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SERUM APOLIPOPROTEIN AI & B, LIPOPROTEINS, LIPIDS LEVELS IN INDIAN PATIENTS WITH ANGIOGRAPHICALLY DEFINED CORONARY ARTERY DISEASE

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Research Article

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ABSTRACT

The association serum lipids, lipoproteins, and apolipoproteins between angiographically defined coronary artery disease (CAD) was evaluated in 251 Indian men and women in order to assess the predictive power of apolipoproteins as a 'marker' of coronary artery disease (CAD). Patients with 70% or greater narrowing of at least one coronary artery or ⩾50% stenosis of the left main coronary artery (n=234, CAD+) were compared to those with lesions of < 50% stenosis (n = 186, CAD-) for total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), very low density lipoprotein (VLDL-C), triglycerides, apolipoprotein A-I, apolipoprotein B, and apolipoprotein A-I/B. Information on nonlipid risk factors was obtained from questionnaires. CAD+ compared with CAD- had higher frequencies of diabetes (P=<0.001), hypertension (P=<0.05), and smoking (P<0.001). CAD+ patients had higher plasma concentrations of apoB (145.57±18.52 vs. 93.22±9.11mg/dl, P<0.001), Apo AI decreased plasma concentration (89.90±19.26 vs. 131.01±22.55, P<0.001). Total cholesterol, TGs and VLDL- chol, were found not significant after correction of age where as LDL-chol (P<0.001), and HDL-chol (P<0.001) had significant change. Ratio of Apo AI/Apo B had most significant decreased in CAD+ patients. Apo AI, Apo and ratio of Apo AI/Apo B showed the most significant relation with the number of stenotic vessels and was associated with CAD in the normolipidemic subgroup. In conclusion, by using multiple logistic regression analysis, and adjusting for age & other traditional lipid measures Apo AI, apoB and ratio of Apo AI/Apo B was superior to chol, LDL-chol, HDL-chol, TG, in discriminating between CAD+ and CAD-.

KEYWORDS: Apolipoproteins; Coronary disease; Lipids; Lipoproteins

Introduction

Cardiovascular disease is the most common cause of death worldwide. Incidence of coronary heart disease has shown an upward trend in Indians in the last decade [1, 2] Atherosclerosis is the major cause of coronary heart disease.

Initially the estimation of serum lipids like cholesterol and triglycerides were used to assess the risk of coronary heart disease. However, the inconsistency in the correlation between serum lipid profile and coronary heart disease, led to the development of better indicators [3]. Among them the estimation of serum apolipoproteins as a risk factor in coronary heart disease and also as a marker has shown great promise. Earlier LDL was thought to be a marker for risk CAD and was later replaced by HDL. Now attention has been directed towards identifying components

of HDL because there was inconsistency in correlation between HDL and risk of coronary heart disease.[4] In this light Alaupovic came with the estimation of one of the component of HDL-apolipoprotein-AI, as a better marker for coronary heart disease [5].Various subfraction of atherogenic LDL and protective HDL as better discriminator of coronary heart disease.

Apolipoproteins are the protein components of lipids. Apo-AI is the major protein constituent of HDL. Apo-AI and HDL are protective; Apo-B and LDL are atherogenic. HDL has 2 molecules of Apo-AI, whereas cholesterol content varies in each of these lipoprotein particles. Therefore measuring Apo-AI is an determinant of the number of antiatherogenic particles in circulation, than the cholesterol content, which varies [6]. The atherogenic lipoprotein particles LDL, VLDL remnants, or IDL, and chylomicron remnants each contain 1 molecule of apoB as the structural protein. The plasma apoB concentration reflects the number of atherogenic lipoproteins, and studies in men have demonstrated that apoB can be a valuable predictor for CAD. [7, 8] Many case control studies have shown that apolipoproteins AI and B are good markers for CHD [9].The purpose of this study is to assess the ability of Apolipoprotein-A1, Apo B and ratio of Apo A1/Apo B to predict the risk of coronary heart disease.

MATERIALS AND METHOD:

Design:

This cross-sectional study was performed in the Government super speciality hospital and the Government medical college at Nagpur. All subjects gave their informed consent before participation in the study.

Study Population

The study population consisted of men & women who were undergoing their coronary angiography between January 2009 and January 2011. The indications for angiography were suspicion of CAD or preoperative screening for CAD in subjects with valvular disease. Patients using lipid-lowering medication were excluded from analysis. Plasma concentrations of chol, TGs, HDL-chol, LDL-chol, VLDL-chol, apoA-I, and apoB were determined after an overnight fast during the week preceding the angiography. Coronary angiographies were performed according to the standard Judkins technique.[10] Patients were classified as CAD+ if 1 or more coronary arteries had a stenosis >50% on visual examination. The other patients were classified as CAD-.

Lipids and Apolipoproteins Measurment:

Chol and TG concentrations were measured enzymatically (Angstrom, Co. Baroda, India). HDL-chol was measured by kit (Accurex Bio-Medicals Pvt. Lt. Thane, India), Plasma LDL-chol was calculated by using the Friedewald formula[11] (total chol-[HDL-chol]-[0.45xTG]).VLDL-chol was calculated by TG/5. ApoA-I and apoB were measured by immunoturbidometric method (Orion Diagnostica kit) using a semi-autoanalyzer (transasia Chem 5 Plus).

Clinical and Lifestyle Characteristics:

Questionnaires were sent to the participants to retrospectively obtain self-reported information about clinical and lifestyle characteristics during the year preceding coronary angiography. Height and weight were recorded. Ages at menarche and, if appropriate, at menopause (surgical or natural) were recorded. Finally, the premenopausal use of oral contraceptives and the postmenopausal use of HRT in any form were recorded.

Statistics:

Logistic regression was used to analyze the

influence of continuous and dichotomous variables on the presence of CAD (the dependent variable). ANOVA with age as a covariate was used to analyze the effect of lipid and apolipoprotein values on 1-, 2-, or 3-vessel disease. Student's *t* tests for independent samples were used to analyze differences in Apo AI, apoB concentrations between CAD- and CAD+ groups for each quartile of the other lipid or apolipoprotein variable. Values are expressed as mean±SD. Two-tailed *P* values <0.05 were considered significant. The GraphPad Prisam software program was used.

RESULT:

Clinical and Lifestyle Characteristics:

Table 1 Shows 156 male and 78 female out of 234 CAD+ patients and 133 male and 53 female out of total 186 CAD- patients(**Table No. I**). Age of CAD+ patients (57.26±15.62) were significantly no difference than CAD- patients (56.18±14.21). Diabetes, smoking, and hypertension were significantly associated with CAD+ after correction for age. Postmenopausal factor was not significantly associated with CAD+ (**Table No. II**). But after correction for age, smoking and hypertension, the only nonlipid risk factor that was significantly associated with CAD+.

Table-I Age & Sex distribution in CAD- & CAD+ Patients

Sex	CAD-patients (n=186)	%	Age Yrs. (Mean ± S.D.)	CAD + Patients (n=234)	%	Age in Yrs. (Mean ± S.D.)
MALE	133	71.50	56.18±14.21	156	66.66	57.26±15.62
FEMALE	53	28.50	53.34±12.61	78	33.33	55.31±13.53

Table- II. Age and Frequency Distribution of Clinical Characteristics in CAD- and CAD+ as Assessed by Angiography

	CAD-(n=186)	%	CAD+ (n=234)	%	P^1	P^2(Age as Covariate)
Age in Yrs	54.76±13.41		56.28±14.57		NS	NS
Diabetes	10	5.37	22	9.40	<0.001	>0.05
Smoking	21	11.29	45	19.23	<0.001	<0.001
Hypertension	44	23.65	65	27.77	<0.05	<0.001
Postmenopausal	46(n=53)	86.79	67(n=78)	85.89	NS	NS

Lipids and Apolipoproteins:

Plasma concentrations of chol. were significant in CAD+ but after age correction it was not significant, while VLDL-chol & TGs, were not significant. Apo-B was significantly higher and HDL-chol was significantly lower in CAD+ than in CAD- patients. Apo-AI and ratio of Apo-AI/Apo-B significantly decreased (**Table No.III**), and this association remained

so after correction for age. The extent of CAD, expressed as the number of stenotic coronary arteries, was associated with chol, LDL-chol, apo-B, and age. After correction for age, Apo-B remained the most significant parameter (**Table No.III**). In a normolipidemic subgroup, apo-B, Apo AI, ratio of Apo AI/Apo B and LDL-chol were the only parameters associated with CAD+ after correction for age (**Table No. IV**).When CAD+ Male compared with CAD+ Female no parameter found significant change.

Frequency distributions of apoB and apo AI in CAD+ and CAD- are shown in **Figures I and II.** Of the CAD+ , 79.48% had an elevated apoB concentration (>135mg/dl). Of the CAD- women, 90.32% had a normal apoB concentration (<135mg/dl). In the CAD+ group, apo AI concentration decreased (<135mg/dl) in 94.44% which significant as compaired to CAD- patients.

Table -III Fasting Plasma Lipids and Lipoproteins in CAD- and CAD+ patients as Assessed by Angiography

PARAMETER	CAD-(n=186) (Mean±S.D.)	CAD+(n=234) (Mean±S.D.)	P^1	P^2(Age as Covariate)
Cholesterol (mg/dl)	191.96±23.17	206.96±36.63	<0.05	NS
TGs(mg/dl)	141.16±34.67	150.53±26.16	NS	NS
HDL-chol (mg/dl)	38.75±3.02	31.62±3.56	<0.001	<0.001
VLDL-chol (mg/dl)	28.18±7.05	30.27± 5.48	NS	NS
LDL-chol (mg/dl)	125.01±20.71	145.05± 32.89	<0.001	<0.001
Apo A-I, (mg/dl)	131.01± 22.55	89.90± 19.26	<0.001	<0.001
Apo B, (mg/dl)	93.22±9.11	145.57±18.52	<0.001	<0.001
Apo AI/Apo-B	1.4664±0.4008	0.6275±0.1522	<0.001	<0.001

[1] **By logistic regression.**

[2] **Logarithmically transformed**

Table-IV: Fasting Lipids and Lipoproteins in Women with 1-, 2-, and 3-Vessel Disease on Coronary Angiograms

PARAMETER	1Vessel(n= 102)	2 Vessel(n=85)	3 Vessel(n=47)	P[1](Age as Covariate)
Cholesterol (mg/dl)	195.32 ± 25.12	198.86 ± 33.58	209.54 ± 26.72	>0.05
TGs(mg/dl)	146.26 ± 44.74	149.52 ± 32.11	151.43 ± 26.55	NS
HDL-chol (mg/dl)	36.64 ± 5.16	34.32 ± 2.75	31.62 ± 3.56	<0.001
VLDL-chol (mg/dl)	27.88 ± 6.12	29.36 ± 5.11	30.39 ± 6.44	NS
LDL-chol (mg/dl)	141.21 ± 26.46	148.31 ± 31.92	151.52 ± 35.43	<0.001
Apo A-I, (mg/dl)	101.34 ± 07.63	93.90 ± 19.26	89.90 ± 15.48	<0.001
Apo B, (mg/dl)	143.36 ± 10.16	148.75 ± 13.28	149.84 ± 21.92	<0.001
Apo AI/Apo-B	0.8394 ± 0.3021	0.7443 ± 0.2561	0.6135 ± 0.1420	<0.001

[1] **General factorial ANOVA with linear contrast and age as a covariate.**

Table V: Fasting Lipids and Apolipoproteins in Normolipidemic[1] CAD- and CAD+ patients as Assessed by Angiography

PARAMETER	CAD-(n=78) (Mean±S.D.)	CAD+(n=104) (Mean±S.D.)	P[1]	P[2](Age as Covariate)
Cholesterol (mg/dl)	181.96±18.52	194.16±6.03	<0.05	NS
TGs(mg/dl)	140.23±5.76	142.53±6.28	NS	NS
HDL-chol (mg/dl)	35.21±2.15	30.27±4.74	<0.05	NS
VLDL-chol (mg/dl)	29.21±6.52	30.70± 4.83	NS	NS
LDL-chol (mg/dl)	135.14±12.16	144.51± 13.79	<0.001	<0.05
Apo A-I, (mg/dl)	132.61± 27.58	88.48 ± 19.26	<0.001	<0.001
Apo B, (mg/dl)	92.31±8.53	144.73±19.48	<0.001	<0.001
Apo AI/Apo-B	1.5158±0.3981	0.5582±0.4571	<0.001	<0.001

[1] **Plasma chol <200 mg/dl and TG <150 mg/dl.**

[2] **By logistic regression**

FIG.1-The frequency distribution of Apo-B levels in CAD+ & CAD- patients

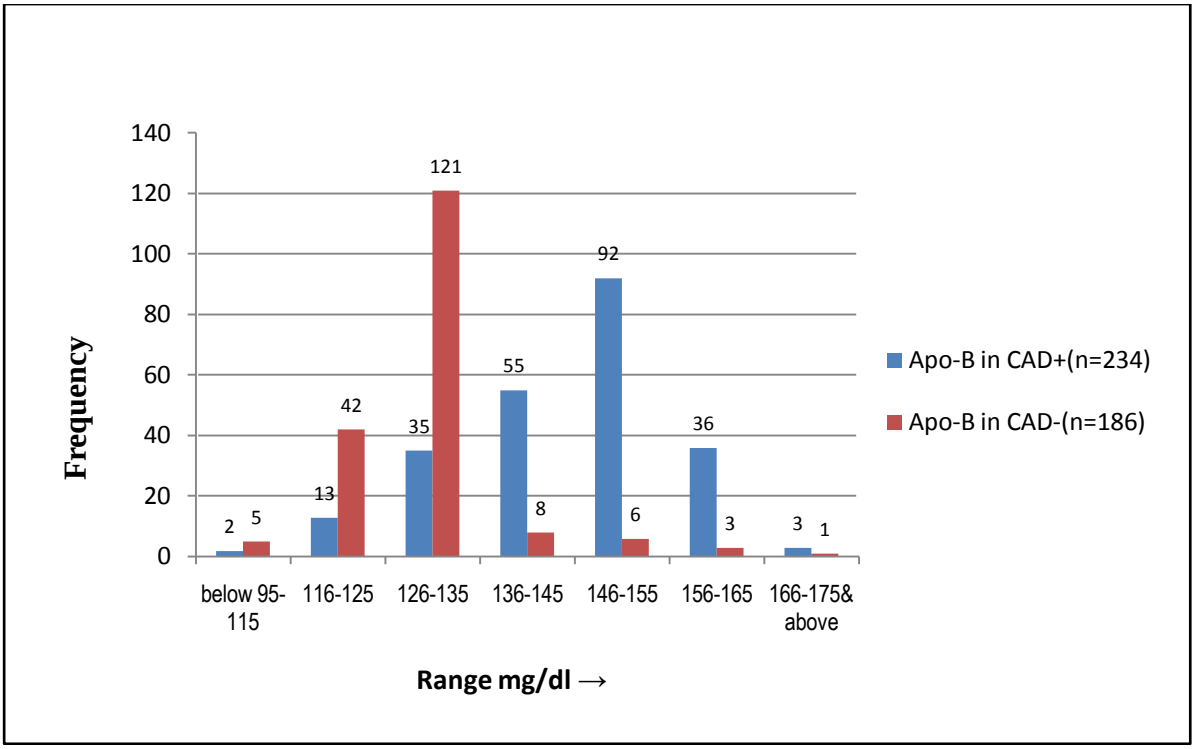
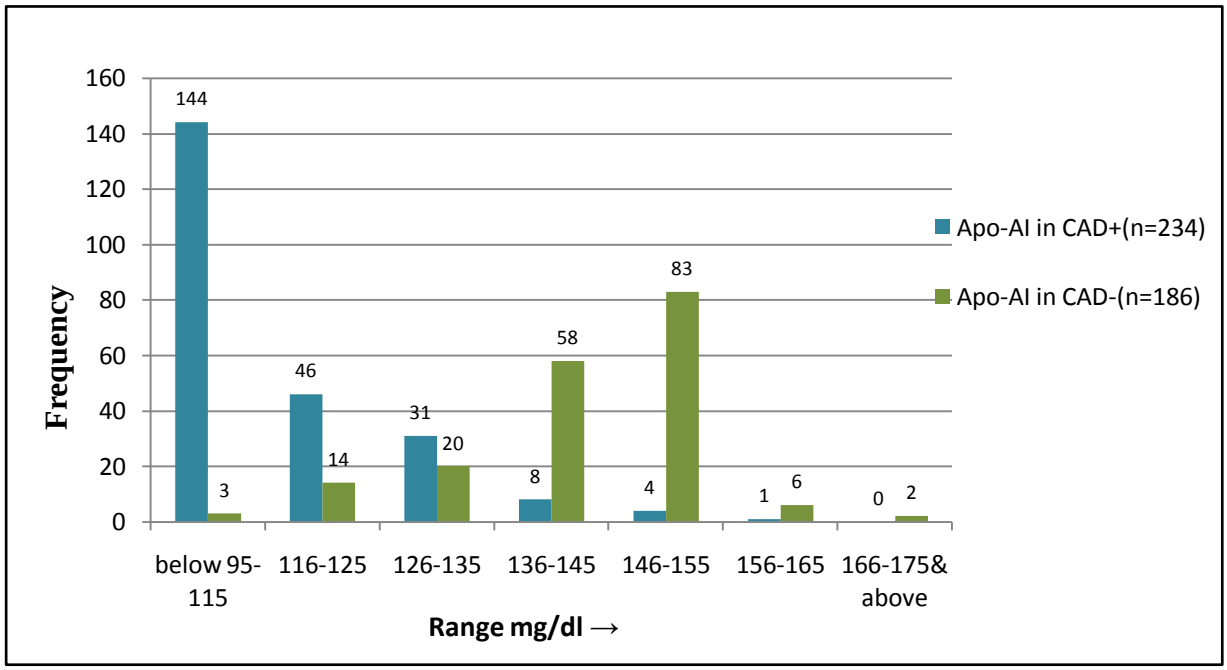


FIG.2- The frequency distribution of Apo-AI levels in CAD+ & CAD- patients



DISCUSSION

In this study we report the association between plasma apo A1, apo-B and ratio of apoAI / apo B in CAD patients who were referred for angiography. Chol, VLDL-chol, TGs, were not significant in CAD+ patients than CAD- patients and apoA1, apo-B, ratio of apo AI / apo B, LDL-chol, HDL-chol were significant risk factors for CAD+ after correction for age. ApoAI, apo-B, ratio of apoA1/apo B, LDL-chol, HDL-chol was superior to the "traditional lipids" chol, LDL-chol, HDL-chol, and TGs in predicting the presence or absence of CAD. Chol, LDL-chol, TGs, or HDL-chol gave no additional information for normolipidemic patients. ApoAI, apo-B, ratio of ApoAI/apo-B, HDL-chol, LDL-chol was also associated with the extent of CAD, expressed as the number of vessels involved, which has recently been reported to predict cardiovascular mortality.[12]

Clinical and epidemiological studies have established the association between coronary risk and high serum levels of cholesterol and LDL-C, apo-B, as well as of low concentrations of HDL-C and apoA-I. [13] The results from the study indicate that the apo-B, apo A1, apo-B/apoA-I ratio are independent risk factors for CAD and are superior to any of the cholesterol ratios. [14]

Apolipoproteins are the protein components of lipoproteins. Each class of lipoprotein contains a variety of apolipoproteins in differing proportions, with the exception of low-density lipoprotein, which contains only apo B. Apolipoprotein A consists of apo A-I and apo A-II, apo A-I being the major protein constituent of high-density lipoprotein. [15] Some studies have suggested that the plasma concentrations of apolipoproteins (apo) A-I and B are better discriminators of patients with CAD than are traditional lipid measures.[16-20]

In this study found that increased levels of apo B was significant in CAD+ patients than CAD- patients. These findings are in good agreement with the findings of Wolfgang Schwantzkopff et al [21],P.P.Jadhav et al[3],Vinay K Bahl et al[22],Wallidus G, Jungmer [23].

Gran Wallidus et al [24] demonstrated that value of apo-B as risk predictor was evident, even at LDL-chol levels below the median. Apo B was a better index of risk than the total cholesterol and LDL-chol in Quebec [25] and the European Atherosclerosis Research Study (EARS). [26]

In the present study, shows that apo AI is significantly decreased in CAD+. This findings correlate with the findings of Wolfgang Schwantzkopff et al [21] ,P.P.Jadhav et al[3] ,Vinay K Bahl et al[22], Wallidus G, Jungmer [23],Johan Franzen and Goranfex.[27]

The statistical analysis revealed strong relations between apo A-I, apo-B, ratio of Apo AI/apo-B and the presence of CAD as defined by the observation of vessel stenosis. Hence, this study directly documents the role that the extent of CAD plays in the link between blood apoA-I and apo-B concentration levels and clinical events. Moreover, apoA-I, apo-B and ration of apoAI/apo-B exhibited a highly significant relationship to the number of stenosed coronary vessels. In the absence of an association between traditional lipids, lipoproteins and CAD, concentrations of apoA-I and apo-B can prove to be a valuable tool in the risk assessment of a population and the severity of coronary stenosis. Less evidence exists on the relationship between apoA-I and apo-B levels and the severity of CAD, although

Garfagnini et al have shown that the apoA-I and apoA-I/apo-B ratio are better than HDL-C in assessing the severity of coronary damage. [28]

In conclusion, the present study revealed that various well-known coronary risk factors of lipid metabolism are powerful discriminators of both the presence and the extent of CAD. This suggests that the measurement of apoAI, apo-B and ratio of ApoAI/apo-B should be routinely added to the routine lipid profile in order to assess the atherogenic potential of lipid disorders.

Selected Abbreviations and Acronyms

CAD+, CAD-	with, without coronary artery disease
chol	Cholesterol
HRT	hormone replacement therapy
TG	Triglyceride

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