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# Correlation of Apolipoprotein B and Apolipoprotein A1 with Metabolic Syndrome – Single Centre Experience from Delhi

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## Abstract

***Background:** Metabolic syndrome is characterised by insulin resistance, visceral adiposity, atherogenic dyslipidaemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress. Apo-B, Apo-A-1 (major apolipoproteins in lipid transport and atherosclerosis) and their ratio are good predictors of metabolic syndrome, cardiovascular disease, and stroke. Our study aimed at assessing the correlation of these apolipoproteins and the metabolic syndrome.*

***Material and methods:** 50 cases (metabolic syndrome) and 50 controls were included in this cross-sectional observational study of both male and female subjects > 18 years at a large hospital in Delhi. Participants were evaluated by history, examination and laboratory analysis for diagnosis and characterisation of metabolic syndrome and for levels of Apo-B and Apo-A-1.*

***Results:** The study showed that metabolic syndrome is prevalent in the age group between 41 - 60 years. Apo-B levels were higher in cases than controls. Apo-A-1 levels were lower in cases than controls. Apo-B/Apo-A-1 ratio is associated with metabolic syndrome. Apo-B/Apo-A-1 ratio correlated positively with SBP, VLDL, and HOMA-IR.*

***Conclusions:** Apo-B and Apo-B/Apo-A-1 ratio correlated positively whereas Apo-A-1 had a negative correlation with metabolic syndrome, its components and insulin resistance. Thus these are added associations with metabolic syndrome with clinical implications yet to be discerned. Screening individuals with Apo-B, Apo-A-1, and Apo-B/Apo-A-1 can hence help in the diagnosis of metabolic syndrome as an additional marker.*

***Key words:** Metabolic syndrome, apolipoproteins, insulin resistance.*

## Introduction

Metabolic syndrome is defined by interconnected physiological, biochemical, clinical, and metabolic factors such as insulin resistance, visceral adiposity, atherogenic dyslipidaemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress[1].According to the harmonised definition metabolic syndrome is present when atleast 3 of the following 5 criteria are fulfilled[2]:

1. Fasting blood glucose ≥ 100 mg/dl.
2. Blood pressure ≥ 130/85 mmHg.
3. Triglyceride ≥ 150 mg/dl.
4. HDL-C ≤ 40 mg/dl(males), ≤ 50 mg/dl (females).
5. Waist circumference ≥ 90 cm (males); ≥ 80 cm (females).

Metabolic syndrome patients havea 5-fold risk of type 2 diabetes and a 2-fold risk of cardiovascular disease and all-cause mortality[3,4]. Lipoprotein abnormalities including elevated triglycerides, low HDL-cholesterol, and increased small dense LDL cholesterol are common in metabolic syndrome[5,6]. Apo-B and Apo-A-1 are the two major apolipoproteins involved in lipid transport and in the processes causing atherosclerosis and its complications. Apo-B is an important parameter in assessing cardiovascular risk in patients of diabetes and metabolic syndrome, since these patients tend to have small, dense LDL particles with relatively normal LDL-C but high Apo-B levels[7]. Apo-A-1 reflects the anti-atherogenic potential in HDL particles; the higher the value the better the protection against CV risk[8].

Many studies have demonstrated that the Apo-B , Apo-A-1 and their ratio are good predictors of metabolic syndrome[9], cardiovascular disease[10], and stroke[11]; however, Indian data for these parameters is lacking. The aim of our study was to bridge this gap and assess correlation of apolipoproteins and metabolic syndrome.

## Material and methods

Our study was a cross-sectional observational study at a large teaching hospital in Delhi. Subjects > 18 years of age satisfying criteria of metabolic syndrome according to the harmonised definition as described were included as cases and a same number of controls were also included. Patients

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with hepatic, renal dysfunction, thyroid disorder, malignancy, pregnancy, smokers, alcoholics and those on drugs affecting the levels of lipoproteins (beta blockers, statins, diuretics, progesterone, oestrogen, niacin, fibrates, glitazones, insulin, HIV on anti-retroviral therapy) were excluded from the study.

Ethical clearance was taken from Institutional Review Board. The participants were enrolled for study after an informed consent. Detailed history and examination were undertaken. Anthropometric data was collected. Enrolled participants were required to fast overnight for around 12 hours and venous samples were collected. Blood was drawn from the ante cubital vein, and blood specimens were collected in an EDTA and plain vials, which were then sent for lab analysis. The rest of the samples, were centrifuged at 3,000 rpm for 5 - 10 minutes at room temperature and stored in aliquots. These samples were stored at -80 degree for analysis on a later date.

Height was measured by Stadiometer to nearest 0.1 cm, weight by Digital Weighing machine and BMI was calculated by standard formula Wt (kg)/ $[Ht(m)]^2$. Waist circumference was measured by cross tape method at mid-waist during end expiration. Blood pressure was recorded by Anaeroid Sphygmomanometer and average of three readings taken. Blood glucose and serum cholesterol were measured by enzymatic method (Randox kit), HDL cholesterol by enzymatic clearance assay and serum triglycerides, by Enzymatic automated calorie method. VLDL, LDL were calculated by Friedewald's equation. Glycated Hb (HbA1c) was measured by Boronate affinity chromatography (Bio-Rad in2it system). Serum insulin was determined by Radioimmunoassay (Mercodia ELISA machine) and HOMA-IR was calculated by the formula = FPG x fasting insulin/ 405. Apo-B and Apo-A-1 were measured by Immunochemistry (VITROS reagent).

Data was analysed by SPSS version 20. Description of categorical variables, i.e., sex, presence of various risk factors (diabetes, hypertension) and descriptive of continuous variables (age, BMI, SBP, DBP, HDL, TG, total cholesterol, Apo-B, Apo-A-1) were presented as mean and standard deviation. Association of two categorical variables was seen using Chi-square statistics. Statistical significant differences between two means was analysed using Student's t test. Pearson's test was used for determination of correlation. A p - value of $\leq 0.001$ was taken as level of statistical significance.

## Results

A total of 100 subjects (males and females) aged > 18 years with 50 cases (of metabolic syndrome) and 50 controls (no features of metabolic syndrome) were included in the study. The mean age of the study population was 53.29 ± 6.21 years. In cases and controls, the mean age was 55.60 ± 5.66 years and 50.98 ± 6.76 years respectively with no statistically significant difference. There was no significant difference in the sex distribution of the cases and controls (Table I). The subjects were clearly delineated as cases and controls based on characteristics of metabolic syndrome (Table I).

**Table I: Mean values and standard deviation of the main anthropometric, clinical and biochemical characteristics of the subjects.**

| Parameter | Cases (Mean ± SD) | Controls (Mean ± SD) |
|---|---|---|
| Age (in years) | 55.60 ± 5.66 | 52.98 ± 6.76 |
| Sex | M = 28, F = 22 | M = 25, F = 25 |
| BMI (kg/m²) | 27.78 ± 1.98 | 22.13 ± 2.07 |
| WC (cms) | 87.80 ± 5.65 | 80.14 ± 6.91 |
| SBP (mmHg) | 143.28 ± 8.88 | 122.76 ± 6.05 |
| DBP (mmHg) | 88.00 ± 4.71 | 74.26 ± 3.46 |
| FBS ( mg/dl) | 150.64 ± 54.46 | 85.94 ± 8.31 |
| HBA1C (%) | 8.39 ± 2.12 | 5.10 ± 0.52 |
| F insulin (µIU/ml) | 11.06 ± 3.88 | 7.42 ± 0.82 |
| HOMA-IR | 4.13 ± 2.16 | 1.56 ± 0.22 |
| T CHOL (mg/dl) | 193.46 ± 32.83 | 151.94 ± 18.62 |
| HDL- C (mg/dl) | 43.40 ± 9.31 | 59.42 ± 5.00 |
| LDL - C (mg/dl) | 114.04 ± 33.27 | 76.16 ± 19.05 |
| VLDL (mg/dl) | 36.00 ± 15.47 | 16.32 ± 4.88 |
| TG (mg/dl) | 179.86 ± 57.98 | 112.68 ± 16.50 |
| Apo-B | 148.21 ± 31.43 | 80.62 ± 20.07 |
| Apo-A-1 | 89.06 ± 24.10 | 173.13 ± 24.11 |
| Apo-B/Apo-A-1 | 1.93 ± 1.18 | 0.48 ± 0.13 |

Apo-B was significantly higher in cases compared to controls. The mean Apo-B in cases was 148.21 mg/dl vs 80.62 mg/dl in controls (p value < 0.001) (Table I). In cases the Apo-B levels were higher in males (151.06 mg/dl) compared to females (144.57 mg/dl) whereas in the control group, the Apo-B levels in males and females were similar (79.82 and 81.43 mg/dl respectively) (Table II).

Apo-A-1 levels were much lower in cases than in controls. The mean Apo-A1 level in cases was 89.06 mg/dl and in controls was 173.13 mg/dl (Table I). Mean Apo-A-1 was higher in males (184.32 mg/dl) than females (161.93 mg/dl) in the control group. In the case group, mean Apo-A-1 was lower in males (85.53 mg/dl) than females (94.82 mg/dl) (Table II).

**Table II: Mean value of Apo-B, Apo-A-1 and Apo-B/ Apo-A-1 ratio in the study group.**

| Apo-B | Males | Females | Total | P value |
|---|---|---|---|---|
| Cases (mg/dl) | 151.06 | 144.57 | 148.21 | < 0.001 |
| Controls (mg/dl) | 79.82 | 81.43 | 80.62 | |
| **Apo-A-1** | | | | |
| Cases (mg/dl) | 85.53 | 94.82 | 89.06 | < 0.001 |
| Controls (mg/dl) | 184.32 | 161.93 | 173.13 | |
| **Apo-B/Apo-A-1** | | | | |
| Cases | 2.05 | 1.78 | 1.93 | < 0.001 |
| Controls | 0.42 | 0.55 | 0.48 | |

The observed differences in Apo-B and Apo-A-1 levels between the cases and controls makes Apo-B/Apo-A-1 ratio a strong correlator for metabolic syndrome as is seen in our study with mean ratio of 1.93 in cases and 0.48 in controls with a p value < 0.001 (Table II). In the cases, the levels were higher in males than in females with a mean of 2.05 and 1.78, respectively. The control group had a ratio of 0.42 in males and 0.55 in females. On detailed analysis of correlation of apolipoproteins with individual components of the metabolic syndrome it was observed that Apo-B positively correlated with SBP, TG and HOMA-IR. On the other hand, Apo-A-1 correlated negatively with waist circumference and VLDL and positively correlated with HDL. Apo-B/Apo-A-1 ratio had a positive correlation with SBP, VLDL, and HOMA-IR (Table III).

**Table III: Correlation of Apo-B, Apo-A-1 and Apo-B/ Apo-A-1 ratio with components of metabolic syndrome.**

| Parameters | Correlation co-efficient (r) | | | Significance level (p) | | |
|---|---|---|---|---|---|---|
| | Apo-B | Apo-A-1 | Apo-B/ Apo-A-1 ratio | Apo-B | Apo-A-1 | Apo-B/ Apo-A-1 ratio |
| WC | 0.247 | -0.243 | 0.178 | 0.04 | 0.05 | 0.216 |
| SBP | 0.233 | -0.175 | 0.308 | 0.103 | 0.233 | 0.03 |
| DBP | 0.054 | -0.095 | 0.201 | 0.711 | 0.513 | 0.162 |
| FBS | -0.168 | 0.09 | -0.157 | 0.242 | 0.536 | 0.484 |
| HDL | -0.186 | 0.227 | -0.188 | 0.195 | 0.05 | 0.413 |
| TG | 407 | -0.119 | 0.135 | 0.003 | 0.41 | 0.35 |
| VLDL | 0.340 | -0.317 | 0.456 | 0.016 | 0.025 | 0.001 |
| LDL | 0.043 | -0.018 | -0.041 | 0.767 | 0.902 | 0.778 |
| Non HDL | 0.199 | -0.158 | 0.199 | 0.167 | 0.274 | 0.167 |
| BMI | 0.049 | -0.112 | 0.029 | 0.738 | 0.439 | 0841 |
| HOMA-IR | 0.415 | 0.218 | 0.286 | 0.003 | 0.128 | 0.044 |

## Discussion

This study is a significant observation on correlation of apolipoproteins and metabolic syndrome in Delhi as there have been no such studies till now. In our study the mean BMI (27.78 ± 1.98 kg/m$^2$ in cases and 22.13 ± 2.07 kg/m$^2$ in controls) were comparable to the study by Jing *et al* (BMI of 26.47 kg/m$^2$ in cases and 22.43 kg/m$^2$ in controls)[12]. Our study clearly demonstrated significant higher Apo-B levels in cases compared to controls (148.21 mg/dl vs 80.61 mg/dl), as was observed by other studies like Lind *et al* (137 mg/dl vs 122 mg/dl)[13] and Atanasovaalva *et al* (104.87 mg/dl vs 85.24 mg/dl)[14]. This study also clearly demonstrated significant inverse relationship of Apo-A-1 with metabolic syndrome (mean value in cases vs controls of 89.06 mg/dl and 173.13 mg/dl respectively). Similar findings have been reported by Wang *et al*[15], Soloymoss *et al*[16] and Stewart *et al*[17].

The combined effect of Apo-B and Apo-A-1 is seen in the Apo-B/Apo-A-1 ratio with highly significant correlation with metabolic syndrome (mean value in cases and controls 2.05 and 0.65 respectively). Similar correlation has been reported by Johnson *et al*[18], Zhong *et al*[19]. ROC analysis was performed in our study to assess the cut-off diagnostic value of Apo-B/Apo-A-1 ratio for metabolic syndrome. The optimal cut-off value of Apo-B/Apo-A-1 ratio for metabolic syndrome detection was 0.68. In a similar study Chang *et al* showed a ratio of 0.65 in men and 0.63 in women[20]. However, Pistavos *et al* suggested a ratio of 0.73 as an optimal cut-off for predicting metabolic syndrome, with a sensitivity of 74% and a specificity of 67% in Greek population[21] and Walldius *et al* demonstrated higher cut-off for metabolic syndrome, which is 0.7 in men and 0.6 in women in Swedish population[22]. These differences could be due to the geographical variation, ethnicity, diet, genetic polymorphisms and difference in sample size.

## Conclusions

The study showed that metabolic syndrome is prevalent in the age group 41 - 60 years. Apo-B showed positive correlation with WC, TG, VLDL and HOMA-IR and Apo-B/ Apo-A-1 ratio positively correlated with SBP, VLDL and HOMA-IR. In summary, Apo-B and Apo-B/Apo-A-1 ratio was associated with metabolic syndrome, its components and insulin resistance. Thus they can be used as indicators of metabolic syndrome. We recommend screening individuals in the age group of 40 - 60 years with measurement of Apo-B, Apo-A-1, Apo-B/Apo-A-1 ratio as part of early diagnosis of metabolic syndrome.

## Limitations

The main limitation of this study is its small sample size.

More studies need to be done on larger populations to unveil the hidden epidemic of metabolic syndrome and its characteristics in order to initiate early management to prevent morbidity and mortality. Second, the causal relationship between the Apo-B/Apo-A-1 ratio and metabolic syndrome cannot be conclusively established because of the cross-sectional nature of the study. Also prospective studies in the Indian population are needed to determine whether serum apolipoproteins precede the development of metabolic syndrome and insulin resistance.

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