

# Can apolipoproteins should be consider as better index of risk factor than total cholesterol and traditional lipids?

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## Abstract

**Introduction:** It is essential to identify and manage risk factors for coronary heart disease in order to prevent its development in asymptomatic individuals (primary prevention) as well as to avoid its recurrence in patients with established disease (secondary prevention). Although low density lipoprotein (LDL) is recognized as the primary lipid related risk factor, and therefore the primary target for lipid lowering therapy, there are in fact several limitations of only using LDL cholesterol as the primary risk variable. New data are accumulating which speak in favor of apolipoproteins as more informative risk indicator/factors. **Aims and Objectives:** a) To find the relationship between serum Apolipoprotein A-I and B and lipid profile in Coronary Heart Disease patient and age and sex matched healthy control. b) To evaluate, whether Apolipoprotein A-I and B should be consider as better index of risk factor than total Cholesterol or Lipid profile. **Materials and methods:** The present study was conducted at Government Medical College and Hospital, Aurangabad. Levels of Apolipoprotein A-I and B and lipid profile in 60 Coronary Heart Disease patients admitted with first episode of coronary heart disease in ICCU were compared with 60 healthy apparently normal age, sex matched individuals. **Results:** It was observed that levels of apolipoprotein A-I and the ratio of apolipoprotein A-I and B were decreased in CHD patients where as levels of apolipoprotein B was increased in CHD patients as compared to control group. And the difference was also statistically significant. Also lipid profiles in case group showed significant difference as compared to control group except triglyceride and VLDL levels in male group. **Conclusion:** Levels of serum Apolipoprotein A-I and B and lipid profile in Coronary Heart Disease patient showed significant change as compared to control group. And the concentration of apo A-I, apo B and its ratio can be a useful summary index of risk factor.

**Key Word:** Apolipoproteins, Lipids.

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Received Date: 05/05/2014 Accepted Date: 01/06/2014

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DOI: 01 June 2014

## INTRODUCTION

It is essential to identify and manage risk factors for coronary heart disease in order to prevent its development in asymptomatic individuals (primary prevention) as well as to avoid its recurrence in patients with established disease (secondary prevention). Risk factor management should be conceived as prevention of coronary atherosclerosis itself and, as such, should be included as an integral part of any management plan for the many acute and chronic manifestation of this disease. Atherosclerosis of coronary artery is the main cause of coronary disease and the Lipid fractions of blood have proved to be among the most potent and best

substantiated risk factors for atherosclerosis in general and coronary heart disease in particular.<sup>2</sup> In India prevalence of coronary heart disease is increasing. The prevalence is higher in men as compared to women in both urban and rural population. Coronary artery disease risk is two to three fold more common among urban subjects compared to rural population in both sexes, which is due to greater sedentary behavior, diabetes mellitus, hypertension, obesity, smoking and hypercholesterolemia.<sup>3</sup> Although low density lipoprotein (LDL) is recognized as the primary lipid related risk factor, and therefore the primary target for lipid lowering therapy, there are in fact several limitations of only using LDL cholesterol as the primary risk variable. New data are accumulating which speak in favor of apolipoproteins as more informative risk indicator/factors. Apo B, which indicates the number of potentially atherogenic lipoprotein particles, and apo A-I, which reflects anti-atherogenic high density lipoprotein (HDL) particles, may be additional lipid related variables that more accurately indicate cardiovascular risk than LDL cholesterol. Thus, several studies have shown that apo B and apo A-I are strong predictors of myocardial infarction.<sup>4</sup> Thus in our study we compared various lipid parameters like total cholesterol, triglyceride, HDL, LDL, VLDL and apolipoproteins A-I and B in 60 Coronary Heart Disease patients admitted with first episode of coronary heart disease in ICCU of Government Medical College, Aurangabad with 60 healthy apparently normal age, sex matched individuals.

**AIMS AND OBJECTIVES**

- To find the relationship between serum Apolipoprotein A-I and B and lipid profile in Coronary Heart Disease patient and age and sex matched healthy control.
- To evaluate, whether Apolipoprotein A-I and B should be consider as better index of risk factor than total Cholesterol or Lipid profile.

**MATERIAL AND METHODS**

**Study Design:** The present study was conducted at Government Medical College and Hospital, Aurangabad among the subjects those who were diagnosed of Coronary Heart Disease and admitted with either myocardial infarction or angina pectoris or ischemic Heart Disease in ICCU.

**Study duration:** January 2005 to January 2006.

**METHODOLOGY**

**Selection of cases and control**

**Cases Group** 60 patients with Coronary Heart Disease admitted to ICCU including male and female were taken with following inclusion and exclusion criterion.

**Inclusion criteria**

- Hospitalization with first time chest pain and fresh ECG showing sign of Ischemic changes.
- Patient between age group of 45-65 years.

**Exclusion criteria**

- Smoking
- Diabetes Mellitus
- Lipid lowering Drugs

**Control Subjects** 60 healthy individuals with Age and sex matched were taken

**Inclusion criteria**

- Age and sex matched with patients
- No s/o ischemia or infraction like chest pain, sweating, vomiting etc.
- ECG not suggestive of myocardial infarction or ischemia.

**Exclusion criteria**

- Smoking
- Diabetes mellitus
- Lipid lowering Drugs (Statins)

All the details about the study were explained to the subject and informed consent was taken. Detail history of cases and controls was entered on proforma. Fasting blood sample were collected and analyzed for lipid profile, Apolipoprotein A-I and Apolipoprotein B. ratio of apolipoprotein A-I and B was also calculated. And the findings were also entered in proforma. The arithmetic mean (x), standard deviation (S.D) were calculated for case and control group separately and compared by using unpaired t test.

**RESULTS**

**Table 1:** Age and sex wise distribution of CHD patients and normal control subjects.

Variable	CHD Patients (n=60)	Controls (n=60)
Male	39	42
Female	21	18
Age(yrs)	59.92 ± 5.40	55.18 ± 5.23

The study included a total number of sixty (60) coronary heart disease patients admitted in Medicine ICCU. Same number (60) age and sex matched apparently healthy normal subjects were studied as controls. It was observed there were 39 male and 21 female with an average age of 59.92 yrs suffering from CHD and control group of 42 male and 18 female with an average age of 55.18 yrs.

**Table 2:** Comparison of Lipoproteins, Apolipoprotein A-I and B in CHD cases and control subjects

Parameters (mg/dl)	Cases (n=60)	Controls (n=60)	Unpaired t test	P value
	Mean ± S.D	Mean ± S.D		
Total	209.46 ±	196.94 ±	2.59	< 0.01
Cholesterol	33.02	17.39		
Triglyceride	148.24 ±	137.13 ±	3.19	< 0.001

	17.86	20.18		
HDL	38.95 ± 2.77	40.75 ± 3.886	2.92	< 0.01
VLDL	29.717 ± 3.68	27.4 ± 3.988	3.31	< 0.001
LDL	140.8 ± 29.59	128.78 ± 18.01	2.68	< 0.01
Apo A-I	107.88 ± 13.33	133.07 ± 21.45	7.726	< 0.001
Apo B	128.12 ± 20.44	97.75 ± 13.989	9.497	< 0.001
Apo A-I/B Ratio	0.8567 ± 0.1365	1.3796 ± 0.2625	13.689	< 0.001

It was observed that highly significant increase in Total Cholesterol, LDL-cholesterol, and very high significant increase in Triglyceride, VLDL-cholesterol and Apolipoprotein B. Very high significant decrease in Apolipoprotein A-I, ratio of Apolipoprotein A-I/B and Significant decrease is seen in HDL-cholesterol.

**Table 3:** Comparison of Lipoprotein Apolipoprotein A-I and B in Male CHD cases and control subjects

Parameters (mg/dl)	Cases (n=39) Mean ± S.D	Controls (n=42) Mean ± S.D	Unpaired t test	P value
Total Cholesterol	210.13 ± 37.55	198.14 ± 17.29	11.85	< 0.05
Triglyceride	145.61 ± 17.31	139.24 ± 20.30	1.54	NS
HDL	38.77 ± 2.59	40.40 ± 4.08	2.16	< 0.05
VLDL	29.18 ± 3.59	27.78 ± 4.04	1.65	NS
LDL	142.18 ± 32.42	129.95 ± 17.48	2.09	< 0.05
Apo A-I	108.69 ± 12.99	133.98 ± 21.94	7.37	< 0.001
Apo B	126.97 ± 19.76	98.31 ± 14.69	7.36	< 0.001
Apo A-I/B Ratio	0.8726 ± 0.1454	1.3698 ± 0.2615	10.67	< 0.001

Analysis of levels of Lipoprotein, Apolipoprotein A-I and B especially in male CHD cases and control subjects it was observed that very high significant increase in Apolipoprotein B and decrease in Apolipoprotein A-I and ratio of Apolipoprotein A-I/B. Significant increase was also seen in Total Cholesterol and LDL-cholesterol whereas non significant increase was seen in Triglyceride and VLDL-cholesterol and significant decrease was seen in HDL-cholesterol, in male CHD patients(n=39) as compared to control male(n=42).

**Table 4:** Comparison of Lipoprotein Apolipoprotein A-I and B in Female CHD cases and control subjects

Parameters (mg/dl)	Cases (n=21)	Controls (n=18)	Unpaired t test	P value
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	Mean ± S.D	Mean ± S.D		
Total Cholesterol	208.28 ± 23.12	194.11 ± 16.39	2.22	< 0.05
Triglyceride	153.09 ± 16.99	132.22 ± 18.05	3.69	< 0.001
HDL	39.28 ± 2.95	41.55 ± 3.10	2.33	< 0.05
VLDL	30.71 ± 3.44	26.5 ± 3.51	3.76	< 0.001
LDL	138.28 ± 20.45	125.05 ± 17.92	2.15	< 0.05
Apo A-I	106.38 ± 13.19	130.78 ± 19.07	4.57	< 0.001
Apo B	130.24 ± 20.62	96.44 ± 11.52	6.43	< 0.001
Apo A-I/B Ratio	0.8205 ± 0.1045	1.3743 ± 0.2617	8.42	< 0.001

Levels of Lipoprotein, Apolipoprotein A-I and B in female CHD cases and control subjects were also compared. It was observed that very high significant increase in Triglyceride, VLDL-cholesterol, and Apolipoprotein B. Decrease in Apolipoprotein A-I and ratio of Apolipoprotein A-I/B was observed. While significant increase was seen in Total Cholesterol and LDL-cholesterol whereas significant decrease was seen in HDL-cholesterol, in female CHD patients (n=21) as compared to control female (n=18).

## DISCUSSION

The present study was conducted with the objective to find the relationship between serum Apolipoprotein A-I and B and lipid profile in Coronary Heart Disease patient. And also to evaluate, whether Apolipoprotein A-I and B should be consider as better index of risk factor than total Cholesterol or Lipid profile. For that we compared lipoproteins, apolipoproteins A-I and B in 60 Coronary Heart Disease patients admitted with first episode of coronary heart disease in ICCU of Government Medical College, Aurangabad with 60 healthy apparently normal age, sex matched individuals. There were 39 male and 21 female with an average age of 59.92 yrs suffering from CHD and control group of 42 male and 18 female with an average age of 55.18 yrs. It was observed in our study that serum Total Cholesterol levels were significantly increased in CHD patients as compared to normal controls. Serum Cholesterol levels were also found to be significantly increased in male and female CHD patients and female CHD patients when compared to their normal counter parts. The relationship between cholesterol and atherosclerosis enjoys a wide acceptance. The emergence of data from cohort studies, such as that began in Framingham in 1950s, bolstered the relationship between cholesterol and CHD. This study, as well as others performed in different population around the world,

established more firmly the concept of cholesterol as a culprit in coronary heart disease.<sup>5</sup> Substantiation of the relationship between total cholesterol and CHD risk emerged from the Multiple Risk Factor Intervention (MRFIT) Trial (1986)<sup>6</sup>, the Prospective Cardiovascular Munster (PROCAM) cohort (1992)<sup>7</sup>, and recently, the Atherosclerosis Risk In Communities (ARIC) study (2001)<sup>8</sup>. Grundy SM *et al* (1986)<sup>9</sup> has also shown a curvilinear association between CHD and cholesterol. Serum Triglyceride showed very highly significant increase in CHD patients as compared to normal healthy group ( $148.24 \pm 17.86$  vs  $137.13 \pm 20.18$  mg/dl,  $p < 0.001$ ). Female CHD patients also had very high significant increase in serum triglyceride levels ( $153.09 \pm 16.99$  vs  $132.22 \pm 18.05$  mg/dl,  $p < 0.001$ ). Male CHD patients also showed increase in sr. triglyceride levels as compared to control group, but the increase was not found to be statistically significant ( $145.61 \pm 17.31$  vs  $139.24 \pm 20.30$  mg/dl). In contrast to the compelling evidence favoring a causal role for cholesterol in atherogenesis, the role of triglycerides still engenders controversy.<sup>10</sup> Our finding of triglycerides correlate with Michael F Reardon *et al* (1985)<sup>11</sup> who found in their study that in men, the score for severity of atherosclerosis was strongly related to LDL and apo B concentration, whereas in women it was related to the triglyceride concentration in plasma. Avins A.L. *et al* (2000)<sup>12</sup> concluded that in men, measurement of serum triglyceride levels does not provide clinically meaningful information about CHD risk. Austin M.A. *et al* (1989)<sup>13</sup> stated that from a statistical point of view, triglyceride often is not a significant predictor of coronary heart disease in multivariate statistical models because of the large variation in triglyceride measurements and the strong inverse relation between HDL cholesterol and triglyceride. Melissa A Austin *et al* (1998)<sup>14</sup> demonstrated that increased plasma triglyceride was associated with just 37% increase in risk of cardiovascular disease in men and a 76% increase in the risk of cardiovascular disease in women. In our study, HDL cholesterol was decreased in total CHD patients and also in males and females patients. Our findings were similar with the finding of Gordon *et al* (1977)<sup>15</sup>, John Albers *et al* (1978)<sup>16</sup>, Lynn Rosenberg *et al* (1983)<sup>17</sup>, Gred Assmann *et al* (1992)<sup>18</sup>, Korhonen T. *et al* (1996)<sup>19</sup>. All of them found significant decrease in HDL cholesterol in CHD irrespective of sex and age. Niemien M.S. *et al* (1992)<sup>20</sup> found that in men serum HDL cholesterol had highest power to discriminate for CAD. P.P. Jadhav *et al* (1993)<sup>21</sup> found decrease in HDL levels in CHD as compared to controls but the decrease was not found to be significant. Table 2 shows very highly significant increase in VLDL in cases as compared to controls ( $29.71 \pm 3.68$  vs  $27.4 \pm 3.98$  mg/dl,

$p < 0.001$ ), in males VLDL was increased in cases as compared to controls but the increase was not statistically significant ( $29.18 \pm 3.59$  vs  $27.78 \pm 4.04$  mg/dl) while very highly significant increase was also found in female CHD patients with  $30.71 \pm 3.44$  mg/dl as compared to  $26.5 \pm 3.51$  mg/dl in control females. Our findings were in accordance with Michael Reardon *et al* (1985)<sup>11</sup> and Singh R.B. *et al* (1997)<sup>3</sup>. LDL in our study was found to be significantly increased in all the groups, in males the reading were  $142.18 \pm 32.42$  mg/dl in CHD patients against  $129.95 \pm 17.48$  mg/dl in controls with  $p < 0.05$ , in females CHD patients LDL was  $138.28 \pm 20.45$  mg/dl against  $125.05 \pm 17.92$  mg/dl with  $p < 0.05$ . The overall concentration of LDL in population was  $140.8 \pm 29.59$  mg/dl in CHD patients against  $128.78 \pm 18.01$  mg/dl in controls with  $p < 0.01$ . In our study table 2, 3, 4 show that apo A-I was decreased with very high statistical significance in CHD patients as total and also in male and female group. Transport of cholesterol and formation of HDL-cholesterol are the basic role of apo A-I, low levels of this protein have been identified as a risk factor in the development and progression of coronary damage.<sup>22</sup> It was suggested by Avogaro P *et al* (1979)<sup>23</sup> that plasma apo A-I measurements may provide more information than HDL levels in the assessment of CHD risk. Gerald Luc *et al* (2002)<sup>24</sup> in PRIME study stated that among the parameters related to HDL, apo A-I appears to be the strongest independent risk factor. P.P. Jadhav *et al* (1993)<sup>21</sup> and Johan Franzen *et al* (1986)<sup>25</sup> found significantly decrease levels of apo A-I in survivors of myocardial infarction with normal levels of HDL. Apo B in our study was increased in CHD patients as total group and also in male and female CHD group as compared with their age and sex matched controls, statistically showing very high significance. Apo B was found to be better index of risk in many prospective studies like AMORIS (2001)<sup>26</sup>, Quebec (1996)<sup>27</sup>, and EARS (1994)<sup>28</sup>. In P.N. Durrington's study (1988)<sup>29</sup> apo B emerged as the main lipoprotein determinant of coronary disease risk. Peter O. Kwiterovich *et al* (1992)<sup>30</sup> concluded that 'nontraditional risk factors' (plasma apo A-I and B levels) are better predictor of premature coronary heart disease than are plasma lipoprotein. C. Snehalatha *et al* (2002)<sup>31</sup> found that hyper apo B was more common than hyper LDL cholesterol in CAD subjects and apo B abnormalities exist in large percentage of CAD subjects despite having normal levels of LDL cholesterol. Measurements of apolipoprotein (apo A-I and apo B) are internationally standardized, automated, more convenient and precise than those for LDL cholesterol.<sup>32</sup> LDL cholesterol is calculated using Friedewald formula and is not measured and is calculated from several unstandardized assays, each of which necessarily involves

its own errors in measurements.<sup>33</sup> The ratio of apo A-I and apo B was found to be the most significant of all the parameters in our study. It was  $0.8567 \pm 0.1365$  in CHD patients against  $1.3796 \pm 0.262$  in controls ( $p < 0.001$ ). In male CHD patients the ratio was  $0.8726 \pm 0.145$  and  $1.369 \pm 0.261$  in male controls ( $p < 0.001$ ). In females  $0.8205 \pm 0.104$  was the ratio of apo A-I, B in CHD patients and  $1.3743 \pm 0.261$  in normal matched controls with  $p < 0.001$ . The ratio of apo A-I to apo B reflects the balance of cholesterol transport in a simple way. It is a useful summary index of risk and that it is at least as good as, and often better than, the conventionally used LDL-C. There are a number of user friendly reasons for adopting this ratio into clinical practice. Since the analyses can be made on non-fasting samples this is of great practical advantage for patients and physicians over the other methods, which usually need fasting. Furthermore, the results can be expressed as one number for the ratio only, rather than by many values for LDL, HDL, triglycerides and lipid ratio.<sup>4</sup> Bahl V.K. *et al* (1994)<sup>34</sup> reported that apo B and triglyceride levels showed larger univariate difference between the normal group and the group with CAD. The variable with the strongest predictive power of CAD was the ratio of apo A-I to B. Goran Walldius *et al* (2001)<sup>26</sup> in their AMORIS study suggested that apo B, apo B/apo A-I and apo A-I should be regarded as highly predictive in evaluation of cardiac risk. Adnan I. Qureshi *et al* (2002)<sup>35</sup> found that apo A-I to B ratio was inversely associated with myocardial infarction and may be an important protective clinical marker for atherosclerosis. At the same time apo B concentration alone were not found associated with myocardial infarction by him. Christa Meisinger *et al* (2004)<sup>36</sup> stated that the result for apo B levels and the apo B/A-I ratio remained significant even when adjusted for age, smoking, alcohol, body mass index, diabetes and hypertension. From the above discussion, we can state that the concentration of apo A-I, apo B and its ratio can be a useful summary index of risk and that it is at least as good as, and often better than, the conventionally used lipid parameters. This can be supported by various following reasons

1. Measurements of apolipoproteins are internationally standardized, automated, more convenient and precise against LDL cholesterol which is calculated, not measured, and is calculated from several unstandardized assays, each of which necessarily involves its own errors in measurements.
2. The requirement of fasting sample for lipid profile sharply limits the time of day when samples can be obtained and more importantly imposes the burden of fasting on the patients. While analyses of apo A-I and B can be made on non-fasting samples which is of

great practical advantage for patients and physicians over the other methods.

3. The ratio of apo A-I to B reflects the balance of cholesterol in a simple way. Lower the value of apo A-I/B ratio, the more cholesterol is likely to be deposited in the arterial wall, thereby provoking atherogenesis and hence also increasing the risk of CHD.
4. The blood sample required for the measurement of apo A-I and B is very less about 1-2 ml as compared to the lipid profile measurement for which 4-5 ml of blood is required.

The only limiting factor for apo A-I and B in developing countries like India is the cost of test. The cost of reagents for each test of apo A-I and B is about 120-150 rupees against the cost of lipid profile reagents which is 30-40 rupees. As our knowledge and awareness about apolipoproteins increases and technology permits, in the interest of clinical laboratories, physicians and, most of all, our patients, the estimation of apolipoproteins should be done routinely in health screening.

## CONCLUSION

Thus in the end we can state that levels of serum Apolipoprotein A-I and B and lipid profile in Coronary Heart Disease patient showed significant change as compared to control group. We can also state that the concentration of apo A-I, apo B and its ratio can be a useful summary index of risk and that it is at least as good as, and often better than, the conventionally used lipid parameters.

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Source of Support: None Declared  
Conflict of Interest: None Declared