrumentation necessary to measure apolipoproteins, we strongly recommend Apo B, Apo AI and Apo B /Apo AI ratio assessment in CAD risk prediction.

5. Conclusion

The observation of declined levels of Apo AI and elevated levels of Apo B among CAD subjects proved to be efficient biomarkers for CAD. Moreover our study demonstrated that subjects with elevated Apo B were more insulin resistant and had higher CAD risk profile, being reflected in increased inflammatory, endothelial dysfunction/prothrombotic markers namely hs-CRP and lower HDL-C levels. Thus for dyslipidemic subjects with elevated cardio-metabolic risk, we strongly recommend Apo B to be a more reliable marker of risk for CAD than LDL-C.

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