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Difference between calculated and direct-measured low-density lipoprotein cholesterol in subjects with diabetes mellitus or taking lipid-lowering medications

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OBJECTIVE: We evaluated factors that caused differences between calculated low-density lipoprotein cholesterol (C-LDL-C) and direct-measured LDL-C (D-LDL-C) and compared them in subjects with diabetes mellitus (DM) or taking lipid-lowering medications.

METHODS: 21,452 subjects (9,177 women, 12,275 men; 8.1% with DM and 8.5% on lipid-lowering medications) were included in the analysis. Participants were classified into 3 groups, i.e., group 1: the subjects without DM and not on lipid-modifying drugs (n = 18,287), group 2: without DM and on lipid-modifying drugs (n = 1,423), and group 3: with DM (n = 1,742). LDL-C concentrations were either directly measured by a homogenous method or calculated by Friedewald formula.

RESULTS: There was a significant correlation between C-LDL-C and D-LDL-C ($r = 0.966$, $P < .001$). The absolute values of the differences between two LDL-C values were 7.0 ± 6.2 mg/dl and 6.6 ± 7.3% (6.6 ± 5.9 mg/dl and 6.0 ± 6.5%, 8.8 ± 6.7 mg/dl and 9.1 ± 9.7%, and 10.1 ± 7.3 mg/dl and 10.7 ± 10.1% in group 1, 2, and 3 respectively, $P < .001$). The subjects with the absolute value of the differences of LDL-C ≥10% was 20.2% (17.3%, 31.3%, and 41.1% in group 1, 2, and 3 respectively, $P < .001$). In the multiple logistic regression analysis, high triglyceride (≥150 mg/dl), low high-density lipoprotein cholesterol (HDL-C) (<40 mg/dl), male gender, obesity (body mass index ≥25 kg/m^2), DM and taking lipid-lowering drugs were significant associated with high LDL-differences (the absolute value of the differences ≥10% or ≥10 mg/dl).

CONCLUSION: D-LDL-C was generally higher by 5 mg/dl or 5% than C-LDL-C. The differences C-LDL-C and D-LDL-C were higher in subjects with DM and on lipid-lowering medications. Male gender, high triglyceride, low HDL-C, and obesity were also associated with the greater differences between C-LDL-C and D-LDL-C.

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for the development of ischemic heart disease, and the lowering of LDL-C decreases mortality in patients with coronary heart disease.[1] LDL-C can be measured directly or calculated by Friedewald formula. Friedewald formula drives LDL-C from total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) in fasting state[2]: [LDL-C] = [TC] − [HDL-C] − [TG]/5. According to the third report of the National

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Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III,[3] LDL-C is the primary target for the diagnosis and treatment of hypercholesterolemia largely based on early epidemiologic studies that established the link between lipoproteins and cardiovascular disease. Most of these studies used chemical precipitation methods for HDL-C, and β-quantification or the Friedewald calculation for LDL-C.[3] Although calculated LDL-C (C-LDL-C) is also convenient for clinical practice, it is not recommended for use in nonfasting state or when TGs are greater than 400 mg/dL. Indeed, Friedewald formula should be used with precaution in several pathologic states, such as diabetes mellitus (DM) hepatopathy, nephropathy, even if the TG concentrations are between 200 mg/dL and 400 mg/dL.[4,5] Comparisons between C-LDL-C and direct-measured LDL-C (D-LDL-C) show good agreement and the latest European guidelines for the management of dyslipidemia has recommended D-LDL-C whenever available.[6] In our community-based study, we evaluated factors that caused differences between C-LDL-C by Friedewald formula and D-LDL-C by using a homogenous method and compared them in subjects with DM and taking lipid-lowering medications.

Methods

Patient population

The study population consisted of asymptomatic subjects free of acute cardiovascular disease and acute illness who visited Seoul National University Hospital Healthcare System Gangnam Center between January 2010 and December 2010. All subjects had general health checkups, including fasting lipid measurements for screening purpose on patients' demand. Medical histories and current medications were derived from medical questionnaires. Of 25,505 participants, subjects with TG concentration ≥400 mg/dL (4.52 mmol/L; n = 186, male 92.0%), aged older than 80 years, with renal insufficiency (creatinine >1.4 mg/dL), untreated hypo- or hyperthyroidism (thyroid-stimulating hormone <0.4 or >4.1 μIU/mL), hepatopathy (aspartate aminotransferase ≥100 IU/L or alanine aminotransferase ≥100 IU/L), or who receiving steroid medication or hormone-replacement therapy after menopause were excluded. After exclusion of 4,053 subjects, 21,452 participants (9,177 women, 12,275 men) were enrolled in the present study.

Hypertension was defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg without medication in the outpatient clinic on at least two separate measurements or on antihypertensive medications. DM was defined as fasting blood glucose ≥126 mg/dL, 2-hour blood glucose after oral glucose tolerance test ≥200 mg/dL, plasma hemoglobin A1c (HbA1c) ≥6.5% or use of medication for diabetes. Obesity was defined as body mass index (BMI) ≥25 kg/m^2, according to the criteria from the World Health Organization's Asia-Pacific guideline.[7] The study protocol was confirmed and approved by the Institutional Review Board of Seoul National University Hospital. Because the study was performed retrospectively with the use of medical records, informed consent was not obtained from study subjects.

Lipid measurement

We performed our analyses with measuring 12-hour fasting blood samples. Serum TC and TG concentrations were measured by enzymatic methods and LDL-C and HDL-C concentrations by a homogenous method with Architect Ci8200 (Abbott, Abbott Park, IL). LDL-C was also calculated with the Friedewald formula.

We evaluated the differences and percent differences between C-LDL-C and D-LDL-C concentrations by subtracting C-LDL-C from D-LDL-C concentrations and also evaluated the absolute vales of the differences and percent differences of LDL-C.

$$\%\ \text{difference of LDL-C} = [\{(\text{D-LDL-C}) - (\text{C-LDL-C})\}/(\text{C-LDL-C})] \times 100$$

The total errors of TC, TG, HDL-C, and D-LDL-C were 2.8%, 3.9%, 4.4%, and 6.5% respectively, with the reference measurement procedures performed at the Centers for Disease Control and Prevention (CDC). The analytical performances for the measurements of the lipids and lipoproteins met the NCEP goals for inaccuracy, imprecision, and total error.

Statistical analysis

The study subjects were grouped into two, according to the genders. Participants were also classified into three groups according to clinical characteristics, ie, group 1: the subjects without DM and not on lipid-modifying drugs, group 2: without DM and on lipid-modifying drugs, and group 3: with DM. Data are expressed as mean ± SD and median (interquartile range) for continuous variables and as frequencies and percentages for categorical variables. For TG which was highly skewed, we used log-transformed values for statistics analysis. Groups were compared by the use of *t*-test and analysis of variance for means and Mann-Whitney and Kruskal-Wallis test for medians for continuous variables and χ^2 test for categorical variables.

Several approaches were used to assess the agreement between C-LDL-C and D-LDL-C. First, linear regression, scatter-plots, and paired *t*-test analyses were performed to assess significant differences in LDL-C concentrations obtained by calculation and direct measurement. Second, C-LDL-C and D-LDL-C measures were tabulated on the basis of modifying LDL-C goals recommended by the NCEP ATP-III guidelines,[3] that is, 100 mg/dL, 130 mg/dL, and 160 mg/dL. κ Statistics were used to assess and test for