Is calculated LDL-C by using the new modified Friedewald equation better than the standard Friedewald equation?

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The patients who have CHD or CHD risk equivalents should have LDL-C level less than 100 mg/dL because of the great reduction of risk for major coronary events. Direct measurement of LDL-C is the most accurate but is expensive. But with the practical use of the Friedewald equation for calculating LDL-C, the authors noticed that the accuracy declined with triglyceride level being higher than 300 mg/dL. The authors determined the correlation of direct measurement of LDL-C with calculation LDL-C from the Friedewald equation and postulated the new modified Friedewald equation for calculating LDL-C by using 1/6 triglyceride to minus. From a total of 1079 fasting serum samples analysis, and determining the correlation of LDL-C from the direct measurement (dm LDL) while calculating LDL-C from equations of the standard Friedewald (sf LDL), and the new modified Friedewald (mf LDL) , by using 1/6 triglyceride to minus instead of 1/5 triglyceride, if triglyceride was over 200 mg/dL. The authors found an excellent correlation within 0 $\pm$ 10% difference of dm LDL and sf LDL if triglyceride was less than 200 mg/dL, but sf LDL is less accurate when the triglyceride level is high, and mf LDL has better correlation with dm LDL within 0 $\pm$ 10% that sf LDL vs mf LDL, 72.3% vs 91.6% (p = 0.0001), and 58.3% vs 83.3%, (p = 0.01) when the triglyceride level is 200 -299, and 300–399 mg/dL respectively. It is shown that sf LDL has more underestimation than mf LDL when compared with dm LDL (more than 10 mg/dL) as 26.9% vs 2.5% (p < 0.0001) and 41.6% vs 5.6% (p = 0.0003) with triglyceride of 200-299, and 300–399 mg/dL respectively, although mf LDL showed overestimation of more than 10 mg/dL difference with dm LDL as sf LDL vs mf LDL of 0.8% vs 5.8% (p = 0.03), and 0.0% vs 11.1% (p= 0.03) if the triglyceride is in the range of 200-299 and 300-399 mg/dL respectively, even with a triglyceride level of 400-499 mg/dL, mf LDL still has good correlation with dm LDL up to 75.0%. The authors conclude that the standard Friedewald equation is excellent for LDL calculation if triglyceride is less than 200 mg/dL, but the accuracy is declined when triglyceride is over 200 mg/dL, the authors offer a new modified Friedewald equation to calculate LDL-C if triglyceride is in the range of 200-499 mg/dL which has a better correlation with direct measured LDL-C. However this new modified Friedewald equation needs to be testified again especially with dyslipidemic patient sera.

Key word : *Calculating LDL-C, Friedewald equation, New modified Friedewald equation, Ban Paew Project*

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It has been accepted that persons with coronary heart disease (CHD) or CHD risk equivalent should have low density lipoprotein cholesterol (LDL-C) level less the 100 mg/dL[1] because of a greater reduction of risk for major coronary events[1-6]. The first step in the treatment of lowering the LDL-C level is lifestyle modification including diet, weight reduction, exercise and increasing physical activity[7-9]. If the LDL-C level is not achieved, the lipid lowering drug should be added to the therapy, which is costly and may have adverse drug reactions, so it is necessary to know the exact LDL-C level. Direct measurement of LDL-C from the serum is the most accurate, but it is expensive especially in developing countries, so physicians usually use the Friedewald equation to calculate LDL-C, if the serum triglyceride is less than 400 mg/dL[10]. Calculating LDL-C from the Friedewald equation has shown good correlation with direct measurement of LDL-C, however the authors noticed that the LDL-C level from the direct measurement

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was higher than calculating one if the serum triglyceride is higher than 300 mg/dL.

The authors determined the correlation of LDL-C from direct measurement with LDL-C from calculation by using the standard Friedewald equation[10], the authors also postulated the new modified equation for calculating LDL-C and correlating with direct measured LDL-C.

Material and Method

During the period of February to April 2002 and the same months in 2003, there were 1079 fasting (from 8 pm to 8 am or more) blood samples taken from villagers randomly selected in Ban Paew District, Samutsakorn Province in Central Thailand. One volunteer was taken from each house. Their ages ranged from 40-69 years. This study was part of the Epidemiology of coronary artery disease at Ban Paew Project. The serum was separated from the blood, and kept in a test tube with a plastic cap, and put in an icebox. Specimens were transferred to a special refrigerator, kept at -60°C and analyzed later. The serum lipid profiles were measured by the analytic enzymatic method (Hitachi 917) at the Central Laboratory of Rajavithi Hospital.

Calculation of LDL-C by using the standard Friedewald equation if serum triglyceride was less than 400 mg/dL[10] as follows:

LDL = total cholesterol - HDL- 1/5 triglyceride

The authors also postulated the new modified Friedewald equation as follows:

LDL = total cholesterol - HDL -1/6 triglyceride

The authors correlated the serum level of direct measured LDL-C (dm LDL) with calculating LDL-C by using the standard Friedewald equation (sf LDL), and also with the new modified Friedewald equation (mf LDL).Statistical analysis by using Chi square test.

Results

There were 1079 fasting serum samples to be analyzed which 900, 119, 36, 12 and 12 samples having triglyceride levels of less than 200, 200-299, 300-399, 400-499 and 500 or more mg/dL, respectively. The authors calculated the difference by direct measured LDL-C (dm LDL) minus with calculating LDL-C from the standard Friedewald equation (sf LDL), and also dm LDL minus by calculating LDL-C from the new modified Friedewald equation (mf LDL), the results are shown in Table 1.

The data showed that sf LDL of 847 samples (94.1%) correlated with dm LDL of 900 samples with the difference of 0 $\pm$ 10 mg/dL, compared with mf LDL of 822 samples (91.3%) correlated with dm LDL as the above amount and the difference, when triglyceride was less than 200 mg/dL (Table 1). When triglyceride levels of 200-299, 300-399 mg/dL, sf LDL declined in accuracy with dm LDL within 0 $\pm$ 10 mg/dL difference, even though mf LDL decreased in accuracy the same as the above comparison, but it was less than sf LDL, the results were sf LDL vs mf LDL as 86 (72.3%) vs 109 (91.6%) p = 0.0001,and 21

Table 1. The difference of LDL-C from direct measurement and calculation by using standard Friedewald and new modified Friedewald equations

Triglyceride level (mg/dL)	Direct measured LDL-C minus by Calculated LDL-C (mg/dL)										Total
	> +20		+11 to + 20		0$\pm$10		-11 to -20		> -20		
	sf	mf	sf	mf	sf	mf	sf	mf	sf	mf	
< 200	0	0	30	9	847	822	23	69	0	0	900
	0.0%	0.0%	3.3%	1.0%	94.1%	91.3%	2.6%	7.7%	0.0%	0.0%	100%
200-299	3	0	29	3	86	109	0	6	1	1	119
	2.5%	0.0%	24.4%	2.5%	72.3%	91.6%	0.0%	5.0%	0.8%	0.8%	100%
300-399	3	0	12	2	21	30	0	3	0	1	36
	8.3%	0.0%	33.3%	5.6%	58.3%	83.3%	0.0%	8.3%	0.0%	2.8%	100%
400-499	4	1	5	0	3	9	0	2	0	0	12
	-	8.3%	-	0.0%	-	75.0%	-	16.7%	-	0.0%	100%
$\geq$500	6	1	1	0	5	8	0	3	0	0	12
	-	8.3%	-	0.0%	-	66.7%	-	25.0%	-	0.0%	100%

sf = standard Friedewald equation, using 1/5 triglyceride to minus
mf = new modified Friedewald equation, using 1/6 triglyceride to minus

(58.3%) vs 30 (83.3%) p = 0.01,respectively; and the difference of dm LDL with sf LDL was more than +10 mg/dL compared to dm LDL with mf LDL difference as the above, sf LDL vs mf LDL as 32 (26.9%) vs 3 (2.5%) p < 0.0001, and 15 (41.6%) vs 2 (5.6%) p = 0.0003, respectively; although as the above comparison with the difference of more than -10 mg/dL, sf LDL vs mf LDL as 1 (0.8%) vs 7 (5.8%) p = 0.03, and 0 (0.0%) vs 4 (11.1%) p = 0.03, respectively (Table 1, 2, and Fig. 1).

Discussion

The authors showed an excellent correlation of LDL-C between dm LDL and sf LDL which was up to 94.1% with 0 ± 10 mg/dL difference if fast serum triglyceride level was less than 200 mg/dL, but the correlation became good to fair when the triglyceride level was in the range of 200-299 and 300-399 mg/dL which was 72.3% and 58.3% of the correlation respectively. When the new modified Friedewald equation was used, the difference of dm LDL and mf LDL with 0 ± 10 mg/dL difference, which was very good, the correlation was up to 91.6% and 83.3% with triglyceride level in the range of 200-299 and 300-399 mg/dL, respectively (Table 1) which was statistically significant, $p < 0.05$, when compared between using the standard Friedewald equation and the new modified Friedewald equation (Table 2, Fig.1). The standard Friedewald equation is based on an estimate of VLDL-C (very low density lipoprotein cholesterol) concentration, which assumes that all plasma triglyceride is carried on VLDL-C, and triglyceride: VLDL-C ratio is about 5:1[10]; the presented data support the study of Benlian et al[11] and the comments of Nauck M et al , that the accuracy declines with triglyceride over 2,000/L if using the Friedewald equation for calculating LDL-C[12]. In CHD or CHD equivalent, LDL-C should have tight control, keeping below 100 mg/dL[1-3], it is not good for underestimation of the LDL-C level, because from ASAP trial showed that when the mean LDL-C level was 118 mg/dL or above, the carotid intima was thicker after follow up for 2 years in familial hypercholesterolemia, but it was thinner when the mean LDL-C level was kept extensively low[2]. The standard Friedewald equation showed more underestimation of LDL-C significantly than the new modified one, which was more than 10 mg/dL if the triglyceride level was 200-399 mg/dL (Table 2). It is possible that when fast triglyceride is 200 mg/dL or more, it may be carried on VLDL-C as the ratio of about 6:1 instead of 5:1. The authors reviewed the English literatures and could not find any equation using 1/6 triglyceride to minus as the authors (LDL = total cholesterol - HDL - 1/6 triglyceride). So the authors offer the new modified Friedewald equation to calculate LDL-C if the fast triglyceride level is 200-499 mg/dL, but do not recommend it if it is 500 mg/dL or more, because of fair correlation with the direct measurement (Table 1), although 5.8%, 11.1%, and 16.7% of mf LDL was overestimated more than 10 mg/dL when compared to dm LDL with the triglyceride level of 200-299, 300-399, and 400-499 mg/dL, respectively; which may cause using more lipid lowering drug than it should, and the patients have

Table 2. The significant difference of LDL-C between using standard Friedewald equation and new modified Friedewald equation by correlating to direct measured LDL-C in each triglyceride level

Triglyceride level (mg/dL)	Direct measured LDL-calculated LDL (mg/dL)		
	0 ± 10		P value
	standard Friedewald	new modified Friedewald	
200-299	86 (72.3%)	109 (91.6%)	0.0001
300-399	21 (58.3%)	30 (83.3%)	0.01
	> + 10		
200-299	32 (26.9%)	3 (2.5%)	< 0.0001
300-399	15 (41.6%)	2 (5.6%)	0.0003
	> -10		
200-299	1 (0.8%)	7 (5.8%)	0.03
300-399	0 (0.0%)	4 (11.1%)	0.03

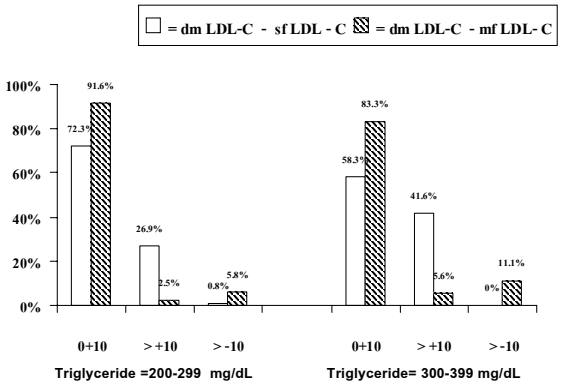

Fig. 1 Comparison of the difference of LDL-C by using standard Friedewald and new modified Friedewald equations in each triglyceride level

to pay more but they have saved some money from the test of LDL-C already, and also they would have a further reduction of coronary events[1,2,6]. This new modified Friedewald equation needs to be testified again especially with dyslipidemic patient sera.

New modified Friedewald equation:

LDL = total cholesterol - HDL - 1/6 triglyceride, when fasting triglyceride in the range of 200 - 499 mg/dL.

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การคำนวณค่า LDL-C ด้วยสูตร new modified Friedewald ดีกว่าสูตร standard Friedewald จริงหรือ?

วิไล พัววิไล, ดอนพิชิต เหล่ารักพงษ์

เป็นที่ยอมรับว่าผู้ป่วยโรคหลอดเลือดแดงที่หัวใจตีบหรือมีปัจจัยเสี่ยงเทียบเท่าควรต้องมีระดับไขมัน LDL-C ต่ำกว่า 100 มก/ดล เพื่อช่วยลดผลแทรกซ้อนของโรคหลอดเลือดแดงที่หัวใจตีบ การวัดค่า LDL-C โดยตรงจากน้ำเลือด (dm LDL) นั้นให้ค่าถูกต้องที่สุด แต่เสียค่าใช้จ่ายสูงขึ้น ดังนั้นจึงใช้ค่า LDL-C จากการคำนวณด้วยสูตร Friedewald equation (sf LDL) ซึ่งคณะผู้วิจัยสังเกตว่าค่า sf LDL นี้มีความถูกต้องลดลงเมื่อระดับ triglyceride มากกว่า 300 มก/ดล คณะผู้วิจัยได้ทำการศึกษาเปรียบเทียบค่า dm LDL กับ sf LDLและคิดสูตรใหม่ เป็น new modified Friedewald equation คำนวณค่า LDL-C (mf LDL)โดยใช้ค่า 1/6 triglycerideไปลบ แทนค่า 1/5 triglyceride

จากการศึกษาตัวอย่างน้ำเลือดจำนวน 1079 ตัวอย่าง พบว่า sf LDL มีความสัมพันธ์อย่างดีมากถึง 94.1% กับ dm LDL โดยมีค่าแตกต่างกัน 0 $\pm$ 10 มก/ดล เมื่อ triglyceride มีค่าน้อยกว่า 200 มก/ดล แต่ความสัมพันธ์นี้ลดลงเมื่อระดับ triglyceride สูงขึ้น และ mf LDL จะมีความสัมพันธ์กับ dm LDL ดีกว่า โดยมีค่าแตกต่างกัน 0$\pm$ 10 มก/ดล คือ sf LDL vs mf LDL มีค่า 72.3% vs 91.6% (p = 0.0001), 58.3% vs 83.3% (p = 0.01) เมื่อระดับ triglyceride 200-299, 300-399 มก/ดล ตามลำดับ และในช่วง 400-499 มก/ดล นั้น mf LDL มีความสัมพันธ์ระดับดีกับdm LDL ถึง75.0%โดยมีความแตกต่างกัน 0 $\pm$ 10 มก/ดล และยังพบว่า sf LDL มีค่าต่ำกว่าความเป็นจริงมากกว่า mf LDL เมื่อเปรียบเทียบกับ dm LDL โดยแตกต่างกันมากกว่า 10มก/ดล คือ sf LDL vs mf LDL มีค่าต่ำกว่าความเป็นจริง 26.9% vs 2.5% (p < 0.0001), 41.6% vs 5.6% (p = 0.0003) ในช่วง triglyceride 200-299 และ 300-399 มก/ดล ตามลำดับ แต่ sf LDL vs mf LDL มีค่ามากกว่าความเป็นจริงเกิน 10 มก/ดล เพียง 0.8% vs 5.8% (p = 0.03), และ 0.0% vs 11.1% (p= 0.03) เท่านั้น โดยทั้งหมดดังกล่าวมีค่า triglyceride 200-299, 300-399 มก/ดล ตามลำดับ คณะผู้วิจัยสรุปผลวิจัยคือ สูตร standard Friedewald นั้นใช้ในการคำนวณค่า LDL-C ให้ค่าถูกต้องมากถ้าระดับ triglyceride น้อยกว่า 200 มก/ดล และคณะผู้วิจัยขอเสนอสูตรใหม่คือ new modified Friedewald equation โดยใช้ 1/6 triglyceride เป็นตัวลบแทน ถ้าระดับ triglyceride 200 -499 มก/ดล ซึ่งสูตรใหม่นี้จะให้ค่า LDL-C ได้ถูกต้องมากกว่า standard Friedewald equation แต่สูตรใหม่นี้จำเป็นต้องถูกทดสอบอีกโดยเฉพาะอย่างยิ่งจากน้ำเลือดของผู้ป่วยที่มีไขมันผิดปกติ