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Comparison of the various lipid ratios and indices for risk assessment in patients of myocardial infarction

Binita Goswami [a,*], Medha Rajappa [b], Baidarbhi Chakraborty [c], S.K. Patra [d], Suresh Kumar [e], V. Mallika [f]

[a] Department of Biochemistry, Lady Hardinge Medical College & Associated hospitals, New Delhi-110001, India
[b] Department of Biochemistry, PGIMER, Pudducherry, India
[c] Department of Biochemistry, D Y Patil Medical College, Mumbai, India
[d] Department of Biochemistry, Lady Hardinge Medical College, New Delhi, India
[e] Department of Medicine, Maulana Azad Medical College and Associated Lok Nayak Hospital, New Delhi-110002, India
[f] Department of Biochemistry, G. B. Pant Hospital, New Delhi-110002, India

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ABSTRACT

Objectives: Coronary artery disease (CAD) has emerged as the major cause of morbidity and mortality among Asian Indians in the recent past. The following study was undertaken to assess the predictive value of novel biomarkers of dyslipidemia for risk assessment for CAD in the Indian population.
Design and methods: The study group comprised of 100 clinically assessed patients of myocardial infarction and 100 age and sex matched healthy controls. Apolipoprotein-A (Apo-AI) and Apolipoprotein-B (Apo-B) were estimated and small dense LDL was derived mathematically.
Results: The cases showed significantly high levels of total serum cholesterol, triglycerides, LDL cholesterol, Apo-B, sdLDL, and non-HDL cholesterol. On carrying out multivariate regression analysis, Lp(a)/HDL ratio emerged as the best determinant of CAD risk
Conclusion: The above data clearly underlines the role of these novel biomarkers in the risk assessment for CAD in the Indian context.

Introduction

Studies conducted over the past few years have highlighted that India will become the CAD capital of the world with more than half the worldwide cardiovascular disease burden borne by the Indian subcontinent in the next decade. The risk factor profile is unique among the Asian Indians and the control measures, proven effective in other populations, have clearly failed to address the cardiovascular disease-related morbidity and mortality, and its rise among Asian Indians worldwide [1,2].

The process of atherosclerosis, which is fundamental to the occurrence of cardiovascular disease, is recognized as the consequence of the interplay of a plethora of genetic, biochemical and environmental factors, but lipoproteins remain the foundation of its pathogenesis [3]. Identification of a highly specific and sensitive lipid biomarker is the need of the hour to identify high risk populations and hence initiate corrective measures [4]. A simple blood test that can be carried out as an outpatient procedure, involving minimum infrastructure and patient preparation would be beneficial in patient identification even in remote villages.

Although, the measurement of serum cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) have been the mainstay of the fundamental lipid profile analysis since decades, recent studies have demonstrated the superior discriminatory value of apolipoproteins such as Apo-AI and -B100. The measurement of the apolipoprotein levels gives a better reflection of the total number of pro and anti-atherogenic particles in blood [5]. Recent years have seen the advent of several lipid ratios and indices as determinants of CAD risk. These include LDL/HDL, apolipoprotein B100/apolipoprotein A, total cholesterol/HDL, triglycerides/HDL, comprehensive lipid tetrad index (CLTI) and lipid pentad index (LPI) etc.

Comprehensive lipid tetrad index (CLTI), proposed by Enas EA, is designed to magnify the subtle abnormalities of the various atherogenic and anti-atherogenic lipoproteins and is derived by multiplying the three commonly measured lipids directly associated with CAD and dividing the product by HDL, which is inversely associated with CAD (total cholesterol × triglyceride × Lp(a)/HDL) [6].

Since Apo-B100/Apo-AI ratio is better than the LDL-C/HDL-C ratio, Das et al. have defined a new index (Lipid Pentad Index, LPI) incorporating

* Corresponding author.
E-mail addresses: binita.dr@gmail.com (B. Goswami), linkmedha@gmail.com (M. Rajappa), dr.baidarbhi@gmail.com (B. Chakraborty), drsurajeetlhmc@gmail.com (S.K. Patra), linkbinita@rediffmail.com (S. Kumar), drvmallika@gmail.com (V. Mallika).

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this ratio into the known Lipid Tetrad Index to express the total dyslipidemia, defined as, LPI = total cholesterol × triglyceride × Lp(a) × Apo-B/Apo-AI [7].

The Third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program (NCEP) has recommended the use of non-HDL cholesterol as a secondary target of lipid lowering in cases where the triglyceride level is more than 200 mg/dl [8]. It is easier to calculate, circumvents the intraindividual variability of triglyceride level and can be determined in the nonfasting state also. The term Atherogenic Index of Plasma (AIP), calculated as log (TG/HDL-C) was proposed by Dobiasova and Frohlich as an indicator of atherogenic risk [9]. The availability of so many lipid ratios and indices has led to a lot of confusion regarding their applicability as well as their contribution to the existing knowledge regarding CAD risk profile.

We evaluated various ratios of proatherogenic to antiatherogenic lipoprotein measurements, including total to HDL cholesterol (total/HDL cholesterol), LDL to HDL cholesterol (LDL/HDL cholesterol), and Apo-B100 to Apo-AI (Apo-B/AI) etc. as potential markers of risk for CAD in patients of myocardial infarction. Our endeavor was aimed at determining the most appropriate ratio in the Indian scenario. This will help in devising diagnostic algorithms specific for the disease prone Indian population.

Methods

The study population comprised of 100 cases of acute myocardial infarction, presenting to the medical emergency of Lok Nayak Hospital, New Delhi. Acute myocardial infarction was diagnosed based on clinical, electrocardiographic and biochemical criteria. Patients with history suggestive of hepatic or renal disease were excluded. History of any endocrine or metabolic disease and intake of lipid lowering drugs known to affect the study parameters also amounted to exclusion from the study. The patients were enrolled in the study group, after informed consent and filling of a structured questionnaire including details of classical risk factors such as family history of CAD, hypertension and smoking. Body mass index (BMI) values were derived from Quetlet's formula (weight in kg/height in m^2). Approval was taken from the ethical committee of the institution, before commencing the study. One hundred non-diabetic age and sex matched healthy controls were also enrolled who satisfied the following criteria: normal glucose tolerance test, absence of angina (Rose questionnaire), absence of history of any vascular disease (AMI, Stroke or intermittent claudication) and normal 12-lead resting electrocardiograms.

A patient is diagnosed with AMI, if there is clinical history of ischemic type chest pain lasting for more than 20 min, substantiated by electrocardiographic evidence of Q waves, ST elevation/depression, with rise in cardiac troponins/CK-MB [10]. Arterial hypertension was diagnosed in patients with resting blood pressure values above 140/90 mm Hg measured repetitively (at least twice) [11]. Diabetes was diagnosed based on the criteria of the American Diabetic Association expert committee on diagnosis and classification of diabetes mellitus, i.e., fasting plasma glucose ≥ 126 mg/dl, 2 h post load glucose ≥ 200 mg/dl or two random plasma glucose values ≥ 200 mg/dl [12].

A fasting blood sample was taken within 12 h of presentation to the hospital and serum separated and stored at −70 °C, until the assays were performed. Total cholesterol and triglycerides were measured using commercially available kits on the Olympus RU400 auto analyzer using commercial kits provided by Randox Industries, UK. The within run and between run precision for total cholesterol was determined by calculating CV%. The CV% ranged from 1.71% to 3.84% and 1.00% to 1.39% for intra assay and interassay comparisons respectively. Same analysis for the triglyceride kit revealed good inter assay and intra assay precision. The CV% for within run analysis was 1.55%–3.39% respectively. The corresponding figures for between run precision was 1.33%–3.51% respectively.

HDL cholesterol was determined, after precipitation of Apo-B containing particles by phosphotungstic acid-$MgCl_2$. The inter assay and intra assay CV ranged from 1.65% to 3.52% for intra assay variations and 1.52% to 2.20% for inter assay precision analysis. LDL-cholesterol was calculated for subjects with fasting serum triglyceride levels (<400 mg/dL) using Friedwald's formula [13].

Apo-B and Apo-AI were assayed using commercial kits based on an automated immunoturbidimetric method (Randox, UK). The run to run imprecision for measurement of Apo-B was 7.1% at a 110-mg/dl concentration, 6.5% for Apo-A at a 100-mg/dl concentration.

Lp (a) levels were estimated by immunoturbidimetric method using a commercially available kit by Randox Industries, UK. The within run CV ranged from 1.7% to 2.5% while the between run CV was 2.99% to 6.09%. The sensitivity was 3 mg/dl. There were no significant interactions and pro zone effect was not observed up to 341 mg/dl.

Small dense LDL was calculated by the formula of Hattori et al. [14].

$$\mathrm{sdLDL} = 0.94^{*}\mathrm{chol} - 0.94^{*}\mathrm{HDL} - 0.19^{*}\mathrm{TG/Apo\text{-}B} - 0.09^{*}\mathrm{chol} + 0.09^{*}\mathrm{HDL} - 0.08^{*}\mathrm{TG}.$$

Statistical analysis

Statistical analyses were performed with SPSS for windows version 12 (SPSS Inc.). All the values are expressed as mean ± S.D. Continuous variables were compared by Mann Whitney *U* test as the parameters followed a non-Gaussian distribution in the study population. Multiple logistic regression analysis was performed to ascertain the roles of the different risk factors for CAD in our study Receptor operating curves (ROC) were plotted for different parameters to ascertain their discriminative value. Sensitivity, specificity, likelihood ratio, positive and negative predictive values were calculated to determine the best plausible biomarker among the parameters evaluated in the study. P values < 0.05 were considered significant.

Results

The clinical characteristics of the study group are shown in Table 1. The study groups are age and sex matched. Risk factor analysis showed prevalence of smoking and alcohol in 38% and 17% of the cases respectively. In comparison with control subjects, patients with AMI had higher BMIs ($p = 0.0002$). Significantly elevated levels of total cholesterol, triglycerides, LDL cholesterol, Apo-B and non-HDL cholesterol was observed in patients with AMI, as compared with healthy control subjects (Table 2). The patients with AMI also exhibited lower HDL cholesterol and Apo-AI, as compared with controls (Table 2). However, there was no statistically significant difference between Apo-AI levels of patients and controls. Tables 3 and 4 illustrate the values of the various lipid indices in the cases and controls. It can

Table 1
Demographic features of the study population.

	AMI patients (n = 100)	Controls (n = 100)
Age (years)	53.1 ± 11.6	52.8 ± 12.7
Sex (M/F)	86/14	90/10
BMI (kg/m^2)	26.6 ± 3.7[a]	21.5 ± 2.11
Systolic BP (mm Hg)	132 ± 9.4	119 ± 10.1
Diastolic BP (mm Hg)	87 ± 4.5	75 ± 5.2
Past history of CAD	–	–
Family history of CAD (%)	5	–
Smoking (%)	38	–
Alcohol (%)	17	–
Diabetes mellitus (%)	5	–
Hypertension (%)	8	–

[a] Significantly high compared with control group ($p < 0.001$).