Original Article

The Apolipoprotein-B/ Apolipoprotein-A1 Ratio in Normal Individuals Verses Patients with Metabolic Syndrome in Tertiary Care Units of District Peshawar, KPK

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ABSTRACT

Objective: The main objective of the study was to determine the ratio of Apo-B/Apo-A1 in normal individuals and patients with metabolic syndrome.

Study Design: Comparative / case control study.

Place and Duration of Study: This study was conducted at the Department of Pharmacology, KGMC, Peshawar from June 2015 to December 2015.

Materials and Methods: Total of 200-cases, including 150-Met-S and 50-controls were enrolled in different tertiary care hospitals of Peshawar. After formal consent, detail history and clinical examination, data was collected about height, weight, socioeconomic condition, blood pressure and waist circumference and diagnosis of Met-S was made accordingly. Blood glucose levels, Apo-B and Apo-A1 and lipid profile was done in all patients and normal individual.

Results: Among 200-study population, 150 were cases having Met-S, while 50 were normal control. The mean age was 47.75±4.79 years in patients, while it was 45.16±3.84 years in control group. In both cases and control groups, male-female ratio was 61/89 and 32/18 respectively. The ratio of Apo-B/Apo-A1 was calculated to measure the relative risk for coronary heart disease. The study showed ½ average risks in subjects with Met-S, was 4.9% in males and 1.1% in females. In control, it was 3.1% in males and 5.5% in females. In my study majority of the cases in both Met-S (68.8% male, 70.7% female) and controls (96.8% male & 88.8% female) fall in twice-average risk category group. There was threefold risk in Met-S patients was 26.2% in male and 28% in female. No such association was found in the controls.

Conclusion. It is concluded from the study that ratio of Apo-B/Apo-A1 can be used as one of the best variable to quantitate the risk of coronary heart disease in normal individuals and patients with metabolic syndrome.

Key Words: Metabolic Syndrome (Met-S), Apolipoprotein, And Coronary Heart Disease.

Citation of article: Anjum N, Jamil A, Nizamuddin, Parvez A, Yasmin A. The Apolipoprotein-B/ Apolipoprotein-A1 Ratio in Normal Individuals Verses Patients with Metabolic Syndrome in Tertiary Care Units of District Peshawar, KPK. Med Forum 2017;28(3):123-127.

INTRODUCTION

Metabolic syndrome (Met-S) is a cluster of different components characterized by increased body fat around the waist, increased blood pressure, a high blood glucose level, raised triglycerides in the blood and reduced high density cholesterol that occur together[1 2]. These factors increase the chance of having coronary heart disease, T2DM and stroke[3].

The prevalence of Met-S is increasing worldwide and approximately affects 20 to 25% people. There is three-fold increase in stroke and coronary heart disease and two fold increased incidence of mortality rate in such patients, compared to people without this syndrome. They also have fivefold risk of having Type 2 diabetes mellitus[4]. The contributing factors being age, race, obesity, gestational diabetes, family history of diabetes, non alcoholic fatty liver disease and polycystic ovarian syndrome[5 6].

Although LDL-Cholesterol, and more recently non HDL-Cholesterol are used for cardiovascular risk evaluation and for those patients who are using lipid lowering drugs, but newer studies have shown that in contrast to single lipid fractions, lipid ratios are stronger cardiovascular risk markers[7]. Nowadays, Apo-B/Apo-A1 ratio is one of the best variables to quantitate the risk of coronary heart disease[8 9]. Research reveals that there would be great advantage of integrating Apolipoprotein into clinical practice[10]. According to a recent study done in Chinese population, Apo-B/Apo-A1 ratio of 0.80 & 0.85 in women & men respectively, proved to be a highly significant biomarker of Met-S[11]. Studies carried out by Makaridze, Giorgadze, and

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Received: January 22, 2017; Accepted: February 20, 2017

Asatiani at Tbilisi state university Georgia revealed strong association of Apo B/ApoA1 ratio with Met-S as well as its components[12]. Prospective risk studies such as, EPIC Norfolk[13] AMORIS[14] MONICA / KORA[15] and ULSAM[16] show that Apo-B/Apo-A1 is an effective marker of fatal and non-fatal myocardial infarction (MI).

Apo-B and Apo-A1 are responsible for the transport of lipids and if deranged, have the potential to cause atherosclerosis and its related complications[17]. Apo-B is a 550 KD protein, synthesized in liver and is considered atherogenic and abnormal values are seen in familial combined hyperlipidemia, acquired hyperlipidemia, acute angina & Myocardial Infarction (MI). The reference range is 40-125 mg/dl.Apo-A1 comprises 75% in HDL and is considered anti-atherogenic. Apo-A1 levels are inversely proportional to the risk of CAD. The reference range of Apo-A1 varies with sex i.e greater than 120 mg/dl in males & greater than 140 mg/dl in females. The ratio of Apo-B/Apo-A1 is a balance of atherogenic & antiathrogenic particles and high values indicate high cardiovascular risk. It is a much more precise and adequate index of statin therapy as compared to LDL[18 19]. In clinical practice, accurate detection of glucose intolerance and dyslipidemia is very important so as to find out patients at high risk for cardiovascular disorders[20]. Various studies consider Apo-B/Apo-A1 ratio as an additional independent variable for the evaluation of this risk, especially in individuals with normal lipid profile[21 22].

Therefore, this present study was carried out in our population to assess its significance in normal individuals and patients with Met-S in tertiary care units of district Peshawar, KPK. This study can be helpful in assessing individuals at high risk of cardiovascular complications, future treatment and follow up.

MATERIALS AND METHODS

This study, conducted from June 2015 to December 2015, enrolling total of 200-subjects, including 150-Met-S and 50-controls. After formal consent, data was collected about height, weight, and socioeconomic condition, blood pressure and waist circumference. The diagnosis of Met-S was made accordingly. Blood glucose levels, Apo-B and Apo-A1 and lipid profile was done in all patients and normal individual. All male and female with age 40 and above with metabolic syndrome were included. Non co-operative patients, patients who do not meet the criteria's mentioned in the definition of Met-S, smoker, pregnant women, patients using oral contraceptives and statins and patients with Nephrotic syndrome and hypothyroidism were excluded. In control all male and female with age group 40 and above and those who do not meet the criteria's mentioned in the definition of Met-S were included, while control with diagnosed Met-S, non co-operative individuals, smokers, pregnant ladies, diabetics and central obesity (WC ≥ 90cm for male) and (WC ≥ 80cm for female) were excluded.

Data Collection: Data was collected from total 150-cases and 50-controls visiting outdoor clinics and fulfilling the inclusion and exclusion criteria. They were enrolled in a consecutive manner. After ethical committee approval and informed consent, the demographic information of the subjects such as names, age and gender were recorded. Blood glucose, TG, LDL, HDL, Cholesterol and Apo-B and Apo-A1 were done using, AKENZA MAX biochemistry analyzer and ARCHITECT analyzer ci8200. All collected information was recorded on pre-designed Performa.

Data Analysis: Analysis of the data was done by SPSS version 17. Results were expressed in the form of mean and standard deviation. Apo-B and Apo-A1 were determined and ratio was calculated. Comparison between Apo-B/Apo-A1 ratio with WC and comparison of WC among gender was done. Statistical significance was weighed when $P \leq 0.05$.

RESULTS

In studied 200 cases, 150 individuals fulfill the criteria and considered as cases, while 50 adults are taken as control. Age of all the participants both patient and controls ranges between 40 -55.

Age, gender, waist circumference, blood pressure and biochemical characteristics among all the subjects, due to the absence or presence of the Met-S are shown in Table-1.

Table No.1: Demographic characteristic of Met-S patients and Controls

	Met S (150)	Control (50)	P-value
Age (mean±SD)	47.75±4.79	45.16±3.84	NS
Sex (male/female)	61/89	32/18	NS
ApoA-I (mg/dl)	121.73 ±32.30	131.66 ±18.65	.041
ApoB (mg/dl)	114.01 ±94.82	84.40 ±18.11	.030
ApoB/ApoA-I ratio	1.02 ±1.08	0.61 ±0.10	.007
SBP (mmHg)	140.99 ±24.08	132.0 ±20.07	.018
DBP (mmHg)	90.90 ±10.57	86.90 ±9.19	.018
WC (cm)	105.78 ±11.31	84.80 ±5.11	.001
TC(mg/dl)	222.04 ±52.18	184.02 ±43.47	.001
HDL-C (mg/dl)	38.47 ±22.33	42.06 ±6.91	.085
LDL(mg/dl)	143.33 ±49.45	115.78 ±43.60	.001
TG (mg/dl)	221.79 ±91.49	124.66 ±31.90	.001
FBS (mg/dl)	131.41 ±59.37	86.78 ±12.24	.001

Mean & standard deviations of WC, age, sex, systolic, diastolic blood pressure, TG, TC, LDL, and blood glucose were highly significant ($p<0.001$) & HDL-C levels were reduced in Met-S group as compared to

control group. A value of Apo-B/Apo-A1 ratio in patients with Met-S was highly significant with p≤0.007 while Apo-B and Apo-A1 separately were also significant with p≤0.03 and p≤0.04 respectively in both the groups. This Study included 53.5% female and 46.5% male subjects.

The comparison of waist circumference has been shown between male and female subjects. It was divided into three groups i.e. group-1, WC >90, group-2, WC ranges from 91-100 while group-3, WC>100. In this data it was shown that, WC of females is more than males. The mean and standard deviation in female is 104.69±14.53 while in male is 95.75±10.68. WC is highly significant. P value is<0.001.

Table No.2: Descriptive characteristics between genders

	Female (*n*=107; 53.5%)	**Male (*n* = 93; 46.5%)**	**P value**
Age	47.36±4.70	46.76±4.64	0.366
ApoB/ApoA1 ratio	0.96±1.03	0.87±. 85	0.505
ApoA1 (mg/dl)	125.89±32.62	122.28± 26.12	0.394
ApoB (mg/dl)	115.84±110.15	95.98± 30.03	0.094
SBP (mmHg)	140.83±20.40	136.34± 26.39	0.177
DBP (mmHg)	92.94±9.29	86.40± 10.49	0.001
WC (cm)	104.69±14.53	95.75± 10.68	0.001
TC(mg/dl)	222.55±54.33	201.01± 48.52	0.004
HDL-C (mg/dl)	38.08±9.737	40.85± 26.94	0.323
TG (mg/dl)	209.88±99.84	183.28± 77.96	0.039
FBS (mg/dl)	129.76±63.41	109.31±41	.009

Anthropometric and biochemical characteristics were presented on gender basis and no difference was found in both the groups as shown in Table 2.The value of Apo-B/Apo-A1 ratio and Apo-B and Apo-A1 separately in patients with Met-S as well as in control group was not significant with p value of p≤0.5, p≤0.09 and p≤0.3 respectively.

Cardiovascular risk assessment in patients with Met-S and controls by Apo-B/Apo-A1 ratio is presented in Table 3. The ratio of Apo-B/Apo-A1 provides us the relative risk levels for future coronary heart disease. The study showed ½ average risks in subjects with Met-S in males 4.9% and in females it is 1.1%. In control males it is 3.1% and control females it is 5.5%. In my study, majority of cases in both Met-S (68.8% male, 70.7% female) and controls (96.8% male & 88.8% female) fall in twice-average risk category group. There was threefold risk in male Met-S patients i.e. 26.2% and in females it was 28%. No such association was found in the controls.

Table No.3: Cardiovascular risk assessments, among Met-S adults and control, by Apo-B/Apo-A1 ratios.

	Met-S(150)		**Control(50)**	
	Male (61)	**Female (89)**	**Male (32)**	**Female (18)**
1/2 Average Risk. (Male=0.4, Female=0.3)	3 (4.9%)	1 (1.1%)	1 (3.1%)	1 (5.5)%
Twice Average Risk(Male=0.5-1.0, Female=0.4-0.9)	42 (68.8%)	63 (70.7%)	31 (96.8%)	16 (88.8%)
Three Times Average Risk(Male ≥1.1, Female≥ 1.0)	16 (26.2%)	25 (28.0%)	0%	0%

DISCUSSION

Metabolic syndrome is a worldwide health problem. Met-S is the fastest growing chronic disease worldwide including Pakistan[23]. For the diagnosis of Met-S and risk evaluation of cardiovascular disease, diabetes mellitus, hypertension and familial hyperdyslipedemia, there are certain biomarkers including lipid profile, including total cholesterol, TG, HDL-C, LDL, IDL and VLDL Apo-A1, Apo-B and their ratios [9 10 11]. The researchers thought about a new approach to find out more convenient biomarkers for the diagnosis of Met-S patients as well as for those who are on lipid lowering treatment and for those who have a family history.

The two major apolipoproteins are Apo-B and Apo-A1, which are considered the new determinants of Met-S, before and after the development of the disease &all its components. The major protein in very low-density lipoproteins (VLDL) is Apo-B, as well as in the intermediate-density lipoproteins (IDL), and low-density lipoproteins (LDL), one protein per particle. The major protein in high-density lipoprotein (HDL) particles is Apo-A1[6]. Apo-B/Apo-A1 ratio being a strong, new risk factor for cardiovascular disease and a target for lipid-lowering therapy has been reevaluated several times in healthy subjects and in patients with different clinical manifestations of atherosclerosis[24].

Laboratory services in the pathology department of university of lowa United State gives the values of Apo-B/ApoA-1 ratio as relative risk factors in 2015, to find out the cardiovascular risk. These are

Apolipoprotein B/A	Male	Female
1/2 Average Risk	0.4	0.3
Twice Average Risk	1.0	0.9
Three Times Average Risk	1.6	1.5

In the present study it was found out that those individuals who are included in control group having WC 80-90cm in men and 70-80cm in female was at future CV risk. ½ average risk was 3.1% in male while 5.5% in female while twice-average risk in male was

96.8% and 88.8% in female. In our study patient with Met-S showed ½ average CV risk 4.9% in male, 1.1% in female, twice average risk 68.8% in men, 70.7% in female, three times risk 26.2% in male and 28% in female.

Many authors have studied the importance of Apo-B, Apo-A1, and Apo-B/Apo-A1 ratios as significant markers of CV risk. Prospective risk studies, such as AMORIS[14] INTERHEART[25], EPIC-Norfolk study[13]and ULSAM[16] indicated that Apo-B/ApoA-1 ratio is a valuable marker of risk of myocardial infarction. Interheart, a case-control study done in 52 countries, investigated that Apo-B/Apo-A1 ratio was the strongest factor in explaining risk of acute MI with Odd ratio of 3.25(2.81-3.76) with 95% confidence interval. It was also the most prevalent risk factor of all the nine conventional risk factors irrespective of sex, race, age and other lipids or lipid ratios[25].

Similar finding to our study were present in study done by Min Lu[9] in china in 2011, showed that in Met-S group blood pressure, blood sugar, TC,TG, LDL Apo-B and Apo-B/Apo-A1 ratio were high while Apo-A1 and HDL were low.

Hanan Belfki and Samer Bin Ali have studied in a Tunisian population (330 adults aged 35–74) including Met-S subjects & a control group, showed that Apo-B/Apo-A1 ratio was very strongly associated with Met-S ($p<0.001$). This study also showed that Apo-B (0.97 ± 0.23) and Apo-A1 (1.49 ± 0.28) were highly significant in Met-S group versus controls with $p < 0.001$[26]. In our study Apo-B/Apo-A1 ratio showed strong correlation with Met-S versus controls (1.02 ± 1.08) with $p<0.007$, however Apo-B ($p<0.03$), Apo-A1 ($p<0.04$) independently were also significant.

The present study showed that WC of females was more than males. The mean and standard deviation in female is 104.69±14.53 while in male is 95.75±10.68. WC is highly significant p value is<0.001. Similar findings were observed in study of Tunisian population conducted in 2011 whose finding for WC were 100.1±13.0 for female and 99.4±11.1 for male[12]. It is also found out in our study that mean and standard deviation in Met-S group is 105.78±11.31 verses 84.80±5.11 in control group with p value of .001, the results of our study are in concordance with the above mentioned Tunisian study showing 104.7±10.9/ 95.5±12.4 in Met-S/controls[12]. IDF recommended that the primary target of intervention in Met-S and without Met-S should be obesity[1].

Central obesity, which is the basic component of Met-S, is more important than body mass index (BMI). In Epic Norfok study and Arsenault, S Rana studied in Norfolk UK population that physical inactivity and central obesity are the main killers of our population. Men and women both shows great variations in lipid profile analysis and Apo-B/Apo-A1 ratio even in those whose waist circumference is borderline i,e 80-90cm for men and 70-80cm for women[27]. Anastasiya M. Kaneva studied 157-normolipidemic men aged 20-59. The median of Apo-B/Apo-A1 ratio was 0.52. Apo-B/Apo-A1 ratio >0.9 was 19.1%.

Zaza Makaridze found in Georgian population in 2014 that previously in lipid profile, LDL-C was thought to be an independent risk factor for CV diseases and was recommended as first line diagnostic tool by different clinical guidelines but now the Apo-B/Apo-A1 ratio is more important predictor of CV risk. They found positive correlation of Apo-B/Apo-A1 with, blood glucose and TG (all $p<0.001$) and negative correlation with HDL in both sexes[12].

G Leroux, I Lemieux and B Lamarche showed in their study that the levels of triglycerides in blood have a positive effect on the levels of Apo-B/Apo-A1 ratios there is a strong correlation between TG and Apo-B/Apo-A1 ratio ($p<0.001$) [17]. Our study also demonstrated a strong correlation between TG and Apo-B/Apo-A1 ratio, that higher the TG level, higher will be Apo-B/Apo-A1 ratios.

On the Basis of the new studies, now it is the time to include Apo-B, Apo-A1 and the Apo-B/Apo-A1 ratio into new guidelines in our country as leading risk variables of parallel or higher importance than LDL, TC, TG and HDL C. The Apo-B/Apo-A1 ratio is a simple and precise test, can be done on non-fasted subjects. Also LDL-C, HDL-C, TG and lipid ratios are explained in many cumbersome numbers while Apo-B/Apo-A1 ratios can be expressed as only one number[25]. There are some limitations like small sample size and the positive relation between the Apo-B/Apo-A1 ratio and Met-S cannot be established fully because this was a cross-sectional study. Multiple risk factors, including dyslipidemia, diabetes mellitus & hypertension and other metabolic abnormalities were also affecting the finding.

CONCLUSION

It can be concluded from the present study that Apo-B, Apo-A1 and Apo-B/Apo-A1 ratio are newer and valuable markers for prediction of cardiovascular disease risk in Met-S patients & in normal population. It can be used as a follow up test to evaluate the response of lipid lowering drugs. Further studies addressing the all-possible confounders with huge sample size is recommended for further validation.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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