Editorial / Editöryal Yorum

Is it time to abandon Friedewald formula? New equations for LDL-C calculation

Friedewald formülünü bırakma zamanı mı? LDL-C hesaplaması için yeni denklemler

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Lipoproteins and their cholesterol contents play an important role in the initiation and progression of atherosclerosis. There is a causal relationship between cumulative low density lipoprotein cholesterol (LDL-C) arterial burden and atherosclerosis.[1] Therefore, it is crucial to measure these particles accurately. However, it is not easy to measure LDL-C with the reference method, which requires beta-quantification ultracentrifugation. This technique is tedious, time consuming, and expensive. Historically, Friedewald and colleagues developed an equation to estimate LDL-C values using total cholesterol, high density lipoprotein cholesterol (HDL-C), and triglycerides (TG).[2] They originally intended to find a less time consuming and inexpensive method to classify hyperlipoproteinemia to use in epidemiological studies; however, this method has been widely adopted into clinical practice since then. The Friedewald formula was based on two observations. First, there was a constant TG to very low density lipoprotein cholesterol (VLDL-C) ratio (5:1) in normal subjects; and second, most of the TGs were contained in the VLDL when chylomicrons were not detectable.[2] Although Friedewald formula served well for over 40 years, the discovery of new drugs to lower LDL-C to very low levels and the well-known limitations of the equation (e.g. high TG levels) led to questioning of the accuracy of this equation. The original formula was proposed in 1972 when lipid lowering therapies were not widely available, and very low LDL-C values were not recommended. However, accumulating evidence suggested lower LDL-C targets, and it has become possible to achieve these very low targets with new drugs. The Friedewald formula tends to underestimate the LDL-C values in low levels (e.g. <70 mg/dL) and cannot be used at high levels of TG (i.e., >400 mg/dL). Direct chemical assays could be used to measure LDL-C in these circumstances; however, they are not free of charge.

Underestimation of LDL-C with the Friedewald equation was most evident in high-risk patients in whom accuracy was most crucial. Hence, new formulas for more precise calculation of LDL-C were proposed and validated in large studies.[3-6] High levels of TG was another problem for the Friedewald formula, and a new formula was developed to overcome this problem, which allowed to calculate LDL-C for TG <800 mg/dL.[7] All these formulae seem to be more accurate than the old Friedewald formula; however, their validation in large epidemiological studies is lacking. The strengths and limitations of these formulae are summarized in Table 1. One major limitation of all the new formulae is that the Friedewald formula has been widely used in all the clinical trials until now, and the guideline recommendations were made accordingly. However, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor trials used beta

Abbreviations:	
HDL-C	High density lipoprotein cholesterol
LDL-C	Low density lipoprotein cholesterol
PCSK9	Proprotein convertase subtilisin/ kexin type 9
TG	Triglycerides
VLDL	Very Large Database of Lipids
VLDL-C	Very low density lipoprotein cholesterol

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Table 1. Comparison of the strengths and limitations of formulas for LDL-C calculation

	Friedewald[2] LDL-C	Martin/Hopkins[3] LDL-C	Anandaraja[4] LDL-C	Chen[5] LDL-C	Cordova[6] LDL-C	Sampson[7] LDL-C
Formula	LDL-C= TC – HDL-C – TG/5	LDL-C= TC – HDL-C – TG/adjustable factor	LDL-C= (0,9 T-C) – (0,9TG/5) – 28	LDL-C= (Non-HDL-Cx 90%) – (TG × 10%)	LDL-C= ¾ (TC – HDL-C)	LDL-C= (T-C/0,948) – (HDL-C/0,971) – [(TG/8,56) + (TG x non-HDL-C)/2140) – (TG2/16100)] – 9,44
Reference method used for direct LDL-C measurement	Beta quantification	Vertical spin density-gradient ultracentrifugation	Heparin/sodium citrate precipitation	Roche Diagnostics homogeneous method	Select FS (DiaSys), a Wako (Richmond, VA, USA) method	Beta quantification
Sample database	Samples of 448 subjects	Very Large Database of Lipids 1,340,614	Derived in 1000 Indian patients and internally validated in 1008 patients	2180 Chinese patients	10,664 Brazilian patients	18,715 samples from 8656 NIH patients
Validation studies	Extensive use in clinical studies, validation in multiple datasets	External validation in multiple datasets	External validation in Asian populations	External validation in some Asian populations	External validation in some international studies	External validation in some international datasets
Comparison with reference method and other formulas	Acceptable accuracy comparing gold standard	Better performance when compared to Friedewald formula	Better performance when compared to Friedewald formula	Better performance when compared to Friedewald formula	Better performance when compared to Friedewald formula	Better performance than Friedewald and Martin formulas
TG<400 mg/dL	Lowest accuracy among all formulas	Better accuracy especially in low LDL-C values	Better accuracy comparing Friedewald	Better accuracy comparing Friedewald	Better accuracy comparing Friedewald	Better accuracy comparing Friedewald, similar accuracy to Martin
TG>400 mg/dL	The formula is not recommended for this population	The formula is not recommended for this population	The formula is not recommended for this population	The formula is not recommended for this population	The formula is not recommended for this population	Can be used for patients 400-800 mg/dL. There might be errors up to 30 mg/dL
Fasting/ Non-fasting	Fasting state is required	Better accuracy comparing Friedewald formula non-fasting	Fasting samples were used for comparison	Fasting samples were used for comparison	Fasting samples were used for comparison	Better accuracy comparing Friedewald formula in non-fasting
Summary	Old extensively validated formula Major drawback is accuracy in levels of low LDL-C and high TG	Better performance comparing Friedewald in low LDL-C (<100 mg/dL) and high TG (150-400 mg/dL)	Better performance comparing Friedewald formula	Better performance comparing Friedewald formula	Better performance comparing Friedewald formula	Better performance comparing Friedewald formula Comparable performance with Martin formula can be used in higher TG (400-800 mg/dL)

HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; NIH: National Institutes of Health; TG: triglycerides; TC: total cholesterol.

quantification as a reference method for patients who had very low LDL-C values.[8] Lower LDL-C values were safe and effective for lowering the risk of cardiovascular disease, and no level of LDL-C below which a safety concern arises has been defined. These new data should reassure the safety of low LDL-C and to ensure all patients are benefitted, there is a need for an accurate measurement.

In the current issue of the Archives of the Turkish Society of Cardiology, the authors have compared Friedewald and Martin formulae with the direct method for LDL-C estimation in Turkish population.[9] They found a strong correlation between the formulae and direct LDL-C measurement. Although Martin formula showed better performance than Friedewald formula, they both underestimated LDL-C values. The Martin formula was derived by Martin et al.[3] in 2013 from the Very Large Database of Lipids (VLDL) in a clinical sample of >1,300,000 subjects. Unlike Friedewald formula, Martin et al.[3] used an adjustable factor for the TG/VLDL ratio. This adjustable factor was calculated according to HDL-C and TG values of the patients, and they performed a 180 cell table for the formula. In this study, this factor changed between 3.5 and 11.9, and this dynamic structure provided better LDL-C calculation according to authors.[9] An online version of the formula was used to calculate LDL-C values of the patients in this study. However, its 180 factor table was patented and might need licensing agreements for routine implementation into clinical practice in our country. Nevertheless, the vigorous external validity of the formula in several external cohorts led to widespread adoption by clinical laboratories in the United States and worldwide. In September 2021, the National Lipid Association issued a new statement on lipid measurements and recommended to prefer Martin/Hopkins equation, especially in patients with an LDL-C level below 100 mg/dL and TG of 150-400 mg/dL. Similar to Friedewald, the Martin formula cannot be used in patients with hypertriglyceridemia (>400 mg/dL). Notwithstanding, this new formula outperforms Friedewald at TG levels of 150-400 mg/dL. When we consider the fact that almost every one of three adults in our population has hypertriglyceridemia, the accuracy of the formula used to calculate LDL-C becomes more significant in our country and for countries having a high percentage of metabolic syndrome.[10] Similar to previous studies, misclassi-fication of cardiovascular risk was most pronounced in high-risk patients in this study.[9] Although 92% of patients had an LDL-C of >100 mg/dL according to direct LDL-C measurement, 82% and 73% had an LDL-C of >100 mg/dL according to Martin and Friedewald formulae, respectively. This misclassification of risk might lead to under-treatment of high-risk patients as mentioned by the authors. One of the most important limitations of the study is the direct LDL-C method used as a reference method. The authors did not use beta-quantification ultracentrifugation (gold standard method); however, they claimed that the method had been standardized against it. Although there are a dozen of new formulae for LDL-C calculation, the authors preferred to use the Martin formula as a comparator in their study. It might be defended as it has been the most intensively studied formula, but a new formula proposed by Sampson et al.[7] could also be used in the study. The new equation has comparable results to the Martin formula and can be used in patients with hypertriglyceridemia. It also does not need a 180-cell table and is thus freely available. The authors also used a relatively small population, and there is a need for a larger number of subjects with different lipid status for generalizability of the equation in the Turkish population. Nevertheless, their efforts will give us perspective regarding the use of new formulas for better LDL-C calculation and better risk classification of our patients.

In conclusion, LDL-C (the primary lipid target for cardiovascular risk reduction) is underestimated by the Friedewald formula in high-risk patients. This underestimation is pronounced in patients with low LDL-C (<100 mg/dL) and relatively high TG (150-400 mg/dL) levels. The Martin formula can be used as an alternative calculation method, which has better correlation with direct LDL-C measurements. This study, being the first validation of the Martin formula in Turkish population, adds to our knowledge. We should move forward to validate these new equations in our population and seek a way to implement new formulae for LDL-C calculation in high-risk patients.

Conflict of interest: None.

REFERENCES

1. Ference B, Ginsberg H, Graham I, Ray K, Packard C, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemi-

ologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2017;38:2459-72. [Crossref]

2. Friedewald W, Levy R, Fredrickson D. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502. [Crossref]

3. Martin S, Blaha M, Elshazly M, Toth P, Kwiterovich P, Blumenthal R, et al. Comparison of a novel method vs the Friedewald equation for estimating low-density lipoprotein cholesterol levels from the standard lipid profile. JAMA 2013;310:2061-8. [Crossref]

4. 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. [Crossref]

5. 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. [Crossref]

6. de Cordova CMM, de Cordova MM. A new accurate, simple formula for LDL-cholesterol estimation based on directly measured blood lipids from a large cohort. Ann Clin Biochem 2013;50:13-9. [Crossref]

7. Sampson M, Ling C, Sun Q, Harb R, Ashmaig M, Warnick R, et al. A new equation for calculation of low-density lipoprotein cholesterol in patients with normolipidemia and/or hypertriglyceridemia. JAMA Cardiol 2020;5:540-8. [Crossref]

8. Martin S, Giugliano R, Murphy S, Wasserman S, Stein E, Ceška R, et al. Comparison of low-density lipoprotein cholesterol assessment by Martin/Hopkins estimation, friedewald estimation, and preparative ultracentrifugation: insights from the FOURIER trial. JAMA Cardiol 2018;3:749-53. [Crossref]

9. Alpdemir M, Alpdemir MF. Comparison of Martin and Friedewald equation for estimated LDL-C in adults. Turk Kardiyol Dern Ars 2021;49:619-26.

10. Kayikçioğlu M, Tokgözoğlu L, Kiliçkap M, Göksülük H, Karaaslan D, Özer N, et al. Data on prevalence of dyslipidemia and lipid values in Turkey: systematic review and meta-analysis of epidemiological studies on cardiovascular risk factors. Turk Kardiyol Dern Ars 2018;46:556-74.