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COMPARATIVE ESTIMATION OF SERUM APOLIPOPROTEIN A_1, Apolipoprotein B_{100} And hsCRP IN ISCHEMIC HEART DISEASE AMONG MANIPURI POPULATION: A CASE CONTROL STUDY

Biochemistry

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ABSTRACT

Background: Apolipoprotein A1,Apolipoprotein B100 and hsCRP play a pivotal role for the diagnosis of ischemic heart disease. Among these , Apolipoprotein A1 is a component of HDL or so called "Good cholesterol"which promotes reverse cholesterol transport producing an antiatherogenic effect in our body.Apolipoprotein B100 or Apo B100 is a major apolipoprotein of LDL has atherogenic property. hsCRP or high sensitive C reactive protein is an positive acute phase protein which has atherogenic property. The aim of the study is to evaluate concentrations of Apo A1 , Apo B100 and hsCRP among the ischemic heart disease patients and healthy controls and to provide inter-relationships between Apo A1, Apo B100 and hsCRP among the patients. **Methods:** A case control study was performed from November 2021 to January 2023 in the department of biochemistry in collaboration with department of medicine, Shija Hospital and Research Institute,Imphal,Manipur.60 ischemic heart disease patients and 60 healthy controls were taken for the study population. **Results:** the results of this study shows that the serum level of Apo A1 is decreased significantly in cases as compared to controls and levels of apolipoproptein B100 and hsCRP are increased significantly in cases than controls and no significant correlation has been found between these three cardiac biomarker in this study. **Conclusions:** The present data represents the measurement ofApo B100 hsCRP as an important screening tool for the risk measurement of ischemic heart disease.Therefore,this study suggests the urgency of routine measurement of Apo A1,Apo B100 and hsCRP in the diagnosis of Myocardial infarction or ischemic heart disease and thus helps in initial detection of myocardial damage which provides in time intervention leading to lowered morbidity and mortality.

KEYWORDS

Apolipoprotein A1, Apolipoprotein B100,hsCRP, ELISA., Myocardial Infarction, Ischemic heart disease.

INTRODUCTION

APOLIPOPROTEINS A_1

The major apolipoproteins of HDL are apolipoprotein A_1 and apolipoprotein A_2. Most attention has been focused on apolipoprotein A_1 since it is the major apoprotein in HDL, constituting about two-thirds of the total HDL protein and is probably a major component of each HDL particle. In humans, the mature protein contains 243 amino acids with the last 199 amino acids of the protein composed of a series of ten repeating amphipathic α-helices. Eight of these helices have 22 amino acids and two have 11 amino acids. The amphipathic α-helices are class A helices in which hydrophobic residues occupy one face whereas neutral and negatively charged residues occupy the other (polar) face with the positively charged lysine and arginine residues found between the two faces of the helix. A major and much studied function of HDL and apolipoprotein A_1 is the promotion of reverse cholesterol transport involving the transfer of cholesterol from peripheral tissue, including the macrophage foam cells of the atherosclerotic lesions, through the plasma to the liver whence it is excreted either as free cholesterol or bile salt into the faeces ,thus producing an anti atherogenic effect in body.[1]

APOLIPOPROTEIN B_{100}

Apolipoprotein B exists in 2 forms: apolipoprotein B_{100} and apolipoprotein B_{48}. The two proteins are known to be translation products of a single structural gene. Apolipoprotein B_{100}, a single polypeptide of more than 4500 amino acids, is the full length translation product of the apolipoprotein B gene. In humans, apolipoprotein B_{100} is made in the liver and secreted into plasma as part of VLDL. Apolipoprotein B_{100} is the major apolipoprotein of LDL, the end product of VLDL catabolism. Each VLDL particle contain one molecule of apolipoprotein B_{100} and remains with lipoprotein as it is catabolized to LDL. Apolipoprotein B_{48} contains 2152 amino acids and is identical to the amino terminal portion of apolipoprotein B_{100}. Apo B_{48} results from posttranscriptional modification of internal apolipoprotein B_{100} mRNA, in which a single base substitution produces a stop codon corresponding to residue 2152 of apolipoprotein B_{100}. Apolipoprotein B_{48} is made in the intestine and is the major component of chylomicrons. Both apolipoprotein B_{100} and apolipoprotein B_{48} play an important role in the secretion of VLDL and chylomicrons, respectively. Apolipoprotein B is recognized by the LDLR in hepatic and peripheral tissues and allows the receptor mediated internalization of LDL.[2]

Familial defective apolipoprotein B_{100}: It is the result of a mutation in apolipoprotein B gene. The defective apolipoprotein B has a decreased affinity for LDL receptor thus causing plasma LDL cholesterol to be increased. These individuals have an increased incidence of CAD.[3]

HIGH- SENSITIVITY C-REACTIVE PROTEIN (hsCRP)

CRP has been shown to be an acute phase reactant and important in the nonspecific host defence against inflammation. Chronic inflammation is an important component in the development and progression of atherosclerosis and numerous epidemiological studies have demonstrated that increased serum CRP concentrations are positively associated with a risk of future coronary events such as coronary artery disease, cerebrovascular disease or peripheral arterial disease. The use of CRP for these purposes requires the use of hsCRP assays having detection limits less than 0.3 mg/l. A number of automated immunoturbidimetric and immunonephelometric assays are commercially available and capable of sensitive and precise measurements at low concentrations of CRP.

BIOCHEMISTRY:

CRP consists of five identical, nonglycosylated polypeptide subunits noncovalently linked to form a disk- shaped cyclic polymer with a molecular weight of 115 kDa. It contains little or no carbohydrate and is synthesized in the liver. Its production is controlled by interleukin-6 and it binds to polysaccharides present in many bacteria, fungi and protozoal parasites and polycations, such as histones.

CARDIOVASCULAR DISEASE AND hsCRP:

Of all other markers, only hsCRP has fulfilled the required criteria for a novel biomarker of CHD risk, and national guidelines for its measurement in the primary prevention of CHD have recently been issued jointly by the American Heart Association (AHA) and CDC (AHA/ CDC). Prospective epidemiological studies have consistently shown that a single hsCRP measurement is a strong predictor of myocardial infarction, stroke, peripheral vascular disease and sudden cardiac death. The association between hsCRP and future CHD reflects the current understanding of vascular biology because it is known that chronic inflammation plays a pivotal role in atherogenesis.[4]

C-reactive protein (CRP) is a protein produced by liver found in the blood in response to inflammation. High sensitivity C Reactive Protein (hsCRP) is useful in the assessment of very low levels of CRP (< 0.01) in blood. Inflammation plays a major role in atherothrombosis , and measurement of inflammatory biomarkers such as hsCRP can provide detection of high risk for IHD. First discovered in 1930 through a reaction with the somatic c polysaccharide of Streptococcus pneumonia in patients afflicted with pneumonia. Its link to CHD was reported more than 60 years later. CRP has been prodigiously investigated, largely facilitated by its relative stability as a frozen sample, long plasma half-life of 19 h, and ease of testing with a standardized assay.CRP is an acute-phase reactant and nonspecific marker of inflammation, produced predominantly in hepatocytes as a pentamer of identical subunits in response to several cytokines.

Interleukin (IL)-6, one of the most potent drivers of CRP production, is released from activated leukocytes in response to infection or trauma and from vascular smooth muscle cells in response to atherosclerosis. CRP directly binds highly atherogenic oxidized low-density lipoprotein cholesterol (LDL-C) and is present within lipid-laden plaques. The possible mechanistic role of CRP in plaque deposition is highly complex, exerting pro atherogenic effects in many cells involved in atherosclerosis. CRP may facilitate monocyte adhesion and transmigration into the vessel wall, a critical early step in the atherosclerotic process. Furthermore, M_1 macrophage polarization, catalyzed by CRP, is a pro inflammatory trigger in plaque deposition , leading to macrophage infiltration of both adipose tissue and atherosclerotic lesions.

Many studies of lipid profile in IHD patients have been carried out. But the study of apolipoprotein A_1, apolipoprotein B_{100} and hsCRP has not been routinely carried out in IHD patients. The present study is undertaken to assess the levels of these parameters and to determine if there is any association with the disease. The study will be useful to predict, monitor, intervene and prognosticate with diagnostic utility that will have a great impact on risk of IHD. These parameters may also be useful biomarkers for potential screening and therapeutic implications.

AIMS AND OBJECTIVES

A) To evaluate:
i) Concentrations of Apolipoprotein A_1 (Apo A_1)
ii) Concentrations of Apolipoprotein B100(Apo B100)
iii) Concentrations of high sensitive C Reactive Protein(hsCRP) in Ischemic Heart Disease patients or cases and healthy controls .

B) To establish:
i) Inter-relationships,If any, between Apolipoprotein A_1, Apolipoprotein B100 high sensitive C Reactive Protein among the patients.

MATERIALS AND METHODS

The study has been conducted after the approval from the institutional ethical committee. The informed written consent of the patients or their relatives has been obtained prior to the test.

Study Design: Case control study

Study Settings:
The study has been conducted in the Department of Biochemistry in collaboration with the Department of Medicine, Shija Hospital and Research Institute, Imphal, Manipur.

Duration Of Study:
The study has been carried out for a period of 22 months with effect from January 2021 to November 2023.

Study Population:
Consecutive patients with IHD attending SHRI, Imphal.

Subjects:
A total number of 120 subjects participated in the study, of which 60 were cases and 60 were controls.

Inclusion Criteria
- All patients with already diagnosed ischemic heart disease who attended Cardiac clinic/Medicine OPD or admitted in the Medicine ward or ICCU.
- All patients above 18 yrs of age, irrespective of sex, religion and socio economic status.

Exclusion Criteria
Ischemic heart disease patients with
- Hepatic and renal disease
- Sepsis
- Malignancy
- Diabetes mellitus
- Anemia
- Hypolipidemic drugs

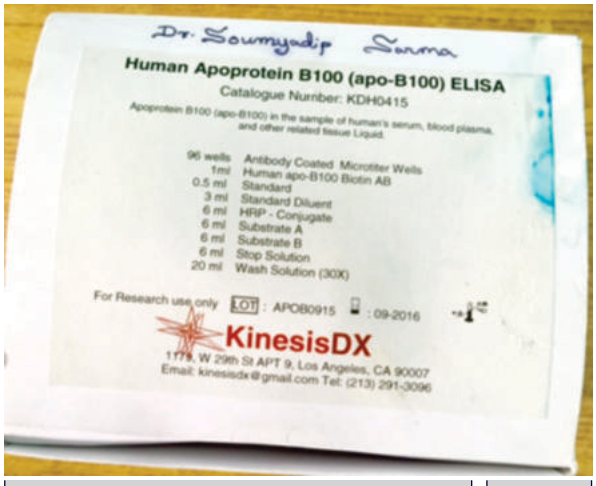
Collection Of Blood Samples:
About 6 ml of venous blood was drawn under aseptic conditions in a sterile vacationer from selected subjects after a period of overnight fasting of 12 hours. Serum was instantly separated by centrifugation and used for analysis of Apolipoprotein A_1, Apolipoprotein B100 and hsCRP.

Human Subject Protection:
There was no physical risk to the participants in the study. The participants were informed that their participation was voluntary and that they were free to withdraw at any time. The study was approved by the Research Ethics Board of SHRI, Imphal.

Statistical Analysis:
Statistical analysis was done using SPSS version-20 software. Results were reported as mean + SD (standard deviation) for quantitative variables and number of cases along with percentages for the categorical/quantitative variables. Chi-square test, independent sample T test were applied whenever necessary. All comparisons were two-sided and the P- values of < 0.05 and < 0.01 were used as the cut-off values for significance and highly significance respectively.

Ethical Issues:
- Approval was sought from Research Ethics Board, SHRI, Imphal.
- Consent taken before taking blood samples.
- Confidentiality maintained**.**

Materials
Serum Apolipoprotein $A_{1\ \text{and Apolipoprotein B100}}$ were measured by using KinesisDX's Enzyme Linked Immunosorbent assay ELISA^{PRO}KIT and hsCRP was measured in DBC ELISA pro kit respectively, manufactured by KinesisDX Los Angeles, CA 90007, USA, and marketed by KinesisDX India Private Limited, as described by Nakajima K et al.[5]



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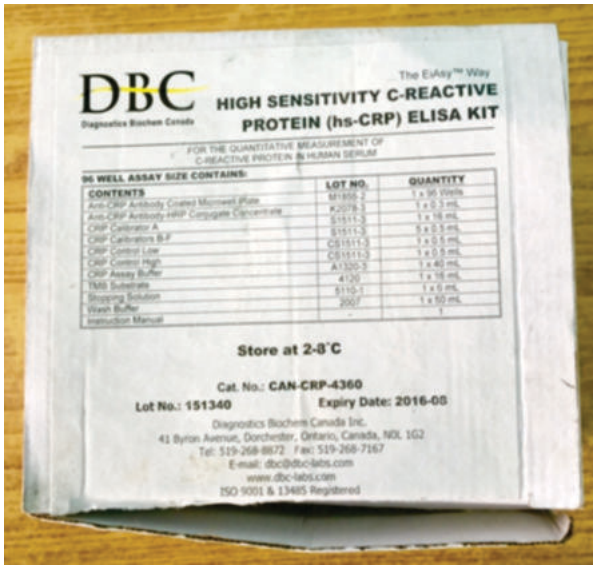

RESULTS

Table 1. Variation Of The Concentration Of Apolipoprotein A_1, Apolipoprotein B_{100} And hsCRP Among Different Age Groups In Case And Control:

	31-40 years	41-50 years	51-60 years	>60 years	ANOVA significance
apoA1 (µg/ml)	1371.42± 447.95 µg/ml	1211.76± 706.11 µg/ml	1199.03± 718.82 µg/ml	1282.43± 1105.05 µg/ml	f=0.19 p=0.90
Apo B100 (mg/ml)	1.05±0.72 mg/ml	1.17±0.87 mg/ml	1.48±1.12 mg/ml	1.57±0.88 mg/ml	f=1.41 p=0.24
hsCRP (µg/ml)	1.55±0.97 µg/ml	2.13±0.95 µg/ml	2.44±1.76 µg/ml	2.33±1.56 µg/ml	f=1.30 p=0.27

Table 2. Variation Of The Concentration Of Apolipoprotein A_1 , Apolipoprotein B_{100} And hsCRP Among Both Sex Groups In Case And Control:

	Male(32)	Female(28)	Significance t test
Apo A1 (µg/ml)	1265.75± 676.63 µg/ml	1217.02± 1024.39 µg/ml	t=0.314 p=0.754
Apo B100 (mg/ml)	1.29± 0.91mg/ml	1.61± 1.06 mg/ml	t=-1.754 p=0.082
hsCRP (µg/ml)	2.18± 1.55 µg/ml	2.37± 1.52 µg/ml	t=-0.678 p=0.499

Table 3. Distribution Of The Respondents By Serum Concentrations Of Apo A1, apo B100 and hsCRP

Variable	Mean ± SD
Ischemic heart disease	
apo A1	748.3±821.7 µg/ml
apo B100	2.1±0.8 mg/ml
hsCRP	6.5±1.6 µg/ml
Healthy controls	
apo A1	1745.0 ±444.5 µg/ml
apo B100	0.6±0.3 mg/ml
hsCRP	1.2 ±0.5 ng/ml

Table 4. Correlation Between Apo A1, Apo B100 and hsCRP

Variable	Mean ±SD	Unpaired t-test
Apo A1 (µg/ml)		
Case	748.3±821.7 µg/ml	t=8.2
Control	1745±444.5 µg/ml	P<0.001
Apo B100(mg/ml)		
Case	2.1±0.8 mg/ml	t=12.33
Control	0.6±0.3 mg/ml	P<0.001
hsCRP(µg/ml)		
Case	3.2 ±1.6 µg/ml	t=8.89
Control	1.2 ±0.5 µg/ml	P<0.001

Table 1 shows variation of the concentration of apolipoprotein A1 , apolipoprotein B100 and hsCRP among different age groups where apo A1 concentration gradually decreases where concentration of apo B100 has been gradually increases with increment of age. The concentration of hsCRP is gradually increases from lower age group to 51-60 years and thereafter it is found to be decreased in the age group of >60 years.Comparison between different age groups among cases and controls by ANOVA test was statistically insignificant (p>0.05).

Table 2 shows variation of the concentration of apolipoprotein A1, apolipoprotein B100 and hsCRP among both male and female groups in study group,Where apoA1 has been found significantly higher among males(32),and apo B100 and hsCRP has been found higher among females(28)which has been found insignificant(p>0.05).

Table 3 depicts that mean with standard deviation of apo A1,apo B100 and hsCRP were 748.3±821.7 µg/ml,2.1±0.8 mg/ml and 6.5±1.6 µg/ml respectively for ischemic heart disease and for healthy controls 1745.0±444.5µg/ml,0.6±0.3 mg/ml and 1.2±0.5 µg/ml.

Table 4 significantly shows that on comparing various level of ApoA1,Apo B100 and hsCRP of cases with the controls,for ApoA1 cases had lower level than controls(748.3±821.7 vs 1745±444.5) but for Apo B100 and hsCRP cases had higher values than controls.All findinds are statistically significant (p<0.05).

DISCUSSION

A study of serum Apolipoprotein A1, apolipoprotein B_{100},and hsCRP in patients with Ischemic heart disease(IHD) and healthy controls has been conducted in the Department of Biochemistry in collaboration with Department of Medicine ,SHRI. The present study was taken to elaborate the association of various risk factor variables to detect the presence of IHD. The details of the study group is described in the results.

In the first part of the results, an effort has been taken to find out prevalence of IHD within different demographic variables as age, sex, religion, inhabitancy and socioeconomic group As depicted in the Table 1 , the peak incidence of IHD was observed between 51- 60 years(43.3%), similar study was conducted by Tanna NA et al[6] which implicated age wise distribution of Coronary Artery Disease risk factors. The data for this study was collected from Baroda Heart Institute & Research Centre (BHIRC). The total 208 patients were considered for study of CAD. The majority of the patients were from age group of 60-69 years i.e. 67 (32.21%) and only 10 patients (4.32%) were in the age group of ≥80 years. Amongst all patients, 93.27% were lacking exercise, 39.42% were hypertensive, 28.85% were obese, 27.88% diabetic, 10.58% had family history of CAD and 5.28% were smokers. It is essential to identify CAD risk factors amongst the Indians to tackle the problem. So this study was of great help in this direction.

Similar study by Jackson CF et al[7] who has found prevalence of IHD in the same age group in a case control study. The aging of the population worldwide will result in increasing numbers of elderly patients, among whom heart disease is the leading cause of death. Changes in cardiovascular physiology with normal aging and prevalent co-morbidities result in differences in the effects of common cardiac problems as well as the response to their treatments. Patient-centered goals of care such as maintenance of independence and reduction of symptoms may be preferred over increased longevity. New less-invasive treatments are likely to improve outcomes in elderly patients who previously have been considered at prohibitive risk for traditional procedures. Clinical trials enrolling elderly patients are limited and recommendations for management from younger patients frequently lack evidence-based support in patients aged >75 years.

The study shows variation of the concentration of Apolipoprotein A_1,Apolipoprotein B_{100} and hsCRP among different age groups where Apo A_1 concentration gradually decreases where concentration of Apo B_{100} has been gradually increases with increment of age. The concentration of hsCRP is gradually increases from lower age group to group of 51-60 years and thereafter it is found to be decreased in the age group of >60 years.Comparison between different age groups among cases by ANOVA test was statistically insignificant (p>0.05).

This finding correlated with study by Talmud PJ et al[8] who compared the pairwise combinations of total cholesterol, TGL, apolipoprotein B, HDL-C, LDL-C and apolipoprotein A_1,apolipoprotein B_{100} and hsCRP on CHD risk prediction in middle -aged men and younger age groups and concluded aforementioned markers significantly altered with increment of age so that the combined evaluation of apolipoprotein B

with TGs provides useful diagnostic criteria for CHD.

Ridker PM et al[9] reported that C reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level among middle age group than yonger counterpart in a comparative study. Ariyo AA et al[10] observed in older U.S. adults that all Apolipoproteins play an important part in atherothrombogenesis and predicting increased risk of vascular disease in older men.

In a study of 1,846 men and 2,703 women between the ages of 45 and 74 years from 13 American Indian communities Howard VB et al[11] shows Statistically significantly greater adverse differences in those with diabetes versus those without diabetes. Those were observed in women than in men for waist-to-hip ratio, HDL cholesterol, apolipoprotein B, apolipoprotein A_1, fibrinogen, and LDL size. In multiple linear regression models adjusting for age, center, sex, and diabetes, the diabetes by sex interaction terms were statistically significant for waist-to-hip ratio, LDL cholesterol, HDL cholesterol, apolipoprotein B, apolipoprotein A_1, fibrinogen, and LDL size among elder age group (51-60 years) and younger ones.

Backer GD et al[12] in their study, serum cholesterol, HDL cholesterol (HDL-C), and apolipoproteins, A_1, A_2 and B were determined in 70 male survivors of myocardial infarction and in an equal number of healthy controls, matched for age, sex and body mass index. In univariate analyses, the apolipoprotein B/ apolipoprotein A_1 ratio discriminated the best between cases and controls, giving a 72% exact classification. In a multivariate analysis, the apolipoprotein B/ apolipoprotein A_1 ratio, HDL-C and the apolipoprotein A_2/ apolipoprotein A_1 ratio contributed independently to the discrimination of cases from controls while the overall exact classification was 82%. These promising results were comparable in younger and older subgroups. Thus, the determination of apolipoproteins yielded complementary information in this cross-sectional survey and warrants further study in a prospective setting.

Taking sex incidence, as depicted in Table 2 and ,men had higher incidence (about 32 patients) when compared to women (28 patients). In a study conducted by Mandal S et al[13] in Siliguri authors tried To determine the prevalence of ischemic heart disease and the associated risk factors among the urban population of Siliguri. A cross-sectional survey of a random sample of the population aged ≥40 years old in the Municipal Corporation area of Siliguri. Study variables were age, sex, occupation, addiction, food habit, physical activity, body mass index, blood pressure, and electrocardiogram change. Out of 250 individuals who took part in this study, 29 (11.6%) had ischemic heart disease (IHD) and 118 (47.2%) had hypertension. Males had a higher (13.5%) prevalence of IHD than females (9.4%). About 5% of the patients had asymptomatic IHD. IHD among the study population is significantly associated with hypertension and smoking.

In a community-based cross sectional study by Krishnan MN et al[14] , they selected 5167 adults (mean age 51 years, men 40.1 %) using a multistage cluster sampling method. Information on socio-demographics, smoking, alcohol use, physical activity, dietary habits and personal history of hypertension, diabetes, and CAD was collected using a structured interview schedule. Anthropometry, blood pressure, electrocardiogram, and biochemical investigations were done using standard protocols. CAD and its risk factors were defined using standard criteria. Comparisons of age adjusted prevalence were done using two tailed proportion tests. The overall age-adjusted prevalence of definite CAD was 3.5 %: men 4.8 %, women 2.6 % (p<0.001). Prevalence of any CAD was 12.5 %: men 9.8 %, women 14.3 % (p < 0.001). There was no difference in definite CAD between urban and rural population. Physical inactivity was reported by 17.5 and 18 % reported family history of CAD. Other CAD risk factors detected in the study were: overweight or obese 59 %, abdominal obesity 57 %, hypertension 28 %, diabetes 15 %, high total cholesterol 52 % and low level of high density lipoprotein cholesterol 39 %. Current smoking was reported only be men (28 %). However, the incidence of IHD in women increased after 50 years in some study probably due to the decreased protective mechanism of oestrogen in the postmenopausal period.

The study also shows variation of the concentration of apolipoprotein A_1 apolipoprotein B_{100} and hsCRP among both male and female groups in case,Where ApoA_1 has been found insignificantly higher among males(32),and Apo B100 and hsCRP has been found insignificantly higher among females(28) (p>0.05).

This study is in favour of Brown G et al[15] who reported that regression of CAD as a result of intensive lipid lowering therapy in men with high levels of apolipoprotein B and inversely proportional to high level of Apolipoprotein in both sex groups.

Kamstrup PR et al[16] reported that extreme apolipoprotein levels predict a 3 to 4 fold increase in risk of MI in the general population and absolute 10-year risks of 20% and 35% in high risk women and men and male have a higher chance of having IHD as compared to female.

Benn M et al[17] showed that apolipoprotein B predicts ischemic cardiovascular events in both genders, and is better than low-density lipoprotein cholesterol in this respect. They suggest that prediction of future ischemic cardiovascular events could be improved by measuring apolipoprotein B.They studied 9231 asymptomatic women and men from the Danish general population followed prospectively for 8 years and observed the following incident events: ischemic heart disease 591, myocardial infarction 278, ischemic cerebrovascular disease 313, ischemic stroke 229, and any ischemic cardiovascular event 807. Women with apolipoprotein B in the upper versus the lower tertile had hazard ratios for ischemic heart disease of 1.8 (1.2 to 2.5), for myocardial infarction 2.6 (1.4 to 4.7), and for any ischemic cardiovascular event 1.8 (1.3 to 2.3), and men had hazard ratios for ischemic heart disease of 1.9 (1.5 to 2.6), for myocardial infarction 2.4 (1.5 to 3.6), and for any ischemic cardiovascular event 1.6 (1.3 to 2.1). Women had similar hazard ratios for ischemic cerebrovascular disease and ischemic stroke. Apolipoprotein B had a higher predictive ability than low-density lipoprotein cholesterol in the prediction of ischemic heart disease, myocardial infarction, any ischemic cardiovascular event, and any nonfatal ischemic cardiovascular event in both genders (p=0.03 to <0.001). Finally, in smokers older than 60 years with systolic blood pressure >160 mm Hg, apolipoprotein B contributed 11% in women and 15% in men to the increase in absolute 10-year risk from the lower to the upper apolipoprotein B tertile.

The religion wise distribution of cases in the present study shows that the maximum number of cases of IHD belongs to Hindu,(61.7%) as showed in Table 5 and Fig 3.The reason for the higher percentage of cases among Hindu religion in the present study may be because of the fact that the study has been undertaken in RIMS Hospital located at Hindu dominated area.

It has also been found that a higher prevalence of IHD was seen in rural area(Table 6 and fig 4),which is similar to the findings of Mendagudali RR et al[18] whose study was undertaken to find out the prevalence of Coronary Heart Disease (CHD) in the age group of 20 years and above among the rural population of Bagalkot, Karnataka. A cross sectional study was conducted in Shirur, a rural field practice area of S. Nijalingappa Medical College, Bagalkot between 1st January 2011 to 31st October 2012, to study the prevalence of CHD among individuals aged 20 years and above. The systematic random sampling method was used to draw the sample of 1226 respondents from 7015 eligible individuals.

The present study revealed the prevalence of CHD as 7.58% with the prevalence of symptomatic CHD (4.81%) was higher compared to asymptomatic (2.77%) cases. CHD was found to be significantly associated with increasing age in both genders (p<0.001) with male (60.22%) predominance. Higher prevalence of CHD was found among Hindu individuals, married people, illiterate and also among the individuals belonging to lower socio economic class.

Higher prevalence of CHD was found in the study in Shirur; a village of North Karnataka is a matter of concern and has to be addressed by regular screening and health education in rural areas regarding the risk factors and lifestyle modification.

Nissen SE et al[19] showed that although low levels of high-density lipoprotein cholesterol (HDL-C) increase risk for coronary disease. Apolipoprotein A_1 milano is a variant of apolipoprotein A_1 identified in individuals in rural Italy who exhibit very low levels of HDL. Infusion of recombinant apolipoprotein A_1 milano-phospholipid complexes produces rapid regression of atherosclerosis in patient models. A recombinant apolipoprotein A_1 milano/phospholipid complex (ETC-216) administered intravenously for 5 doses at weekly intervals produced significant regression of coronary atherosclerosis as measured by IVUS. Although promising, these results require confirmation in larger clinical trials with morbidity and mortality end

points. In a small village in northern Italy called Limone sul Garda live approximately 40 carriers with a naturally occurring variant of apolipoprotein A_1 known as apolipoprotein A_1 milano. Individuals with apolipoprotein A_1 milano are characterized by very low levels of high-density lipoprotein cholesterol (HDL-C) (10-30 mg/dl [0.25-0.78 mmol/l]), apparent longevity, and much less atherosclerosis than expected for their HDL-C levels. The apolipoprotein A_1 milano protein differs from native apolipoprotein A_1 in that cysteine is substituted at position 173 for arginine allowing disulfide-linked dimer formation. Recombinant apolipoprotein A_1 milano has been formulated in a complex with a naturally occurring phospholipid to mimic the properties of nascent HDL (ETC-216, Esperion Therapeutics, Ann Arbor, Mich).

Joshi R et al[20] found mortality rates of nearly 31% for ischemic heart disease and stroke combined in rural Andhra Pradesh; however, according to the Global Burden of Disease estimates, ischemic heart disease and stroke deaths are estimated to be approximately 20% and 10%, respectively, for the South Asian Region, which includes India. Other studies in India around the same time as the Global Burden of Disease study suggest that the prevalence of and death rates due to CVD are as much as 2 to 3 times higher in urban areas than in rural areas. If this is true, we may be grossly underestimating the burden of CVD in South Asian countries today. In these aforementioned studies including ours, non healthy lifestyle with smoking and alcohol can be causative factors.

This study shows that majority of IHD cases belong to middle class of socioeconomic group. In Table 7 and fig 5 it is clearly been depicted that middle socio economic status constituted the majority(43.3%) of the cases and low socioeconomic status was more(36.7%) than high socio-economic status(20%).Similar to above tables socioeconomic status was also comparable both the case and control groups and Chi-square test value obtained was statistically insignificant (p>0.05).

This finding is supported by Finegold JA et al[21] who analysed IHD deaths world-wide between 1995 and 2009 and used the UN population database to calculate age-specific and directly and indirectly age-standardised IHD mortality rates by country and region.IHD is the single largest cause of death worldwide, causing 7,249,000 deaths in 2008, 12.7% of total global mortality. There is more than 20-fold variation in IHD mortality rates between countries. Highest IHD mortality rates are in Eastern Europe and Central Asian countries within middle and lower economic status groups; lowest rates in high income countries. For the working-age population, IHD mortality rates are markedly higher in low-and-middle income countries than in high income countries.Over the last 25 years, age-standardised IHD mortality has fallen by more than half in high income countries, but the trend is flat or increasing in some low-and-middle income countries. Low-and-middle income countries now account for more than 80% of global IHD deaths.The global burden of IHD deaths has shifted to low-and-middle income countries as lifestyles approach those of high income countries. In high income countries, population ageing maintains IHD as the leading cause of death. Nevertheless, the progressive decline in age-standardised IHD mortality in high income countries showed that increasing IHD mortality is not inevitable. The 20-fold mortality difference between countries, and the temporal trends, may hold vital clues for handling IHD epidemic which is migratory, and still growing.

Since economic status mostly related to day to day activity also, Leddy J et al[22] showed dietary fat may be associated with coronary heart disease (CHD) among groups from higher economic status. Studies suggested that restricting fat intake may compromise endurance performance and that increasing fat intake may improve endurance performance. They studied the effects of varying dietary fat intake on CHD risk factors in workers. Twelve male and 13 female workers from lower economic status increased fat from 16% to 30% of daily calories (4 wk each). Of this group, six males and six females increased fat to 42% of daily calories (4 wk). Physiological and lipoprotein risk factors were measured after each diet. Results were analyzed by repeated measures ANOVA. Increasing dietary fat from 16% to 42% of daily calories did not change adiposity, weight, heart rate, blood pressure, serum triglycerides, total cholesterol, LDL cholesterol. apolipoprotein B, or the apolipoprotein A_1/ apolipoprotein B ratio. Compared with those eating higher fat, subjects eating 16% fat had lower HDL cholesterol (50 +/- 3 vs 62 +/- 3 mg.dl-1, P < 0.0001) and apolipoprotein A_1 (111 +/- 6 v. 134 +/- 6 mg/dl, P < 0.0005) and a higher TC/HDL-C ratio (4.05 +/- 0.27 vs 3.42 +/- 0.24, P < 0.0005). Runners who increased fat intake to 42% further raised HDL cholesterol (64 +/- 6 to 69 +/- 5 mg.dl-1, P < 0.04) without adversely affecting other lipoproteins.

Ischemic heart disease is one of the important cause of morbidity and mortality in most countries of the world. The debate on the value of lipids as a predictive risk factor for atherogenesis has centered for many years on total cholesterol, triglycerides and low density lipoprotein. Recently the interest has been focused on role of Apolipoprotein A_1 apolipoprotein B_{100}, hsCRP and other inflammatory marker in atherogenesis.

We see that the mean serum concentrations of hsCRP in controls and in patients with ischemic heart disease was in the range of 3.2 ± 1.6 and 1.2 ± 0.5 µg/mL, respectively. The concentration of hsCRP was increased in patients with ischemic heart disease when compared to healthy normal individuals. This study showed a positive association between ischemic heart disease and hsCRP level and the results were in agreement with those of Chowta MN et al[23] Main objective was to correlate the highly sensitive CRP (hsCRP) level to individual components of metabolic syndrome and coronary vascular disease. Forty patients who were diagnosed clinically with metabolic syndrome were included in the study. Detailed history with regard to diabetes mellitus, hypertension and other CVD was collected from each patient. All the patients underwent complete physical examination, including ECG. Height, weight, fasting blood glucose and lipid levels were measured in all the patients. CVD was assessed with the following: new-onset angina, fatal and non-fatal myocardial infarction or stroke, transient ischemic attack, heart failure or intermittent claudication. In the findings**,** the mean hsCRP level was higher in patients with CVD compared with those without CVD. The CRP level correlation with CVD showed a statistically significant correlation. hsCRP level was very high in eight hypertensive patients, whereas it was very high in five normotensives. But, statistical analysis has not shown any significant correlation between hypertension and hsCRP level. Similarly, although a higher hsCRP level was seen in diabeteics, statistical analysis failed to show a significant correlation between diabetes and the hsCRP level. Analyses of hsCRP correlation with body mass index, fasting glucose, cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein did not show a significant correlation with the hsCRP level. It could be concluded that increased hsCRP levels are associated with an increase in the incidence of CVDs. Higher values of hsCRP were observed in patients with hypertension and diabetes. No correlation was seen between hsCRP and components of the metabolic syndrome.

Another study by Sabatine MS et al[24] supports our result where they measured hsCRP in 3771 patients with stable coronary artery disease from the Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial, a randomized placebo-controlled trial of the angiotensin-converting enzyme inhibitor trandolapril. Patients were followed up for a median of 4.8 years for cardiovascular death, myocardial infarction, or stroke, as well as new heart failure and diabetes. After adjustment for baseline characteristics and treatments, higher hs-CRP levels, even >1 mg/L, were associated with a significantly greater risk of cardiovascular death, myocardial infarction, or stroke (hs-CRP 1 to 3 mg/L: adjusted hazard ratio, 1.39; 95% CI, 1.06 to 1.81; P=0.016; hs-CRP >3 mg/L: adjusted hazard ratio, 1.52; 95% CI, 1.15 to 2.02; P=0.003). Similarly, elevated hs-CRP levels were an independent predictor of new heart failure (adjusted P<0.001 for trend) and new diabetes (adjusted P<0.001 for trend). There were no significant interactions between hs-CRP levels and the effects of trandolapril on any of the above outcomes.

Third study is by Ghodke SS et al[25] Who aimed to evaluate the relationship between pre procedural high sensitive C- reactive protein and angiographic signs in patients presenting with acute coronary artery disease. The diagnosis was based on the ECG and enzyme profile. Increased total LDH level was taken as criteria for selection of patients. Total 100 cases were studied with coronary artery disease in the age group 40 to 70 years. They were followed for 7 days or until discharge. The high sensitive Creactive protein levels were estimated in these 100 patients and the results were compared with 100 age and sex matched healthy controls in the same age group. The mean value of high sensitive C- reactive protein was 4.63±1.43 was significantly higher (p<0.001) when compared to healthy controls.

Clearfield MB[26] conducted a study with the aid of The Centers for

Disease Control and Prevention and the American Heart Association who therefore proposed joint guidelines for the use of hs-CRP in determining cardiovascular disease risk. The author reviews numerous studies examining the prognostic value of hs-CRP and outlines ongoing efforts to assess the effect of statin therapy in healthy individuals with low levels of low-density lipoprotein cholesterol and high levels of hs-CRP.

Regarding our primary objective,as per Table 10,the mean serum concentration of Apolipoprotein A_1 was lower in IHD subjects when compared to controls suggesting a negative association to ischemic heart disease. These results were in accordance with the studies of Sherpa LY et al[27] conducted in Lhasa Tibet.The aim of this study was to determine the prevalence of abnormal lipid levels and its association with selected coronary heart disease (CHD) risk factors in the Tibetan population living at 3660 meters above sea level in Lhasa, Tibet. Three hundred seventy one randomly selected male and female, aged 30 to 70 yr took part in the study. Based on the National Cholesterol Education Programme (NCED) adult treatment panel ATP-III 2004 criteria, the age-adjusted prevalence of hypertriglyceridemia was 12.0%; high triglycerides (TG), 33.4%; high low-density lipoprotein cholesterol (LDL-C), 4.8%; and low high-density lipoprotein cholesterol component of Apolipoprotein A_1; 24.3%. After adjusting for age, sex, smoking, alcohol, physical activity, diet, hemoglobin (Hb) concentration, and systolic and diastolic blood pressure (BP), an increase in waist-to-hip ratio (WHR) by 0.1 unit was associated with a statistically significant increase in TG, total cholesterol (TC) and LDL-C by 0.25 mmol/L, 0.24 mmol/L, and 0.18 mmol/L, respectively. Female gender increased HDL-C by 0.18 mmol/L when compared with males. Age-adjusted prevalences of Framingham CHD risk score for males and females were 16.3% and 0.6%, respectively. This study demonstrated a high prevalence of hypertriglyceridemia in males, a higher prevalence of low Apolipoprotein A_1 in females, and a high hypercholesterolemia prevalence in both genders. However, further longitudinal studies assessing CHD risk factors in high altitude natives are required.

Another study done by Ibrahim MM et al[28] conducted in Egyptian patients with IHD.Plasma lipid profile may differ according to ethnic origin and geographic area.The main objective was to identify plasma lipid abnormalities in Egyptians with CAD and define the role of age, type of CAD, and the presence of hypertension (HT) on lipid profile.A Retrospective consecutive sampling of lipid profile of 1000 patients with CAD. Results were compared to a control group of 1920 non-coronary individuals. Patients' age range was 19–90 years. HT was present in 56.7% of patients. The commonest isolated lipid abnormality was a reduced Apolipoprotein A_1 in men and increased plasma triglycerides (TG) in women. Patients with myocardial infarction (MI) had a lower Apolipoprotein A_1 than those with angina pectoris (AP). Abnormalities were more severe and more prevalent in the young age group. No significant difference in lipid profile was present between normotensive (NT) and hypertensive (HT) CAD patients.So by this study it could be concluded that Dyslipidemia is common among Egyptians with CAD. Lipid profile was influenced by age, gender, type of CAD, but not by the presence of HT. The high prevalence rate of risk factors particularly among young Egyptians is remarkable and can explain the epidemic of CAD among Egyptians.

The mean value of apolipoprotein B_{100} in controls and in patients with ischemic heart disease was in the range of 0.6 ± 0.3 and 2.1 ± 0.8 mg/mL, respectively.

The apolipoprotein B_{100} concentration was increased in patients with ischemic heart disease when compared to age matched healthy normal individuals. This study showed a positive association between ischemic heart disease and apolipoprotein B_{100} level and the results were in agreement with study of Miremadi S et al[29] which was conducted to examine whether measurement of a single marker (apo B_{100}) led to the same categorization of risk as the traditional five indices (lipid profile). If both apo B_{100} and lipid profile indicated that the patient was either within or outside their respective treatment targets, the indices were considered concordant. If not, the indices were considered discordant. Concordance/discordance was examined in 215 patients at their first and last clinic visit.As an outcome Concordance was high in both higher (88% at the first and 92% at the last clinic visit) and lower (76% at the first and 78% at the last clinic visit) risk groups at both the initial and final visits. Discordance was virtually restricted to the group with hypertriglyceridemia with increased concentrations of apo B_{100} in cases than controls, a group in which little independent evidence points to any substantially increased risk of vascular disease.

Another study by Ansari KMH et al[30] supports our findings where 300 non-diabetic patients afflicted with CAD been divided in three groups of low, medium, and high extremity. Due to attained results, the patients afflicted with high CAD had a higher level of insulin (18.3 ± 0.8) in relation with low and medium groups ($P < 0.001$). As it was observed, the level of serum apo-lipoproteins of A1 (APO-A1) in low group of CAD (175 ± 36.4) is meaningfully higher than its quantity in high-CAD group (158 ± 42.4, $P < 0.001$). Furthermore, the quantity of serum apo-lipoproteins of B_{100} in mild CAD group (139 ± 30.4) is meaningfully less than severe CAD group (155.21 ± 29.7, $P <$ 0.001).So authors concluded that insulin, APO-A1, APO-B100, and total cholesterol measurement is a good case for defining the severity of coronary artery involvement, while high-density lipoprotein, low-density lipoprotein, and triglyceride are not important risk-factors.

Third study which supports our findings is by Ramjee V et al[31] in USA.In anticipation of the Adult Treatment Panel IV (ATP IV) guidelines from the National Cholesterol Education Program (NCEP), there exists controversy regarding the comparative performance of the 2 foremost markers, apolipoprotein B_{100} and non-high-density lipoprotein cholesterol (non-HDL-C), as they relate to the current standard of risk assessment and treatment: low-density lipoprotein cholesterol (LDL-C). Although some emerging markers may demonstrate better performance compared with LDL-C, certain fundamental characteristics intrinsic to a beneficial biomarker must be met prior to routine use. Collectively, studies have found that non-HDL-C and apolipoprotein B_{100} perform better than LDL-C in CVD risk prediction, both on- and off-treatment, as well as in subclinical CVD risk prediction. The performance of non-HDL-C compared with apoB_{100}, however, has been a point of ongoing debate. Although both offer the practical benefits of accuracy independent of triglyceride level and prandial state, non-HDL-C proves to be the better marker of choice at this time, given established cutpoints with safe and achievable goals, no additional cost, and quick time to result with an easy mathematical calculation. The purpose of this review was to assess the performance of these parameters in this context and to discuss the considerations of implementation into clinical practice.

Moreover , Ryoo JH et al[32] conducted a study to examine the association between serum apolipoprotein B_{100} (apoB) and the risk of coronary heart disease (CHD) using Framingham risk score (FRS) in healthy Korean men. A total of 13,523 men without medication history of diabetes and hypertension were enrolled in this study. The FRS is based on six coronary risk factors. FRS ≥ 10% was defined as more-than-a-moderate risk group and FRS ≥ 20% as high risk group, respectively. The logistic regression analyses were conducted. When quartile 1 (Q1) set as a reference, in unadjusted analyses, the Q2, Q3, Q4 of apoB_{100} level had increased odds ratio (OR) for the risk of CHD in both more-than-a-moderate risk and high risk group, respectively. After adjusting for confounding variables, multivariable-adjusted logistic regression analyses showed a strong relationship between the quartiles of apoB_{100} level and more-than-a-moderate risk and high risk group, respectively. These associations were attenuated, but still remained statistically significant. ApoB100 is found to be independently related to the risk of CHD using FRS in healthy Korean men, and the link between apoB_{100} and the risk of CHD is dose-dependent.

ROC curve shows relation between Apo A1 and hsCRP ROC curve shows Apo B100 had an accuracy of 96% , hsCRP had an accuracy of 86% and Apo A_1 has accuracy of 44%.Similar findings are by Lu M et al[33] who investigated the relationship of apolipoprotein B/apolipoprotein A_1 ratio and coronary heart disease (CHD) in persons who were overweight or obese.. In the overweight and obesity group, the area under ROC curve (AUC) was the highest for apolipoprotein B100/ apolipoprotein A_1 (0.655). The cut-off point of apolipoprotein B100/apolipoprotein A_1 for optimal sensitivity and specificity was at 0.80, with a sensitivity of 57.19% and a specificity of 71.72%,while apolipoprotein B100 has better sensitivity and specificity. In conclusion, apolipoprotein B and apolipoprotein A_1 were simple clinical indicators, and the apolipoprotein B100/apolipoprotein A_1 ratio was closely related with CHD in overweight and obese patients. The apolipoprotein B100/apolipoprotein A_1 ratio may provide some useful information in

the differential diagnosis.

CONCLUSION

The present study considered a small number of cases and the period was relatively short. Thus, the incidence and observation obtained may not reflect the true relationship between Apolipoprotein A_1,apolipoprotein B_{100} ,hsCRP and prevalence of IHD in population.

Therefore, the present study suggests the use of apolipoprotein B100 to be a more specific biomarker in the prediction of ischemic heart disease when compared to other two biomarkers. Inflammation plays a major role in atherothrombosis and measurement of inflammatory markers such as hsCRP may provide a promising novel biochemical marker for detecting individuals at high risk of plaque rupture. So, the present data suggest that hsCRP has the potential to play an important role in risk assessment in ischemic heart disease.

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