

Potential role of apolipoprotein B/A1 ration in obese and non-obese female patients of coronary artery disease

Sunita Mahto¹, Suman Bala Sharma², Shridhar Dwivedi², Mani Sethi³, Rahul Saxena⁴

¹Assistant Professor, Department of Biochemistry, Indira Gandhi Medical College, Shimla, H.P, ²Professor, Department of Biochemistry, University College of Medical Sciences, New Delhi, ³Research Scholar, Department of Biochemistry, University College of Medical Sciences, New Delhi, ⁴Assistant Professor, Department of Biochemistry, SAHS, Sharda University, Greater Noida, U.P. 201036

Submitted: 28-09-2015

Revised: 27-10-2015

Published: 10-01-2016

ABSTRACT

Background: Obesity and hyperlipidemia are considered to be risk factor for cardiovascular diseases. Many patients who develop coronary artery disease (CAD) are non obese and have normal lipoprotein cholesterol. Assessment of apolipoproteins can improve future risk of cardiovascular complications. **Aims and Objectives:** We have investigated effect of weight in relation with lipoprotein and apolipoprotein levels as efficient marker of CAD in North Indian females. **Materials and Methods:** The study population consist of 90 subjects categorized into three groups: Group 1: Healthy controls; Group 2: Non obese patients of CAD and Group 3: Obese patients of CAD (n= 30 each group). Serum lipid profile along with apolipoprotein B and A1 were measured and apolipoprotein B/A1 ratio were calculated. **Results:** Total cholesterol and triglycerides levels were significantly high in obese patients as compared to non-obese and controls. LDL-C and HDL-C were altered insignificantly ($p < 0.1$) in Group 2 and Group 3 as compared to Group 1. Apo B and apo A1 were significantly high in obese and non-obese CAD patients as compared to controls whereas insignificant difference was observed ($p < 0.1$) when Group 3 patients were compared with Group 2. ApoB/Apo A1 ratio was increased significantly ($p < 0.01$) in patient groups as compared to controls. **Conclusion:** Although LDL-C and HDL-C were normal in subjects of CAD, increase in Apo B, A1 and its ratio authenticates the fact that these markers are more efficient in detection of CAD risk in obese and non obese patients than conventional lipid profile parameters.

Key words: Apolipoprotein B, Apolipoprotein A1, Lipid profile, Coronary heart disease

Access this article online

Website:

<http://nepjol.info/index.php/AJMS>

DOI: 10.3126/ajms.v7i3.13504

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality in all over the world despite major advances in treatment and prevention. The overall figure of CAD in the population represents approximately a 10 folds increase in the prevalence of CAD in urban India during the last 40 years.¹⁻³ It has been well predicted that by the year 2020 there would be an almost 75% increase in the global cardiovascular disease burden, and thus, received much attention for early prediction of CAD.^{4,5}

Obesity is one of the reasons which is more prevalent in men until 45 years and in women after that age.⁶ The risk

of cardiovascular events is increased especially in subjects with central obesity because of the concomitance of hyperlipidemia or other risk factors.⁷ In fact the metabolic syndrome, defined by the presence of three or more of risk factors which includes central obesity.⁸ However hyperlipidemia linked cardiovascular risk increase cannot be explained in non obese patients. The Apolipoprotein-related mortality risk (AMORIS) studies were published demonstrating that the concentrations of apolipoprotein B (ApoB) and apolipoprotein A1 (Apo A1) as well as the ratio of Apo-B/Apo A1 improved prediction of CHD risk.⁹ Whether apolipoproteins provide any additional predictive information over and above the usual lipid measurements remains controversial to date. Some early

Address for Correspondence:

Dr. Rahul Saxena, Department of Biochemistry, SAHS, Sharda University, Plot No. 32-34, Knowledge Park III, Greater Noida, U.P. 201036. India. **E-mail:** rahulapril@gmail.com. **Mobile:** 09958255816.

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case-control studies found Apo-B and ApoA-I to be better predictors of coronary heart disease (CHD) than the usual lipids.^{10,11} This idea was supported by several cohort studies.^{12,13} However other prospective studies did not confirm these findings.^{14,15} In the present study, we therefore have investigated the role of Apo-B, Apo A1 and Apo B/A1 ratio in relation to central obesity and lean subjects of CAD.

MATERIALS AND METHODS

The present study was done in ninety female subjects of age between 30-60 years comprising thirty healthy controls and sixty patients of coronary artery disease admitted in medical wards and/or coronary care unit of University College of Medical Sciences and Guru Teg Bahadur Hospital. Control group included people without hypertension, diabetes mellitus, obesity and hypothyroidism. All the subjects were matched for age and informed consent was taken from all subjects. Study was approved by ethical committee of University College of Medical Sciences, Delhi. Ninety subjects were divided into Group 1 consisting of 30 healthy controls, Group 2 consisting of 30 obese patients of coronary artery disease, Group 3 consisting of 30 non-obese patients of coronary artery disease. Central obesity was defined as waist circumference of >80cms in females. Measurement was taken at navel level for central obesity and CAD was defined on the basis of history, clinical examination, ECG findings, elevated cardiac enzymes and troponins.

Four ml venous blood was withdrawn under aseptic condition within 12 hrs of admission. Then one ml of venous blood was transferred in vacutainer containing sodium fluoride in fasting state for plasma glucose. Plasma glucose level was estimated using standard method. Rest 3ml of venous blood was transferred in plain vacutainer. Sample was centrifuged at 3000 rpm for 10 minutes for serum separation. Serum was collected and separated into two portions. First portion was analysed for lipid profile on the same day of collection using standard methods. Second portion was stored at -70°C for measurement of apolipoproteins. Apolipoproteins B, A1 were done using immunoturbidity method (Randox kit) and ApoB/A1 ratio was calculated.

Statistical analysis

The data from both the study group subjects and controls were expressed as Mean \pm SD and comparison was made between study group and control group by using one way ANOVA with two Turkey's test at 5% significance level.

RESULTS

As shown in Table 1, all the groups were matched for age. There was no statistically significant difference of age in group 2 (non-obese) and group 3 (obese) as compared to group 1 (control). Waist circumference was highly significant ($p < .001$) in group 3 (obese) as compared to group 2 and group 1 (controls). Systolic and diastolic blood pressure were significant in group 2 (non-obese) and group 3 (obese) as compared to group 1 (controls). Fasting blood sugar in group 2 (non-obese) and group 3 (obese) was significantly higher as compared to group 1 (controls).

Serum total cholesterol (TC) was significant ($p < .01$) in group 3 (obese) as compared with controls whereas TC was found insignificant in obese as compared to non-obese (Table 2). Insignificant difference was also found for HDL-C and LDL-C among the study groups (Table 2). TG levels were found highly significant ($p < .001$) in group 3 (obese) as compared to the group 2 (non obese) and group 1 (controls), whereas insignificant levels were found in group 2 as compared to group 1 (Table 2).

The level of Apo B was found significantly high ($p < .001$) in group 2 (non-obese) and group 3 (obese) as compared to group 1 (controls), whereas insignificant level was found in obese group as compared with non-obese group (Table 3). Level of Apo-A1 was found significantly lower ($p < .001$)

Table 1: Demographic profile of the study groups (mean \pm SD)

Parameter	Group I (n=30)	Group II (n=30)	Group III (n=30)
Age (years)	54.3 \pm 6.75	49.00 \pm 9.48	53.1 \pm 12.40
Waist circumference (cm)	74.37 \pm 4.15	75.5 \pm 4.5	96.2 \pm 10.9 ^{b,c}
Systolic blood pressure (mmHg)	114 \pm 4.31	132.93 \pm 32.0 ^a	150.80 \pm 32.24 ^b
Diastolic blood pressure (mmHg)	74.7 \pm 3.64	96.97 \pm 20.73 ^a	103.90 \pm 28.47 ^b
Fasting blood sugar (mg/dl)	95.67 \pm 17.21	135.90 \pm 45.62 ^a	135.67 \pm 42.62 ^b

Where, ^aGroup 1 vs. Group 2 ($p < .001$), ^bGroup 1 vs. Group 3 ($p < .001$), ^cGroup 2 vs. Group 3 ($p < .001$)

Table 2: Comparison of serum lipid profile in study groups (mean \pm SD)

Parameter	Group I (n=30)	Group II (n=30)	Group III (n=30)
Total cholesterol (mg/dl)	142.63 \pm 1.73	158.13 \pm 41.97	169.53 \pm 41.2 ^a
HDL-cholesterol (mg/dl)	36.5 \pm 7.0	35.5 \pm 10.33	37.43 \pm 7.29
LDL-cholesterol (mg/dl)	88.07 \pm 20.12	95.50 \pm 38.5	94.6 \pm 35.5
Triglycerides (mg/dl)	104.4 \pm 44.4	125.7 \pm 56.0	178.56 \pm 82.6 ^{a,b}

Where, ^aGroup 1 vs. Group 3 ($p < 0.001$), ^bGroup 2 vs. Group 3 ($p < 0.004$)

Table 3: Comparison of Apo-B, Apo-A and Apo-B/A1 ratio in the study groups (mean±SD)

Parameter	Group I (n=30)	Group II (n=30)	Group III (n=30)
Apo-B (mg/dl)	90.37±17.00	111.37±27.04 ^a	119.63±24.62 ^b
Apo-A (mg/dl)	141.27±28.2	97.47±19.05 ^a	86.7±31.86 ^b
Apo-B/A1	0.66±0.15	1.20±0.36 ^a	1.48±0.51 ^b

Where, ^aGroup 1 vs. Group 2 (p<0.001); ^bGroup 1 vs. Group 3 (p<0.001)

in group 2 (non-obese) and group 3 (obese) as compared group 1 (controls), whereas insignificant level was found in group 3 as compared to in group 2 (Table 3).

Apo-B/A1 ratio was significantly higher (p<.001) in non obese and obese patients as compared to control whereas insignificant difference of ratio was found between obese and non obese patients (Table 3).

DISCUSSION

Plasma levels of TC and LDL-C are correlated with prevalence of CAD.¹⁶ High levels of LDL-C predisposes to premature CAD.¹⁷ Still many patients with CAD do not have elevated LDL-C or other detectable lipoprotein lipid level.¹⁸ Many patients with advanced coronary atherosclerosis have elevated levels of Apo B but normal LDL-C.¹⁸ Patients with premature coronary heart disease (CHD) have over production of LDL-apo B and yet normal concentration of LDL-C, enhanced production of LDL-apo B may cause accelerated atherosclerosis.¹⁸ There are three major components of the dyslipidemia that occur in obesity: increased fasting and postprandial triglyceride-rich lipoproteins (TRLs), decreased HDL and increased small dense LDL particles. There is also evidence from case control studies that apoB and apo A1 may be superior to LDL and HDL in discriminating Ischemic heart disease (IHD) case subjects.¹⁸ In the present study, levels of HDL-C and LDL-C were found insignificant. We also found that levels of TG and total cholesterol were highly significant in obese patients as compared to non-obese and controls whereas non significant levels of total cholesterol was found in non obese patients as compared to obese and controls.

Many researchers found that apolipoproteins are the better predictors found of risk for CAD as compared to controls. Apo-B synthesis is required for the hepatic secretion of VLDL and Apo-B remains associated with particle during the triglycerides hydrolysis and lipid exchange cascade until its clearance from the circulation as LDL or IDL particles. There is abundance of evidence from case control reports to support the role of Apo-B as an important risk factor for IHD.¹⁹ In our study Apo-B was highly significant in non obese and obese patients of CAD as compared to controls

whereas Apo-B levels are not significant in obese patients as compared to non-obese patients. High numbers of Apo-B containing lipoproteins will results in the presence of an elevated number of small dense LDL particles which have been associated with an enhanced risk of CAD.²⁰ There may also an increased secretion of VLDL apo-B particles synthesis, a condition that may favour the formation of small, dense, atherogenic LDL particles.²⁰⁻²² The range of values for apoB secretion among the obese was wide and partly related to central adiposity, insulin resistance and genetic factors.²³⁻²⁵ Increase in Apo-B in non-obese patients could be because of other pathophysiological abnormalities and associated risk factor that could lead to formation of small dense LDL. These works suggest that abnormalities in metabolism of Apo-B which are not necessarily revealed by concentration of LDL-C may cause acceleration of atherosclerosis.

It has been suggested that Apo-A1 measurements may provide more information than HDL cholesterol levels in the assessment of ischemic heart disease risk.²⁶ Levels of apo A-I are strongly correlated with those of HDL-C, and expression of apo A-I may be largely responsible for determining the plasma level of HDL. Apo A-I also acts as a cofactor for lecithin cholesterol acyl transferase (LCAT) which is important in removing excess cholesterol from tissues and incorporating it into HDL for reverse transport to the liver. Furthermore, apo A-I is the ligand for the ATP-binding cassette (ABC) protein, ABCA1 and hence is involved in the docking procedure by which excess cholesterol in peripheral cells is externalized to HDL for further reverse cholesterol transport either directly or indirectly via LDL back to the liver. ApoA-I also manifests anti-inflammatory and antioxidant effects.²⁷ The anti-atherogenic properties of apoA-I were recently documented.²⁸ In our study, Apo-A1 was significantly decreased in non obese and obese compared to controls whereas Apo-A1 levels were not significantly decreased in obese patients as compared to non-obese patients of CAD.

The ratio of Apo-B/ApoA1 has also suggested that predicating of the severity of CAD.²⁹ The two largest of these studies are the AMORIS³⁰ and the INTERHEART³¹ studies which both show a very strong direct relation between a high apoB/apoA-I ratio and an increased risk of fatal MI⁷ and acute MI (AMI).⁹ These results are in line with the findings in the INTERHEART study, which was based on almost 15 000 AMI compared with 15 000 age- and sex-matched controls.³¹ In that study the apoB/A-1 ratio was the strongest of all risk factors including smoking, hypertension, abdominal obesity, diabetes, alcohol, psycho-social stress, vitamin intake, and exercise. The results were independent of age, gender, and ethnicity. Furthermore, the apo B/A1 ratio also

remained the strongest of all risk factors in multivariate analyses.³¹ Our study showed that Apo-B/Apo-A1 ratio are significant in non-obese and obese patients of CAD as compared to controls whereas Apo-B₁₀₀/Apo-A1 ratio were not significantly changed in obese as compared to non obese.

CONCLUSION

These findings suggest that increase in concentration of Apo B and decrease Apo A1 can be considered to be risk factor for CAD in cases of normolipidemic profile where HDL-C and LDL cholesterol are not significantly changed in study population. Both obese and non obese patients showed increase in ApoB, Apo A1 ratio and non significant difference between these two groups. Therefore, altered levels of apolipoproteins are independent risk factor of CAD irrespective of obesity and early assessment of apolipoproteins (Apo-B, apo-A1, Apo-B/Apo-A1 ratio) can be effective in prediction of CAD complications.

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Authors Contribution:

S - Biochemical analysis, Data collection; **SBS** - Principal investigator, Planning & Formulation of study; **SD** - Facilitate the sample collection, Manuscript Editing; **MS** - Evaluation and Literature search; **RS** - Preparation of manuscript, Manuscript editing, Statistical analysis, Literature search.

Source of Support: Nil. **Conflict of Interest:** None.