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Original Article

Is Lipid Tetrad Index a Promising Atherogenic Index in Acute Coronary Syndrome?

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Abstract

Introduction: Coronary heart disease (CHD) is expected to be the most important cause of death in India by 2020. Increased concentration of atherogenic lipoprotein plays an important role in the development of atherosclerosis leading to premature myocardial infarction. Etiology of CHD is multifactorial; a single biomarker is unlikely to provide information for coronary artery disease occurrence. Hence, the present study is on the calculation of lipid tetrad index (LTI) in acute coronary syndrome (ACS).

Aims and Objectives: To estimate lipoprotein(a) (Lp[a]), lipid parameters, to calculate LTI, and to explore the diagnostic importance of LTI as a risk factor in ACS.

Materials and Methods: Study group comprised 50 subjects admitted in the intensive coronary care unit (ICCU) with ACS which includes 38 ST-elevation myocardial infarction (STEMI), 2 non-ST STEMI, and 10 unstable angina patients. Fifty healthy gender- and age-matched subjects were taken as control group. The fasting venous sample was collected. plasma Lp(a) total cholesterol (TC), triglycerdies (TGL) and high density lipoprotein (HDL) estimated. LTI was calculated by the product of TC, TGL, and Lp(a) divided by high-density lipoprotein and compared between two groups.

Results: The mean Lp(a), LTI were significantly elevated in study group compared to control group (P = 0.0001).

Conclusion: Elevated LTI depicts it as a risk factor in ACS and a promising atherogenic index for assessment in ACS compared to other lipid parameters.

Key words: Acute coronary syndrome, Coronary artery disease, Lipid parameters, Lipid tetrad index, Lipoprotein (a)

INTRODUCTION

The acute coronary syndrome (ACS) is the clinical manifestation of the critical phase of coronary artery disease (CAD). ACS describes the spectrum of clinical manifestations which follow disruption of coronary arterial plaque, complicated by thrombosis, embolization, and varying degrees of obstruction to myocardial perfusion.[1] The myocardial ischemia occurs when oxygen supply does not meet the myocardial demand, usually seen in atherosclerotic disease of the epicardial coronary artery. When ischemia is severe, prolonged necrosis or infarction occurs.[2] The clinical features depend on extent and severity of myocardial ischemia. ACS refers to a range of myocardial ischemic states which includes patient with ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina.

It has been predicted that CAD might become the most prevalent disease in India by the year 2020.[3] CAD is a chronic process that begins during adolescence and slowly progresses throughout life. CAD evolves often unnoticed over decades, often culminating in myocardial infarction. The myocardial infarction and its complications are the principal cause of death in patients with CAD.[4] The prevalence of CAD is 4-fold higher in urban India and

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2-fold higher in rural India than in the USA. This is again high in South Indians compared to North Indians, 7% in rural and 14% in urban areas. The CAD rates in urban India are similar to more affluent overseas Indians.[5]

Several factors appear to have contributed to the acceleration of CAD epidemic in India in recent times such as demographic transition to the older population, as a result of increasing life expectancy and confluence of both conventional and non-conventional risk factors. Conventional risk factors such as hypertension, diabetes mellitus, hypercholesterolemia, and smoking are increased in Indians due to urbanization and Western acculturation. Non-conventional factors such as hyperinsulinemia, insulin resistance, and lipoprotein(a) (Lp[a]) are determined by genes, and their high prevalence among Indians probably explains the precocious nature of CAD that typically affects Indians. These multiplicative effects of conventional and emerging risk factors appear to provide an explanation for excess burden of CAD among Indians.[6] The increased concentration of atherogenic lipoproteins plays an important role in the development of atherosclerosis leading to premature myocardial infarction and stroke. Lp(a) is an atherothrombogenic lipoprotein that is inherited as a genetic quantitative trait and is an important emerging risk factor for premature coronary heart disease (CHD).[7]

Lp(a) is an enigmatic lipoprotein, discovered by Berg in human plasma in 1963,[8] also called as deadly cholesterol. Lp(a) contains a lipoprotein moiety that is highly similar to low-density lipoprotein (LDL) both in lipid composition and presence of apolipoprotein B (apoB) and contains unique glycoprotein apo(a). Lp(a) particles contain apo(a) and apoB100 in a 1:1 molar ratio. Lp(a) has also been identified as a risk factor for a variety of atherosclerotic disorders such as ischemic stroke and myocardial infarction.[7,9] LP(a) is synthesized in the liver. The metabolism of Lp(a) is independent of other lipoproteins. Lp(a) concentration in plasma varies 1000-fold in human population ranging from undetectable to >100 mg/dl and difference is primarily due to production rather than catabolism of the particle.[9] Plasma levels of Lp(a) do not vary with the age of the subjects and fully expressed in the first year of life.[10]

Since the underlying etiology of CHD is multifactorial, it is, therefore, unlikely that a single biomarker will provide accurate information for CAD occurrence. Hence, the present study is on simultaneous measurement of several lipid biomarkers and calculation of lipid tetrad index (LTI). This index eliminates the need for numerous ratios and cutoff points that are confusing and frustrating for the clinicians. The LTI is derived by multiplying three lipids which are directly associated with CAD and dividing the product by high-density lipoprotein (HDL) which is inversely associated with CAD.

$$\text{Lipid tetrad index} = \frac{\text{Total cholesterol} \times \text{Triglycerides} \times \text{Lipoprotein (a)}}{\text{High density lipoprotein}}$$

MATERIALS AND METHODS

The study was conducted at a tertiary care hospital in South India after getting approval from the Ethical Committee. In the present study, the age group of both study and control groups ranged from 30 to 65 years, males and females were included, and informed consent obtained from them. Fifty subjects (30 males and 20 females) who were admitted in the intensive coronary care unit with clinical findings suggestive of STEMI (n = 38), non-STEMI (n = 2), and unstable angina (n = 10) were included in the study group. Fifty gender- and age-matched individuals without any history or clinical evidence of ACS from the general population were taken as control group.

Inclusion Criteria

1. Patients admitted with a history of chest pain, electrocardiogram changes showing ST elevation or ST depression exceeding 2 mm, T wave inversion, presence of Q waves more than 1 mm
2. Based on elevated creatine kinase-MB (CK-MB) levels.

Exclusion Criteria

Patients with nephrotic syndrome, chronic renal failure, hypothyroidism, diabetes mellitus, previous history of ACS, on drugs such as steroids, lipid-lowering drugs (statins, fibrates), and hormone replacement therapy were excluded from the study.

Blood Collection

Fasting venous blood samples (the day after the admission with ACS) were collected under aseptic conditions. Five milliliters of blood was drawn by the intravenous route. Two milliliters of blood was transferred to ethylenediaminetetraacetic acid (EDTA) tubes for Lp(a) estimation, and 3ml was transferred to plain vacutainers for estimation of total cholesterol (TC), triglycerides (TGL), HDL, fasting blood sugar, urea, creatinine, and CK-MB. The samples in the EDTA tube were centrifuged, plasma diluted (1:8000), and stored at −20°C in a deep freezer for Lp(a) estimation. Human Lp(a) assay was done using ELISA kit (assay maximum human Lp[a] kit-Assaypro). The estimation of TC, TGL, and HDL was done using enzymatic kits in XL 300 auto analyzer. Friedewald's formula was used to calculate LDL values. LTI was calculated using the formula:

$$\text{Lipid tetrad index} = \frac{\text{Total cholesterol} \times \text{Triglycerides} \times \text{Lipoprotein (a)}}{\text{High density lipoprotein}}$$

Statistical Analysis

Data were entered in IBM SPSS version 20 software. The analysis was done using Student's *t*-test. Pearson correlation was done between LTI and lipid parameters. Descriptive statistics like percentage used. The significance of various parameters is expressed by means of *P* values as per *P* <0.05 – significant, *P* <0.001 – highly significant, and NS – Not significant.

RESULTS

Table 1 shows general descriptive of control and study groups, age and sex were matched between study and control groups, and there was no significant difference between two groups. Sixty percent were males, and 40% were females in both control and study groups.

Table 2 shows that the mean plasma Lp(a), TC, TGL, VLDL, and LTI are higher in study group compared to control group and HDL is lower in study group compared to control group which is statistically highly significant ($P = 0.0001$).

Table 3 shows there is no statistically significant gender difference in mean plasma Lp(a) and LTI in control and study groups.

Table 4 shows plasma Lp(a), and LTI values in study group are higher compared to control group for their respective age distribution and are statistically significant.

From Table 5, Pearson correlation analysis in the study group shows that there is a highly significant positive correlation between LTI and Lp(a) ($r = 0.699$, $P < 0.01$), TC ($r = 0.650$, $P < 0.01$), TGL ($r = 0.670$, $P < 0.01$) levels. There is a negative correlation between LTI and HDL which is statistically significant ($r = -0.395$, $P < 0.01$).

DISCUSSION

CAD in Indians has been rising steadily over the past 40 years affecting mainly younger age group in the absence of traditional risk factors. Elevated Lp(a) concentration is related to atherothrombogenesis and may be a key link between lipid and CAD occurrence. Rising affluence, sedentary and stressful lifestyle are additional risk factors for CAD at a younger age group. LTI is calculated to assess the total burden of dyslipidemia[11,12] in patients with ACS.

In Indian population, Enas *et al.* suggested Lp(a) of 20 mg/dl as the upper limit of normal.[13] Lp(a) is higher in African population compared to Caucasians and Asians. For risk categorization, Lp(a) levels are desirable <14 mg/dl, borderline risk: 14-30 mg/dl, high risk: 31-50 mg/dl, and very high risk: >50 mg/dl.[14]

In the present study, the mean plasma Lp(a) of study group is higher than the control group which is statistically significant ($P = 0.000 < 0.05$). Higher mean plasma Lp(a) levels in study group correlated with mean Lp(a) levels in CAD group was observed by Rajasekhar *et al.*[15] and Isser *et al.*[16] There is no gender difference in plasma Lp(a) values in our study and control groups. A study done by Pedreno *et al.* has shown no gender difference in Lp(a) levels in both patients and controls. However, Rajasekhar *et al.* have reported higher Lp(a) values in females compared to males. Higher levels are seen in post-menopausal women.

Although influence on sex on Lp(a) is not yet established in literature, the lowering effect of testosterone could be the cause of lower Lp(a) levels in males.[13]

Lp(a) is categorized as an emerging lipid risk factor by Adult Treatment Panel III of National Cholesterol Education Programme, elevated Lp(a) level, increases the individual risk to a higher level. High levels of Lp(a) correlate with prematurity, severity, extent, and progression of coronary atherosclerosis as well as occurrence and recurrence of

Table 1: General descriptive of study and control groups

Variables	Control (*n*=50)	Study (*n*=50)
Age (years)	51.18±9.26	52.1±9.250
Sex (male/female)	30/20	30/20
BMI (kg/m^2)	25.48±1.75	25.51±3.35
Systolic BP (mmHg)	120.12±7.33	131.48±19.78
Diastolic BP (mmHg)	79.52±3.78	83.96±11.08

Data were expressed as mean±SD. BMI: Body mass index, BP: Blood pressure, SD: Standard deviation

Table 2: Plasma Lp (a), lipid parameters, and LTI in control and study groups

Variables	Control (*n*=50)	Study (*n*=50)	*P*
LP (a) (mg/dl)	10.37±2.96	23.43±7.40	0.0001**
TC (mg/dl)	181.62±14.20	215.68±33.88	0.0001**
TGL (mg/dl)	133.86±17.34	208.00±36.8	0.0001**
HDL (mg/dl)	42.94±3.50	37.54±3.64	0.0001**
VLDL (mg/dl)	27.64±5.97	41.96±7.30	0.0001**
LDL (mg/dl)	111.98±14.76	134.74±32.33	0.0001**
LTI	6046.44±2257.65	29,624.63±16,295.62	0.0001**

Data were expressed as mean±SD, **P<0.001 - HS: Highly significant. Lp (a): Lipoprotein (a), TC: Total cholesterol, TGL: Triglycerides, HDL: High-density lipoprotein, VLDL: Very low-density lipoprotein, LDL: Low-density lipoprotein, LTI: Lipid tetrad index, SD: Standard deviation

Table 3: Mean plasma Lp (a) and LTI values in males and females

Variables	Control			Study		
	Male (*n*=30)	Female (*n*=20)	*P*	Male (*n*=30)	Female (*n*=20)	*P*
Lp (a) mg/dl	10.42±3.02	10.30±2.96	0.886 (NS)	23.82±7.40	22.86±7.56	0.661 (NS)
LTI	5971.00±2193.57	6159.59±2403.78	0.771 (NS)	30,062.53±15,033.69	28,967.77±18,414.93	0.826 (NS)

Data were expressed as mean±SD. NS: Not significant, Lp (a): Lipoprotein (a), LTI: Lipid tetrad index, SD: Standard deviation

Table 4: Lipoprotein (a), lipid tetrad index in different age groups

Age group (years)	Variables	Control		Study		*P*
		n	Mean±SD (mg/dl)	*n*	Mean±SD (mg/dl)	
<40	Lp (a) (mg/dl)	7	10.11±2.14	5	26.48±4.63	0.0001**
	LTI	7	5866.05±941.12	5	41,083.04±22,710	0.002*
41-50	Lp (a) (mg/dl)	17	11.68±4.40	16	24.25±6.23	0.0001**
	LTI	17	7224.60±3038.74	16	30,100.36±14,165.79	0.0001**
51-60	Lp (a) (mg/dl)	19	9.70±1.585	19	20.60±7.68	0.0001**
	LTI	19	5318.60±1697.47	19	26,884.66±18,469.52	0.001*
>60	Lp (a) (mg/dl)	7	9.27±0.58	10	26.00±8.70	0.0001**
	LTI	7	5341.13±1108	10	28,340.18±10,430.79	0.0001**

*P<0.05 - S: Significant, **P<0.001 - HS: Highly significant. Lp (a): Lipoprotein (a), LTI: Lipid tetrad index, SD: Standard deviation

Table 5: Pearson correlation between LTI and lipid parameters in study group

LTI (mg/dl)	Correlation value	Statistical inference (*P*)
Lp (a)	0.699	<0.01*
TC	0.650	<0.01*
TGL	0.670	<0.01*
HDL	−0.395	<0.01*

*P<0.05 - S: Significant. Lp (a): Lipoprotein (a), TC: Total cholesterol, TGL: Triglycerides, HDL: High-density lipoprotein, LTI: Lipid tetrad index

myocardial infarction among Asian Indians. The risk for CAD increases 3-fold in the absence of other risk factors, increases 8-fold with low HDL, 12-fold with high LDL, 16-fold with diabetes, 25-fold with high TC/HDL ratio[17] when associated with increase in plasma Lp(a) levels.

The mean cholesterol level in the study group is higher than the control group which is statistically significant ($P < 0.05$). This level is slightly higher than the mean level of cholesterol observed in a study done by Singh *et al.* in North Indian population, is due to difference in nature of fat intake.[18]

In this study group, the mean TGL level is higher than the control group which is statistically significant ($P < 0.05$). An increase of TGL from 90 mg/dl to 180 mg/dl is associated with doubling of the incidence of CAD. An increase in TGL by 90 mg/dl and increase in age by 10 years[5] have the same effect on the occurrence of coronary atherosclerosis.

The mean HDL level in the study group is lower than the control group which is statistically significant ($P < 0.05$). Similar values are observed in Singh *et al.*'s study and demonstrated that low HDL increases the risk of CAD.[18] LDL cholesterol of study group is higher than the control group which is statistically significant. Raised cholesterol is recognized as a primary risk factor for CAD by the National Cholesterol Education Programme and Adult Treatment Panel III groups.[18]

TC and LDL levels are similar in Indians and American counterparts, but Lp(a), TGL levels are higher and HDL are lower, even when adjusted for the presence for the presence of diabetes and metabolic syndrome in Indians.[17] When combined with the concomitant elevation of TC, LDL and decreased HDL cholesterol, the pathophysiological effects of Lp(a) are increased exponentially. This is "deadly lipid quartet" commonly seen in Asian Indians. The comprehensive LTI is proposed by Enas *et al.*, is designed to magnify the subtle abnormalities of various atherogenic and antiatherogenic lipoproteins,[19] and described as a single best predictor for CAD risks in diverse population, especially Asian Indians (India, Pakistan, Bangladesh, and Sri Lanka). When measurements are made in mg/dl, an index of <10,000 is desirable, 10,000-20,000 is borderline-high, >20,000 is high. An index of more than 100,000 is usually associated with marked prematurity and severity of CAD, poor outcome from mechanical vascularization including recurrence restenosis after angioplasty and rapid thrombosis of the coronary stent.[20]

The mean LTI in the study group is higher than the mean LTI of control group which is statistically highly significant ($P = 0.000 < 0.05$). In the study group, 78% had LTI above 20,001 (high risk), 14% had LTI between 10,001 and 20,000 (borderline), 8% had LTI below 10,000 (desirable). In the control group, 94% had LTI below 10,000 (desirable) index and 6% between 10,001 and 20,000 (borderline risk).

There is no statistically significant gender variation observed in LTI in our study and control groups. No gender difference in LTI values has been reported by Nwosu *et al.*[14]

Japanese population have a low incidence of CAD with LTI of 4300, Asian Indians in the US have a higher incidence of CAD with lipid tetrad index of approximately 24,000. The mean LTI in native Indians is 12,899 in males and 10,814 in females.[10]

The present study depicts that the effect of lipid parameters as well as Lp(a) on atherogenicity is not additive but multiplicative. Study with large sample size needs to be conducted to confirm the findings of our present study.

CONCLUSION

This study on evaluation of LTI in ACS shows that it is a promising atherogenic index in risk factor assessment when compared to other lipid parameters. LTI facilitates in early identification of individuals with high risk for premature CAD as a result of their genetic predisposition. Since no well-established Lp(a) lowering drugs are available at present, there is a need to create awareness for early detection and modification of other risk factors in young individuals. Early intervention like lipid lowering drugs helps preventing the progression of atherosclerosis and in reducing the morbidity and mortality from ACS.

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