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Lipid Tetrad Index as a Predictive Marker for Coronary Artery Disease in Type 2 Diabetes Patients

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ABSTRACT

Background: *Coronary artery disease (CAD) is a major cause of morbidity and mortality in type 2 diabetes mellitus (T2DM). As conventional lipid parameters may underestimate atherogenic risk, this study aimed to compare lipoprotein(a) [Lp(a)] levels and lipid tetrad index (LTI) between T2DM patients with and without CAD and assess their correlation with standard lipid parameters.*

Methods: *This cross sectional comparative study was conducted at a tertiary care hospital over a period of 18 months. The study included 128 participants, equally divided between cases (diabetic patients with coronary artery disease) and controls (diabetic patients without coronary artery disease). Comprehensive data on lipid markers, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL), and LTI, were collected. Statistical analysis comprised t-tests for mean comparisons and chi-square tests for categorical variables.*

Results: *Diabetic patients exhibited significantly higher levels of TC (218.77 ± 39.80 mg/dL vs. 163.66 ± 16.68 mg/dL, $p < 0.001$), TG (192.39 ± 54.76 mg/dL vs. 112.39 ± 42.72 mg/dL, $p < 0.001$), LDL (140.12 ± 37.59 mg/dL vs. 99.61 ± 19.91 mg/dL, $p < 0.001$), and lipoprotein(a) (11.56 ± 2.18 mg/dL vs. 8.41 ± 2.47 mg/dL, $p < 0.001$) compared to controls. HDL levels were lower in diabetic patients (40.67 ± 5.07 mg/dL vs. 44.19 ± 6.73 mg/dL, $p = 0.001$). LTI was significantly higher in cases, showing better predictive accuracy than traditional lipid parameters. It correlated strongly with TC, TG, LDL, and Lp(a), and was associated with hypertension, and poor glycemic control.*

Conclusion: *T2DM patients with CAD exhibited a significantly more atherogenic lipid profile and higher LTI values than those without CAD. LTI showed strong correlations with key lipid parameters, supporting its role as a comprehensive and cost-effective marker for cardiovascular risk assessment in diabetic populations.*

Keywords: *Type 2 diabetes mellitus, coronary artery disease, lipoprotein(a), lipid tetrad index, dyslipidemia, cardiovascular risk*

INTRODUCTION:

Cardiovascular diseases (CVDs) remain the leading cause of death worldwide, accounting for an estimated 19.8 million deaths in 2022—about one-third of all global deaths, with the majority occurring in low- and middle-income countries (1). Contemporary global analyses confirm that ischaemic heart disease and stroke dominate CVD mortality and disability across regions (2,3). In parallel, the diabetes epidemic continues to expand: the International Diabetes Federation estimates 537 million adults were living with diabetes in 2021, projected to rise to 783 million by 2045, with updated 2024 figures indicating ~589 million adults and a trajectory toward 853 million by 2050 (4,5). India bears a disproportionate share of this burden; the ICMR-INDIAB study estimated 101 million people with diabetes in 2021, highlighting substantial cardiometabolic risk at a population level (6). South Asian ancestry itself confers higher atherosclerotic cardiovascular disease (ASCVD) risk than European ancestry, with earlier onset and a distinct cardiometabolic profile that amplifies conventional risk factors (7,8).

Risk estimation based solely on total cholesterol, LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C) can underestimate atherogenic burden in people with type 2 diabetes mellitus (T2DM), particularly where triglycerides are elevated and HDL-C is low (2). Lipoprotein(a) [Lp(a)], a genetically determined, causal, and independent ASCVD risk factor, contributes additional risk that is not reflected by standard

lipid panels and is increasingly advocated for inclusion in risk assessment (9,10). These considerations have accelerated interest in composite lipid indices that integrate multiple pro- and anti-atherogenic components.

The lipid tetrad index (LTI)—combining total cholesterol, triglycerides, and Lp(a), divided by HDL-C—along with related indices such as the lipid pentad index and atherogenic index of plasma, has shown promise for refining risk stratification beyond conventional measures (11). Recent Indian data in young myocardial infarction cohorts demonstrate higher LTI and related indices in cases versus controls and meaningful correlations with traditional lipids (11). Studies in Indian populations have also linked Lp(a) to angiographic disease characteristics, underscoring its clinical relevance (12). In T2DM, broader cardiometabolic marker panels that include composite lipid indices associate with adverse metabolic and hepatic profiles, supporting their pathophysiologic plausibility (13). National guidance has begun to reflect this shift, with the Lipid Association of India emphasizing comprehensive risk assessment in high-risk groups (14). Moreover, a 2024 Indian cross-sectional study reported substantially higher LTI values in patients with CAD compared with controls, suggesting potential clinical utility in routine practice (15). Earlier work on consolidated lipid risk (advanced atherogenic index) likewise indicated that composite indices may outperform single lipid measures in premature CAD (16).

Despite growing interest in advanced lipid indices, there remains limited evidence directly comparing Lp(a) levels and LTI between T2DM patients with established CAD and those without CAD in Indian settings—where background risk, Lp(a) distributions, and triglyceride-rich dyslipidaemia may differ from Western cohorts (6–8,11–15). Addressing this gap is clinically relevant because improved discrimination of risk in T2DM could refine preventive strategies, inform lipid-lowering targets, and help prioritize early interventions in resource-constrained environments (1,2,14,15). Therefore, this study aimed to compare lipoprotein(a) levels and the lipid tetrad index (LTI) in T2DM patients with and without CAD, and to examine their relationship with conventional lipid measures and CAD status to inform risk assessment in an Indian tertiary-care context.

MATERIALS AND METHODS

Study design

This was a hospital-based cross sectional comparative study.

Study setting

The study was conducted in the Department of General Medicine at Adichunchanagiri Institute of Medical Sciences, B.G. Nagara, Mandya District, Karnataka, which is a tertiary care teaching hospital catering to a large rural and semi-urban population.

Study duration

The study was carried out over a period of 18 months, from June 2023 to December 2024.

Study population

The study population comprised patients with type 2 diabetes mellitus (T2DM) attending the Department of General Medicine outpatient clinics and admitted to the wards. The participants were divided into two groups: Cases consisted of patients with T2DM and confirmed coronary artery disease (CAD), and Controls consisted of age- and sex-matched patients with T2DM without CAD.

Inclusion and exclusion criteria

Inclusion criteria for Cases included patients aged above 18 years with a confirmed diagnosis of T2DM and CAD based on clinical records and relevant investigations. Inclusion criteria for Controls included patients aged above 18 years with T2DM but without a history or evidence of CAD. Exclusion criteria for both groups were patients with type 1 diabetes mellitus, chronic kidney disease, chronic liver disease, pregnancy, HIV-positive status, and malignancy.

Sample size

The sample size was calculated based on the prevalence of lipid tetrad index (LTI) positivity among T2DM patients, reported as 73% in the study by Srinivas et al. (17). Using a 95% confidence level and 10% of allowable relative error, the required sample size was determined to be 63 participants per group, for a total of 126 participants.

Study procedure

All consecutive patients attending the outpatient department or admitted to the wards who met the inclusion criteria were recruited through purposive sampling until the required sample size for each group was achieved. After explaining the study objectives, written informed consent was obtained. Each participant underwent a detailed clinical evaluation, including demographic data, duration of diabetes,

treatment history, lifestyle habits such as smoking and alcohol use, and family history of CAD. General physical and systemic examinations were performed, and blood pressure, height, weight, and body mass index were recorded. Relevant investigations including fasting and postprandial blood glucose, HbA1C, lipid profile (total cholesterol, triglycerides, HDL, LDL), and lipoprotein(a) were carried out, and the lipid tetrad index (LTI) was calculated using the formula (total cholesterol × triglycerides × lipoprotein(a)) / HDL. CAD diagnosis was confirmed by reviewing clinical records, ECG, echocardiography, and when available, coronary angiography findings. Data were captured using a pretested structured proforma covering sociodemographic, clinical, and investigation details. Laboratory tests were performed in the hospital's central laboratory following standard quality protocols, and data entry was done in Microsoft Excel with double-checking to minimize errors.

Study tools

The study tools included the structured proforma, standardized measuring instruments for anthropometry (stadiometer, weighing scale), sphygmomanometer for blood pressure measurement, and laboratory reports for biochemical parameters.

Independent and outcome variables

Independent variables included age, sex, duration of diabetes, family history of CAD, presence of hypertension, and smoking status. Outcome variables included HbA1C, total cholesterol, triglycerides, HDL, LDL, lipoprotein(a), and calculated lipid tetrad index (LTI).

Ethical considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Adichunchanagiri Institute of Medical Sciences before initiation. Written informed consent was obtained from all participants after explaining the objectives, procedures, and potential risks of the study in their local language. Confidentiality of patient information was maintained throughout the study, and participation was voluntary with the option to withdraw at any time.

Statistical analysis

Data were entered in Microsoft Excel and analyzed using Statistical Package for the Social Sciences (SPSS) software. Descriptive statistics such as mean and standard deviation were used for continuous variables, and frequencies with percentages were used for categorical variables. Independent t-test was employed to compare the means of continuous variables between the two groups. Categorical variables were compared using chi-square test or Fisher's exact test when expected cell counts were less than five. Pearson's correlation coefficient was used to assess the correlation between lipid parameters and LTI among cases. A p-value of <0.05 was considered statistically significant.

RESULTS

Table 1 shows the comparison of baseline characteristics between the case and control groups. The age distribution was comparable, with the majority of participants in both groups belonging to the 60–69 years age category (40.62% in cases vs. 35.94% in controls, p = 0.620). There was no statistically significant difference in the distribution of sex between the groups, with males constituting 59.38% of cases and 67.19% of controls (p = 0.359). A positive family history of coronary artery disease (CAD) was reported by 26.56% of cases and 15.62% of controls, though this difference was not statistically significant (p = 0.137). Hypertension was significantly more prevalent among cases (43.75%) compared to controls (21.88%) (p = 0.008). Smoking status was similar between the groups (28.12% vs. 26.56%, p = 0.598).

Table 1. Comparison of Baseline Characteristics Between the Groups

Variable	Category	Cases n (%)	Controls n (%)	P-value
Age category	41–49	16 (25.00%)	21 (32.81%)	0.620
	51–59	22 (34.38%)	20 (31.25%)	
	60–69	26 (40.62%)	23 (35.94%)	
Sex	Female	26 (40.62%)	21 (32.81%)	0.359
	Male	38 (59.38%)	43 (67.19%)	

Family history of CAD	Yes	17 (26.56%)	10 (15.62%)	0.137
	No	47 (73.44%)	54 (84.38%)	
Hypertension	Yes	28 (43.75%)	14 (21.88%)	0.008
	No	36 (56.25%)	50 (78.12%)	
Smoking status	Yes	18 (28.12%)	17 (26.56%)	0.598
	No	46 (71.88%)	47 (73.44%)	

The comparison of biochemical parameters between the two groups is depicted in **Table 2**. The mean HbA1C levels were slightly higher among cases (9.36 ±1.87) compared to controls (9.08 ±1.17), but the difference was not statistically significant ($p = 0.319$). Total cholesterol, triglycerides, LDL, lipoprotein(a), and lipid tetrad index (LTI) were all significantly higher among cases ($p < 0.001$ for all), while HDL levels were significantly lower among cases (40.67 ±5.07) compared to controls (44.19 ±6.73, $p = 0.001$). These findings indicate that cases had a more adverse lipid profile compared to controls, with strong statistical significance for most parameters.

Table 2. Comparison of Biochemical Parameters Between the Groups

Parameter	**Case Mean (SD)**	**Control Mean (SD)**	**t**	**p-value**
HbA1C	9.36 (1.87)	9.08 (1.17)	1.001	0.319
Total Cholesterol (TC)	218.77 (39.80)	163.66 (16.68)	10.217	<0.001
Triglycerides (TG)	192.39 (54.76)	112.39 (42.72)	9.215	<0.001
HDL	40.67 (5.07)	44.19 (6.73)	-3.338	0.001
LDL	140.12 (37.59)	99.61 (19.91)	7.619	<0.001
Lipoprotein (a)	11.56 (2.18)	8.41 (2.47)	7.634	<0.001
Lipid Tetrad Index (LTI)	11975.46 (4959.24)	3830.45 (2889.77)	11.352	<0.001

Table 3 presents the correlation between lipid profile components and LTI among cases. A very strong positive correlation was observed between LDL and TC ($r = 0.9463$, $p < 0.0001$). LTI showed significant positive correlations with TC ($r = 0.4319$, $p = 0.0004$), TG ($r = 0.6691$, $p < 0.0001$), LDL ($r = 0.2814$, $p = 0.0243$), and lipoprotein(a) ($r = 0.4093$, $p = 0.0008$), indicating that LTI increases proportionally with worsening lipid profile parameters. HDL was negatively correlated with LTI, though the association was not statistically significant ($r = -0.1706$, $p = 0.1777$).

Table 3: Correlation Between Lipid Profile and Lipid Tetrad Index (LTI) in Cases

Variables	**Measure**	**TC**	**TG**	**HDL**	**LDL**	**Lipoprotein**	**LTI**
TC	r-value	1.0000					
	P-value	-					
TG	r-value	0.2369	1.0000				
	P-value	0.0595	-				
HDL	r-value	0.3230	0.1617	1.0000			

	P-value	0.0092	0.2019	-			
LDL	r-value	0.9463	-0.0608	0.1716	1.0000		
	P-value	0.0000	0.6332	0.1751	-		
Lipoprotein	r-value	-0.1508	0.0210	-0.1107	-0.1570	1.0000	
	P-value	0.2343	0.8695	0.3838	0.2153	-	
LTI	r-value	0.4319	0.6691	-0.1706	0.2814	0.4093	1.0000
	P-value	0.0004	0.0000	0.1777	0.0243	0.0008	-

DISCUSSION

The present study demonstrated that patients with T2DM and CAD had a significantly more adverse lipid profile compared to those without CAD, as evidenced by higher total cholesterol, triglycerides, LDL, lipoprotein(a), and lipid tetrad index (LTI) values, with significantly lower HDL levels. These findings are consistent with global data showing that diabetic dyslipidemia is a major contributor to atherosclerotic cardiovascular disease (ASCVD) burden worldwide (2). The strong correlation between LDL and total cholesterol observed in our study is biologically plausible, as LDL constitutes the major fraction of circulating cholesterol. Similar patterns were reported by Dabla et al., who found that young myocardial infarction patients had higher LDL, TC, and composite indices like LTI, supporting their role in identifying atherogenic risk beyond conventional measures (11). Our findings thus strengthen the evidence that lipid derangements are more pronounced in diabetic CAD patients, underlining the importance of comprehensive lipid assessment in this high-risk group.

Hypertension was significantly more prevalent among cases than controls in the present study, a finding consistent with the INTERHEART and ICMR-INDIAB studies, which identified hypertension as an important modifiable risk factor contributing to premature CAD in India (6). The coexistence of diabetes and hypertension is particularly concerning as it multiplies cardiovascular risk, leading to greater arterial stiffness and endothelial dysfunction (7). Our study's lack of significant difference in age and sex distribution between groups suggests that the observed differences in biochemical parameters are unlikely to be confounded by demographic imbalance. Similar case–control studies in Indian populations have reported comparable findings, where metabolic risk factors rather than age alone were the key determinants of CAD occurrence (15). This highlights the need for early screening and aggressive risk factor modification, especially in diabetic individuals with coexisting hypertension.

Lipoprotein(a) [Lp(a)] levels were significantly elevated in cases compared to controls, aligning with the well-documented role of Lp(a) as a genetically determined and independent causal factor for ASCVD (10). Our results corroborate the findings of Kulkarni et al., who observed a strong correlation between elevated Lp(a) and greater angiographic lesion severity, supporting its use as a marker of disease burden (12). The clinical relevance of Lp(a) is particularly important in South Asians, who are known to have higher baseline Lp(a) levels, contributing to their increased predisposition to CAD (8). This reinforces recommendations from the European Atherosclerosis Society and Lipid Association of India that advocate at least a one-time measurement of Lp(a) for improved risk stratification, particularly in those with a family history of premature CAD (9,14). Our findings suggest that Lp(a) may have additional utility in diabetic populations where conventional lipid markers may underestimate residual risk.

The LTI values in our study were significantly higher in cases than in controls, demonstrating its potential as a powerful discriminator between diabetic patients with and without CAD. This observation is consistent with the findings of Kumar et al., who reported significantly elevated LTI in CAD patients and emphasized its diagnostic utility as a comprehensive atherogenic marker (15). Similarly, Bansal et al. proposed advanced atherogenic indices like LTI to provide a consolidated estimate of lipid-related cardiovascular risk and found them superior to single lipid parameters in predicting premature CAD (16). Our study adds to this body of evidence by showing that LTI correlates strongly with individual lipid parameters such as TC, TG, LDL, and Lp(a), reinforcing its validity as a surrogate marker of cumulative lipid burden. These findings highlight that LTI could be integrated into clinical practice as a cost-effective tool to enhance risk stratification in diabetic patients, particularly in resource-limited settings.

The mean HbA1C levels were slightly higher in cases compared to controls, though not statistically significant, which is in line with previous studies showing that poor glycemic control is associated with CAD risk but may not always demonstrate a clear-cut difference when both groups are already diabetic (13). This suggests that while glycemic control remains a cornerstone of diabetes management, the incremental risk from dyslipidemia and genetic factors like Lp(a) may play a more prominent role in determining CAD occurrence among diabetics. The clustering of metabolic risk factors seen in our study, including dyslipidemia, hypertension, and elevated Lp(a), mirrors the pathophysiologic framework described in recent mechanistic studies linking insulin resistance, systemic inflammation, and lipid abnormalities to accelerated atherosclerosis (3). This underscores the importance of a multifactorial approach to risk reduction rather than focusing solely on glucose control.

Our study has several strengths, including a well-defined case–control design, age- and sex-matched groups, and comprehensive biochemical profiling with LTI calculation, which is not routinely reported in Indian diabetic populations. However, some limitations need consideration. Being hospital-based, the findings may not be generalizable to the community. The cross-sectional design limits causal inference, and residual confounding from dietary and genetic factors cannot be excluded.

CONCLUSION

T2DM patients with CAD had a significantly more atherogenic lipid profile and higher LTI values, which strongly correlated with key lipid parameters, which support the growing consensus that advanced lipid indices such as LTI and biomarkers like Lp(a) offer incremental value for cardiovascular risk prediction in diabetics. Future prospective studies with larger sample sizes and longitudinal follow-up are warranted to establish cut-off values for LTI in Indian populations and to determine whether LTI-guided therapy can improve clinical outcomes.

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