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Association of Low-Density Lipoprotein-Cholesterol and Its Small, Dense Phenotype with Six-Month Cardiovascular Morbidity

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Abstract

Background: Globally, cardiovascular diseases (CVDs) are the leading cause of death and disability. Elevated low-density lipoprotein-cholesterol (LDL-C) and more specifically, elevation of its small, dense phenotype (sdLDL-C) has been regarded as the key modifiable risk factors associated with atherogenesis. This study aimed to determine the association of LDL-C and sdLDL-C with the development of CVDs in the next six months to establish their predictive efficacy.

Methods: A batch of 162 anonymized serum samples sent for analysis of lipid profile parameters, were classified into tests and controls based on the calculated LDL-C values obtained by Fried Ewald formula. Direct LDL-C was also estimated automatically using assay kits. Using the formula provided by Srisawasdi et al., sdLDL-C was then computed for all samples. Six months later, samples were deanonymized, and the lipid profiles were compared with cardiovascular outcomes of these patients, to determine which parameter had the greatest correlation.

Results: Four control group patients and three test group patients developed the outcome (any cardiovascular event) during the 6-month follow-up period. Binary logistic regression analysis showed that none of the lipid profile parameters: calculated LDL-C (OR= 0.99; 95% CI= 0.97-1.01; p= 0.826), direct LDL-C (OR= 0.99; 95% CI= 0.97-1.01; p= 0.818) or sdLDL-C (OR= 0.99; 95% CI= 0.93-1.04; p= 0.734), were significantly associated with the occurrence of outcome. The median % sdLDL-C both with respect to direct and calculated LDL-C was slightly higher in patients with the outcome.

Conclusions: The levels of LDL-C or its individual phenotypes may not be used singly as indicator of cardiovascular morbidity in the next six months.

Keywords: Biomarkers, Cardiovascular diseases, Cholesterol, LDL, Lipoprotein, Myocardial infarction.

Introduction

The prevalence of cardiovascular pathology is increasing rapidly in developing nations, where it has become the leading cause of death and disability. Cardiovascular diseases (CVDs) affect virtually every age group in society (1). Due to rapid changes in lifestyle brought about by economic development, the rate of heart diseases in India has doubled in rural areas and tripled in urban areas. One of the biggest advances in medicine has been the identification of major risk factors associated with CVDs (2). Dyslipidemia has been identified as an important modifiable risk factors for CVDs. Increased triglycerides (TG), very low-density lipoprotein cholesterol (VLDL- C), low- density lipoprotein

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cholesterol (LDL-C), and reduced high-density lipoprotein cholesterol (HDL-C), are the atherogenic lipid profile indices. Dyslipidemia is associated with elevated plasma LDL-C levels and lowering LDL-C levels has been shown to reduce the risk of heart disease. Hence, patients with elevated LDL-C are prescribed pharmacological agents that reduce LDL-C, such as statins, which have severe adverse effects, such as musculotoxicity, gastrointestinal distress, hepatotoxicity, as well as other medication interactions (3).

Seven subspecies of LDL-C has been identified based on their metabolic behavior and pathological significance (4). Austin et al, have identified two distinct phenotypes of LDL-C particles which are a large and buoyant type called pattern A, lbLDL-C (> 25.5 nm), and a small and dense type called pattern B, sdLDL-C (≤ 25.5 nm) (5).

According to National Cholesterol Education Program Adult Treatment Panel III, sdLDL-C is an emerging risk factor for CVDs (6). sdLDL-C has strongly predicted the rate of coronary heart disease independent of LDL-C in the 13 year follow up Quebec Cardiovascular Study (7). When LDL-C characteristics were investigated by polyacrylamide gel electrophoresis, the strongest association of risk of CVDs was found to be with sdLDL-C (8). The Epic Norfolk Study showed that sdLDL-C is associated with reduction in survival rates in the instance of a CVD (9). Rizzo et al, observed that in metabolic syndrome, sdLDL-C is better than the LDL-C, as a valuable marker for the risk of coronary artery disease (10). It was demonstrated to be an independent risk factor for CVDs even with the use of multivariate logistic and survival models (11).

Determination of LDL-C can be done in two ways namely, (a) arithmetic calculation (cLDL-C) based on total cholesterol (TC) using the Friedewald formula, cLDL-C (mg/dL)= TC – (HDL-C) – (TG/5) and (b) direct estimation (dLDL-C) by using specially designed assays (12,13). On the other hand, various means have been adopted for the assessment of sdLDL-C, which includes gradient gel electrophoresis, tube gel electrophoresis, density gradient ultracentrifugation, and nuclear magnetic resonance (14). These methods are not only exorbitant, arduous, time-demanding, but also technically challenging to be used routinely in clinical practice or for screening a large population. A novel method for the measurement of sdLDL-C has been devised via a simple homogeneous enzymatic assay independent of LDL-C (15). Though this method is simple to perform and could be effectively used for regular clinical practice, the reagent cost being heavily expensive hinders its general as well as screening application.

Srisawasdi et al, developed cost-effective method for estimation of sdLDL-C concentration based on classic lipid profile indices. This linear regression equation did not significantly vary across different subgroups based on sex, age group, chronic kidney disease stages, and fasting plasma glucose categories and it was suggested to consider using the calculated sdLDL-C in serum samples as a means of assessing CVD risk worldwide in clinical practice (16, 17).

This study was primarily undertaken to determine and validate any actual association of LDL-C or its phenotype – sdLDL-C, with the occurrence of cardiovascular diseases within six months, in order for them to be utilized as surrogate markers for prediction and prevention of future cardiovascular events.

Materials and Methods

Study Design, Setting and Population

Over a period of six months, this prospective cohort study was conducted at Kasturba Medical College, Manipal, in the Department of Biochemistry. The Institutional Ethics Committee approved the study prior to its commencement (IEC No: 567/2016), and the study followed the principles of the Declaration of Helsinki. For the study, 81 samples of normal and high LDL-C were required in order to estimate the sensitivity of sdLDL-C at 80% with 5% precision and 95%

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confidence level. Hence, leftover samples from 162 subjects with fasting lipid profiles were used (17).

Data Collection

The lipid profile data obtained from the laboratory of all the 162 samples include: Total Cholesterol (TC, in mg/dL), Triglyceride (TG, in mg/dL), High Density Lipoprotein-Cholesterol (HDL-C, in mg/dL) and calculated Low Density Lipoprotein-Cholesterol (cLDL-C, in mg/dL, calculated using Friedewald formula) (12). Based on the lipid profile values, 81 samples, each containing optimal levels of all the lipid profile parameters, and 81 samples containing greater than optimal levels of cLDL-C, ≥ 130 mg/dL, irrespective of the values of other lipid profile parameters, were classified into two groups, and identified as: Group 1 (Control) - contains 81 normal samples (i.e., subjects who are not at risk from CVDs in the immediate future), and Group 2 (Test) - contains 81 test samples (that is, subjects who maybe at high risk of CVD).

Optimal is defined as: TC: 150-200 mg/dL, TG: 70-150 mg/dL, HDL: 40-60 mg/dL, and cLDL: < 100 mg/dL. This study assumed that subjects with cLDL-C≥ 130 mg/dL, are at risk for developing CVD (18). A total of 162 anonymized samples were subsequently processed to estimate direct-LDL cholesterol (dLDL cholesterol, in mg/dL), using LCL cholesterol plus 2nd generation kits obtained by Roche and Hitachi Cobas 501.

We then calculated the sdLDL-C cholesterol levels for all samples using the formula provided by Srisawasdi, et al.: sdLDL-C (in mg/dL) = (non-HDL-C) + (direct LDL-C) – (calculated LDL-C) - 12.05. The non-HDL-C here is (TC-HDL-C) (16). In addition, the % sdLDL-C, both compared to cLDL-C and dLDL-C, was also calculated in all samples. The sdLDL-C value is considered normal if it is less than 30% of LDL-C.

Six months after the laboratory analysis of all samples, they were deanonymized and cross-checked for their clinical outcomes with the medical records obtained from Kasturba Hospital's Medical Records Department. They were checked for any cardiovascular events that may have occurred during the 6-month period, any form of atherosclerotic or ischemic heart disease. The socio-demographic details, associated comorbidities, and personal histories for all the participants could not be obtained due to unavailability, so was not studied.

Statistical anlaysis

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 16 (SPSS, South Asia, Bangalore). Continuous variables have been described with medians and interquartile ranges. At less than 0.05 p-value, statistical significance was set in all tests. Mann-Whitney U test was used to compare means of continuous variables between the groups. Univariable logistic regression analysis was also performed using the occurrence of cardiovascular morbidity as the outcome variable and different lipid profile parameters as independent variables.

Results

Serum samples from 162 consecutive patients, 81 each fulfilling the eligibility criteria for control and test groups, were considered for the final analysis. These included 91 male and 71 female subjects, aged between 25 to 87 years. Table 1 shows the median and interquartile range of lipid profile parameters for both groups, Control and Test. A Mann-Whitney U test was used to compare the two groups. Based on the results and 95% confidence level, we have expressed the resistance rate as a percentage. There is a clear statistical difference between these two groups with respect to all lipid profile parameters. There was also a statistically significant association ($r= 0.985$, $p< 0.001$) observed between cLDL-C and dLDL-C values.

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Table 1. Median and interquartile range of lipid profile indices in both control and test groups.

Reference Parameters	Group 1 (Control) (n= 81) Median (Q1, Q3)	Group 2 (Test) (n= 81) Median (Q1, Q3)	p-Value
Total Cholesterol (TC, in mg/dL)	146 (124.5, 161)	237.00 (214.50, 268.50)	0.000*
Triglycerides (TG, in mg/dL)	108 (82, 148.5)	127.00 (99.50, 180.50)	0.030*
High-Density Lipoprotein-Cholesterol (HDL-C, in mg/dL)	44 (31.50, 51)	46.00 (39.50, 54.50)	0.005*
Calculated Low-Density Lipoprotein-Cholesterol (cLDL-C, in mg/dL)	74 (59.5, 89.5)	154.00 (142.50, 184.50)	0.000*
Direct Low-Density Lipoprotein-Cholesterol (dLDL-C, in mg/dL)	74 (57.5, 91)	157 (147, 187.5)	0.000*
Small, Dense Low-Density Lipoprotein-Cholesterol (sdLDL-C, in mg/dL)	21.63 (16.23, 29.30)	46.867 (39.995, 58.90)	0.000*

*p-values are obtained using Mann-Whitney U tests to compare groups.

After a six-month period, the review of all the participant's medical records revealed that 4 participants from Group 1 (Control) and 3 participants from Group 2 (Test) had developed the outcome in the form of a cardiovascular event. Table 2 summarizes the descriptive statistics of selective lipid profile parameters, with comparisons using Mann-Whitney U test, between these two populations based on the outcome of interest, where *(a)* - participants with no cardiovascular events in 6-months (n= 155), and *(b)* - with cardiovascular events in 6-months (n= 7).

Table 2. Median and interquartile range of lipid profile indices in Groups **(a)** and **(b)**, based on outcome of interest.

Reference Parameters	Group (a) (n= 155) Median (Q1, Q3)	Group (b) (n= 7) Median (Q1, Q3)	p-Value
Calculated Low-Density Lipoprotein-Cholesterol (cLDL-C, in mg/dL)	131 (86,152)	90 (81, 142)	0.468
Direct Low-Density Lipoprotein-Cholesterol (dLDL-C, in mg/dL)	119 (92, 155)	100 (91,150)	0.615
Small, Dense Low-Density Lipoprotein-Cholesterol (sdLDL-C, in mg/dL)	34.97 (24.84, 45.33)	28.29 (26.11, 37.52)	0.642
% sdLDL-C with respect to cLDL-C, (sdLDL-C/cLDL-C) *100	29.12 (26.4, 32.95)	30.63 (28.43, 32.9)	0.720
% sdLDL-C with respect to dLDL-C (sdLDL-C/dLDL-C) *100	27.74 (25.58, 31.18)	29.73 (27.2, 30.89)	0.683

*p-values are obtained using Mann-Whitney U tests to compare groups.

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The group (a) had higher median cLDL-C, dLDL-C and sdLDL-C values compared to group (b). The group (b) had slightly higher median % sdLDL-C with respect to cLDL-C values as well as % sdLDL-C with respect to dLDL-C values compared to group (a), as opposed to the previous parameters, which could be inferred to be better predictors of the outcome, however this difference is not statistically significant (p> 0.05). As none of the lipid profile indices showed any significant statistical difference (p> 0.05), box plots were charted, to study the variability of parameters assessed between groups (a) and (b) (Fig. 1).

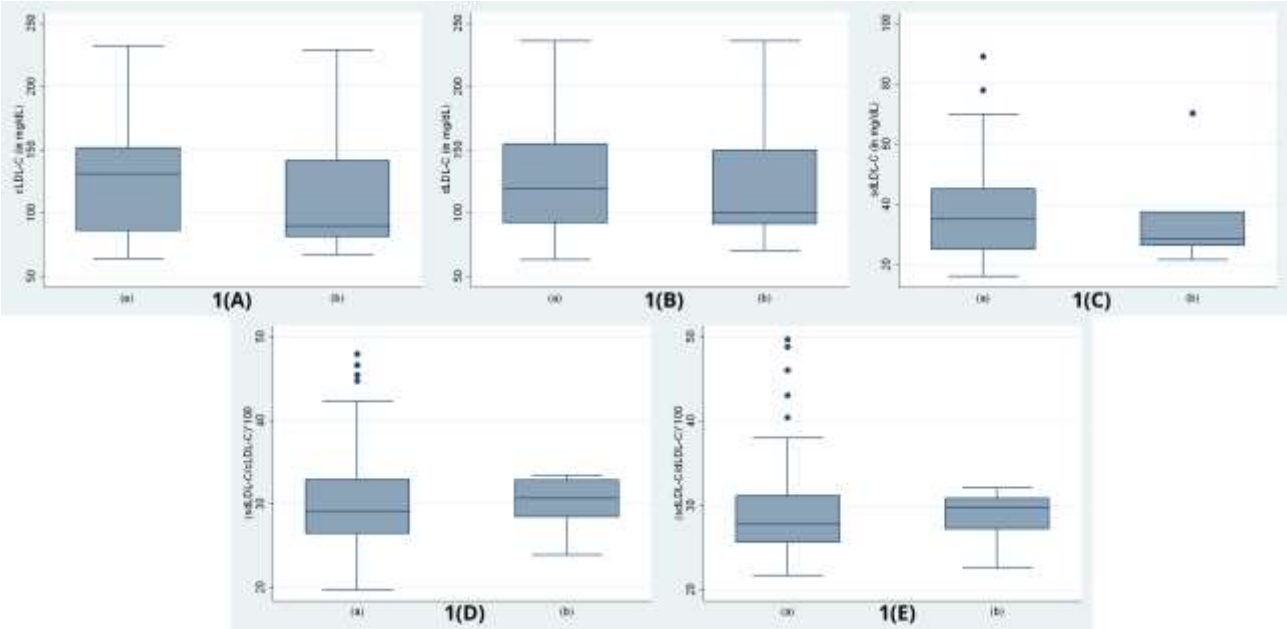

Fig. 1. Box and Whisker plots showing the comparison and median differences in calculated LDL-C (1A), direct LDL-C (1B), calculated sdLDL-C (1C), % sdLDL-C w.r.t. cLDL-C (1D), and % sdLDL-C w.r.t. dLDL-C (1E), amongst group (a) (n= 155), and group b (n= 7).

Binomial logistic regression analysis was performed using the different lipid profile parameters as independent variables and occurrence of a cardiovascular event during the 6-month follow-up period as the outcome variable. Table 3 represents the univariate analysis using logistic regression along with odds ratios and 95% confidence intervals. Multivariable analysis was not conducted due to lack of access to data for confounding variables (Table 3).

Table 3. Univariable logistic regression analysis for 6-month cardiovascular morbidity**.**

Reference Parameters	Odds Ratio	95% Confidence Interval	p-Value
TC	0.99	0.97 – 1.01	0.659
TG	0.99	0.98 – 1.01	0.822
HDL-C	0.96	0.88 – 1.04	0.387
cLDL-C	0.99	0.97 – 1.01	0.826
dLDL-C	0.99	0.81 – 0.97	0.818
sdLDL-C	0.99	0.93 – 1.04	0.734
(sdLDL-C/cLDL-C) *100	0.99	0.85 – 1.15	0.933
(sdLDL-C/dLDL-C) *100	0.99	0.84 – 1.17	0.939

*p-values are obtained using Univariable logistic regression analysis.

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Discussion

According to the literature review, previous studies indicate that high levels of LDL-C are associated with atherogenesis (8, 19). In contrast, neither the population with elevated cLDL-C nor the population with elevated dLDL-C developed CVDs in the 6-month follow-up period during our study. Based on these findings, neither calculated or laboratory estimated LDL-C could singly serve as potential markers or risk factors for CVDs in the immediate future.

A study conducted had previously shown that nearly 75% of patients hospitalized for a heart attack had cholesterol levels that were not indicative of high risk of CVD based on current national cholesterol guidelines (20). Patil RS et al also failed to demonstrate that LDL-C was a major primary lipid parameter associated with the severity or occurrence of CVDs in their study on premature CVDs in the Indian population (21). Our study concurs with the findings in the above published studies.

Recent studies suggest that elevated levels of sdLDL-C can predict the risk of incident CVDs, even in individuals considered to be at low risk for CVDs based on their LDL-C levels (22). Studies from University of Zurich showed the pathological significance of sdLDL-C in development of atherosclerosis (23). The present study, on the other hand, failed to find any such association. Despite having similar LDL-C levels, Goel PK et al observed higher sdLDL-C levels in Indian patients with established CVD when compared to individuals without established CVDs (24). However, even the calculated sdLDL-C failed to show any significant difference in our study, whereas the percentage of sdLDL-C showed higher predictive values, as indicated by the box plots.

Our study did not find a significant difference between calculated and directly estimated LDL-C as the correlation coefficient, $r= 0.985$ ($p< 0.001$), unlike the study conducted by Kannan et al on Indian population (25). In most healthcare institutions and laboratories, especially in low-middle-income countries, only cLDL-C is obtained if a clinician wishes to treat a patient with cholesterol-lowering drugs such as statins, during assessment of risk for atherosclerotic cardiovascular diseases (26, 27). There is, however, scope for large-scale studies to delineate the association between calculated and estimated LDL-C within the Indian population (28).

Indian healthcare providers rely on guidelines and normative data provided for the western population, to assess and manage the patient population in India, despite there being a staggering difference in the genetic makeup of both (29). Keeping this in mind, it is also beneficial to have normative laboratory data for our own population, based on large-scale studies carried out on Indians that would aid in appropriate mode of management for different diseases.

The authors would like to highlight that the follow-up duration of this study was only 6-month period. We used only calculated sdLDL-C in our study to make conclusions, due to lack of availability of funding for carrying out laboratory-based sdLDL-C estimation. Also, larger sample size within the representative Indian population would be required to be implemented as confirmatory evidence, and this study could serve as a pilot for the same. Lack of participant's socio-demographic details, history of exposure to risk factors for CVDs, previous medical/treatment history and associated comorbidities could be taken into consideration to perform a multivariate regression analysis, and hence this study could be a basis on which other researchers can work upon at a larger scale.

It is concluded from this study that LDL-C levels alone or the levels of its individual phenotypes cannot be used as surrogate markers for predicting the occurrence of any cardiovascular event in the immediate future. Moreover, it also alerts a clinician not to rely solely on prescription of LDL-C lowering

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medications as measure to counterfeit CVDs, as various genetic, environmental, metabolic, and multifarious biochemical factors interplay in cardiovascular contingencies.

Developing validated scales for grading the likelihood of future CVD, based on combinations of various individual determinants, with rigorous validation of inclusive parameters used for arithmetic discernment. The clinician could use this as a guide to determining treatment and outcomes.

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