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Reevaluating The Necessity of Fasting Lipid Profiles: Non-HDL Cholesterol in Non-Fasting State as A Practical and Reliable Alternative in Clinical Practice for Atherogenic Risk Assessment

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Conflict of interest: Nil

Abstract

Objectives: Atherosclerosis, a major cause of cardiovascular morbidity and mortality, is closely linked to dyslipidemia. This study aims to assess the interchangeability of fasting and non-fasting lipid profiles and examine the correlation between non-HDL cholesterol and apolipoprotein B (apo B).

Materials and Methods: A comparative study was conducted on 132 patients. Blood samples were collected in both fasting and postprandial states and analyzed for lipid profile parameters, including apo B and apo A1.

Statistical Analysis: Paired t-tests were used to compare fasting and postprandial lipid parameters. Bland-Altman analysis assessed the agreement between fasting and postprandial measurements, while Pearson correlation was used to evaluate the relationship between postprandial non-HDL cholesterol and apo B.

Results: No significant differences were observed between fasting and postprandial levels of total

cholesterol (183.9 ± 41.4 vs. 185.7 ± 42.2 mg/dL, P = 0.223), HDL cholesterol (41.9 ± 10.1 vs. 42.4 ± 8.6 mg/dL, P = 0.182), or non-HDL cholesterol (143.7 ± 40 vs. 141.5 ± 37 mg/dL, P = 0.122). Bland-Altman analysis demonstrated minimal bias and clinically acceptable agreement between fasting and postprandial states for total cholesterol and non-HDL cholesterol. A strong correlation was found between non-HDL cholesterol and apo B (r = 0.980, P < 0.001), indicating its reliability as a surrogate marker.

Conclusion: The findings support the use of non-fasting non-HDL cholesterol as a practical and reliable marker for atherogenic risk assessment. Eliminating the need for fasting simplifies testing, enhances patient compliance, and maintains diagnostic accuracy.

Keywords: Non-fasting, Atherosclerosis, Non-HDL cholesterol, HDL cholesterol, Total cholesterol, Apoprotein B

Introduction

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, significantly impacting both developed and developing nations.[1] In India, the burden of CVD is particularly severe, with death rates exceeding the global average, as highlighted by the Global Burden of Disease study.[2] Among the various contributors to CVD, atherosclerosis stands out as the predominant cause of ischemic conditions affecting the heart and brain. The formation of atheromatous plaques within arterial walls restricts blood flow, leading to insufficient tissue perfusion and life-threatening events such as myocardial infarction and stroke.

Dyslipidemia is a major risk factor for atherosclerosis and is strongly associated with increased CVD-related mortality.[3] Extensive research underscores the pivotal role of low-density lipoprotein cholesterol (LDL-C) in the initiation and progression of atherosclerosis. The process begins with the uptake of modified LDL particles by macrophages via scavenger receptors, culminating in the formation of foam cells and subsequent plaque development.[4] Thus, the measurement of lipid profiles, particularly LDL cholesterol concentration, has long been a cornerstone for assessing the risk of CVD.[5]

Recent studies have highlighted that, in addition to LDL cholesterol, other lipoproteins containing apolipoprotein B (apo B), such as VLDL, IDL, and other remnant lipoprotein molecules, can also be targeted by macrophages and exhibit atherogenic properties comparable to LDL.[6] These lipoproteins contribute to the formation of foam cells and exacerbate atherosclerotic processes. Therefore, measuring apo B levels or Non-HDL cholesterol (calculated as total cholesterol minus HDL cholesterol) provides a comprehensive assessment of atherogenic lipoprotein burden. Non-HDL cholesterol, in particular, offers valuable insights as it encompasses all cholesterol carried by atherogenic lipoproteins and is emerging as a robust predictor of acute coronary events.[7,8]

Conventionally, lipid and lipoprotein levels are measured in fasting plasma samples to mitigate the postprandial rise in triglycerides, which can interfere with LDL-C calculations using the Friedewald formula.[9] However, the necessity of fasting for evaluating atherogenic risk using Non-HDL cholesterol—largely independent of triglyceride levels—remains uncertain. Addressing this uncertainty, the present study aims to compare Non-HDL cholesterol levels in fasting and postprandial states to determine whether fasting is mandatory for assessing the atherogenic risk. Additionally, it investigates the association between postprandial Non-HDL cholesterol

and apo B, providing further insights into the utility of non-fasting lipid profiles in assessing atherogenic risk.

Materials & Methods

This comparative study was conducted at the tertiary care hospital in Andhra Pradesh, over a two-month period from February to March 2021. The study protocol was approved by the Indian Council of Medical Research-STS and reviewed by the Institutional Ethics Committee (IEC). Ethical approval was obtained on October 3, 2020.

Study Population

A total of 132 patients were recruited based on the inclusion criteria of having at least two non-lipid risk factors for cardiovascular disease, as defined by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines. The non-lipid risk factors included:

- Cigarette smoking within the past month.
- Blood pressure > 140/90 mmHg or current antihypertensive treatment.
- Family history of premature coronary heart disease.
- Age > 45 years for males and > 55 years for females.

The sample size was calculated using OpenEpi 3.0 software, with an alpha error of 0.05 and a beta error of 0.10.

Study Procedure

The study procedure was explained to all participants in their local language, and written informed consent was obtained prior to enrolment. Blood samples were collected from each participant in two states:

- Fasting State: After an overnight fast of 10–12 hours.
- Postprandial State: Two hours after consuming a meal.

The collected blood samples were centrifuged to isolate serum, which was subsequently analyzed using a fully automated Beckman Coulter DXC 700AU analyzer. The following parameters were measured:

- Total Cholesterol (TC): Measured using the cholesterol oxidase-peroxidase (COD-POD) method.
- High-Density Lipoprotein Cholesterol (HDL-C): Measured using the Accelerator Selective Detergent (ASD) methodology.
- Non-HDL Cholesterol: Calculated as Total Cholesterol minus HDL-C.
- Apolipoprotein B (Apo B) and Apolipoprotein A1 (Apo A1): Measured using immunoturbidometric assays.

Statistical Analysis

Data were analysed using SPSS version 22.0. The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test, confirming that the variables were normally distributed. Statistical methods included:

- Paired t-test: Used to compare mean values of fasting and postprandial parameters, expressed as mean ± standard deviation (SD).
- Pearson Correlation Analysis: Conducted to examine associations between postprandial Non-HDL cholesterol and Apo B.
- Bland-Altman Analysis: Performed to assess the agreement between fasting and postprandial values for Total Cholesterol and Non-HDL Cholesterol.

A p-value ≤ 0.05 was considered statistically significant for all analyses.

Results

The study included 132 patients, with demographic characteristics summarized [Table 1]. The mean age of the participants was 51 ± 10 years, with a near-equal distribution of males (51.5%) and females (48.5%). The majority of participants (59.1%) were diabetic.

Table 1: Demographic characteristics of study population

Baseline characters	
Age(years)	51±10
Male (n (%))	68(51.5)
Female (n (%))	64(48.5)
Diabetic (n (%))	78(59.1)

The mean levels of serum cholesterol (183.9±41.4 vs. 185.7±42.2mg/dl; *P* = 0.223), HDL-c (41.9±10.1 vs. 42.4±8.6 mg/dl; *P* = 0.182), and non-HDL-c (143.7±40 vs. 141.5±37 mg/dl; *P* = 0.122) were not significantly different between fasting and non-fasting states [Table 2].

Table 2: Comparison of fasting & non fasting lipid parameters

Parameter	**Fasting(mean±SD)**	**Non-Fasting(mean±SD)**	**p value**
Total cholesterol	183.9±41.4	185.7±42.2	0.223
HDL-cholesterol	41.9±10.1	42.4±8.6	0.182
Non-HDL-cholesterol	143.7±40	141.5±37	0.122

The Bland-Altman analysis comparing fasting and postprandial cholesterol levels [Fig 1] revealed a mean difference (bias) of 1.73 mg/dL, indicating that fasting cholesterol values were, on average, slightly higher than postprandial values. The 95% limits of agreement (LOA) ranged from -29.95 mg/dL to 33.41 mg/dL, suggesting that while there is a small systematic difference, individual variability is present. The majority of data points fell within the limits of agreement, signifying acceptable agreement between fasting and postprandial cholesterol measurements for clinical or research purposes. However, the observed variability should be taken into account when interpreting individual patient results.

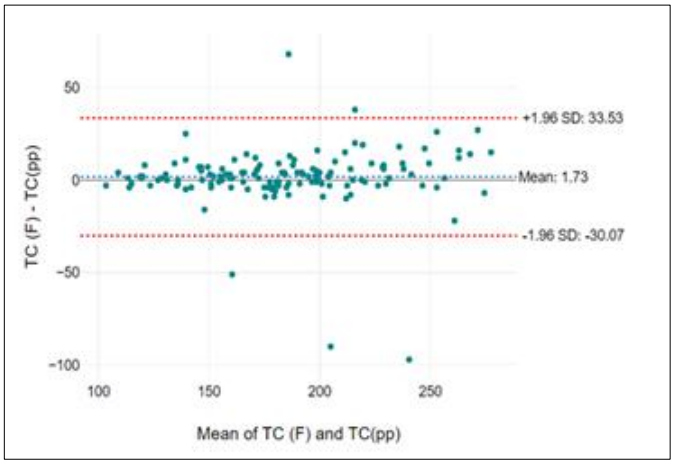

Figure 1: Agreement between Fasting and Postprandial Total Cholesterol

For Non-HDL cholesterol, the Bland-Altman plot [Fig 2] demonstrated a mean difference (bias) of -0.67 mg/dL, indicating that postprandial Non-HDL cholesterol levels were marginally higher than fasting levels on average. The 95% limits of agreement ranged from -22.65 mg/dL to 21.31 mg/dL, reflecting a narrower range of variability compared to total cholesterol. The majority of data points were within the limits of agreement, showing a consistent

and clinically acceptable agreement between fasting and postprandial Non-HDL cholesterol measurements. These findings support the potential interchangeability of fasting and postprandial Non-HDL cholesterol in assessing atherogenic risk, with caution for individual cases outside the limits of agreement.

A significant and strong positive correlation was observed between postprandial non-HDL cholesterol and Apo B levels ($r = 0.980$, $P < 0.001$), as well as between non-HDL cholesterol and the Apo B:Apo A1 ratio ($r = 0.779$, $P < 0.001$) [Table:3].

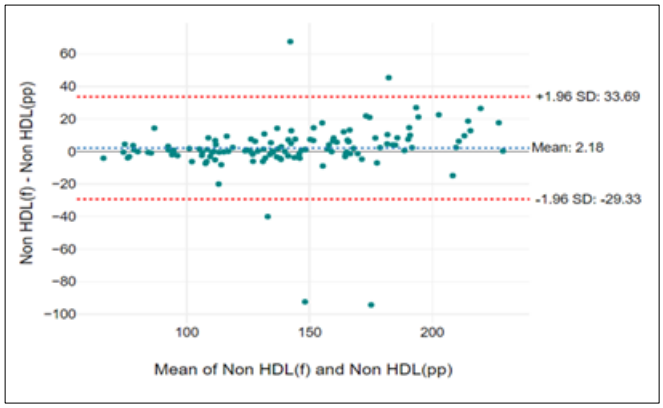

Figure 2: Agreement between Fasting and Postprandial Non-HDL Cholesterol

Table 3: Correlation between non fasting Lipid parameters with apoproteins & ratios

Parameter	r value	p value
Total cholesterol vs apoB	0.954	0.000
HDL cholesterol vs apoB	0.877	0.000
Non HDL cholesterol vs apoB	0.980	0.000
Total cholesterol vs apoB/A1	0.664	0.000
HDL cholesterol vs apoB/A1	-0.184	0.262
Non HDL cholesterol vs apoB/A1	0.779	0.000

Discussion

Atherosclerosis remains a leading cause of mortality and morbidity in India, accounting for 24.8% of deaths nationwide. Studies from the World Health Organization (WHO) and the Global Burden of Disease Study have documented an alarming rise in years of life lost (YLLs) and disability-adjusted life years (DALYs) due to coronary heart disease (CHD) in India.[10] Atherosclerosis is a multifactorial disease driven by genetic and environmental factors, with key risk factors including dyslipidemia, diabetes mellitus, smoking, hypertension, obesity, sedentary lifestyles, unhealthy diets, aging, and family history. Elevated levels of homocysteine and lipoprotein (a) have also been implicated in its pathogenesis.[11] Among these, dyslipidemia—characterized by low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, and an increased number of small dense low-density lipoprotein (LDL) particles—is a major modifiable contributor to atherosclerosis and cardiovascular risk.[12]

The pathogenesis of atherosclerosis begins with the deposition and oxidation of LDL within the arterial wall.

LDL, rich in cholesterol and containing apolipoprotein B100 (apoB100), is normally cleared by peripheral tissues via LDL receptors. ApoB100 serves as a ligand for receptor binding, leading to endocytosis and cholesterol uptake.[13] However, when cholesterol levels exceed cellular requirements, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibits further uptake by degrading LDL receptors.[14] This process leads to the accumulation and oxidation of LDL in the bloodstream, triggering a cascade of inflammatory responses, foam cell formation, and plaque development[15] Consequently, serum LDL cholesterol and apoB levels are key determinants of atherogenic risk.[16]

Traditionally, LDL cholesterol levels are calculated using the Friedewald formula, which requires fasting samples to account for postprandial triglyceride fluctuations. However, fasting lipid testing presents logistical challenges, including reduced patient compliance, delayed testing, and missed follow-ups. Additionally, direct LDL cholesterol measurements may underestimate cardiovascular risk, particularly in individuals with complex dyslipidemia.[17] These limitations have prompted a shift towards non-HDL cholesterol, which encompasses all atherogenic lipoproteins, as an alternative marker for atherogenic risk. Non-HDL cholesterol offers the advantage of being measurable in non-fasting samples and has demonstrated superior predictive value for atherogenic risk compared to LDL cholesterol in various studies. Bjornnson et al. concluded in their study that non-HDL cholesterol could be a superior marker for predicting atherogenic risk compared to LDL cholesterol.[18] Non-HDL cholesterol can better predict atherogenic risk than LDL cholesterol in cases of more complicated dyslipidemia patterns.[19]

However, there are conflicting reports regarding the use of non-HDL cholesterol in non-fasting states. Some studies have suggested that non-HDL cholesterol provides less useful cardiovascular disease risk information when measured in non-fasting samples, despite small changes in its concentrations.[20] Therefore, our study aimed to estimate non-HDL cholesterol levels in both fasting and non-fasting samples and determine whether non-fasting non-HDL cholesterol can be used as a tool to assess atherogenic risk. Our study found no significant differences between fasting and non-fasting levels of total cholesterol, HDL cholesterol, and non-HDL cholesterol. These findings align with prior studies from Copenhagen and Calgary, which reported minimal variations in lipid profiles between fasting and non-fasting states. Specifically, non-HDL cholesterol exhibited stability across fasting states, reinforcing its utility as a reliable and practical marker for cardiovascular risk assessment.[21,22]

The Bland-Altman plots demonstrated clinically acceptable agreement between fasting and postprandial measurements for both total cholesterol and non-HDL cholesterol. The mean difference (bias) was minimal, with most values falling within the 95% limits of agreement for both parameters. Notably, the narrower range of variability observed for non-HDL cholesterol compared to total cholesterol underscores its stability and potential utility as a robust marker for assessing cardiovascular risk, regardless of the fasting state. These findings support the growing body of evidence advocating for the adoption of non-HDL cholesterol in routine lipid assessments. Additionally, the strong correlation observed between non-HDL cholesterol and apoB, as well as the apoB: Apo A1 ratio, underscores its role as a surrogate marker for atherogenic lipoprotein

burden. Non-HDL cholesterol provides a comprehensive measure of cholesterol in all atherogenic particles, including LDL, very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), and lipoprotein(a), and effectively captures the risk associated with triglyceride-rich remnants.[23]

Recent studies, such as those by Klop et al., have demonstrated the utility of non-fasting lipids, including non-HDL cholesterol and apoB, as treatment targets in secondary prevention of cardiovascular disease.[24] However, evidence supporting the use of non-fasting lipid profiles for primary prevention remains limited, particularly in direct comparisons of fasting and non-fasting values within the same cohort. The results of our study support the routine use of non-fasting lipid profiles, particularly non-HDL cholesterol, as a practical and effective tool for assessing atherogenic risk. This approach offers significant advantages in clinical practice, including improved patient compliance and streamlined testing workflows. However, further research is needed to validate these findings across diverse populations and to establish standardized guidelines for non-fasting lipid testing in cardiovascular risk assessment.

Limitations

- The study participants may not be representative of the general population due to the specific inclusion criteria involving only high risk patients with minimum two non-lipid risk factors according to NCEP ATP III guidelines. This can limit the generalizability of the findings to broader populations.
- Non-fasting samples were obtained 2 hours after breakfast which may not validate its use in any time of the day.
- The study did not investigate the direct association between fasting and non-fasting lipid levels and cardiovascular outcomes, limiting the clinical implications of the findings in terms of risk stratification.

Conclusion

In conclusion, our study challenges the conventional requirement of fasting for plasma lipid and lipoprotein measurements. The absence of significant differences in total cholesterol, HDL cholesterol, and non-HDL cholesterol levels between fasting and non-fasting states highlights the potential of non-fasting lipid profiles as a reliable alternative for assessing atherogenic risk. Non-fasting non-HDL cholesterol, in particular, emerges as a practical and accurate marker for evaluating the risk of atherosclerosis, encompassing all atherogenic lipoproteins. Eliminating the need for fasting in lipid testing offers several advantages, including enhanced patient compliance, streamlined procedures, and fewer missed appointments or delays in diagnosis. By adopting non-fasting non-HDL cholesterol assessments, healthcare providers can efficiently evaluate cardiovascular risk, making lipid testing more accessible and patient-friendly. These findings pave the way for integrating non-fasting lipid profiles into routine clinical practice, supporting a more convenient and effective approach to dyslipidemia management and cardiovascular risk assessment.

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