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RESEARCH ARTICLE

APOB/APOAI RATIO – PREDICTOR FOR CORONARY ARTERY DISEASE IN NORTH WEST PUNJABI POPULATION

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ABSTRACT

Previously considered a cholesterol storage disease, we now view atherosclerosis as an inflammatory disorder. Lower levels of serum ApoAI and higher levels of serum ApoB and ApoB/ApoAI ratio are considered to be independent risk factors for CAD. In the present case-control study we analyzed the serum levels of apolipoproteins in a total of 600 samples which included 300 CAD patients and 300 normal healthy individuals. The results revealed significant positive associations between higher ApoB levels and ApoB/ApoAI ratio and CAD events. Logistic regression model showed ApoAI provides protection towards CAD susceptibility (OR=.979; 95% CI (.964-.995) among North-West Punjabi population. ApoB/ApoAI has highest AUC of 0.73(>0.50) (p<0.001).

INTRODUCTION

Epidemiological data suggests that India is host to 3-40 million patients with Coronary Heart disease and the prevalence is increasing (Gupta *et al*., 2008). This is also the largest cause of mortality in the country. Chronic Inflammation contributes to the development of atherosclerosis, cardiovascular disease (CVDs) and Type 2 diabetes (Theodore *et al*., 2008; Peter *et al*., 2002; Russell, 1999). In 21st century clinical mantra for CAD is markedly attenuated, if not eliminated. For this purpose, considerable research has focused on novel CAD risk biomarkers, among which are apolipoproteins (Goran *et al*., 2001). Measurement of these biomarkers is useful to stratify patients according to disease risk. Apolipoprotein B (ApoB) indicates the number of potentially atherogenic lipoprotein particles, and Apolipoprotein A (ApoAI), associates with anti-atherogenic HDL particles, were two main apolipoproteins which have shown significant association with CAD (Rong *et al*., 2011; Michael, 2009; Goran and Ingmar, 2004). ApoAI reflects the antiatherogenic potential in HDL particles, the higher the value of HDL, the better defense it gives to CAD risk. ApoB 100 is the structural protein for atherogenic lipoproteins and facilitates the transport of lipid from the liver to peripheral tissues (Michael, 2009; Marcovina and Packard, 2006; Michel *et al*., 2011). In all atherogenic particles a single ApoB100 molecule is present. ApoB100 concentration is a better measure of LDL particle number concentration and is a more reliable risk indicator (Navid *et al*., 2014; Tripta and Sharma, 2013). ApoB/ApoAI ratio indicates cholesterol balance is a robust and specific marker for CAD is also well documented. In the clinical setting ApoB/ApoAI ratio can be measured at any time without any fasting (Santica *et al*.,1994) .Considering paucity of data on the association and predictive value of Apolipoproteins with CAD, the present study aims to evaluate the effectiveness of apolipoproteins and analyzing whether these parameters are better predictors of CAD.

METHODS

The present case-control association study has been approved by the Ethics Committee of Govt. medical college, Amritsar. A signed informed consent was obtained from all the participants in the study prior to sample collection. A total of 600 individuals from Punjab (North-West India) were included in

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the study. Coronary artery disease cases were selected from the wards and out-patient department of the medicine department, Guru Nanak Dev Hospital, Amritsar. All the cases were clinically diagnosed by the physician on a past history of documented myocardial infarction or ECG changes suggestive of ST-segment depression or Q-wave changes or T- wave changes (Mohan *et al*., 2001). Ethnicity matched 300 normal healthy individuals above the age ≥ 35 years without any evident symptom of CAD or any past history of the disease were included as controls from the general population. Alcohol abuse history was defined as alcohol consumption ≥ 100 g per day. As to smoking, the patients were classified as smokers (if they reported to smoke regularly during the past 1 year). Family history was deemed positive if any of these criteria were present: the diagnosis of CAD in any first-degree male relative < 55 years of age or in any first-degree female relative < 65 years of age. An overnight fasting blood samples were taken for estimation of ApoAI and ApoB. Blood was allowed to clot and serum was used for biochemical investigations. Apolipoprotein AI and B concentration in serum was estimated with immune turbidimetric method using kits from ERBA Diagnostics Mannheim GmbH. Sample containing human ApoAI and ApoB were made to react with the respective specific antiserum to form an insoluble complex which was measured turbidometrically at 340nm. *Preferred Cutoff Values*: Cut off values for ApoB/ApoAI ratio above 1 was considered to be at risk.

Table 1 Comparison of serum Apolipoprotein AI, Apolipoprotein B and ApoB/ApoAI ratio in CAD cases and controls

	Cases (n=300)	Controls (n=300)	p-value
Age(years)	59.72±10.97	54.73±10.62	0.00
Men[n%]	169(56.3%)	167(55.6%)	-
Women[n%]	131(43.6%)	133(44.3%)	-
Alcohol abuse [n (%)]	91(30.33%)	78(26%)	-
Family history of CAD [n (%)]	47(15.6%)	0(0%)	-
History of T2DM [n (%)]	101(33.6%)	0(0%)	-
Smoking [n (%)]	34(11.3%)	13(4.3%)	-
ApoAI(mg/dl)	109.57±27.69	128.76±27.99	0.00*
ApoB(mg/dl)	109.70±30.04	93.10±31.25	0.00*
ApoB/ApoAI ratio	1.07±.43	.76±.31	0.00*

ApoAI, ApolipoproteinAI; ApoB, Apolipoprotein B *p < 0.05 significant, Results were expressed as Mean±S.D mg/dl; n= number of subjects

Table 2 Apolipoprotein Concentration by Gender in of the Two Groups

Variables	Women		p-value	Men		p-value
	cases	controls		cases	controls	
N						
ApoAI (mg/dl)	117.7 ±29.3	132.4±28.1	0.00*	103.2 ± 24.6	125.9 ±27.6	0.00*
ApoB (mg/dl)	106.7±29.7	81.5 ±30.8	0.00*	112.0±30.1	102.1±28.5	0.002*
ApoB/Apo AI (mg/dl)	.99±.45	.65 ±.30	0.00*	1.14±.40	.84±.29	0.00*

Significant at< 0.05

Table 3 ROC Curve analysis for ApoAI, ApoB and ApoB/ApoAI ratio

Indicators	AUC [a]	p-value	95% CI	
			Lower	Upper
ApoAI(mg/dl)	.322	0.00	.279	.365*
ApoB(mg/dl)	.647	0.00	.603	.691*
ApoB/ApoAI ratio	.733	0.00	.693	.772*

a-Area under curve *Significant at< 0.05

Table 4 Logistic Regression for predicting Coronary rtery Disease according to ApoAI, ApoB and ApoB/ApoAI ratio

Variables	Odds Ratio (O.R)	p-value	95% CI for Exp(B)	
			Lower	Upper
ApoAI(mg/dl)	.979	0.01*	.964	.995
ApoB(mg/dl)	1.013	0.12	.996	1.031
ApoB/ApoAI ratio	1.946	0.47	.310	12.204

ApoAI, Apolipoprotein AI; ApoB, Apolipoprotein B; *p < 0.05 significant

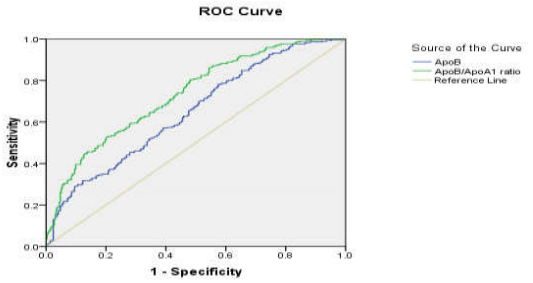

Figure 1 Receiver operating characteristic curve of ApoB and ApoB/A1 ratio for Coronary artery disease patients

Statistical Analysis

The Statistical analysis was performed using Statistical Package for Social Science Program (SPSS version 16.0; SPSS, Chicago, IL). Baseline clinical characteristics of the case and control continuous data was expressed as mean±S.D, significance of any difference in means was tested by student t-test. Discriminatory power of independent parameters was quantified in terms of Receiver Operating characteristics (ROC) curve analysis.

RESULTS

Data for the baseline characteristics of individuals investigated in the present study has been summarized in Table 1.

Demographic Characteristics

In Normal Healthy Individuals (controls) 55% were Male and 44% were female. Among CAD patients 56% were Male and 43% were female. Compared with control group, CAD group had a greater percentage of individuals with positive family history of CAD, Diabetes mellitus and smokers (all p< 0.05).

ApoAI, ApoB and ApoB/ApoAI ratio in the study population

Mean values of ApoAI were 128.76±27.99 and 109.57±27.69 in Normal healthy control individuals and CAD patients. The serum levels of ApoB, ApoB/ApoAI ratio was higher in CAD patients as compared to controls with mean values of 109.70±30.04, 1.07±.43 and the difference was statistically significant. We also found a decrease in serum concentration levels of ApoAI in relation to CAD (p<0.05) (Table 1). On gender stratification analysis, mean value of ApoB and ApoB/ApoAI ratio was found to be more in male CAD patients than females, whereas mean value of ApoAI was more in Normal healthy control females (Table 2).

The area under curve (AUC) of ApoAI, ApoB and ApoB/ApoAI for predicting CAD was 0.322, 0.647 and 0.733 respectively. ApoB and ApoB/ApoA1 were > 0.50 (p<0.001) (Fig 1).

The risk relationship between ApoAI, ApoB and ApoB/ApoAI ratio was expressed as Odds Ratio (OR). ApoAI provides protection towards CAD predisposition (OR=.979; 95% CI (.964-.995) ApoB and ApoB/ApoAI ratio are potent markers of CAD risk (OR=1.013; 95% CI (.996-1.031) (OR=1.946; 95% CI (.310-12.20), but the difference is not statistically significant (Table 4).

DISCUSSION

In a quest to find whether Apolipoproteins stand out to be better markers for CAD, this case-control study was carried out. We estimated the association between ApoAI, ApoB and ApoB/ApoAI ratio and compared their predictive effectiveness for CAD. Apolipoproteins are referred to as risk predictors for CAD events. Elevated levels of ApoB and/or low levels of ApoAI have consistently been associated with an increased risk of CAD events in clinical studies. These emerging biomarkers appear to be more accurate than traditional risk factors in predicting coronary artery disease and thus are useful for clinician in diagnosing patients with borderline risk factors. Methods for measuring ApoB and ApoAI are now internationally standardized by the World Health Organization-International Federation of Clinical Chemistry (WHO-IFCC) (Santica *et al*., 1993; Santica *et al*., 1994).

In the present study, the risk seemed to be more pronounced in males having increase number of atherogenic particles (ApoB) and decreased number of anti-atherogenic particles (ApoA1). Both ApoB level and the ApoB/ApoA1 ratio are believed to be useful predictors of cardiovascular events (*Sierra et al., 2009*). The predictive value of ApoB as the strongest single lipid association risk factor has been shown in large observational studies (Marianne, 2009; Kuo-Liong *et al*., 2007; Marianne *et al*., 2007).

We found a significant association between higher ApoB levels and CAD events. Measurement of ApoB has been shown to be a predictor of CAD events. Our results are in accordance with these studies (Navid *et al*., 2014). Ding *et al*., 2014, in their findings have emphasized stronger risk relationship association of high levels of ApoB with the CVD risk mortality. ApoAI initiates the Reverse Cholesterol Transport process in peripheral tissues. It is involved in anti-inflammation, anti-oxidation, antiprotease activity, anti-apoptotic and anti-thrombotic functions (Goran and Ingmar, 2006). In the present study CAD patients showed a clear trend of low levels of ApoA1which was in concordance with these studies (Ding *et al*., 2014; Arthur *et al*., 1999).

ApoB/ApoAI ratio is a promising marker for predicting the occurrence of CAD events. Different studies and published data have suggested ApoB/ApoAI ratio as better indicator of risk for CAD (Tripta and Krishna Sharma, 2013; Goran *et al*., 2001; Gyarfas *et al*., 2006 ; Fangyuan *et al*., 2014; Rasouli M, 2006) . In addition, Binita *et al*., 2008 have highlighted the significance of Apo ratio as better discriminator of CAD risk in the Atherosclerosis prone Indian population. The Statistical analysis confirmed sturdy relations between ApoAI and ApoB levels and Coronary artery disease. Hence this study documents the role of Apolipoprotein levels in serum and the clinical events causing CAD. The present study concludes that the levels of ApoAI are consistent discriminator of atherosclerosis burden among Coronary artery disease patients. The results of the present study are in accordance with the study conducted by Jeetesh *et al*., 2010.

Based on the findings of the current study and prospective studies, especially the AMORIS (Goran *et al*., 2001; Goran and Ingmar, 2004) and the INTERHEART studies (Salim, *et al*., 2004), 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/ApoAI ratio into clinical practice in order to simplify risk evaluation and to optimize lipid lowering therapy. Apolipoproteins are simple, robust, accurate risk indicators of great value in health screening. Moreover there are also a number of user friendly reasons for incorporating apolipoproteins into the clinical practice. We strongly recommend Apo B, Apo AI and Apo B /Apo AI ratio assessment in CAD risk prediction.In conclusion, the present study suggests that the measurement of ApoB, ApoAI and ApoB/ApoAI ratio appears to be novel powerful discriminator markers to assess the CAD and they should be routinely added to the lipid panel to assess the atherogenic potential of CAD patients.

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