Original Article

Is evaluation of non-HDL-C better than calculated LDL-C in CAD patients? MMIMSR experiences

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ABSTRACT

Objective: The present study aimed to establish a better marker for the assessment of coronary artery disease (CAD).

Methods: One hundred patients of CAD (aged 20–60 years) of both sex and patients of hypertension with symptoms of CAD were selected for the study. 50 age and sex matched healthy controls were chosen for the present study. Serum total cholesterol, triglycerides and HDL-C were estimated in Siemens Dimensions RxL. LDL-C, VLDL-C were calculated by Friedwald Formula while non-HDL-C was calculated by subtracting HDL-C level from total cholesterol level. The comparison of non-HDL-C and friedwald calculated LDL-C was made in terms of independent t-test, serum TG levels (TG ≤ 200 mg/dl and TG > 200 mg/dl) and area under receiver operating characteristic (AUROC) curve.

Results & conclusion: The non-HDL-C levels (mean ± S.D) were higher in both test and control groups to that of the levels of friedwald calculated LDL-C. The area under receiver operating characteristic (AUROC) curve was significantly higher for non-HDL-C than for friedwald calculated LDL-C. The predictive value of non-HDL-C and friedwald calculated LDL-C were also compared in group A (serum TG ≤ 200 mg/dl) and group B (serum TG > 200 mg/dl). Non-HDL-C levels showed a significant difference in both the groups while the results were non-significant to that of friedwald calculated LDL. Thus, non-HDL-C is much specific and sensitive parameter for assessment of CAD risk. Moreover, non-HDL-C levels can also be done in non-fasting state with accuracy, thereby, it is patient friendly parameter. Therefore, the authors strongly suggest the incorporation of non-HDL-C in routine lipid profile panel.

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1. Introduction

Cardiovascular disease is the foremost cause of mortality and morbidity across the globe. According to the WHO data of the year 2019, 17.9 million people die owing to cardiovascular disease (CVD) each year1. Dyslipidemia has been clearly identified as most important atherosclerotic risk factor eventually leading to the progression of cardiovascular disease2. The World Health Organization had also reported that dyslipidemia is significantly associated with more than half of global cases of ischemic heart disease3.

The traditional approach to the management of dyslipidemia focuses mainly on Low density lipoprotein cholesterol (LDL-C) which is frequently considered as a primary target of lipid lowering therapy for cardiovascular diseases. LDL-C on the routine lipid panel is mostly calculated by Friedwald equation considering it as a cost-effective valuable tool and primary laboratory method over many decades. Despite its extensive use in predicting cardiovascular risk, it has become a sub-optimal marker for a plethora of reasons. Firstly, LDL-C concentration reflects only the amount of cholesterol present in LDL particles. Secondly, in hypertriglyceridemia (TG > 200 mg/dl), this equation gives inaccurate results as already reported by Japan Atherosclerotic Society (JAS) 2012 guidelines, and several other studies conducted recently3-5.

Surprisingly, even in healthy individuals LDL-C has been giving erroneous results with range of 13.3–13.5%6. Besides these limitations, the estimation of LDL-C requires fasting sample which results in delay in reporting thereby, causing inconvenience for both patients and clinicians.

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Therefore, latest diagnosis of the lipid related disorders should be based on such a parameter which is unaffected by these limitations. Several recent epidemiologic studies have documented that non-HDL-C is more strongly associated with coronary artery disease risk than calculated LDL-C\(^9\)\(^{10}\)\(^{11}\)\(^{12}\). Moreover American and European Cardiological Societies, International Atherosclerosis Society, Expert Dyslipidemia Panel and the National Lipid Association have strongly recommended non-HDL-C in routine lipid profile panel whose value can be simply calculated at no additional cost by subtracting HDL level from Total Cholesterol level and it further helps in quantifying total atherogenic burden by measuring aggregate amount of cholesterol\(^14\)\(^{15}\).

Unfortunately, non-HDL-C has been neglected so far despite its efficacy in comparison to LDL-C in CAD risk reduction. Although Lipid Association of India has recommended non-HDL-C as a co-primary target but still several premier institutions and hospitals have not acknowledged its incorporation in routine lipid profile panel\(^15\). The present study was aimed to assess the usage of non-HDL-C evaluation in the primary prevention of cardiovascular disease risk.

2. Methods

This is a case–control study conducted in department of Biochemistry in collaboration with department of Cardiology in MM Superspeciality Hospital, Mullana, Ambala. Patients of CAD (aged 20–60 years) who presented for the first time in cardiology OPD were included in the study and the patients of hypertension with symptoms of CAD were also included in the study. One hundred consecutive patients were taken for the study. Patients of Acute MI, Diabetes mellitus, Kidney disorders, Liver diseases as well as patients on follow up/on extensive medical treatment and on lipid lowering drugs were excluded from the present study. Fifty age and sex matched healthy individuals were selected as controls. The study was duly approved by institutional ethical committee and informed consent was taken from all participants of the study.

Detailed history of the patients was recorded. 3 ml blood was collected in plain vial and serum was separated using standard protocol. After the collection of blood sample, serum total cholesterol (TC), triglycerides (TG), High Density Lipoprotein-Cholesterol (HDL-C) were estimated by Simens Dimensions RxL in the clinical biochemistry lab, Department of biochemistry, MMIMSR. LDL and VLDL were calculated by Friedwald Formula and non-HDL-C was calculated by subtracting the HDL level from Total Cholesterol level i.e. TC−HDL-C. Quality control was maintained throughout this study.

2.1. Statistical analysis

The significance between the groups was determined using independent student\(t\) test. Significance is considered only at \(p < 0.05\). To compare the predictive values of non-HDL-C and friedewald calculated LDL-C, ROC analysis was done. The area under ROC (AUCROC) is considered a global performance indicator for a prognostic factor\(^16\). Greater area under curve of the ROC curve indicates better marker of the study. Further, both the parameters were also compared in terms of serum triglyceride levels (TG < 200 mg/dl and TG > 200 mg/dl). All the statistical analysis was done using SPSS 20 version.

3. Results

Among the 150 individuals who had participated in the study, males outnumbered females. The maximum number of the patients were of age group 40–50 years. The blood pressure of less than 120/80 mm/Hg was considered normal.

Serum TC, TG, HDL, LDL, VLDL and non-HDL were measured for all the subjects. The results (mean ± S.D) of friedewald calculated LDL-C and non-HDL-C are illustrated in Fig. 1.

To compare the predictive values of non-HDL-C and friedewald calculated LDL-C with respect to serum triglycerides levels, patients were divided into 2 groups; Group A (serum TG ≤ 200 mg/dl) and Group B (serum TG > 200 mg/dl). On comparison non-HDL-C levels showed a significant difference in both the groups while the results were non-significant for friedewald calculated LDL-C (Table 1).

To compare the predictive values of non-HDL-C and friedewald calculated LDL-C, ROC curve analysis was done and on comparison area under Receiver Operating Characteristic curve (AUCROC) for non-HDL-C was found to be significantly higher (0.835 at 95% Confidence Interval; 0.771, 0.898) than for friedewald calculated LDL (0.667 at 95% Confidence Interval; 0.582, 0.752) (Fig. 2).

4. Discussion and conclusion

Low-density lipoprotein cholesterol (LDL-C) has been recommended as the primary treatment target on lipid management in coronary artery disease as reported earlier. Despite of having so many advantages over friedewald calculated LDL-C, incorporation of non-HDL-C in routine lipid panel has been neglected so far. In view of this, the present study was done to study the usefulness of non-HDL-C in CAD risk assessment at MMIMSR, Ambala.

There are growing evidences which also suggest the role of non-HDL-C in predicting the CAD risk\(^17\)\(^{18}\)\(^{19}\). Studies conducted by Seki R et al\(^17\), Bhavan Kumar et al\(^7\), Aggarwal J et al.\(^5\) and Lawrence Baruch et al.\(^18\) compared the LDL-C (both direct and calculated) and non-HDL-C levels to confirm the predictive value of both the parameters in assessment of CAD. Seki R et al and Aggarwal J et al. compared non-HDL-C and LDL in terms of ROC analysis, pearson correlation and independent \(t\) test while Bha-van Kumar et al. and Lawrence Baruch et al. compared non-HDL-C and LDL in terms of student \('t\) test, ANOVA and Fisher’s \(z\)-transformation. Interestingly, non-HDL-C was found to be more significantly associated with CAD than friedewald calculated LDL-C as well as direct LDL.

In the present study, the non-HDL-C and friedewald calculated LDL were also compared with respect to serum triglyceride levels (TG < 200 mg/dl and TG > 200 mg/dl). Non-HDL-C was found to be significantly associated while results were non-significant for friedewald calculated LDL-C (Table 1). This is a major landmark change in strategy which we normally follow. This study demonstrated the superiority of non-HDL-C over friedewald.

![Fig. 1. Friedewald calculated LDL-C and non-HDL-C levels in control and test group.](image-url)
considered statistically significant. Moreover, 2018 guidelines have also highlighted the utility of HDL-C instead of LDL-C. These results are in accordance with recent studies leading to the conclusion that non-HDL-C offers coronary artery disease risk.

Non-HDL-C level can be estimated via non-fasting sample thus, making it more patient friendly and fastens the clinical decision as well. Moreover, 2018 guidelines have also highlighted the utility of non-fasting sample in clinical decision making thereby, allowing the non-HDL-C as primary therapeutic target. It would certainly benefit the patients as well as entire healthcare system. Henceforth, the authors strongly suggest the incorporation of non-HDL-C in routine lipid profile panel for the better diagnosis and treatment of coronary artery disease risk.

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Conflicts of interest
All authors have none to declare.

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References
1. https://www.who.int/health-topics. Accessed December 6, 2019. Accessed on.
2. Gupta Rajeev, Rao Ravinder S, Misra Anoop, Sharma K Samin. Recent trends in epidemiology of dyslipidemias in India. Indian Heart J. May-Jun 2017;69(3): 382–392.
3. World Health Organization. Quantifying selected major risks to health. In: The World Health Report 2002—reducing Risks: Promoting Healthy Life. Chapter 4. Geneva: World Health Organization; 2002:47–97.
4. Teramoto T, Sasaki J, Ishibashi S, et al. Comprehensive risk management for the prevention of cardiovascular disease executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan-2012 version. J Atheroscler Thromb. 2012;20:603–615.
5. Aggarwal Jyoti, Reddy Sreenivas, Nagtilak Suryakant. Non-HDL-C: an alternate to LDL-C for the diagnosis of cardiovascular disease. J Dent Med Sci. Feb 2016;15(2):18–9. ISSN: 2279-0861,1–4 (ISSN-JBMS): 2279-0853.
6. Cui Y, Blumenthal RS, Flaws JA, et al. Non-high-density lipoprotein cholesterol level as a predictor of cardiovascular disease mortality. Arch Intern Med. 2001;161:1413–1419.
7. Kumar Vengala Bhawan, Guntakalla Yeshwanth Reddy, Thomas Zachariah, Rajasekaran Uma Rani, Gnanaasekaran Prabhu. Role of non high density lipoprotein cholesterol (non-HDL-C) in predicting coronary artery disease. Indian J Pharm Pract. Oct-Dec.2015;8(4).
8. Miller Wg, Myers Gl, Sakurabayashi I, et al. Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. Clin Chem. 2010;56:977–986.
9. Kastelein John JF, Van der steeg Wim A, Ingarholme Michael Gaffney, et al. Lipids, apolipoproteins and their ratios in relation to cardiovascular events with statin treatment. Circulation. 2008;117(2):3002–3009.
10. Liu Jain, Sempo Christopher, Donahue Richard P, Dorn Joan, Trevisan Maurizio, Grundy Scott M. Joint distribution of non-HDL-cholesterol and LDL-cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabet Care. 2005;28(8):1916–1921.
11. Arsenault Bj, Rana JS, Stroes ES, et al. Beyond low-density lipoprotein cholesterol: respective contributions of non-HDL levels, triglycerides, and the total cholesterol/high density lipoprotein cholesterol ratio to coronary heart disease risk in apparently healthy men and women. J Am Coll Cardiol. 2009;55(1):35–41.
12. Liu Jain, Sempo Christopher, Richard PD, Dorn Joan, Trevisan Maurizio, Scott MG. Non-HDL lipoprotein and VLDL cholesterol and their risk predictive values in coronary heart disease. Am J Cardiol. 2006;98(10):1363–1368.
13. Sniderman, Williams Ken, Contois H John, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol and apolipoprotein B as markers of cardiovascular risk. Circulation: Cardiovasc Qual Outcme. 2011;4:337–345.
14. Ramjee Vimal, Sperling S Laurence, Jacobson A Terry. Non-high-density lipoprotein cholesterol versus apolipoprotein B in cardiovascular risk stratification. J Am Coll Cardiol. 2011;58:457–463.
15. Seshadri Iyengar Shamanna, Raman Puri, Narasigand SN, et al. Lipid association of India expert consensus statement on management of dyslipidemia in Indians 2016: Part 1. J Assoc Phys India. 2016 March;64(3):7–52.
16. Greiner M, Pfeiffer D, Smith. Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. Prev Vet Med. 2000;45:23–41.
17. Seki R, et al. Non-HDL cholesterol is better than friedewald-estimated LDL cholesterol to associate with cardiometabolic markers. Biomed Res Clin Pract. 2017;2(2):2–6, 2017.
18. Baruch Lawrence, Chiong Valerie J, Aggarwal Sanjay, Gupta Bhana. Discordance of non-HDL and directly measured cholesterol: which lipid measure is preferred when calculated LDL is inaccurate? Hindwai Publish Corp. Circ. 2013, 502918. Article ID.
19. Grundy etal Scott M, AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NMA/PNA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation. 2019;139:e1082–e1143.