The Reliability of Calculated Low-Density Lipoprotein Cholesterol from Four Different Formulas in Thai Diabetic Patients

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Background: *Low-density lipoprotein cholesterol (LDL-C) is usually calculated by the Friedewald formula but it has certain limitations, especially in hypertriglyceridemia and diabetes mellitus (DM).*

Objective: *Assess the reliability of LDL-C levels calculated from four formulas (Friedewald, Anandaraja and colleagues, Chen et al, and Vujovic et al) when compared to direct LDL-C measurement (dLDL-C) in DM with various triglycerides (TG) levels.*

Material and Method: *The present study included 2,967 fasting Thai diabetic patients with TG levels less than 400 mg/dl. The total cholesterol and TG levels were measured by enzymatic colorimetric assay. The high-density lipoprotein cholesterol and dLDL-C levels were measured by homogeneous enzymatic colorimetric assay. The calculated LDL-C (cLDL-C) from each formula was compared to dLDL-C. In addition, the degree of agreement between the methods was assessed.*

Results: *The mean and standard deviation (SD) of dLDL-C was 122.3 (37.1) mg/dl, the mean (SD) of cLDL-C from the formula of Friedewald (F-LDL-C), Anandaraja and colleagues, Chen et al, and Vujovic et al (Vu-LDL-C) were 115.2 (35.8), 120.8 (35.2), 116.6 (34.2), and 123.9 (37.4) mg/dl, respectively. In aspect of the accuracy defined as the percentage of dLDL-C minus the cLDL-C within -10 to 10 mg/dl; the accuracy of Vu-LDL-C were higher than the other cLDL-C in overall and the most of subgroups of TG levels, except in the subgroup of TG levels <100 mg/dl which the accuracy of F-LDL-C was the highest. The overall number of dLDL-C minus Vu-LDL-C within -10 to 10 mg/dl was 2,655 cases (89.5% with $p<0.001$). The Vu-LDL-C showed a little discordance with dLDL-C at the higher levels of TG. All cLDL-C had systematic differences from dLDL-C, while only Vu-LDL-C had no proportional difference. The Vu-LDL-C yielded the lowest mean of difference between dLDL-C and cLDL-C of -1.60 with SD of 6.31 mg/dl, while F-LDL-C yielded the highest value of 7.06 with SD of 7.91 mg/dl. The Vu-LDL-C had the narrowest range of 95% limits of agreement (-13.97 to 10.77 mg/dl) and the difference neither depended on the magnitude of LDL-C measurements nor had proportional error.*

Conclusion: *The modified Friedewald formula of Vujovic et al provided the most accuracy with acceptable degree of agreement in DM compared to those derived from the original Friedewald formula or the others. The interference caused by hypertriglyceridemia was obviously diminished; thus, the formula of Vujovic et al is more reliable than the others in DM if TG levels are range from under 400 mg/dl to 100 mg/dl.*

Keywords: *Low density lipoprotein cholesterol, LDL-C, Direct measurement of LDL-C, Calculated LDL-C, Friedewald formula, Modified Friedewald formula, Diabetes mellitus, DM*

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The elevation of low-density lipoprotein cholesterol (LDL-C) serum concentration is one of the major risk factors for atherosclerosis and coronary heart disease (CHD). Diabetes mellitus (DM) carries risk for CHD similar to that of people with established CHD, and should have LDL-C levels less the 100 mg/dl[1]. In many clinical studies, LDL-C has been calculated using Friedewald formula[2]. Despite its limitations, the calculated LDL-C (cLDL-C) is still widely used for the estimation of LDL-C concentration due to its simplicity, convenience, and low cost. The recommendations of ESC/EAS guidelines for the management of dyslipidemias suggested that direct methods for determining LDL-C should be used whenever available[3].

The author had reported that the direct homogeneous method showed higher LDL-C concentration than the Friedewald formula indicated in DM and substantial systematic bias between both methods was found[4]. Recently, a few formulas for LDL-C estimation, such as Anandaraja and colleagues[5] from India, Chen et al[6] from People's Republic of China, and Vujovic et al[7] from Republic

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of Serbia, were proposed. Each method was also claimed to be more accurate than Friedewald formula.

The present study was aimed to assess the reliability of LDL-C levels calculated from Friedewald formula and the other three modified formulas when compared to direct LDL-C (dLDL-C) measurement in DM with various triglycerides (TG) levels.

Material and Method

The present study was conducted between June 2009 and May 2010 in the DM clinic at Surin Hospital, which is located in the northeastern region of Thailand. The present study protocol was approved by the Ethics Committee of Surin Hospital. Any participants who had TG level of 400 mg/dl and over, high-density lipoprotein cholesterol (HDL-C) of 20 mg/dl and lower, present of chylomicron in the sera, history of chronic liver disease, or present of jaundice, were excluded from the study. Blood samples obtained in the morning after 12 hours fasting, and were analyzed within one day. The total cholesterol (TC) and triglyceride (TG) levels were measured by enzymatic colorimetric assay. The reagents were Cholesterol CHOD-PAP Cobas and Triglyceride GPO-PAP Cobas, respectively. The HDL-C and dLDL-C levels were measured by homogeneous enzymatic colorimetric assay. The reagents were HDL-C plus third generation Cobas and LDL-C plus second generation Cobas, respectively. All blood lipid analyses were performed by a Roche/Hitachi 917 automatic analyzer, and the total error used in precision assessment for the Roche method met the recommendation by the National Cholesterol Education Program[1]. The reagents were obtained from Roche Diagnostics and the assays had been shown to meet the criteria for precision (CV <4%), accuracy (bias <4%) and for total analytical error (<12%). LDL-C concentrations were calculated using the Friedewald formula (F-LDL-C (mg/dl) = TC - HDL-C - TG/5), the Anandaraja and colleagues formula (An-LDL-C (mg/dl) = 0.9*TC - 0.9*TG/5 - 28), the Chen et al formula (Ch-LDL-C (mg/dl) = 0.9*TC - 0.9*HDL-C - TG/10), and the Vujovic et al formula (Vu-LDL-C (mg/dl) = TC - HDL-C - TG/6.85).

Statistical analysis

The normality of distribution was checked using the Kolmogorov-Smirnov test. The data were presented as numbers and percentages for categorical variables, as means and standard deviations (SD) for continuous variables. The differences in mean values were compared using Friedman test or Wilcoxon signed ranks test. The differences between related groups were compared using Cochran's Q test or McNemar test. Two-tailed tests were used to determine the statistical significance at *p*-value of less than 0.05. The results of cLDL-C were compared to dLDL-C using Passing-Bablok regression[8] with cumulative sum linearity test and the Bland-Altman method[9]. These statistical analyses were performed using the MedCalc version 12.7.

Results

Blood samples were obtained from 2,967 Thai diabetic patients. The age of patients ranged from 15 to 93 years, and 2,123 cases (71.6%) were female. The mean (SD) of duration of DM was 5.6 (4.2) years, and 1,285 cases (43.4%) had hemoglobin E disorders (HbE). The characteristics of diabetic patients in the present study were shown in Table 1. Kolmogorov-Smirnov test was performed to study normality of LDL-C levels. The distribution was not normal for dLDL-C and cLDL-C from all formulas.

The means of cLDL-C, except Vu-LDL-C, were lower than the mean of dLDL-C. In the comparison analysis, Wilcoxon signed ranks test showed significant differences between means of all cLDL-C and dLDL-C ($p<0.001$).

The TG levels were classified into four subgroups as TG <100 mg/dl, TG 100 to <200 mg/dl, TG 200 to <300 mg/dl, and TG 300 to <400mg/dl, respectively. Friedman test showed significant differences among all cLDL-C and dLDL-C in total and each subgroup ($p<0.001$), as shown in Table 2. However, there was no statistical difference between mean of dLDL-C and Vu-LDL-C in the subgroup of TG 300 to <400mg/dl ($p = 0.134$).

In aspect of the accuracy, the difference between dLDL-C and cLDL-C within -10 mg/dl to 10 mg/dl was determined to be the acceptable result of cLDL-C, as shown in Table 3. When compared among cLDL-C, Vu-LDL-C significantly showed the highest percentages of acceptable results in overall (89.5% with $p<0.001$) and in the most of subgroups of TG levels other than subgroup of TG <100 mg/dl, which the accuracy of F-LDL-C was the highest. However, the acceptable results of F-LDL-C and Vu-LDL-C in subgroup of TG <100 mg/dl insignificantly differed (91.3% vs. 89.6% with $p = 0.237$). The accuracies of Vu-LDL-C in the subgroups ranged from 85.5% to 90.0%, and the better were the groups of lower TG levels. Even though Vu-LDL-C, rather

than Ch-LDL-C, showed a little discordance with dLDL-C at the higher levels of TG, the accuracies of Vu-LDL-C were higher than Ch-LDL-C in all subgroups. In contrast, the accuracies of F-LDL-C and An-LDL-C strongly declined at the higher levels of TG.

When studied among the 2,104 cases of dLDL-C at 100 mg/dl and over. The cLDL-C <100 mg/dl by F-LDL-C were 244 cases (11.6%), by An-LDL-C were 174 cases (8.3%), by Ch-LDL-C were 173 cases (8.2%), and by Vu-LDL-C were 54 cases (2.6%). At this cut-off point, Vu-LDL-C had the lowest percentage of underestimation and the highest was F-LDL-C. The mean (SD) of dLDL-C among the underestimation of F-LDL-C was 105.9 (5.4) mg/dl, of An-LDL-C was 108.7 (7.5) mg/dl, of Ch-LDL-C was 104.3 (4.0) mg/dl, and of Vu-LDL-C was 102.9 (2.9) mg/dl. On the other hand, the overestimation among the 863 cases of dLDL-C <100 mg/dl was also evaluated. There were 20 cases (2.3%) by F-LDL-C, 169 cases (19.6%) by An-LDL-C, 17 cases (2.0%) by Ch-LDL-C, and 89 cases (10.3%) by Vu-LDL-C, which

Table 1. Characteristics of 2,967 Thai diabetic patients in the study

	Mean	SD	Median	Minimum	Maximum
Age (year)	59.2	10.7	60.0	15.0	93.0
BMI (Kg/m^2)	23.7	4.1	23.4	12.3	47.2
FPG (mg/dl)	140.9	46.2	132.0	48.0	554.0
TC (mg/dl)	197.4	41.6	193.0	87.0	362.0
TG (mg/dl)	160.4	71.6	145.0	33.0	399.0
HDL-C (mg/dl)	50.1	12.6	49.0	21.0	130.0
dLDL-C (mg/dl)	122.3	37.1	118.0	34.0	271.0
BUN (mg/dl)	16.7	7.2	15.0	3.0	100.0
Creatinine (mg/dl)	1.1	0.5	1.0	0.4	7.6
Hb (g/dl)	12.0	1.7	12.0	3.7	19.1

SD = standard deviation; BMI = body mass index; FPG = fasting plasma glucose; TC = total cholesterol; TG = triglycerides; HDL-C = high density lipoprotein cholesterol; dLDL-C = low density lipoprotein cholesterol derived from direct measurement; BUN = blood urea nitrogen; Hb = hemoglobin

Table 2. The means of LDL-C levels from direct measurement and each formula among subgroups of different TG levels

	Mean of LDL-C (mg/dl)				
	TG <100 mg/dl mean (SD) range (n = 588)	TG 100 to <200 mg/dl mean (SD) range (n = 1,645)	TG 200 to <300 mg/dl mean (SD) range (n = 568)	TG 300 to <400 mg/dl mean (SD) range (n = 166)	Total mean (SD) range (n = 2,967)
dLDL-C	107.6 (31.8) 41.0 to 247.0	112.8 (36.0) 34.0 to 251.0	133.4 (38.3) 40.0 to 271.0	131.9 (43.6) 38.0 to 263.0	122.3 (37.1) 34.0 to 271.0
Friedewald	106.1 (32.3) 38.0 to 248.8	116.8 (36.4) 24.6 to 263.0	121.0 (38.6) 30.6 to 249.8	112.6 (43.7) 13.6 to 237.0	115.2 (35.8) 13.6 to 263.0
Anandaraja	119.0 (31.6) 40.2 to 255.3	121.9 (34.7) 27.6 to 272.4	121.8 (37.5) 39.1 to 249.7	112.2 (42.2) 12.5 to 227.6	120.8 (35.2) 21.5 to 272.4
Chen et al.	101.9 (29.2) 37.4 to 230.8	116.6 (33.1) 31.1 to 252.3	128.0 (34.7) 49.7 to 242.5	128.8 (39.7) 42.0 to 244.5	116.6 (34.2) 31.1 to 252.3
Vujovic et al.	110.5 (32.4) 40.2 to 253.5	124.5 (36.6) 30.7 to 273.5	133.9 (38.6) 45.6 to 261.7	131.2 (43.9) 33.7 to 258.1	123.9 (37.4) 30.7 to 273.5
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001

* Friedman test

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; SD = standard deviation; dLDL-C = low density lipoprotein cholesterol derived from direct measurement

had the cLDL-C at 100 mg/dl and over. The mean (SD) of dLDL-C among the overestimation of F-LDL-C was 95.6 (6.4) mg/dl, of An-LDL-C was 89.9 (8.0) mg/dl, of Ch-LDL-C was 96.8 (3.4) mg/dl, and of Vu-LDL-C was 95.7 (4.3) mg/dl.

When excluded HbE, Vu-LDL-C significantly had the highest percentage of acceptable results in overall (89.2% with $p<0.001$), whereas F-LDL-C was at 68.8%. Only the subgroup of TG <100 mg/dl that the acceptable results without HbE of F-LDL-C and Vu-LDL-C significantly differed (92.6% vs. 88.1% with $p = 0.021$), otherwise Vu-LDL-C without HbE significantly had the highest percentages of acceptable results in the rest of subgroups (89.5%, 90.0% and 88.0% respectively with $p<0.001$). The other percentages of acceptable results among cLDL-C without HbE were nearly similar to the groups of including HbE (data were not shown).

The comparisons between dLDL-C and cLDL-C using Passing-Bablok regression and Bland-Altman method are shown in Table 4 and the plots are shown in Fig. 1 and 2. The cumulative sum linearity test of all plots showed no statistical difference. All cLDL-C had systematic differences from dLDL-C for the 95% confidence intervals (95% CI) of the interception in Passing-Bablok regression did not contain the value 0 but only the Vu-LDL-C had no proportional difference because the 95% CI of the slope contained the value 1 (0.99 to 1.00).

Table 3. Comparisons of the accuracy defined as direct LDL-C minus calculated LDL-C within -10 to 10 mg/dl among subgroups of different TG levels

	(Direct LDL-C - calculated LDL-C) within -10 to 10 mg/dl (%)				
	TG <100 mg/dl	TG 100 to <200 mg/dl	TG 200 to <300 mg/dl	TG 300 to <400 mg/dl	Total
dLDL	n = 588	n = 1,645	n = 568	n = 166	n = 2,967
Friedewald	537 (91.3)	1,243 (75.6)	217 (38.2)	19 (11.4)	2,016 (67.9)
Anandaraja	259 (44.0)	1,041 (63.3)	200 (35.2)	24 (14.5)	1,524 (51.4)
Chen et al.	459 (78.1)	1,227 (74.6)	431 (75.9)	124 (74.7)	2,241 (75.5)
Vujovic et al.	527 (89.6)	1,475 (89.7)	511 (90.0)	142 (85.5)	2,655 (89.5)
p-value*	<0.001	<0.001	<0.001	<0.001	<0.001

* Cochran's Q test

LDL-C = low-density lipoprotein cholesterol; TG = triglycerides; dLDL-C = low density lipoprotein cholesterol derived from direct measurement

Table 4. Correlations between low density lipoprotein cholesterol levels determined by homogeneous assay and each calculated formula

	Friedewald	Anandaraja	Chen et al.	Vujovic et al.
Passing-Bablok regression				
Regression equation	y = 5.38+1.01x	y = -4.59+1.06x	y = -4.36+1.09x	y = -1.05+0.99x
Interception (95% CI)	5.38 (4.48 to 6.39)	-4.59 (-6.54 to -2.64)	-4.36 (-5.12 to -3.62)	-1.05 (-1.75 to -0.37)
Slope (95% CI)	1.01 (1.00 to 1.02)	1.06 (1.04 to 1.08)	1.09 (1.08 to 1.09)	0.99 (0.99 to 1.00)
RSD (95% CI)	5.60 (-10.98 to 10.98)	10.31 (-20.20 to 20.20)	4.25 (-8.32 to 8.32)	4.46 (-8.74 to 8.74)
Cumulative sum linearity test	$p = 0.44$	$p = 0.22$	$p = 0.92$	$p = 0.62$
Bland-Altman method				
Mean of difference (SD)	7.06 (7.91)	1.53 (14.67)	5.76 (6.66)	-1.60 (6.31)
95% CI of mean (mg/dl)	6.78 to 7.35	1.01 to 2.06	5.52 to 5.60	-1.83 to -1.37
Lower limit (at -1.96SD)	-8.44	-27.22	-7.31	-13.97
95% CI of lower limit (mg/dl)	-8.93 to -7.96	-28.13 to -26.32	-7.72 to -6.90	-14.36 to -13.58
Upper limit (at 1.96SD)	22.57	30.29	18.82	10.77
95% CI of upper limit (mg/dl)	22.09 to 23.06	29.39 to 31.19	18.41 to 19.23	10.38 to 11.16

RSD = residual standard deviation; SD = standard deviation; 95% CI = 95% confidence interval

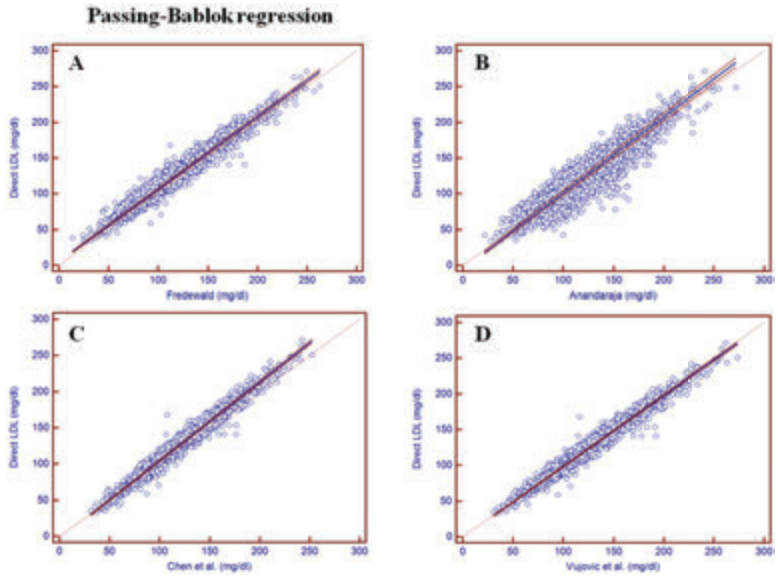

Fig. 1 Illustration of Passing-Bablok regressions between direct LDL-C vs. calculated LDL-C of each formula with 95% confidence interval: A) Friedewald formula, B) Anandaraja and colleagues, C) Chen et al, D) Vujovic et al.

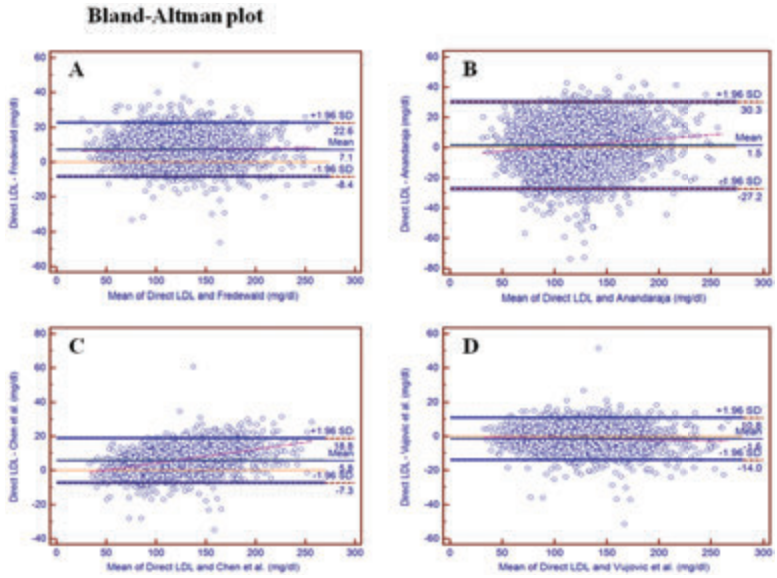

Fig. 2 Illustration of Bland-Altman plots between means difference of direct LDL-C and calculated LDL-C vs. average of direct LDL-C and calculated LDL-C of each formula: A) Friedewald formula, B) Anandaraja and colleagues, C) Chen et al, D) Vujovic et al.

The degrees of agreement between the two methods were assessed using the Bland-Altman graphical technique. The degree of agreement is indicated by calculating the bias, estimated by the mean with SD of the differences and range of 95% CI of the mean difference. According to the Bland-Altman method, Vu-LDL-C had the lowest the mean of difference with SD (-1.60 with 6.31mg/dl) and the narrowest range of 95% limits of agreement (-13.97 to 10.77 mg/dl). The mean of difference of An-LDL-C was only 1.53 mg/dl but the SD was much greater (14.67 mg/dl) and particularly had the widest range of 95% CI of the mean difference (-27.22 to 30.29 mg/dl). The regression line of Vu-LDL-C in Bland-Altman

plot lies nearly parallel to the line of the mean of difference whereas the regression lines of An-LDL-C and Ch-LDL-C are uptrend as shown in Fig. 2. This finding indicates that the accuracy of Vu-LDL-C does not depend on the magnitude of LDL-C nor has proportional error.

Discussion

Many studies show that the use of the Friedewald formula was inferior to dLDL-C measurement in diabetic patients[10-12] because dyslipidemia in DM includes quantitative and qualitative abnormalities in lipoprotein particles including very-low-density lipoproteins (VLDL) and their remnants[13,14]. One function of insulin in non-diabetic people is to maintain balance between intestinally derived and liver-derived triglyceride-rich lipoproteins. The regulation fails in DM and inappropriate production of VLDL by the liver favors hypertriglyceridemia[14]. This mechanism alters the ratio between TG and VLDL and has interference to the estimation of VLDL in Friedewald formula, so the simple division of plasma TG by 5 (for mg/dl) may not give an accurate estimation of VLDL in DM. Many alternative calculations including TG/4, TG/4.5, TG/5, TG/5.5, TG/6, TG/7, and TG/8 (mg/dl) have been proposed[15-17]. However, the postulation of modified formula specified in DM was not established. Furthermore, the cLDL-C derived from Friedewald formula in extreme HDL-C levels especially HDL-C at 20 mg/dl or lower loss their statistical correlation with dLDL-C[18]. The mean of difference with SD between dLDL-C and F-LDL-C of HDL-C at 20 mg/dl and lower in that study was -46.3 with SD of 43.7 mg/dl. Thus, the extreme low HDL-C levels were excluded from present study.

However, the formulas for cLDL-C with more accuracy than Friedewald formula were published worldwide[5-7]. The formula of Anandaraja and colleagues derived from 1,000 subjects by a multiple linear regression analysis at New Delhi[5], whereas the formula of Chen et al derived from calibrated Friedewald formula using different coefficients from a multivariate linear regression analysis between LDL-C (expected value), TG and Non-HDL-C (explanatory variables) performed at Zhongshan Hospital[6]. On the other hand, Vu-LDL-C is considered in a modification of Friedewald formula by changing the VLDL/TG mean ratio. Vujovic et al used TC, TG, LDL-C, and HDL-C measurements in 1,010 patients at Belladonna Clinical Chemistry Laboratory to calculate the VLDL/TG ratio for a Serbian population; however, DM were excluded from their study[7].

The present study favored the formula of Vujovic et al despite the fact that it had trivial overestimation and slightly inferior to Friedewald formula when dLDL-C levels were <100 mg/dl because of the highest percentages of acceptable results in overall, the lowest percentage of underestimation, and the lowest mean of difference with SD when compared to the original formula and the others. In contrast to F-LDL-C and An-LDL-C, the higher levels of TG seldom had interference to the acceptable results of Vu-LDL-C. Even excluding DM from the initial subjects for calculating the TG/VLDL mean ratio in the original study, Vu-LDL-C fitted for the diabetic patients in the present study.

In details, Anandaraja and colleagues did not propose any limitations to their formula and HDL-C is not considered to be a part of the formula; therefore, these make the formula be the most convenient one. The formula was claimed to be better than Friedewald formula[5,19,20]. The mean of difference between dLDL-C and An-LDL-C was lower than those of F-LDL-C and Ch-LDL-C but the degree of agreement of An-LDL-C was the worst because of the widest range of the 95% CI of the mean difference. Moreover, the accuracies of An-LDL-C obviously declined in the groups of higher TG levels; thus, these findings did not support An-LDL-C to apply in DM.

The formula of Chen et al had moderate mean of difference and range of the 95% CI of the mean difference, whereas the percentage of the acceptable results seldom changed between the subgroups of TG. Both of the Ch-LDL-C and Vu-LDL-C, rather than F-LDL-C and An-LDL-C, diminished the interference caused by hypertriglyceridemia. However, the accuracy of Ch-LDL-C was inferior to Vu-LDL-C when the percentage of the acceptable results was used as an indicator (75.5% vs. 89.5%). Although there were a great number of HbE in the present study, HbE had less effect on the comparisons between dLDL-C and cLDL-C.

There are many commercial homogenous assays for LDL-C estimation and each of these has been certified by the Cholesterol Reference Method Laboratory Network (CRMLN) at the Centers for Disease Control and Prevention (CDC)[21]; however, these methods are not routinely used in many laboratories in developing countries as they are expensive, which increase the cost of lipid profile. Instead of the technical disadvantages of Friedewald

formula, the modified Friedewald formula of Vujovic et al may be useful after tested for the reliability in different population, especially in DM.

Conclusion

The present study indicated that LDL-C concentrations of diabetic patients derived from the modified Friedewald formula of Vujovic et al provided the most accuracy in overall compared to those derived from the original Friedewald formula, the formula of Anandaraja and colleagues, the formula of Chen et al The interference caused by hypertriglyceridemia was obviously diminished in this formula. Regarding the satisfactory degree of agreement and the accuracy, the modified Friedewald formula of Vujovic et al is more reliable than the others in DM if TG levels were range from under 400 mg/dl to 100 mg/dl and can be used to calculate LDL-C levels if direct LDL-C measurement was unavailable.

What is already known on this topic?

The direct homogeneous method showed higher LDL concentration than the Friedewald formula indicated in DM[4]. The percentage of LDL levels by direct method was higher than Friedewald formula, significantly increased along the subgroups of higher TG levels, while the dissociation occurred at TG levels of 100 mg/dl and higher. Systematic biases between both methods were found, and the proportional difference between both methods was observed in DM.

The formula of Anandaraja and colleagues[5], the formula of Chen et al[6], and the modified Friedewald formula of Vujovic et al[7] are claimed to be better than Friedewald formula. However, the reliability of each formula in DM with various TG levels had not been published.

What this study adds?

In DM with TG levels of 100 mg/dl or higher, Friedewald formula showed more unreliable values when referred to direct LDL-C measurement. Whereas the modified Friedewald formula of Vujovic et al showed more reliability than the original at TG levels of 100 mg/dl up to <400 mg/dl, and can be used to calculate LDL-C levels if direct LDL-C measurement was unavailable. In overall, the reliability of the modified formula is also better than the others in DM.

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Potential conflicts of interest

None.

References

1. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106: 3143-421.
2. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.
3. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32: 1769-818.
4. Srisurin W. Comparison of low density lipoprotein cholesterol concentrations by direct measurement and Friedewald formula in diabetic patients with and without hemoglobin E disorders. J Med Assoc Thai 2013; 96: 407-15.
5. Anandaraja S, Narang R, Godeswar R, Laksmy R, Talwar KK. Low-density lipoprotein cholesterol estimation by a new formula in Indian population. Int J Cardiol 2005; 102: 117-20.
6. Chen Y, Zhang X, Pan B, Jin X, Yao H, Chen B, et al. A modified formula for calculating low-density lipoprotein cholesterol values. Lipids Health Dis 2010; 9: 52.
7. Vujovic A, Kotur-Stevuljevic J, Spasic S, Bujisic N, Martinovic J, Vujovic M, et al. Evaluation of different formulas for LDL-C calculation. Lipids Health Dis 2010; 9: 27.
8. Passing H, Bablok. A new biometrical procedure for testing the equality of measurements from two different analytical methods. Application of linear regression procedures for method comparison studies in clinical chemistry, Part I. J Clin Chem Clin Biochem 1983; 21: 709-20.
9. Bland JM, Altman DG. Comparing methods of measurement: why plotting difference against

standard method is misleading. Lancet 1995; 346: 1085-7.
10. Rubiés-Prat J, Reverter JL, Senti M, Pedro-Botet J, Salinas I, Lucas A, et al. Calculated low-density lipoprotein cholesterol should not be used for management of lipoprotein abnormalities in patients with diabetes mellitus. Diabetes Care 1993; 16: 1081-6.
11. Hirany S, Li D, Jialal I. A more valid measurement of low-density lipoprotein cholesterol in diabetic patients. Am J Med 1997; 102: 48-53.
12. Branchi A, Rovellini A, Torri A, Sommariva D. Accuracy of calculated serum low-density lipoprotein cholesterol for the assessment of coronary heart disease risk in NIDDM patients. Diabetes Care 1998; 21: 1397-402.
13. Kasama T, Yoshino G, Iwatani I, Iwai M, Hatanaka H, Kazumi T, et al. Increased cholesterol concentration in intermediate density lipoprotein fraction of normolipidemic non-insulin-dependent diabetics. Atherosclerosis 1987; 63: 263-6.
14. Syvänne M, Taskinen MR. Lipids and lipoproteins as coronary risk factors in non-insulin-dependent diabetes mellitus. Lancet 1997; 350 (Suppl 1): SI20-3.
15. DeLong DM, DeLong ER, Wood PD, Lippel K, Rifkind BM. A comparison of methods for the estimation of plasma low- and very low-density lipoprotein cholesterol: The Lipid Research Clinics Prevalence Study. JAMA 1986; 256: 2372-7.
16. Nakanishi N, Matsuo Y, Yoneda H, Nakamura K, Suzuki K, Tatara K. Validity of the conventional indirect methods including Friedewald method for determining serum low-density lipoprotein cholesterol level: comparison with the direct homogeneous enzymatic analysis. J Occup Health 2002; 42: 130-7.
17. Puavilai W, Laorugpongse D, Deerochanawong C, Muthapongthavorn N, Srilert P. The accuracy in using modified Friedewald equation to calculate LDL from non-fast triglyceride: a pilot study. J Med Assoc Thai 2009; 92: 182-7.
18. Timón-Zapata J, Laserna-Mendieta EJ, Pineda-Tenor D, Agudo-Macazaga M, Narros-Cecilia C, Rocha-Bogas MJ, et al. Extreme concentrations of high density lipoprotein cholesterol affect the calculation of low density lipoprotein cholesterol in the Friedewald formula and other proposed formulas. Clin Biochem 2011; 44: 1451-6.
19. Gasko R. Low-density lipoprotein cholesterol estimation by the Anandaraja's formula confirmation. Lipids Health Dis 2006; 5: 18.
20. Gazi IF, Elisaf M. LDL-cholesterol calculation formulas in patients with or without the metabolic syndrome. Int J Cardiol 2007; 119: 414-5.
21. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. Clin Chem 2002; 48: 236-54.

ความน่าเชื่อถือของ 4 สูตรสำหรับคำนวณค่า แอลดีแอล คอเลสเตอรอล ในผู้ป่วยไทยที่เป็นเบาหวาน

วสันต์ ศรีสุรินทร์

วัตถุประสงค์: *เพื่อศึกษาความน่าเชื่อถือของสูตรคำนวณค่าไขมันชนิดแอลดีแอล 4 วิธี คือ วิธีของ Friedewald, Anandaraja และคณะ, Chen และคณะ, และ Vujovic และคณะ โดยเปรียบเทียบกับวิธีวัดโดยตรงในผู้ป่วยไทยที่เป็นเบาหวาน*

วัสดุและวิธีการ: *ทำการศึกษาผู้ป่วยเบาหวานจำนวน 2,967 ราย ซึ่งมีค่าไขมันไทรกลีเซอไรด์ต่ำกว่า 400 มิลลิกรัมต่อเดซิลิตร ในโรงพยาบาลสุรินทร์ วัดค่าไขมันชนิดแอลดีแอลโดยตรงด้วยวิธี homogeneous เปรียบเทียบกับวิธีคำนวณโดยใช้สูตรทั้ง 4 วิธี*

ผลการศึกษา: *พบค่าเฉลี่ยและค่าเบี่ยงเบนมาตรฐานของไขมันแอลดีแอลโดยวิธีวัดตรงคือ 122.3 และ 37.1มิลลิกรัมต่อเดซิลิตร ของไขมันแอลดีแอลโดยการคำนวณด้วยวิธี Friedewald, Anandaraja และคณะ, Chen และคณะ, และ Vujovic และคณะ คือ 115.2 และ 35.8 มิลลิกรัมต่อเดซิลิตร, 120.8 และ35.2 มิลลิกรัมต่อเดซิลิตร, 116.6 และ 34.2 มิลลิกรัมต่อเดซิลิตร, 123.9 และ 37.4 มิลลิกรัมต่อเดซิลิตร ตามลำดับ วิธี Vujovic และคณะมีความแม่นยำมากกว่าวิธีคำนวณอื่นทั้งโดยรวมและในแทบทุกกลุ่มย่อยต่าง ๆ จำแนกตามระดับค่าไขมันไทรกลีเซอไรด์ ยกเว้นช่วงค่าไขมันไทรกลีเซอไรด์ต่ำกว่า 100 มิลลิกรัมต่อเดซิลิตร ซึ่งวิธี Friedewald ดีกว่า โดยพบว่ามีจำนวนผู้ที่ค่าไขมันของแอลดีแอลโดยวิธีวัดตรงลบด้วยวิธีของ Vujovic และคณะ อยู่ในช่วง -10 ถึง 10 มิลลิกรัมต่อเดซิลิตร จำนวน 2,655 ราย คิดเป็นร้อยละ 89.5 ค่าไขมันของแอลดีแอลโดยวิธีของ Vujovic และคณะเบี่ยงเบนเพียงเล็กน้อยเมื่อค่าระดับค่าไขมันไทรกลีเซอไรด์สูงมากขึ้น เมื่อใช้วิธี Passing-Bablok regression พบว่าค่าไขมันแอลดีแอลโดยการคำนวณทุกวิธีมี systematic difference จากค่าไขมันของแอลดีแอลโดยวิธีวัดตรง แต่วิธีของ Vujovic และคณะเท่านั้นที่ไม่พบ proportional difference และเมื่อเปรียบเทียบโดยวิธี Bland-Altman พบว่าค่าเฉลี่ยและค่าเบี่ยงเบนมาตรฐานของค่าความแตกต่างระหว่างค่าไขมันของแอลดีแอลโดยวิธีวัดตรงกับวิธีคำนวณที่ต่ำที่สุดคือค่าของวิธีคำนวณโดยวิธี Vujovic และคณะ (-1.60 และ 6.31มิลลิกรัมต่อเดซิลิตร) และสูงสุดคือค่าของวิธีคำนวณโดยวิธี Friedewald (-7.06 และ 7.91 มิลลิกรัมต่อเดซิลิตร) ค่าความกว้างของ 95% limits of agreement ที่แคบที่สุดคือวิธี Vujovic และคณะ (-13.97 และ 10.77 มิลลิกรัมต่อเดซิลิตร) โดยวิธี Vujovic และคณะ พบว่าค่าความแตกต่างระหว่างค่าไขมันของแอลดีแอลโดยวิธีวัดตรงกับวิธีคำนวณไม่มีความสัมพันธ์กับค่าไขมันแอลดีแอลที่มากขึ้นรวมทั้งไม่พบ proportional error*

สรุป: *ค่าไขมันแอลดีแอลคำนวณโดยวิธี Vujovic และคณะ ในผู้ป่วยเบาหวาน โดยรวมมีความแม่นยำมากที่สุดและมีค่า degree of agreement ดีกว่าวิธี Friedewald, Anandaraja และคณะ, และ Chen และคณะ รวมทั้งพบว่าผลการรบกวนที่เกิดจากค่าไขมันไทรกลีเซอไรด์สูงลดลงอย่างชัดเจน ดังนั้นสามารถใช้วิธี Vujovic และคณะ ซึ่งมีความน่าเชื่อถือสูงกว่าเพื่อคำนวณหาค่าไขมันชนิดแอลดีแอลในผู้ป่วยเบาหวานที่ค่าไขมันไทรกลีเซอไรด์ต่ำกว่า 400 มิลลิกรัมต่อเดซิลิตร ลงมาถึง 100 มิลลิกรัมต่อเดซิลิตร หากไม่สามารถหาค่าไขมันแอลดีแอลโดยวิธีวัดตรง*