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RESEARCH ARTICLE

LIPID TETRAD INDEX –A NEW RISK CALCULATOR IN ACUTE CORONARY SYNDROME

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ABSTRACT

Introduction*:* CAD is a chronic process that begins during adolescence and slowly progresses throughout life. 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. ***Material and Methods***: THIS hospital based prospective case control study was conducted in wards and ICU of department of medicine and cardiology of M. B. Govt. Hospital, Udaipur from June, 2021 to June, 2022 over a period of 1 year. 120 patients from wards or ICU with ACS were selected based on the inclusion/exclusion criteria and 120 normal subjects were taken from relatives of patients and healthy volunteers. Fasting venous blood samples were collected and sent for lipid profile and lipoprotein (a) estimation and Lipid Tetrad Index was calculated. Qualitative data collected were entered in Microsoft excel software and analyzed using SPSS, version 21 for Windows statistical software package. ***Result****:* In our study, there was no significant difference between two groups. 65 percent were males, and 35% were females in both control and study groups. The mean HDL (36.48 vs 40.32) is lower in study group compared to control group which is significant. The mean plasma Lp(a) is greater in study group compared to the control group (37.70 vs 24.13 mg/dl). LTI values in study group are greater compared to control group for their respective age distribution and are statistically significant (24423.60 vs 11807.43). The mean plasma TC, TGL, LDL are greater in study group compared to the control group. ***Conclusion****:* Thus in our study it is concluded that there is a highly significant positive correlation between the LTI and Lp(a) levels. There is statistically significant negative correlation between LTI and the HDL. Thus, the effect of various lipid parameters as well as Lp-a on the atherogenicity is not additive but multiplicative which is well demonstrated by the lipid tetrad index

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INTRODUCTION

Cardiovascular disease is the commonest cause of mortality globally, accounting annually for nearly 12 million deaths, with coronary artery disease (CAD) being the major contributor. There is a steady increase in the prevalence of CAD due to rapid changes in demography and lifestyle consequent to economic development.[1] 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.[2]

ACS refers to a range of myocardial ischemic states which includes patient with ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina.[2,3] Lipoprotein-a (Lp-a) has evolved as a genetically-linked risk factor in thrombosis. High levels of Lp-a have been identified within the atherosclerotic plaque and may represent an important link between atherogenesis and thrombogenesis. Higher Lp-a levels are associated with a 2-3-fold risk of CAD which increases exponentially with concomitant presence of low HDL cholesterol, high total cholesterol/HDL cholesterol ratio ; all of which are common among Asian Indians, a race known to bear the burden of premature CAD.[1,4] The high consistency of Lp(a) levels over many years in an individual, stresses the fact that Lp(a) does not

have any substantial correlation with either lifestyle modifications or any of the established risk factors. This again emphasizes the importance of the LPA locus on Lp(a) levels and, unlike other markers, confers the advantage of assessing CAD risk by a single measurement.[5]

Lipid tetrad index (LTI)[6] is derived by the product of cholesterol, triglycerides and Lp-a values divided by the HDL level. It may be the best estimate of the total burden of dyslipidaemia as it eliminates the need for various cut- off points and ratios involving the lipid subsets. A high index (> 20,000) would indicate the presence of a highly atherogenic lipid profile. This index can serve as a better and novel risk factor for CAD[1,7] 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.

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

AIMS AND OBJECTIVES

- To estimate lipoprotein(a) (Lp[a]), Total cholesterol, Triglycerides, HDL
- To calculate Lipid Tetrad Index (LTI)
- To study that Lipid Tetrad Index (LTI) is a new risk calculator in Acute Coronary Syndrome (ACS).

MATERIAL AND METHODS

STUDY SITE: Patients admitted in wards and ICU of department of medicine and cardiology of M. B. Govt. Hospital, Udaipur were enrolled.

STUDY DESIGN: Hospital based prospective case control study.\

STUDY PERIOD: Eligible cases were studied from June, 2021 to June, 2022 over a period of 1 year.

STUDY POPULATION: Patients admitted in wards and ICU of Department of Medicine and Cardiology of M.B. Govt. Hospital, Udaipur diagnosed with a history of chest pain, electrocardiogram changes showing ST elevation exceeding 1 mm in limb leads or 2 mm in precordial leads, ST depression exceeding 2 mm, T wave inversion, presence of Q waves more than 1 mm, elevated Trop-T/Trop-I level were enrolled in the study after taking proper informed consent.

Inclusion Criteria

- Age group above 18 years both male and female.
- Patients admitted with anginal pain and ECG showing ST-T wave changes.
- Elevated Trop-T/Trop-I level.

Exclusion Criteria

- Patient on Statins and/or Fibrates therapy.
- Patients presenting after 8 weeks of acute myocardial infarction.
- Patients who are taking non cardiac drugs that affect the lipid profile.
- Patient with bleeding disorder.
- Patients who refused to give consent

STUDY METHOD

- 120 patients from wards or ICU with ACS were selected based on the inclusion/exclusion criteria and 120 normal subjects were taken from relatives of patients and healthy volunteers.
- Fasting venous blood samples were collected and sent for lipid profile and lipoprotein (a) estimation .
- Lipid Tetrad Index was calculated using the following formula

$$\textbf{Lipid Tetrad Index} = \frac{\textbf{Total cholesterol} \times \textbf{Triglycerides} \times \textbf{Lipoprotein(a)}}{\textbf{High density lipoprotein}}$$

All the information were recorded in predesigned proforma formed in Microsoft excel for final analysis.

STATISTICAL ANALYSIS

Qualitative data collected were entered in Microsoft excel software and analyzed using SPSS, version 21 for Windows statistical software package. Data were compiled in tabulated form, were expressed as mean and standard deviation and chi sqaure and unpaired 't' test was applied for statistical inference.P value <0.05 was considered as significant.

OBSERVATION AND RESULTS

Table 1. Comparison of Age

AGE(Years)	CASES (n=120)	CONTROL(n=120)
40-50	47	46
51-60	21	22
61-70	37	35
71-80	15	17
TOTAL	120	120
Mean	54.7	57.03
SD	11.51	11.26
P' value	0.1143 (NS)	

Above table shows the age distribution in case and control. Most of the cases were found in age group 40-50 in both case and control group followed by 51-60 and 71-80 years.

Table 2. Comparison of gender

GENDER	CASES(n=120)	CONTROL(n=120)
MALE	79	76
FEMALE	41	44
TOTAL	120	120
P' value	0.561 (NS)	

Above table shows that male preponderance was present over females

Table 3. Mean HDL Comparison

HDL(mg/dl)	CASES(n=120)	CONTROL(n=120)
<30	19	0
30 – 40	63	44
>40	38	76
TOTAL	120	120
Mean	36.48	40.32
SD	7.53	5.20
P' value	<0.001 Significant	

Above table shows mean HDL in case and control group. The mean HDL is low in cases as compared to control (P<0.0001).

Table 4. Mean LP(a) Comparison

Lpa(mg/dl)	CASES(n=120)	CONTROL(n=120)
<30	20	112
30 – 40	58	8
>40	42	0
TOTAL	120	120
Mean	37.70	24.13
SD	11.61	5.02
P' value	<0.001Significant	

Above table shows mean Lp(a) in case and control group. The mean Lp(a) is higher in cases as compared to control (P<0.001).

Table 5. Mean Total Cholesterol Comparison

TC(mg/dl)	CASES(n=120)	CONTROL(n=120)
<200	74	116
≥ 200	46	4
TOTAL	120	120
Mean	192.86	182.62
SD	20.58	17.06
P' value	<0.001 Significant	

Above table shows mean total cholesterol in case and control group. The mean cholesterol is higher in cases as compared to control group (P<0.001).

Table 6. Mean Triglyceride Comparison

TG(mg/dl)	CASES(n=120)	CONTROL(n=120)
<200	78	120
>200	42	0
TOTAL	120	120
Mean	180.86	161.62
SD	32.81	23.74
P' value	<0.001 Significant	

Above table shows mean triglyceride in case and control group. The mean triglyceride is higher in cases as compared to control (P<0.001).

Table 7. Mean Low Density Lipoprotein Comparison

LDL(mg/dl)	CASES(n=120)	CONTROL(n=120)
<100	7	49
≥100	113	71
TOTAL	120	120
Mean	130.39	117.83
SD	16.45	19.63
P' value	<0.001 significant	

Above table shows mean LDL in case and control group. The mean LDL is higher as compared to control group (P<0.001).

Table 8. Mean Lipid Tetrad Index Comparison

LTI	CASES(n=120)	CONTROL(n=120)
<20000	28	120
20000-30000	71	0
>30000	21	0
TOTAL	120	120
Mean	24423.60	11807.43
SD	8556.34	2828.17
P' value	<0.001significant	

Above table shows mean lipid tetrad index (LTI) in case and control group. The mean LTI is higher as compared to control group (P<0.001).

DISCUSSION

This case control study was conducted in patients admitted in wards and ICU of department of medicine and cardiology of M. B. Govt. Hospital, Udaipur, diagnosed with a history of chest pain, electrocardiogram changes showing ST elevation exceeding 1 mm or ST depression exceeding 2 mm, T wave inversion, presence of Q waves more than 1 mm, elevated Trop-T/Trop-I level. In our study there was non significant difference between age group of cases and control. Among cases maximum patients(47) were in 40-50 year age group, followed by 37 patients who were in 61- 70 year age group. Similar pattern was seen in control. There were equal percentage of males and females. Similarly study of Daniel *et al*[8] provides a contemporary estimate of the age- and sex-specific incidence of first-time myocardial infarction in a nationwide setting. We observed a steeper decline among the older age groups (≥70 years) compared to the young and middle aged. While the incidence rate remained higher among males, and the median age at onset remained higher among females, both sexes experienced similar declines in myocardial infarction incidence. The mean HDL (36.48 vs 40.32) is lower in study group compared to control group which is significant. The mean plasma Lp(a) is greater in study group compared to the control group (37.70 vs 24.13 mg/dl). The mean plasma TGL is greater in study group compared to the control group (180.86 vs 161.62mg/dl). The mean plasma LDL is greater in study group compared to the control group (130.39 vs 117.83 mg/dl). LTI values in study group are greater compared to control group for their respective age distribution and are statistically significant (24423.60 vs 11807.43). There is a highly significant positive correlation between the LTI and Lp(a) levels. There is a negative correlation between LTI and the HDL which is statistically significant. The mean plasma TC, TGL, LDL are greater in study group compared to the control group. Thus, the effect of various lipid parameters as well as Lp-a on the atherogenicity is not additive but multiplicative which is well demonstrated by the lipid tetrad index. Dyslipidemia is regarded as a major cause of the excess burden of coronary artery disease among South Asians.[9]. Dyslipidemia occurs when there is an increased level of apolipoprotein (apo) B, TG, Lipoprotein Lp(a) and LDL-C, and low levels HDL-C and apoA1[9]. There are many pieces of evidence suggesting that a decrease in the level of lipoprotein (LDL) levels or an increase in HDL levels can reduce the occurrence of cardiovascular disease[10]. Our study also found that LDL was significantly higher in patients with MI compared to those without MI and HDL was significantly lower in patients with MI compared to those without MI. Various trials Ference BA , Cohen JC and by Baigent C have indicated that long term exposure to lower levels of LDL can reduce the risk of cardiac events[11-13]. In study of Mal K *et al*[14], LDL was higher in participants with AMI compared to those without AMI (94.99 ± 31.97 mg/dl vs 87.12 ± 31.29). In a large scale meta-analysis by Di Angelantonio E, covering almost 170,000 individuals, it was concluded that treatment with statins was associated with a log linear proportional reduction of 22% in major cardiovascular events for every per millimole per litre reduction in LDL-C over a median of five years of treatment.[15].

In this study, HDL was significantly lower in patients with AMI than compared to those without AMI. There are contrary data available on the impact of HDL on cardiovascular disease. Some studies like Holmes MV have established an inverse relationship between HDL level and cardiovascular disease,[16] where Mendelian randomization argues against the causal relation between HDL and cardiovascular disease. In this study, there was no significant difference between triglyceride (TG) levels of patients with AMI and patients without AMI. Emerging risk collaboration in their study concluded that increased level of plasma TG levels are associated with an increased risk of ASCVD, however, after adjusting for non-HDL-C this association becomes null[16]. The coronary artery disease in Indians (CADI) study[17] first reported the existence of high levels of Lp-a in Asian Indians as compared to the United States. Mean lipoprotein- a levels in our study were significantly higher in the study group as compared to the controls (44.90 ± 25.89 mg/dl vs. 14.47 ± 5.92 mg/dl; $p < 0.001$). Lp-(a), in isolation, is a powerful risk factor for atherosclerotic coronary artery disease; the relative cardiovascular risk is significantly increased when elevated Lp-(a) levels are associated with high levels of LDL and apo-B or low value of high density lipoprotein (HDL). The effect of various lipid parameters as well as Lp-a on the atherogenicity is not additive but multiplicative which is well demonstrated by the lipid tetrad index. The mean lipid tetrad index of the patients with CAD was significantly higher than the patients without CAD as has been reported earlier in the studies done by Enas *et al*, Mehdi R and Yusuf S.[17-19] A review done by Yeolekar[20] showed that Asians had a deadly lipid tetrad index which becomes the single predictor of CAD in Asian region.[21]Total cholesterol, Lpa and lipid tetrad index have the specificity of 100% with 100% positive predictive value.

However, the negative predictive value of lipid tetrad index was higher than that of both Lp-a and total cholesterol. Thus we can conclude from our study that patients with premature CAD in the north Indian state of Rajasthan have an atherogenic lipid profile in the form of increased total cholesterol, triglycerides, and LDL cholesterol along with a decrease in HDL cholesterol. The values of lipid parameters and Lp-a in these subjects appear to be different from their southern counterparts and western populations. These differences may be attributed to dissimilar dietary habits in this region in the form of consumption of less amount of saturated fat and higher level of physical activity of the population of this hilly region. In addition, these patients have an increase in Lp-a levels along with a higher lipid tetrad index. Lipid tetrad index due to its higher sensitivity, specificity, positive and negative predictive value emerged as a novel predictor of premature CAD in north Indian subjects as compared to other conventional factors and lipid subsets.

SUMMARY

In our study, 120 cases and controls were included. Age and sex were matched between cases and control groups, and there was no significant difference between two groups. 65 percent were males, and 35% were females in both control and study groups. The mean HDL (36.48 vs 40.32) is lower in study group compared to control group which is significant. The mean plasma Lp(a) is greater in study group compared to the control group (37.70 vs 24.13 mg/dl). LTI values in study group are greater compared to control group for their respective age distribution and are statistically significant (24423.60 vs 11807.43). There is a highly significant positive correlation between the LTI and Lp(a) levels. There is a negative correlation between LTI and the HDL which is statistically significant. The mean plasma TC, TGL, LDL are greater in study group compared to the control group. Thus, the effect of various lipid parameters as well as Lp-a on the atherogenicity is not additive but multiplicative which is well demonstrated by the lipid tetrad index.

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