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Original article

Association of triglyceride-rich lipoproteins-related markers and low-density lipoprotein heterogeneity with cardiovascular risk: Effectiveness of polyacrylamide-gel electrophoresis as a method of determining low-density lipoprotein particle size

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ABSTRACT

Background: Despite well-controlled low-density lipoprotein cholesterol (LDL-C), hypertriglyceridemia is an independent predictor of coronary events. We investigated the risk of atherosclerotic cardiovascular disease through examining the relation between triglyceride (TG) metabolism and LDL-heterogeneity as assessed by polyacrylamide-gel electrophoresis (PAGE).

Methods and results: Estimated LDL-particle size [relative LDL migration (LDL-Rm value)] measured by PAGE with the LipoPhor system (Joko, Tokyo, Japan) was evaluated in 645 consecutive patients with one additional risk factor for atherosclerotic cardiovascular disease.Multivariate regression analysis after adjustments for traditional risk factors revealed an elevated triglyceride-rich lipoproteins (TRLs)-related markers [TG, remnant-like particle cholesterol (RLP-C), very LDL (VLDL) fraction, apolipoprotein (apo) C-II, and apo C-III] level to be an independent predictor of smaller-size LDL-particle size, both in the overall population, and in a subset of patients with serum LDL-C <100 mg/dL. Even among the patients with LDL-C levels <100 mg/dL, the serum levels of atherogenic lipid markers in those with a LDL-Rm value ≥0.40, suggesting the presence of large amounts of small-dense LDL and upper limit (mean + 2 standard deviation) in this population, were significantly higher than in those with a LDL-Rm value <0.40. Moreover, the serum levels of TRLs-related markers showed high accurate area under the receiver-operating characteristic curve (TG, 0.896; RLP-C, 0.875; VLDL fraction, 0.803; apo C-II, 0.778; and apo C-III, 0.804, respectively) in terms of evaluation of the indicators of LDL-Rm value ≥0.40.

Conclusion: To further reduce the risk of atherosclerotic cardiovascular disease, it may be of particular importance to pay attention not only to the quantitative change in the serum LDL-C, but also TG-metabolism associated with LDL-heterogeneity. Combined evaluation of TRLs-related markers and LDL-Rm value may be useful for assessing the risk of atherosclerotic cardiovascular disease.

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Introduction

Large observational studies clearly show that elevated triglyceride (TG) levels are associated with increased coronary artery disease (CAD) risk [1]. Moreover, in recent years evidence of the importance of the substances associated with hypertriglyceridemia as residual risks of CAD has been increasing even in successful low-density lipoprotein cholesterol (LDL-C) reduction trials [2]. TG metabolites, i.e. chylomicrons, very low density lipoprotein (VLDL), and remnant-like particle cholesterol (RLP-C), which are TG-rich lipoproteins (TRLs), and, apolipoprotein (apo) CII and apo CII which are involved in the metabolic process, etc. have been demonstrated to be involved in the progression of atherosclerosis [3].

In addition, conversion of LDL to small particles (small dense LDL, sd-LDL), which hypertriglyceridemia causes, is a powerful promoter of atherosclerotic cardiovascular disease, especially CAD, and has also been reported to be a predictor of ischemic cardiac events [4].

Density gradient ultracentrifugation, nondenaturing gradient gel electrophoresis, and nuclear magnetic resonance spectroscopy are the methods that are usually employed to measure LDL-particle size; but they are difficult to apply in clinical settings due to

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their cost and complexity [5]. On the other hand, estimation of LDL-particle size based on relative LDL migration (LDL-Rm) during polyacrylamide-gel electrophoresis (PAGE) has been reported. Currently, the Lipoprint system, also based on the PAGE system, is used for estimation of the LDL particle size by a simple procedure in the clinical setting, and has been shown to carry high diagnostic accuracy [6]. In Japan, however, the Lipoprint system is not commercially available at present. We used the LipoPhor system (Joko, Tokyo, Japan) for the evaluation of the LDL-particle size in this study. High correlation of the assay results between the two methods has been reported [5,7,8].

The purpose of this study was to evaluate the usefulness of measuring LDL-Rm value as an index of the LDL-particle size by examining the relation between the serum levels of TRLs-related markers (TG, VLDL fraction, RLP-C, apo C-II, and apo C-III) and the LDL-Rm value by the hospital-based cross-sectional study method, and furthermore, to reevaluate the risk of CAD through examining the relations between TG-metabolism and LDL-particle size.

Methods

Study design and populations

This study was designed as a hospital-based cross-sectional study to investigate the relationships between the serum levels of TRLs-related markers as indicators of the risk of atherosclerotic cardiovascular disease and LDL-heterogeneity in patients with the presence of one or more risk factors for atherosclerosis.

The study was conducted on a sample of 700 consecutive outpatients who had undergone regular examinations and blood examinations at Cardiovascular Center, Surugadai Nihon University Hospital between April 2009 and October 2009.

The criterion for patient registration in the cross-sectional study was the presence of one or more risk factors for atherosclerosis. The diagnostic criteria for the coronary risk factors that we used in this study analysis were: a diagnosis of hypertension was made when systolic pressure was 140 mmHg or diastolic pressure was 90 mmHg, or above, or taking medication. Diabetes was defined as a fasting plasma glucose concentrations ≥126 mg/dL and hemoglobin (Hb) A1c ≥6.5% [according to the National Glycohemoglobin Standardization Program (NGSP)], or current treatment with anti-diabetic agents. A diagnosis of dyslipidemia was made when the LDL-C level was 140 mg/dL or above, the TG level was 150 mg/dL or above, or the high-density lipoprotein cholesterol (HDL-C) level was less than 40 mg/dL, or if the patient was already on lipid-lowering medication. The severity of chronic kidney disease (CKD) was determined on the basis of the estimated glomerular filtration rate (GFR) using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation modified by a Japanese coefficient [9].

The Surugadai Nihon University Hospital Ethics Committee approved all study design and purpose.

Measurement of laboratory parameters

Fasting blood samples were collected early in the morning after a 12-h fast. The serum total cholesterol (TC), HDL-C, and TG levels were measured by the standard methods. LDL-C levels were estimated by using the Friedewald formula [10]. The RLP-C level was measured by an immunoadsorption assay (SRL Co., Ltd., Tokyo, Japan). The VLDL fraction was measured by performing PAGE electrophoresis using the LipoPhor system. The serum apo level was determined by turbidimetric latex agglutination assays (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). The malondialdehyde-modified LDL (MDA-LDL) level was measured by an enzyme-linked immunosorbent assay (SRL Co., Ltd.). The high sensitivity C-reactive protein (hs-CRP) level was measured by a nephelometric assay (Behring Diagnostic, Marburg, Germany).

Measurement of LDL-Rm value

LDL-Rm value, an indicator of LDL-particle size, was measured relative to the mobility value of LDL by performing PAGE with the LipoPhor system. LDL-Rm value was calculated as the distance between the VLDL peak and the LDL peak divided by the distance between the VLDL peak and the HDL peak (Fig. 1). Several studies have reported that an LDL-Rm value of 0.40 or more suggests the presence of a large amount of sd-LDL in the LDL fraction [11–13]. The subjects of this study were not healthy persons in the general population, but the upper limit of the reference interval of the subjects' LDL-Rm values (mean ± 2 Standard deviation [covering 95% of the population: 0.350 ± 0.058]) was 0.408, and it was approximately the same as the 0.40 reported above. Accordingly, we conducted this study on the assumption that a large amount of sd-LDL was present in the LDL fraction when the LDL-Rm value was 0.40 in the present study as well.

Statistical analysis

Data are expressed as the mean ± standard deviation for continuous variables and as percentages for discrete variables. Univariate and multivariate regression analyses were performed to identify independent predictors of LDL-Rm value. All variables correlated with the LDL-Rm values at $p < 0.05$ in the univariate regression analysis were entered into the multivariate model. A receiver-operating characteristic (ROC) analysis was performed to determine the TRLs-related marker cut-off values that indicated an LDL-Rm value ≥0.40. Univariate and multivariate logistic regression analyses of variables affecting patient characteristics with LDL-Rm values were ≥0.40 were performed in patients with LDL-C level <100 mg/dL. A p-value less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed with the SPSS software program (SPSS Inc., Chicago, IL, USA) for Windows (version 12.0.1).

Results

Patients

We excluded 55 subjects from the analysis because of missing laboratory data. Therefore, finally, 645 subjects were included in

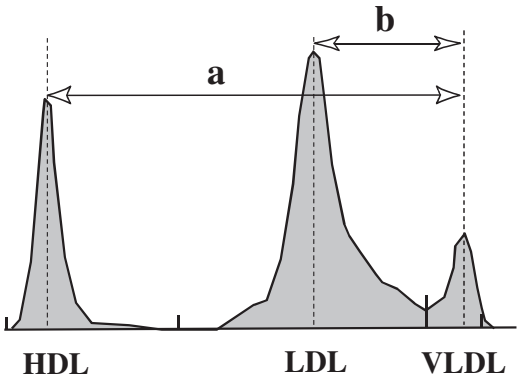

Fig. 1. Measurement of LDL-Rm value by lipoprotein polyacrylamide gel disk electrophoresis. LDL-Rm, relative low-density lipoprotein migration; LDL, low-density lipoprotein; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDL-Rm value calculated from densitometer analysis of polyacrylamide disk gel electrophoresis; LDL-Rm value = b/a.

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