

Non-HDL-C: An alternate to LDL-C for the diagnosis of cardiovascular disease

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Abstract

Background: The present study aims to estimate non-HDL-C in coronary artery disease (CAD) patients.

Materials and Methods: One hundred and ten patients of CAD of either sex and 50 age and sex matched healthy controls were selected. Serum total cholesterol, triglycerides and HDL-C were estimated. LDL-C and non-HDL-C were calculated. A comparison of non-HDL-C and LDL-C was made in terms of area under receiver operating characteristic (ROC) curve.

Results & Conclusion: Area under receiver operating characteristic (ROC) curve was marginally higher for non-HDL-C than for LDL-C. Predictive value of non-HDL-C and LDL-C were compared in group A (subjects with serum triglycerides < 200 mg/dl) and group B (subjects with serum triglyceride >200mg/dl). Non-HDL-C showed statistically more significant difference in both the groups while non-significant results were found for calculated LDL-C. Thus, non-HDL-C yielded marginally better results than LDL-C. Being a calculated parameter, it incurs no additional cost and is more patient friendly, not requiring fasting sample. Non-HDL-C hence should be included in every routine lipid profile.

KeyWords: Atherosclerosis, Coronary Artery Disease, LDL-C, Non-HDL-C, Receiver Operating Characteristic Curve.

I. Introduction

Low density lipoprotein cholesterol (LDL-C) has been established as a predictive marker for the development and progression of coronary artery disease (CAD) ^{1,2}. Considerable educational efforts have been invested and directed towards medical community regarding LDL-C and strategies to lower it to reduce cardiovascular risk. Yet, a large pool of evidence suggests that a narrow focus on LDL-C assessment and treatment is a suboptimal strategy for patient care. Numerous patients were there who in spite of meeting their target "LDL-C" goal still develop complications from atherosclerotic vascular disease and suffer from cardiovascular events; thus bear the burden of having residual risk not identified by using traditional cardiovascular risk markers.

LDL concentration reflects merely the amount of cholesterol contained in LDL particles but fails to provide any information about their number and structure. In addition, LDL-C excludes the participation of other lipoprotein fractions such as Lp (a) and VLDL which also contribute to the development of atherosclerosis. LDL-C is usually calculated with Friedewald formula whereas this method has some limitations, predominantly in patients having hypertriglyceridemia. It was shown that LDL-C is estimated with nearly 17% and 25% error at respective serum triglyceride concentration (TG) of 151-200 mg/dl and 201-300 mg/dl ³.

Modern laboratory diagnosis of lipid disorders/ cardiovascular risk should be based on the use of indicators which reflect full impact of all plasma lipid components involved in the development of atherogenesis. Non-HDL-C measures the sum of cholesterol accumulated in all lipoproteins such as: chylomicrones, VLDL and their remnants, IDL, LDL and Lp(a) with the exception of HDL ⁴. Non-HDL-C is calculated as the difference between the total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), does not require a fasting specimen and reflect the sum of serum cholesterol carried by all the potentially atherogenic lipoproteins-LDL, VLDL, IDL, remnant lipoproteins and lipoprotein(a) ⁵.

Conspicuously, hardly any attention is being paid to the use of non-HDL-C but the latest Guidelines for both European and American Cardiological Societies emphasize the importance of this parameter for assessing the cardiovascular risk ⁶. Therefore the present study was carried out to estimate non-HDL-Cholesterol and to explore its feasibility as an alternate to LDL-C in CAD patients.

II. Methods

Subjects, from November 2010 to August 2013, a total of 110 patients (aged 20-60 years, mean age 41.01 ± 9.20) of coronary heart disease of either sex with a history of acute chest pain, non ST-segment elevation, unstable and stable angina, examined and treated at advanced cardiac centre, PGIMER, Chandigarh were enrolled in the present study. 50 age and sex matched healthy controls (mean age 33 ± 10.32 years) were randomly selected. Patients with diabetes mellitus, nephrotic syndrome, acute or chronic renal failure, thyroid disorders, acute infection or any other systemic illness and on lipid lowering drugs for the past 3 months were excluded from the present study. Regular tobacco, alcohol abusers and smokers were also excluded. The institutional Ethical Committee approved the study and informed consent was obtained from all the participants. The patient's demographic profile, socioeconomic status, behavioural risk factors (sedentary life style, dietary habits) and disease risk factor histories were recorded. Fasting venous blood samples were collected and analyzed by using enzymatic procedures with Johnson & Johnson's Vitros 250 auto analyzer for serum Total Cholesterol, Triglycerides, HDL and LDL-Cholesterol by direct assay. Non-HDL-C was calculated by subtracting HDL-C from total cholesterol.

Statistical Analysis: Results were presented as mean \pm standard deviation. The unpaired 't' test was used to compare the levels of the test and control group. A comparison of non-HDL-C and LDL-C was made in terms of receiver operating characteristic (ROC) curve. A ROC curve is a plot with the 1-specificity on the x-axis and sensitivity on the y-axis obtained for different cut off points. Areas under the curve (AUC) and their 95% confidence intervals (CI) were evaluated as a measure of diagnostic accuracy. Greater AUC of the ROC curve indicated better markers of the study. The area under the ROC curve is considered a global performance indicator for a prognostic factor ⁷. All p-values <0.05 were considered significant. All analyses were performed using the SPSS version 16.0.

III. Results

Among the 110 subjects participating in the study males constituted 67% of the total population compared with females constituting 33%. Among the demographic variables considered the test group showed significantly larger number of sedentary life style subjects and majority of whom were non vegetarians as compared to control group.

Blood lipids (Total Cholesterol, LDL-C, HDL-C, triglycerides) and non-HDL-C levels were measured for all subjects and the results of LDL-C and non-HDL-C are shown in *Figure 1* and *Figure 2* respectively. The levels were not affected by age, gender, diet or life style.

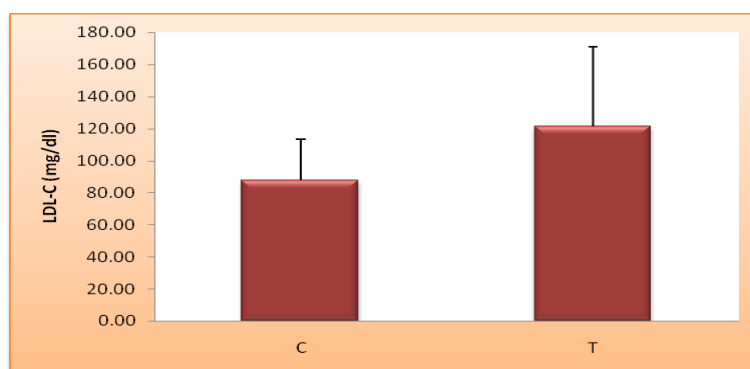


Figure 1: LDL-C levels in patient and control group

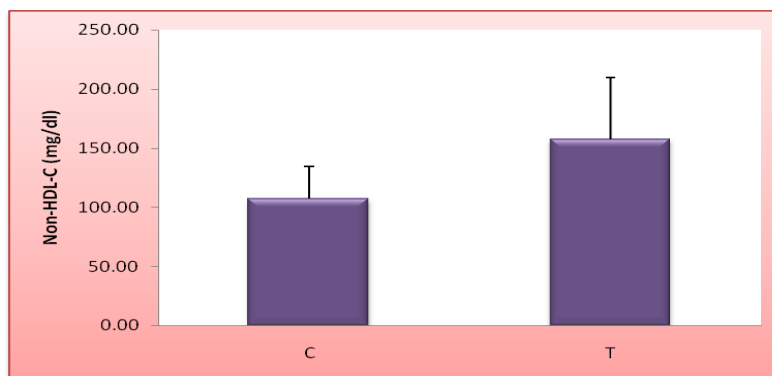


Figure 2: Non-HDL-C levels in patient and control group

To compare the predictive value of non-HDL-C and LDL-C ROC curve analysis was done and further if we compare the AUROC between the two then it was marginally higher for non-HDL-C (0.872) as compared to LDL-C (0.714) **Figure 3**.

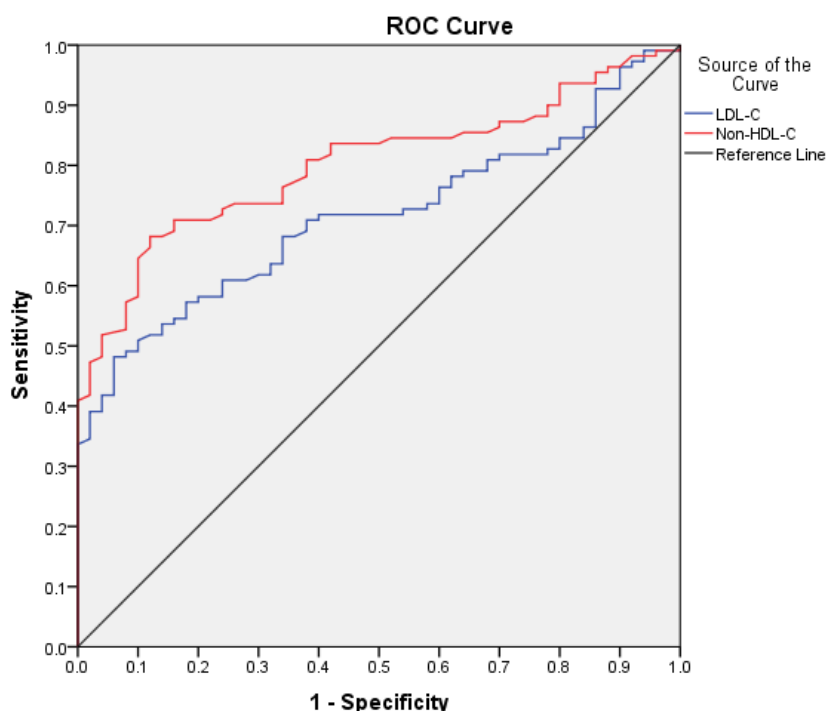


Figure 3: Receiver Operating Characteristic curve for LDL-C and Non-HDL-C in CAD patients. Area under the curve is marginally higher for Non-HDL-C (0.802) than for LDL-C (0.714).

Comparison of Non-HDL-C and calculated LDL-C in hypertriglyceridemic group A (serum triglyceride < 200mg/dl) and group B (serum triglyceride >200mg/dl)

To compare the predictive value of non-HDL-C and calculated LDL-Cholesterol in hypertriglyceridemia, test subjects were divided into 2 groups; group A (serum triglyceride < 200 mg/dl) and group B (serum triglyceride >200 mg/dl). Non-HDL-C showed statistically significant difference in both the groups, while non significant results were found for calculated LDL **Table 1**.

Table 1: Comparison of Calculated LDL and Non-HDL-C in group A (serum triglycerides <200 mg/dl) and group B (serum triglycerides > 200mg/dl)

Parameters	Groups	N	Mean	Std. Deviation	p-value
Calculated LDL (mg/dl)	A	67	119.67	50.21	0.685 NS
	B	43	123.65	49.77	
Non-HDL-C (mg/dl)	A	67	144.82	53.15	<0.001
	B	43	177.50	44.27	

IV. Discussion

So far LDL-C has been an important analyte to be measured for CAD risk assessment however, in recent years there is accumulating evidence to support that the predictive value of non-HDL-C is higher than LDL-C in cardiovascular risk assessment⁸⁻¹³. Recently¹⁶, the American Diabetes Association and the American Heart Association reached an agreement for lipid management according to which non-HDL-C is considered better than LDL-C; in addition it was also recommended that non-HDL-C levels are the primary goal for lipid lowering therapy in high-risk and dyslipidemic patients¹⁴. In the latest guideline of the American Heart Association/American College of Cardiology (AHA/ACC), the use of either LDL-C or non-HDL-C as a cholesterol target is advocated¹⁵. In the National Lipid Association (NLA) Annual Summary 2015, non-HDL-C is considered a co- primary lipid target, apart from LDL-C.

Non-HDL-C can be calculated from a routine lipid panel, which is available as quick and simple measurement in the majority of laboratories worldwide¹⁰. A major advantage for non-HDL-C is that it can be estimated in a non fasting state unlike LDL-C^{10, 17-18}. In addition, cut-off values of non-HDL-C can be easily converted from LDL-C levels by adding 30 mg/dl¹⁸. Incorporating this patient friendly parameter into clinical practice may improve cardiovascular risk prediction.

V. Limitations Of The Present Study:

Considering the diagnostic importance both for the clinicians and the patients, larger sample size in the study would have been appropriate for providing more precise information and accuracy of the non-HDL-C as a predictive marker of coronary heart disease.

VI. Conclusion:

Non-HDL-C was found to be better than LDL-C for atherogenesis. Being a calculated parameter, it incurs no additional cost and is more patient friendly not requiring fasting sample. Non-HDL-C hence should be included in every routine lipid profile panel.

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References

- [1]. Expert panel on detection, Evaluation, and treatment of high blood cholesterol in adults (ADULT TREATMENT PANEL III) JAMA.2001; 285:2486-2497.
- [2]. American diabetes association: Management of dyslipidemia in adults with diabetes. Diabetes care 26:S83-S86, 2003.
- [3]. Fukuyama N., Homma K., Wakana N. et al.: Validation of the Friedewald equation for evaluation of plasma LDL-cholesterol. J Clin Biochem Nutr. 2008, 43(1), 1-5.
- [4]. Bittner V. Non-HDL cholesterol – measurement, interpretation and significance. Adv Stud Med. 2007, 7, 1, 8- 11.
- [5]. Robinson J. G., Wang S., Smith B.J. et al.: Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk. J Am Coll Cardiol. 2009, 53, 316-322.
- [6]. Katarzyna Bergmann.Non-HDL cholesterol and evaluation of cardiovascular risk. eJIFCC. 2010; 21 (3).
- [7]. Greiner, M.,D.Pfeiffer, and R.D. Smith.Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev. Vet. Med.45: 23-41.
- [8]. Kastelein JJP, Van Der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation 2008; 117:3002–3009.
- [9]. Sniderman AD, Williams K, Contois JH, et al. A meta-analysis of low-density lipoprotein cholesterol, non high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes 2011; 4:337–345.
- [10]. Bays HE, Jones PH, Brown WV, Jacobson TA. National lipid association and annual summary of clinical lipidology 2015. J Clin Lipidol 2014; 8:S1–S36.
- [11]. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, et al. (2005) Non-high-density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men.Circulation 112: 3375–3383.
- [12]. Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, et al. (2007) Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 298:776–785.
- [13]. Liu J, Sempos CT, Donahue RP, Dorn J, Trevisan M, et al. (2006) Non-high-density lipoprotein and very-low-density lipoprotein cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol 98: 1363–1368.
- [14]. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care 2008; 31: 811–822.
- [15]. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation 2014; 129(Suppl 2):S49-573
- [16]. Rutger Veerbeek, , G.Kees Hovingh, S.Matthijs Boekholdt. Non-high density lipoprotein cholesterol: Current status as cardiovascular marker. Current opinion in Lipidology Dec 2015; 26(6):502-510.
- [17]. Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011; 32:1769–1818.
- [18]. De Vries M, Klop B, Castro Cabezas M.The use of the non fasting lipid profile for lipid- lowering therapy in clinical practice - Point of view. Atherosclerosis 2014; 234:473–475.