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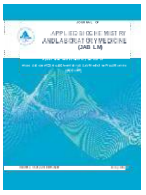

Review Article

Journey of calculated LDL cholesterol in perspective of accuracy

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Density Lipoprotein Cholesterol

ABSTRACT

Low Density Lipoprotein Cholesterol (LDL-c), a key cardiovascular disease marker is often estimated by Friedwald (1972), Martin equation (2013) or other equation but calculating LDL cholesterol is less accurate in patients with low LDL-c or hypertriglyceridemia (TG ≥ 400 mg/dl). Six different formulas were used time to time in different ethnic populations like Chen's formula (2010), Anandaraja's formula (2005), Puavilai formula (2009), Vujovic's formula (2010), de Cordova's formula (2013), Dansethakul formula (2015) with low significant coefficient (r ≥ 0.78) with direct LDL cholesterol measurement in TG < 400 mg/dl. Till now Equation 2 (β quantification) has shown prospect in correlation with direct LDL-c measurement in TG values > 400 mg/dl or low LDL cholesterol values, yet to be on board for small scale laboratories.

INTRODUCTION

Low Density Lipoprotein Cholesterol (LDL-C) is of immense clinical importance and is a treatment target in different world-wide cardiology guidelines. The vintage method of estimation was preparative ultracentrifugation but due to its time, machinery requirements and other problems it has become obsolete.

PHASES OF DEVELOPMENT:

Next came the Friedewald Equation[1] in 1970's; but it was later prone to inaccuracy at low LDL-C or high Triglyceride (TG) levels. Results showed higher Very-Low Density Lipoprotein Cholesterol (VLDL-C) and underestimation of LDL-C.

Then in the year 2013 came the Martin-Hopkins Equation[2,3]. It came as a need from the cardiology community; and from a large population study it was equated by an adjustable factor based on non-High Density Lipoprotein Cholesterol (non-HDL-C) and triglyceride values, where TG value is <400 mg/dl. So, the equation stands as:

LDL-C = Total Cholesterol –HDL-C – TG/adjustable factor

Another formula for estimation of LDL-C was given by Anandaraja et. al[4]is

LDL-C = 0.9 X Total Cholesterol X (0.9 X TG/5) – 28

It overestimates LDL-C at TG level up to 200 mg/dl while it underestimates LDL-C at TG level 201 – 400 mg/dl. Correlation of 0.89 between Anandaraja formula of LDL-C and Direct LDL-C was found by Vujovic et. Al[5]. Kamezaki et. al[6] reported an underestimation of 5.9 mg/dl by Friedewald formula compared to Direct LDL-C measurement.

This improved LDL-C estimation accuracy than prior. Recent AHA/ACC/Multi-society Cholesterol Guideline provided a Class IIa recommendation for using the equation in patients with LDL-C <70 mg/dl[7], but the problem still persisted with TG>400 mg/dl where chylomicrons accumulate and alter the relationship with TG and VLDL-C. Here came several commercial direct assay kits for this purpose which also lacked accuracy and standardization in this high TG values.

In this jeopardy ushered a new equation from a huge number of sample study from NIH (National Institute of Health)Clinical Center[8]. Sampson and colleagues proposed LDL-C (β-quantification)as:

LDL-C = TC/0.948 – HDL-C/0.971 – [TG/8.56 + (TG X nonHDL-C)/2140 – TG2/16100] – 9.44, where TC = Total Cholesterol. This was also known as Equation 2.

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This Equation 2 was compared with Friedewald and Martin/Hopkins, mainly focusing on samples with TG >400 mg/dl (spectrum 0 to >2880 mg/dl) and LDL-C value (spectrum 0 – 800 mg/dl) and statistical analysis showed Root Mean Square Errors (RMSE) with Equation 2(15.2), Friedewald estimation (32)and Martin/Hopkins (25.7). Hence Equation 2 stands good with low RMSE.

Then Mean Absolute Difference (MAD) was calculated between directly estimated LDL-C, β-quantification (i.e., Equation 2) and other equations at various TG and non-HDL-C ranges. Authors found MAD values with Equation 2 (24.9 mg/dl), Friedewald equation (56.4 mg/dl) and Martin/Hopkins (44.8 mg/dl). Hence MAD were also smaller with Equation 2 across the range of triglycerides (0 – 3000 mg/dl) compared to other equations with Direct LDL-C assay (especially Cobas direct LDLC3 estimation by homogeneous enzymatic colorimetric assay).

Reclassification of LDL-C based on guideline LDL-C cut-points were examined on different TG level of <400 mg/dl to 400 – 800 mg/dl and accuracy of Equation 2 was again established. Overall, the authors conclude that Equation 2 is the best for estimation of calculated LDL-C at low LDL-C and/or high TG which can be used by the laboratories with no extra cost.

Sampson et. al's analysis then first gave a blow to Equation 2 by stating:

a) Negative bias for low LDL-C values

b) Derivation of Equation 2 from a low sample population (< 20,000) in contrast to Martin/Hopkin's containing>1 million lipid samples

Now the question is which result will a clinician take up from a standard Lipid Profile; Calculated or directly estimated LDL-C? Answer comes from analysis of different studies:

1. Friedewald LDL-C:

a. worst accuracy at low LDL-C and high TG levels (> 400 mg/dl)

b. LDL-C can be directly measured when TG > 400 mg/dl

2. Martin/Hopkins LDL-C:

a. Best accuracy at LDL-C < 70 mg/dl and TG < 400 mg/dl

b. Not recommended at TG >400 mg/dl. Hence LDL-C should be directly measured.

c. In those with LDL-C < 70 mg/dl (high risk range) and TG<400 mg/dl, this equation is the least likely to underestimate risk by falsely reclassifying patients into lower risk category according to cardiologists and under-treatment in high risks patients at these LDL-C levels is arguably more clinically relevant than over-treatment.

3. Equation 2:

a. Best accuracy at TG >400 mg/dl where other two equation does not stand

b. Clinically relevant margin of error up to 30 mg/dl at TG level of 800 mg/dl. So direct LDL-C measurement is still highly recommended at TG>400 mg/dl.

c. In those with LDL-C< 100 mg/dl this equation is least likely to overestimate risks by falsely reclassifying patients in a high-risk category according to cardio-logical basis. So least likely to cause overtreatment.

Now comes the estimated LDL-C accuracy at high TG levels. Sampson et. al's analysis focused on LDL-C estimation accuracy at high TG value from range 400 – 3000 mg/dl. Martin et. al. assigned only one row of adjustable TG/VLDL-C factors (6 total factors) from a 180-cell table (statistical analysis) to estimate LDL-C at TG values > 400 mg/dl and acknowledged the limited adaptability of the Equation 2 at these higher TG level.

Ultimately AHA/ACC/Multi-society Cholesterol Guidelines specifically note direct LDL-C assays should be used at high TG levels.

Emerging is the era of ultra-low LDL-C measurement due to use of PCSK 9 inhibitors (Protein Convertase Subtilisin/Kexin type 9)[9]. European cholesterol guidelines recommended LDL-C goal <55 mg/dl in very high-risk patient. Here also equation 2 is ahead than other two (i.e., Friedewald and Martin/Hopkins equation) in calculated jonour but still non validated and inaccurate with respect to direct LDL-C measurement. The lower limit of detection in direct LDL-C measurement according to LDL-Cholesterol-Gen.3 kit literature of Cobas is 3.87 mg/dl.

CONCLUSION:

Equation 2 need further testing in the LabCorp dataset (Statistical Analysis) in patients with low or very low LDL-C and TG in varying ranges to get the most accurate LDL-C assessment by simple calculation in place of direct LDL-C measurement to reduce the cost burden for patients and small scales laboratories.

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