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Performance of LDL-C calculated with Martin's formula compared to the Friedewald equation in familial combined hyperlipidemia

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ABSTRACT

Background and aims: A novel method to estimate low density lipoprotein cholesterol (LDL-C) has been proposed by Martin et al. This may permit a more accurate estimation of cardiovascular risk, however, external validation is needed. Here, the performance of LDL-C using this new method (LDL-N) is compared with LDL-C estimated with Friedewald equation (LDL-F) in familial combined hyperlipidemia (FCHL), a common primary dyslipidemia in which apolipoprotein B containing particle composition is abnormal and interferes with LDL-C estimation.

Methods: A total of 410 FCHL subjects were included. LDL-C was estimated with both the Friedewald equation (LDL-F) and the novel formula (LDL-N). Apolipoprotein B levels and non- HDL-C were recorded. The correlation and concordance between LDL-F and LDL-N and both Apolipoprotein B and non-HDL-C levels were calculated. Analysis stratifying for triglyceride tertiles and FCHL lipid phenotypes was also carried out.

Results: The correlations between LDL-N and Apo B and non-HDL-C were $\rho = 0.777$ (95%CI 0.718–0.825) and $\rho = 0.735$ (95%CI 0.648–0.816), respectively. The corresponding correlations for LDL-F were $\rho = 0.551$(95%CI 0.454–0.637) and $\rho = 0.394$ (95%CI 0.253–0.537), respectively. In mixed dyslipidemia or isolated hypertriglyceridemia, these correlations were significantly better using LDL-N. With respect to concordance, LDL-N performed significantly better than LDL-F when considering apoB <90 mg/dL (κLDL-N = 0.495 *vs.* κLDL-F = 0.165) and non-HDL-C <130 (κLDL-N = 0.724 *vs.* κLDL-F = 0.253).

Conclusions: In FCHL, LDL-C estimation using Martin's formula showed greater correlation and concordance with non-HDL-C and Apo B compared with the Friedewald equation.

1. Introduction

Low density lipoprotein cholesterol (LDL-C) remains the principle goal of therapy in the management of dyslipidemia [1–4]. However, many people who achieve LDL-C goals still develop atherosclerotic disease due to residual risk [5]. In certain patients there is a mismatch between the concentration of LDL-C and the number of atherogenic particles, expressed as the number of lipoproteins containing apolipoprotein B. Low density lipoprotein (LDL) particles are heterogeneous with respect to the amount of cholesterol they carry [6]. One person may have large LDLs, rich in cholesterol, while a second person can have small LDLs, which contain only a small amount of cholesterol. Therefore, at the same concentration of LDL-C, the second person will have a greater number of atherogenic particles (LDLs), and consequently increased cardiovascular risk [6]. As a consequence of this discrepancy, several expert panels suggest the use of other parameters to improve the evaluation of cardiovascular risk and determine intensity of therapy. These include apolipoprotein B (ApoB) and non-high density cholesterol (non-HDL-C); both parameters are useful but not equivalent.

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LDL-C represents the mass of cholesterol within LDL particles, whereas the ApoB concentration represents the total number of circulating atherogenic particles [7]. The measurement of this parameter is standardized among laboratories and does not require fasting but it represents a significant additional cost to the patient. Non-HDL-C is calculated by subtracting the concentration of HDL-C from total cholesterol and represents the cholesterol contents of all the atherogenic lipoproteins. It is considered a good therapeutic goal because its value does not change regardless of lipid exchange between VLDL-C and LDL [8]. In summary, non-HDL-C represents the cholesterol content of atherogenic lipoproteins (VLDL, IDL, LDL and Lp(a)), whereas apolipoprotein B measures the total number of atherogenic particles. When the content of cholesterol in the LDL-C particles is normal, both parameters are consistent. This means that they are equal for reporting cardiovascular risk. However, when the cholesterol content in the LDL-C particles is higher or lower than normal, the two parameters are discordant and predict differing risks.

The superiority of ApoB and non-HDL cholesterol for the prediction of cardiovascular risk compared with LDL-C has been shown in several studies [9–14]. The assessment of ApoB and non-HDL cholesterol may be even more relevant in persons with atherogenic dyslipidemias characterized by triglyceride-rich lipoproteins, low levels of HDL-C and increased levels of small dense LDL-C particles, including type 2 diabetes, metabolic syndrome and certain primary dyslipidemias such as familial combined hyperlipidemia (FCHL). In these cases, the total number of LDL-C particles may be higher than the calculated LDL-C level. Thus, using the LDL-C goal alone may not be enough.

FCHL is the most common primary atherogenic dyslipidemia in Mexico, being present in approximately 14% of patients with premature coronary heart disease [15,16]. It is associated with other metabolic abnormalities including obesity, insulin resistance, diabetes and metabolic syndrome [17]. FCHL is characterized by hypercholesterolemia and/or hypertriglyceridemia and elevated apolipoprotein B levels, a fluctuating lipid profile and variable expression within the same kindred. LDL-C may not be the best treatment target in this population, given the frequent presence of hypertriglyceridemia, other lipid targets including non-HDL-C and ApoB levels are probably more relevant in FCHL.

Conventionally, LDL-C is calculated by the Friedewald equation, avoiding the need for an ultracentrifuge [18]. This equation estimates LDL-C as (total cholesterol) − (high-density lipoprotein cholesterol [HDL-C]) − (triglycerides/5) in mg/dL. The final term assumes a fixed ratio of triglyceride levels to very low-density lipoprotein cholesterol (TG:VLDL-C) of 5:1.This estimate is unreliable in patients with triglycerides $\geq$150 mg/dL due to this fixed triglyceride to VLDL-C ratio, and does not consider the variance of this ratio across different concentrations of triglycerides and non-HDL-C [18]. Martin et al. have developed a novel method for estimating LDL-C using an adjustable factor for the TG: VLDL-C ratio (using triglyceride and non-HDL-C concentrations), which offers a greater concordance with measurement of LDL-C by ultracentrifugation [19]. This novel method has not been validated in populations that are characterized by abnormal apolipoprotein B containing particle composition, such as in FCHL; this method might be particularly helpful in such population. The objective of this study is to evaluate the correlation and the concordance of LDL-C, as calculated with the Friedewald equation (LDL-F) and Martin's formula (LDL-N), with non-HDL-C and ApoB targets in patients with FCHL. The results will determine the usefulness of this new method of LDL-C estimation in patients with atherogenic dyslipidemia.

2. Materials and methods

2.1. Study population

Subjects with a previous diagnosis of familial combined hyperlipidemia (FCHL) attending the lipid Clinic at the Instituto Nacional de Ciencias Medicas y Nutricion, Salvador Zubirán (INCMNSZ) in Mexico City were included. All participants gave informed consent. The Human Research Ethics Committee of the INCMNSZ approved the study. All procedures were done in accordance with the Declaration of Helsinki.

2.2. Clinical evaluations

All participants completed a questionnaire which included demographic data, medical history, and lifestyle factors. Patients arrived with the results of a routine lipid profile taken a week before their clinic visit. Diagnostic criteria considered for FCHL were the presence of hypercholesterolemia (total cholesterol >200 mg/dL) or hypertriglyceridemia (triglycerides >150 mg/dL) along with the demonstration of hypercholesterolemia, hypertriglyceridemia and mixed hyperlipidemia in three different first degree relatives and apolipoprotein B level >90th percentile for the Mexican population (>108 mg/dL for men and >99 mg/dL for women). Exclusion criteria included history of an acute illness within the previous six weeks, pregnancy and the presence of any disease or medication known to significantly influence lipid parameters. A complete medical and family history, including use of medications was obtained from all subjects. Subjects were weighed on calibrated scales and height was determined with a floor scale stadiometer. Body mass index (BMI) was calculated as weight in kg divided by the squared product of height in meters.

2.3. Laboratory measurements

Blood samples were obtained after an 8–12 h fast. Plasma glucose concentration was measured by an automated glucose analyzer (Yellow Springs Instruments Co.), serum insulin concentration was measured by using a chemiluminescent immunoassay (Beckman Coulter Access 2). Lipid concentrations (cholesterol, triglycerides, and HDL cholesterol) and apo B measurements were performed using colorimetric assays (Unicel DxC 600 Synchron Clinical System Beckman Coulter). LDL-cholesterol was calculated with the Friedewald equation and the calculation proposed by Martin et al. [18].

2.4. Statistical analyses

Data are presented as mean ± SD or as median and interquartile range. Proportions and medians were compared between groups using the chi-square test and Mann Whitney-U tests. Variables with a parametric distribution were evaluated using Student's t-test. Spearman correlations were performed to evaluate the degree of linear association between LDL-C, LDL-N, apolipoprotein B and non-HDL cholesterol. Linear regression analyses were also performed using logarithmic transformation. Concordance between LDL-C, LDL-N, non-HDL cholesterol and apolipoprotein B targets was assessed using the kappa coefficient in the total population and in subpopulations. We also evaluated correlations and concordance across tertiles of triglyceride levels and according to the differing phenotypes of FCHL, namely isolated hypertriglyceridemia (IHTG), mixed dyslipidemia (MDLP) and isolated hypercholesterolemia (IHCT). Performance of the index was evaluated using areas under

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