Original Research Article

Comparison of Friedewald's and Anandaraja's formula with direct estimation of low-density lipoprotein cholesterol in Shivamogga population

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Abstract

Background: Estimation of low density lipoprotein cholesterol (LDL-C) is crucial in management of coronary artery disease patients. There are many homogenous assays currently available for the estimation of serum LDL-C. Most clinical laboratories determine LDL-C (mg/dl) by Friedewald's formula (FF). Recently Anandaraja and colleagues have derived a new formula for calculating LDL-C. This formula needs to be evaluated before it is extensively applied in diagnosis.
Aim: The aim of this study was to compare the results obtained by direct homogenous assay for LDL-C to those obtained by Friedewald's and Anandaraja's formulas with the assumption that the results obtained by direct assay are the most accurate.
Materials and methods: We measured Lipid profile (TC, TG, HDL-C, D-LDL-C) by direct homogenous method in 715 fasting samples. Simultaneously Friedewald's and Anandaraja's formulas were also used for calculation of LDL-C (FF-LDL-C and AR-LDL-C, respectively).
Results: The mean LDL-C levels were 117.78 ± 13.797, 115.51 ± 12.854 and 112.93 ± 11.671 mg/dl for D-LDL-C, FF-LDL-C and AR-LDL-C respectively. There was a statistically significant difference between the results ($P < 0.001$) obtained by calculation formulas compared to the measured LDL-C. There was underestimation of LDL-C by 2.27 mg/dl and 4.85 mg/dl by Friedewald's and

Anandaraja's formulas respectively. In this study, the Pearson's correlation between FF-LDL-C and D-LDL-C was 0.881 and that between AR-LDL-C and D-LDL-C was 0.880. Bland–Altman graphs showed a definite agreement between mean and differences of the calculation formulas and direct LDL-C with 95% of values lying with in ±2 SD limits.

Conclusion: The results of our study showed that FF is better in agreement with D-LDL-C than Anandaraja's formula for estimation of LDL-C by calculation though both lead to its underestimation.

Key words

Total cholesterol (TC), Triglyceride (TG), HDL-C, LDL-C, Friedewald's formula (FF), Anandaraja's Formula (AR).

Introduction

Elevated serum Low-Density Lipoprotein Cholesterol (LDL-C) concentration is a well-known atherogenic risk factor with a high predictive value for coronary heart disease [1, 2]. The National Cholesterol Education Programme (NCEP) Adult Treatment Panel III (ATP III) recommends a goal of maintaining serum LDL-C concentration < 100 mg/dl as optimal. Based on the serum LDL levels the National Cholesterol Education Program (NCEP) suggests different criteria for decision-making in treatment of hypercholesterolemic patients who have coronary heart disease or other risk factors [3-5]. The reference method for determining LDL-C is β-quantification (the separation of lipoproteins by combining ultracentrifugation and precipitation with poly anions) [6]. It requires ultracentrifugation, uses large volumes of samples and is a time consuming and expensive technique. Therefore, this method is not suitable for routine laboratory testing [7-9]. In 1972, Friedewald, et al. published a landmark report describing a formula to estimate LDL-C as an alternative to tedious ultra centrifugation. In routine practice, most clinical laboratories estimate LDL-C concentrations in serum by Friedewald"s formula from the concentrations of Total Cholesterol (TC), Triglyceride (TG), and High-Density Lipoprotein Cholesterol (HDL-C). TG is mainly from chylomicron and VLDL assuming non HDL-C (TC-HDL-C) has little no change. However, when TG level is too high, LDL-C value is underestimated. This condition occurs in postprandial condition or patient with normal non-HDL-C but high TG level [10]. The calculation of LDL-C by the traditional Friedewald's formula (F-LDL-C) is: F-LDL-C (mg/dl) = TC-(HDL -C + TG/5) [11].

Because VLDL (very low density lipoprotein) carries most of the circulating triglycerides (TG), VLDL-C can be estimated reasonably well from the measured TG divided by 5 for mg/dl units [11]. Although this estimation formula correlates highly with beta quantification, it has certain limitations: it is not valid for samples with chylomicrons, with TG > 400 mg/dl or in patients with dysbetalipoproteinemia. This formula assumes the ratio of total TG to VLDL-C to be constant in all samples. The formula will overestimate VLDL-C and underestimate LDL-C as a consequence if TG rich chylomicrons and chylomicron remnants are present in the serum sample (hence the requirement for a fasting sample [12]. The use of this formula is not recommended for type 2 diabetes, nephrotic syndrome and chronic alcoholic patients because, in these conditions too, the triglyceride to cholesterol ratio in VLDL is altered [13-15].

In spite of the technical disadvantages of FF, it is difficult to displace it from clinical practice unless a method with clear advantages in performance and overall cost effectiveness is developed. Recently a new formula for calculation of LDL-C has been proposed by Anandaraja et al [16].

The calculation of LDL-C proposed by Anandaraja et al., (AR-LDL-C) is

AR-LDL-C (mg/dl) = 0.9* TC- (0.9 *TG/5)- 28 [16].

The use of only two variables- TG and TC in this formula is more likely to reduce analytical errors that are expected when Friedewald's Formula is used. Since the formula does not require HDL-C result for calculation, it can prove to be more economical also.

Many studies done to compare the direct methods of estimation of serum LDL cholesterol with LDL cholesterol calculation by Friedewald's and Anandaraja's formulas have shown conflicting results [17-19].

This study was therefore undertaken, to determine if, and to what extent, LDL-C level is underestimated /overestimated when it is calculated using the formulae compared with direct measurement of LDL-C (D-LDL-C) and to determine which of these calculated formulae (FF-LDL-C, AR-LDL-C) show maximum correlation with D-LDL-C method at different TG levels. Anandaraja's formula has been approved for use in Brazilian and Greek population [19, 20].

The formula needs to be validated before approval for routine use in clinical laboratories. The aim of this study is to compare the results obtained by direct homogenous assay for LDL-C to those obtained by Friedewald's and Anandaraja's formulas with the assumption that the results obtained by direct assay are the most accurate.

Materials and methods

With the approval of the institutional ethics committee and the informed consent of the participants, a total number of 715 participants above 30 years were chosen for the study. All the study participants were free of any confirmed renal, hepatic or cardiovascular disease and diabetes mellitus. After an overnight fast of 10-12 hours, 4 ml of venous blood was collected in a sterile BD vacutainer from antecubital vein from each patient. The serum lipid profile was estimated by the enzymatic CHOD-POD method [21] for TC, GPO-Peroxidase method [22] for Triglycerides, CHOD, CHER-POD method [23] for HDL-Cholesterol, and CHOD,CHER-POD method [23] for LDL-Cholesterol by using Erba Mannheim reagent kits obtained from Transasia Bio-Medicals and all the parameters were estimated using fullyautomated analyser – Erba Mannheim (EM 100). LDL-Cholesterol concentrations were also calculated by Friedewald's formula [11] and Anandaraja's formula [16].

Statistical Analysis

Data obtained was entered into Microsoft Excel sheet and statistical analysis was performed. Results were analysed and presented as numbers and mean± standard deviation (SD).

The study subjects were divided into four groups based on the serum TG levels (mg/dl) - group I: TG - <100 mg/dl, group II: TG – 100-199mg/dl, group III: TG-200-299 mg/dl and group IV: TG-300-399 mg/dl (Set I).

The study subjects were divided into three groups based on the serum HDL-Cholesterol levels (mg/dl) - group I: HDL-C <40 mg/dl, group II: HDL-C 40-49 mg/dl and group III: HDL-C >50 mg/dl (Set-II).

The study subjects were also divided into two groups based on the serum TC levels (mg/dl) – group I: TC <200 mg/dl and group II: TC -200-300 mg/dl (Set –III).

LDL-Cholesterol assay and calculation using the different formulae were compared at different levels of TG, HDL-C and TC. The mean difference and mean percentage difference (%ΔLDL) was calculated as was done by a previous study [24] using the formula: Mean percentage difference calculated LDL-C = (calculated LDL-C – D-LDL-C) / D-LDL-C X 100. Student t test and Pearson's correlation was used for comparing the difference in LDL-C concentrations. The level of significance was

taken as $p<0.05$. Bland Altman graphical plots were used in order to measure or analyse the degree of agreement between the direct LDL-C assay method and formulae for LDL-C calculation.

Results

The comparative study was done on lipid profile values obtained from 715 patients. There were 215,400, 50 and 50 patients in group I, II, III, IV respectively in set-I. There were 222, 443 and 50 patients in group I, II and III respectively in Set II. There were 634 and 81 patients in group I and II respectively in Set III. Out of the 715 samples for which analysis is done, 303 (42.4%) were received from female patients and 412 (57.6%) were from males. The mean age of the patients was 50.8±10.3 years. The mean TC, TG and HDL-C levels were 187.46 ± 13.837, 143.36 ± 66.784, and 41.59 ± 2.537 respectively. The mean LDL-C levels were 117.78 ± 13.797, 115.51 ± 12.854 and 112.93 ± 11.671 mg/dl for D-LDL-C, F-LDL-C and AR-LDL-C respectively (**Table - 1a, 1b**). The calculated formulae underestimate LDL-C by 2.27 mg/dl and 4.85 mg/dl by Friedewald's and Anandaraja's respectively in comparison to the direct method.

Table - 1a: Gender wise distribution of the study subjects.

	Frequency	**Percentage**
F	303	42.4
M	412	57.6
Total	715	100

Table - 1b: Demographic detail of the study subjects.

	N	**Mean ± SD**
Age	715	50.77±10.29
TC	715	187.46 ± 13.837
TG	715	143.36 ± 66.784
HDL	715	41.59 ± 2.537
FF-LDL-C	715	115.51 ± 12.854
D-LDL-C	715	117.78 ± 13.797
AR-LDL-C	715	112.93 ± 11.671

On calculating the mean % difference, it was found that FF-LDL-C differs by 1.93 % from the D-LDL-C which was much lower in comparison to AR-LDL-C 4.12% (**Table - 2**). A strong correlation was found between calculated LDL-C methods and D-LDL-C assay, that is FF-LDL-C versus D-LDL-C (r= 0.881) (**Figure – 1a, 1b**) and A-LDL-C (r=0.880) (**Figure – 2a, 2b**).

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To find the agreement between the direct & calculated LDL- methods, Bland-Altman Plot was prepared (**Figure - 2a, 2b**) but the negative bias in them indicates that although they correlate to one another they cannot be used in place of direct LDL except in the Friedewald's method where the negative bias was minimal.

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Comparison of LDL-C results at different levels of TG showed statistically significant difference ($p<0.001$) between measured values and those calculated by Friedewald's and Anandaraja's formulae (Table/Fig-5a,6a). There was underestimation of LDL-C by calculation at all the levels of TGs. The mean difference between Friedewald's Formula LDL and Direct LDL Cholesterol was highest (5.26 mg/dl) at TG levels 200-299mg/dl and least (1.27 mg/dl) at TG levels <100mg/dl respectively. The mean difference between Anandaraja's Formula LDL and Direct LDL Cholesterol was highest (5.41 mg/dl) at TG levels 200-299mg/dl and least (1.94mg/dl) at TG levels 300-399 mg/dl respectively (**Table – 3a, 3b, 3c**).

Comparison of direct LDL-C with calculated LDL-C at different Levels of Serum Triglyceride was as per **Table – 4a** and **Figure 3a**. Comparison of direct LDL-C with calculated LDL-C at different Levels of Serum HDL-C was as per **Table – 4b** and **Figure – 3b**. Comparison of direct LDL-C with calculated LDL-C at different Levels of Serum TC was as per **Table – 4c** and **Figure – 3c**.

Discussion

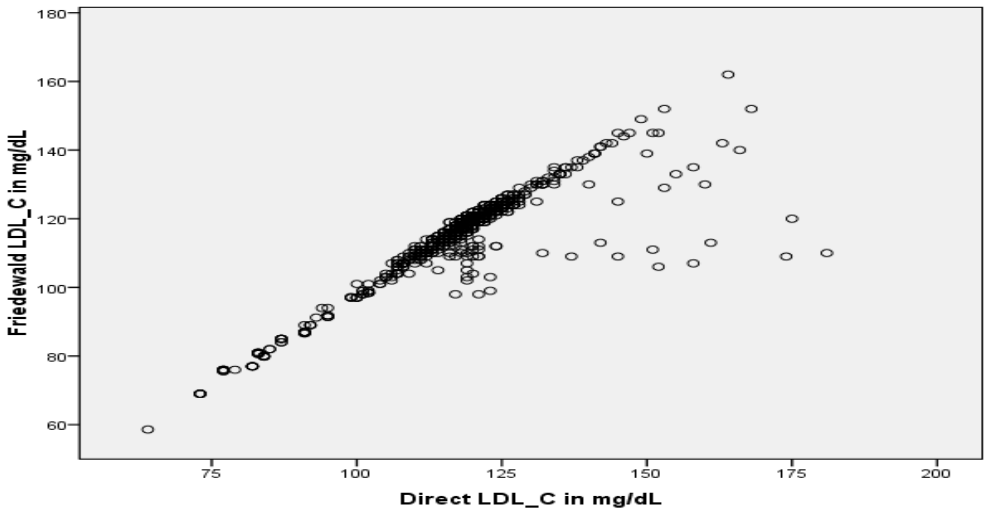
Strategies for treatment of lipid abnormalities are primarily based on LDL-C concentration.

Therefore, LDL-C must be accurately determined to establish a personal CHD risk profile in order to initiate dietary adjustments, drug therapy and to monitor their effects.

Table - 2: Mean percentage difference and pearson's correlation.

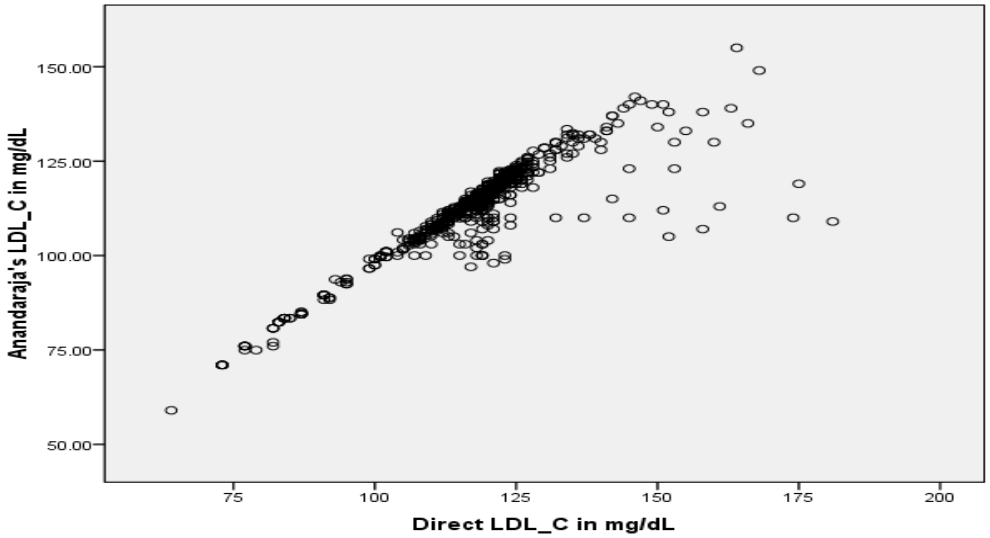
	Mean difference	**Mean percentage difference**	**Correlation coefficient (r)**
FF_LDL vs D_LDL	-2.27	-1.93	0.881 P<0.001, HS
AR_LDL vs D_LDL	-4.85	-4.12	0.880 P<0.001, HS

Figure - 1a: Scatter plot of Friedewald Formula LDL_C vs Direct LDL_C.



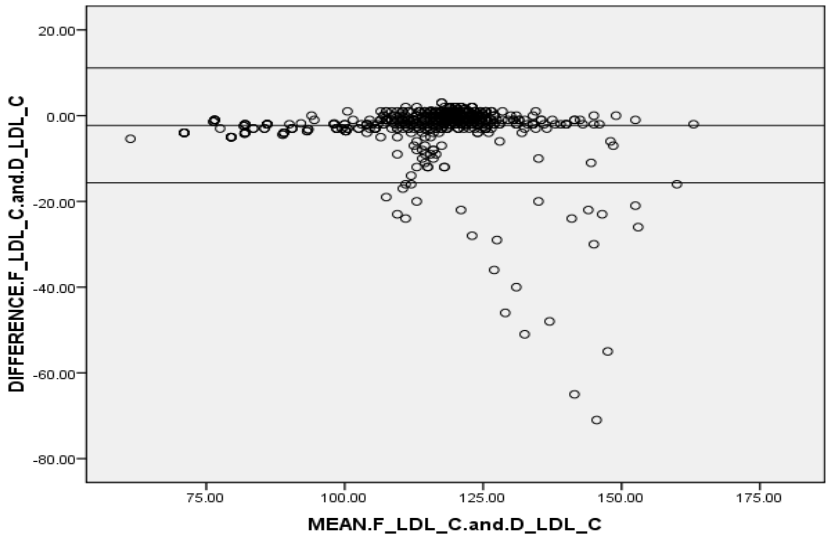
Scatter plot of Friedewald's LDL cholesterol against Direct LDL cholesterol. There was a correlation of r=0.881.

Figure - 1b: Scatter plot of Anandraja's Formula LDL_C vs Direct LDL.



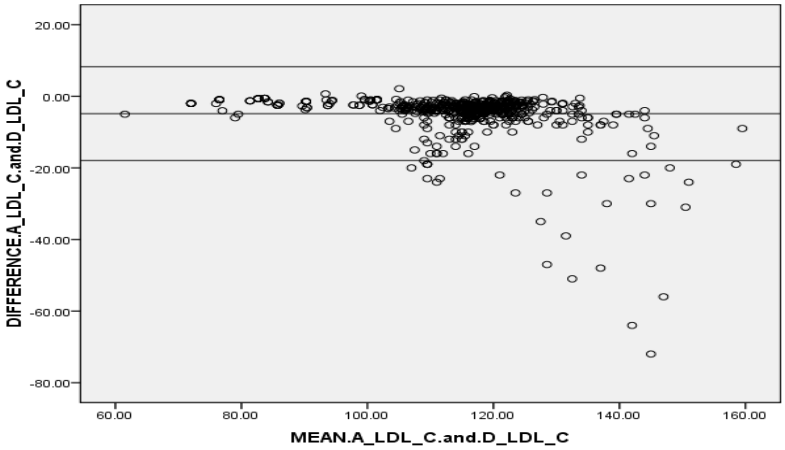
Scatter plot of Anandraja's LDL cholesterol against Direct LDL cholesterol. There was a correlation of r=0.880.

Figure - 2a: Bland-Altman for LDL cholesterol estimated directly and by Friedewald's calculation.



Bland-Altman plot for direct LDL_C and LDL_C calculated by Friedewald's formula showing negative bias. Mean= -2.272, SD=6.6999, mean+2SD=11.1278, mean-2SD=-15.67.

Figure - 2b: Bland-Altman for LDL cholesterol estimated directly and by Anandaraja's calculation.



Bland-Altman plot for direct LDL_C and LDL_C calculated by Anandraja's formula showing negative bias. Mean= -4.849, SD=6.552, mean+2SD= +8.255, mean-2SD= -17.953.

Table - 3a: Mean difference and mean % difference between LDL_D with calculated LDL_C at different levels of TG.

		Mean difference	**Mean % difference**	**p-value**		**Mean difference**	**Mean % difference**	**p-value**
TG<100 N=215	F_LDL vs D_LDL	-1.27	-1.06	<0.001	AR_LDL vs D_LDL	-5.33	-4.44	<0.001
100-199 N=400		-2.32	-1.91	<0.001		-4.89	-4.04	<0.001
200-299 N=50		-5.26	-4.87	<0.001		-5.41	-5.01	<0.001
300-399 N=50		-3.22	-3.53	<0.001		-1.94	-2.12	<0.001

Table - 3b: Mean difference and mean % difference between LDL_D with calculated LDL_C at different levels of HDL_C.

		Mean difference	Mean % difference	p-value		Mean difference	Mean % difference	p-value
HDL<40 N=222	F_LDL vs D_LDL	-0.77	-0.65	<0.001	AR_LDL vs D_LDL	-5.36	-4.56	<0.001
40-49 N=443		-2.21	-1.88	<0.001		-2.42	-3.77	<0.001
≥50 N=50		-42.8	-24.97	<0.05 (P=0.05)		-45	-26.25	<0.05 (P=0.03)

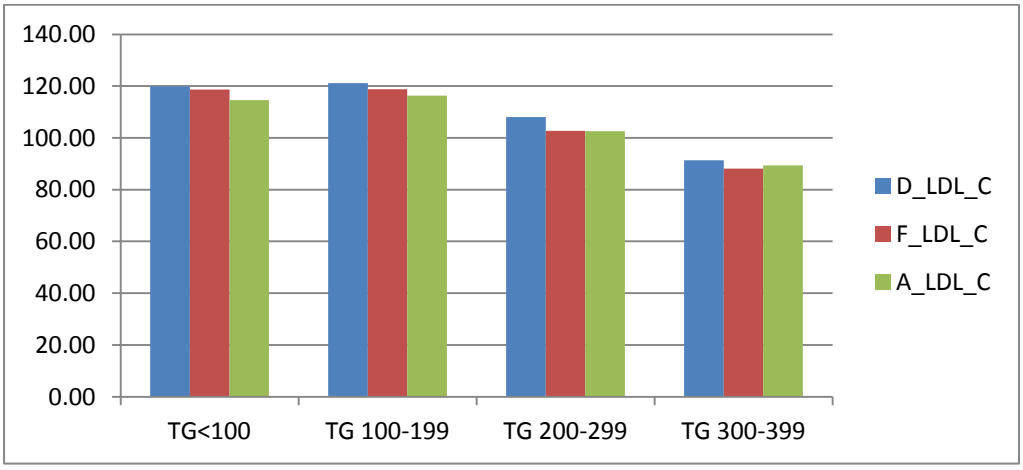
Table - 3c: Mean difference and mean % difference between LDL_D with calculated LDL_C at different levels of TC.

	F_LDL vs D_LDL	Mean difference	Mean % difference	p-value	AR_LDL vs D_LDL	Mean difference	Mean % difference	p-value
TC<200 N=634		-1.26	-1.09	<0.001		-3.86	-3.35	<0.001
200-300 N=81		-10.18	-7.40	<0.001		-12.58	-9.15	<0.001

Table - 4a: Comparison of direct LDL_C with calculated LDL_C at different levels of TG.

	TG<100	TG 100-199	TG 200-299	TG 300-399
D_LDL_C	119.92	121.16	108.02	91.30
F_LDL_C	118.65	118.84	102.76	88.08
A_LDL_C	114.59	116.27	102.61	89.36

Figure - 3a: Comparison of direct LDL_C with calculated LDL_C at different levels of TG.



In the past few decades attempts have been made to derive more accurate formulas for LDL-C calculation than the widely used Friedewald's formula [25-30]. Although the newer formulas offered few advantages over the Friedewald's, they have performed only marginally better, possibly due to diversity in terms of study populations and/or pathologies [14, 15, 31]. Some of them included apolipoprotein concentrations, apoA-I and/or apoB [28-30]. Anandaraja and colleagues [16] described a new formula for LDL-C calculation in an Indian

population of 1000 patients by applying multiple linear regression analysis and validated its accuracy in 1008 patients. Anandaraja and colleagues called for the reliability of their formula to be tested in other populations. The present study was designed to evaluate the performance of this formula in another set of Indian patients. Anandaraja et al. measured direct LDL-C by precipitation method. In our study detergent based homogenous method of Erba Mannheim by Transasia was used. The correlation between FF-LDL-C and D-LDL-C in their study was 0.88. We have found a correlation of 0.881 between these two. Other studies have reported a correlation 0.86 [32] and 0.88 [33] and 0.786 [34], respectively. In a study done in Japan, a positive correlation was found between FF-LDL-C and D-LDL-C with $r^2 = 0.975$ [35]. Anandaraja, et al. [16] reported the Pearson's correlation of 0.97 between LDL-C measured by their formula and D-LDL-C which was better as compared to that for F-LDL-C. This correlation was 0.880 in our study which is similar to that obtained for F-LDL-C (Table/Fig-2). Vujovic, et al. have reported a correlation of 0.89 between AR-LDL-C and D-LDL-C in the study done in Serbian population [36]. Kamal, et al. [34] have also reported a good correlation between these with $r = 0.810$.

Table - 4b: Comparison of direct LDL_C with calculated LDL_C at different levels of TG.

	TC<200	**TC 200-300**
D_LDL_C	115.2603	137.506173
F_LDL_C	113.9984	127.328395
A_LDL_C	111.3976	124.932099

Figure - 3b: Comparison of direct LDL_C with calculated LDL_C at different levels of TG.

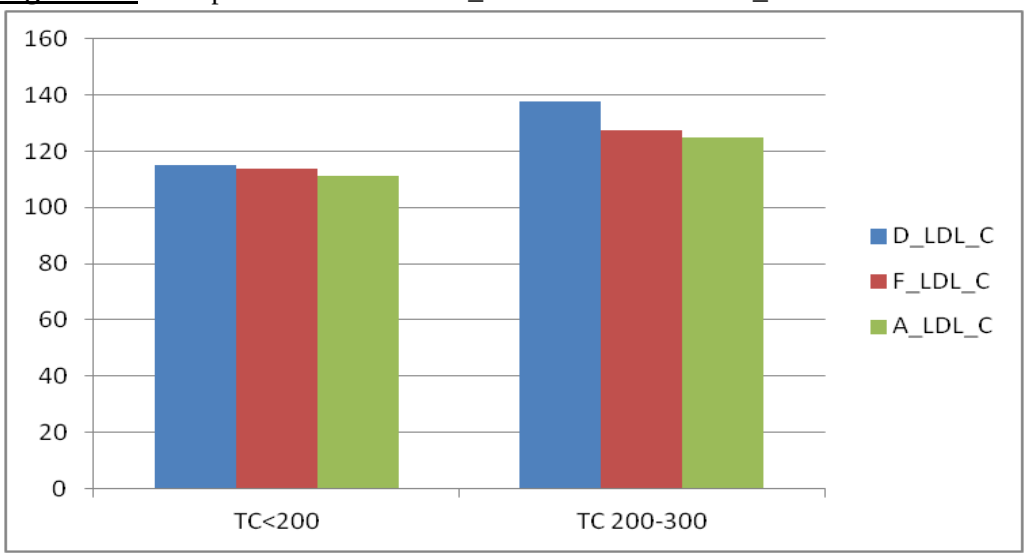
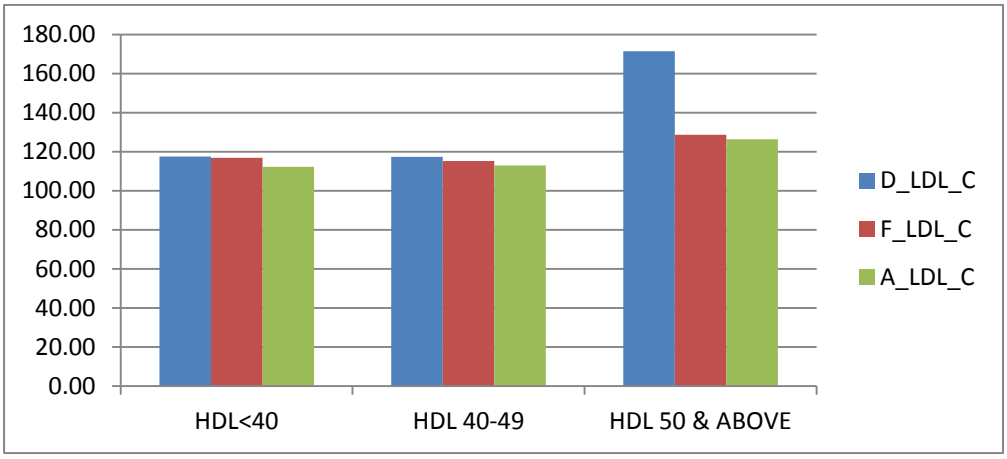


Table - 4c: Comparison of direct LDL_C with calculated LDL_C at different levels of HDL.

	HDL<40	**HDL 40-49**	**HDL 50 and above**
D_LDL_C	117.5804	117.37	171.4
F_LDL_C	116.8089	115.16	128.6
A_LDL_C	112.2174	112.95	126.4

Figure - 3c: Comparison of direct LDL_C with calculated LDL_C at different levels of HDL.



On the other hand, Friedewald's formula has been shown to be relatively reliable and recommended by the NCEP as a routine method [6] for estimation of LDL-C despite it having several well-established constraints. To the best of our knowledge only Paz and colleagues [37] have performed a detailed systematic analysis of the reliability of Anandaraja's formula. They tested the new formula in schizophrenic patients treated with antipsychotic drugs. Their results demonstrated that LDL-$C_{Anandaraja}$ concentrations were underestimated or overestimated compared to LDL-$C_{Electrophoresis}$ and depended on the HDL-C concentrations. They found a higher correlation and a lower estimation error between LDL-$C_{Electrophoresis}$ and LDL-$C_{Friedewald}$ than LDL-$C_{Electrophoresis}$ and LDL-$C_{Anandaraja}$. For that reason improved accuracy of Anandaraja's formula over Friedewald's formula was not claimed. We have found measured LDL-C to be higher than that obtained by calculation using both the formulas. Kamal, et al. [34] have reported an underestimation of 2.27 and 4.85 mg/dl by Friedewald's and Anandaraja's formulas respectively.

Kamazeki, et al. [35] have reported an underestimation of 5.9 mg/dl by FF compared to the directly measured LDL-C. Vujovic et al. [36] have also reported higher values for D-LDL-C. They have found a percentage difference of −6.9% for FF-LDL-C and −3.9% for AR-LDL-C. In our study %ΔLDL-C for Anandaraja's formula was higher at −4.12 compared to that for FF at −1.93% (Table/Fig-2). In the study by Agrawal et al. [38], comparison of FF-LDL-C results with measured LDL-C during three different periods with three different homogenous assays was done. A substantial lack of agreement between direct and calculated LDL-C with higher D-LDL-C values by all the methods in spite of having good correlation coefficients was reported by the authors. Some studies have reported opposite trends with higher results with calculated LDL-C by FF as compared to measured LDL-C [19, 33]. In the study by Gasko, et al. [19], results by Anandaraja's formula were closer to direct measurement with a mean difference of −1 mg/dl. Bland Altman plots showed a negative bias in spite of the good correlation mentioned above.

The difference between measured and calculated LDL-C results can be significant in terms of patient's risk classification for coronary artery disease. According to NCEP ATP III, LDL-C levels of 100, 130 and 160 mg/dl are the treatment goals for low risk, moderate risk and high risk patients for CHD, respectively. Direct measurement leads to approximately 10% more patients being candidate for lipid lowering drug therapy as compared to the use of calculated LDL-C. Vujovic, et al. have also supported their observation and commented that HDL-C should not be omitted from the formula. Our results are similar to their findings. Error in FF-LDL-C results was maximal at HDL-C ≥ 50 mg/dl

(−24.97%) and TG concentration of 201–300 mg/dl (−5.26%). No other study has reported the effect of high HDL-C levels on the results obtained by FF to the best of our knowledge. As TG levels increase, increase in mean difference between the results of direct and FF-LDL-C has been reported in previous studies [34, 39]. Our results support this finding except at TG > 300 mg/dl when mean error was less than that obtained for TG levels of 200–300 mg/dl.

Limitations

A major drawback of the present study was that samples collected for LDL-C estimation in the group IV in Set 1 was only 50 where LDL-C was > 300 mg/dl. The performance of Anandaraja's formula with large sample size could have been done.

Conclusion

We conclude that, calculated LDL-C results and D-LDL-C show good correlation. The negligible negative bias causes a statistically significant difference in results on comparing measured and calculated LDL. AR-LDL-C gives a higher percentage of error compared to FF-LDL-C. Therefore, Friedewald's formula is better than Anandaraja's formula for calculating LDL-C in a more cost effective manner and can be used in large population studies.

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