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Heterogeneous properties of intermediate- and low-density lipoprotein subpopulations

Pornpen Srisawasdi [a], Somlak Vanavanan [a,*], Mana Rochanawutanon [a], Prapaporn Pornsuriyasak [b], Visasiri Tantrakul [b], Khanat Kruthkul [b], Kazuhiko Kotani [c]

[a] Department of Pathology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand
[b] Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok 10400, Thailand
[c] Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke-City 329-0498, Japan

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ABSTRACT

Objective: Intermediate-density lipoprotein (IDL) and low-density lipoprotein (LDL) consist of heterogeneous particles whose subpopulations may have different atherogenic characteristics. This study investigated the associations between these subpopulations and other lipids, lipoproteins and atherosclerosis-related markers.

Design and methods: A total of 416 subjects (124 males and 292 females, mean age: 50.8 years) were enrolled in this study. Using polyacrylamide gel electrophoresis, serum lipoproteins were separated according to their specific electrophoretic mobility based on particle size. The IDL particles were separated into three midbands (MID-A to C), and the LDL particles were separated into seven subfractions (LDL1 to 7).

Results: MID-B, MID-C, LDL2 and LDL3 to 6 (as a small LDL fraction) were significantly and positively correlated with very LDL (VLDL), while MID-A and LDL1 were significantly and inversely correlated with VLDL. MID-A and LDL1 were significantly and positively correlated with high-density lipoprotein (HDL). The correlation patterns between MID-A or LDL1 and triglycerides, apolipoprotein A-I, glucose, the insulin resistance index, creatinine and the mean LDL particle size had similar trends to those between HDL and these parameters.

Conclusions: The respective subpopulations of IDL and LDL particles can vary in their ability to predict cardiovascular disease risks. These variations may partially explain why quantitative assessments using LDL-cholesterol concentrations, as typically performed in conventional practice, are not perfect predictors of cardiovascular disease. Further studies are required to determine the clinical relevance of analyzing the IDL and LDL subpopulations.

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Introduction

The levels of lipoproteins, including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL), are widely used to assess the risk of cardiovascular disease (CVD) and its equivalents [1–5]. In particular, VLDL, IDL and LDL particles, the apolipoprotein (apo) B-containing lipoproteins, have been shown to be crucial for the development of atherogenesis [6]. A large number of studies have indicated that these plasma/serum lipoproteins consist of heterogeneous subclasses of varying density, size, electrophoretic mobility, relative lipid-protein proportions and binding affinity [6–9]. The different IDL and LDL subpopulations can be generated by distinct triglyceride (TG)-rich lipoprotein precursors via different metabolic pathways in which genetic factors are partly involved [7,10]. Consequently, differences in the lipoprotein subpopulations may contribute to differences in atherogenic properties.

Evidence shows that many patients with CVD have LDL-cholesterol (LDL-C) levels in the same range as those of healthy subjects [11,12]. The measurement of LDL subpopulations has been proposed to effectively establish LDL management and accurately stratify the CVD risk [5,13]. In addition, patients with metabolic syndrome, who have an increased risk of CVD, often exhibit low HDL-cholesterol (HDL-C) and high TG concentrations [14]. The dyslipidemic status of metabolic syndrome patients includes the predominance of small LDL particles, an atherogenic LDL subpopulation [6,15]. The predominance of the small LDL, but not large LDL, subpopulation has been reported to

Abbreviations: CVD, cardiovascular disease; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MID, midband: intermediate-density lipoprotein; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; HbA1C, hemoglobin A1C; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein.

* Corresponding author at: Division of Clinical Chemistry, Department of Pathology, Faculty of Medicine Ramathibodi Hospital, Rama VI Road, Rachathavee, Bangkok 10400, Thailand. Fax: +66 2 354 7266.
E-mail address: svanavanan47@gmail.com (S. Vanavanan).

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predict future CVD events [11], while one study reported an association between large LDL and the CVD risk relative to the small LDL subpopulation [16]. Furthermore, the potential atherogenicity of the IDL subpopulations remains to be determined [17], although IDL particles reportedly demonstrate familiarity with the arterial wall [18] and exhibit overlapping characteristics with those of LDL [19]. Accordingly, the LDL-C level, a quantitative measure often used in routine practice, is limited in its ability to predict the CVD risk, and great attention has been recently paid to analyzing lipoprotein subpopulations.

To date, several methodologies for discriminating lipoprotein subpopulations have been developed, including density gradient ultracentrifugation [20], non-denaturing gradient gel electrophoresis [21], tube gel electrophoresis [22], nuclear magnetic resonance (NMR) spectroscopy [23] and ion mobility [24]. Nevertheless, the specific subpopulations of lipoproteins have variously been identified according to the techniques used to separate the particles [25]. One method for performing linear polyacrylamide tube gel electrophoresis (Quantimetrix Lipoprint™, CA) separates plasma/serum lipoprotein particles on the basis of size and, to a lesser extent, charge into VLDL, three subfractions of IDL and seven subfractions of LDL and HDL [22]. This currently used method has been proven valid compared to the NMR method as a gold standard [22].

The aim of this study was to examine how the distinct lipoprotein subpopulations, as defined by polyacrylamide gel electrophoresis, can correlate with other lipids, lipoproteins and atherosclerosis-related markers. The subpopulations were also analyzed in a subgroup with various phenotypic patterns of dyslipidemia (i.e. high or normal TG and LDL-C levels) in order to gain insight into the distinct lipoprotein subpopulations with different pathways of lipid metabolism. This study demonstrates the relative potential atherogenicity of lipoprotein subpopulations, which may partially explain why LDL-C concentrations, as typically measured in clinical practice, are not necessarily perfect predictors of CVD events.

Materials and methods

Study subjects

A total of 416 subjects (124 males and 292 females) were recruited during general health checkups at the clinics of Ramathibodi Hospital. Subjects ≥18 years of age who were residents of Bangkok, Thailand were included. The exclusion criteria were pregnancy or a self-reported past history of cardiovascular disease, cancer, end-stage chronic kidney disease or other serious physical conditions (i.e. thyroid disorders). The study was approved by the Institutional Review Board Committee of the Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Thailand.

Biochemical analysis

Blood samples were collected from each subject after a 10- to 12-hour overnight fast. All samples were analyzed within one day with the samples refrigerated between 2 and 8 °C for biochemical analyses of the following items: total cholesterol (TC), TG, HDL-C, LDL-C, lipoprotein subpopulations, apolipoprotein A-I (apoA-I), apolipoprotein B (apoB) and atherosclerosis-related markers, i.e. glucose, hemoglobin A1C (HbA1C), insulin, high-sensitivity C-reactive protein (hsCRP), creatinine, cystatin C and vitamin D. The serum TC, TG, HDL-C, LDL-C and creatinine and plasma glucose levels were measured on the Siemens Dimension RxL Max using Siemens enzymatic methods (Siemens Medical Solution Diagnostics, Tarrytown, NY 10591-5097). The methods used to determine the TC, TG and HDL-C levels in this study were standardized according to the Centers for Disease Control and Prevention (CDC) National Heart Lung and Blood Institute Lipid Standardization Program. The accuracy and precision of the measurements were within the acceptable criteria of the National Cholesterol Education Program (NCEP). The serum apoA-I, apoB, cystatin C and hsCRP levels were measured on the Siemens BN Prospec (Siemens Medical Solution Diagnostics) using the Siemens immune turbidimetric method. The fasting serum insulin levels were determined on the Immulite H2975 (Siemens Medical Solution Diagnostics) using a two-site chemiluminescent immunoassay. EDTA samples were used to measure the HbA1C levels according to the Cobas Integra immunoturbidimetric method (Roche Diagnostics Ltd., Switzerland). The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated according to the following formula: fasting insulin (μU/mL) × fasting glucose (mg/dL) / 405.

Polyacrylamide tube gel electrophoresis (Quantimetrix Lipoprint™, CA) was used to electrophoretically separate the lipoprotein subpopulations [22]. The test principle is based on the proportional binding of lipophilic dye to the relative amount of cholesterol in each lipoprotein. The prestained lipoproteins underwent electrophoresis, thereby becoming resolved into a maximum of 12 bands ranked according to size, from largest to smallest: VLDL (a diameter of 35–80 nm); IDL (a diameter of 27–35 nm), divided into three midbands (MID-C, MID-B and MID-A); LDL (a diameter of 21.8–27.5 nm) divided into seven subfractions (LDL1 to LDL7); and HDL (a diameter of 7.2–12.9 nm). The LDL1 and LDL2 bands correspond to large LDL, while the LDL3 to LDL7 bands comprise small LDL particles. Using densitometry, the relative area of each lipoprotein band was determined and multiplied by the TC concentration, yielding the amount of cholesterol for each band. The mean LDL particle size was computed by integrating the relative contribution of each subfraction of LDL for a given subject.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD). Categorical variables are presented as numbers and percentages.

Table 1
Characteristics of the study population.

Clinical features	Male Mean (SD)	Female Mean (SD)	*P*-value
Number of subjects, n (%)	124 (29.8)	292 (70.2)	<.001
Age (years)	52.1 (13.9)	50.2 (12.9)	.189
Lipoprotein subpopulation (mg/dL)			
VLDL	36.48 (10.76)	33.09 (8.83)	.003
MID-C	18.15 (5.61)	18.26 (5.86)	.959
MID-B	14.81 (4.86)	15.79 (5.59)	.143
MID-A	18.57 (7.01)	21.98 (8.84)	<.001
LDL1	36.40 (12.40)	43.46 (12.30)	<.001
LDL2	28.06 (10.86)	27.00 (12.15)	.261
LDL3 to 6	12.61 (14.62)	9.12 (11.57)	.012
HDL	46.03 (11.57)	53.04 (12.26)	<.001
Mean LDL-particle size (nm)	26.594 (0.585)	26.812 (0.486)	<.001
TG (mg/dL)	134.6 (67.5)	108.7 (59.8)	<.001
TC (mg/dL)	211.4 (41.0)	222.3 (39.7)	.012
HDL-C (mg/dL)	48.8 (11.1)	57.3 (12.5)	<.001
LDL-C (mg/dL)	131.4 (34.1)	135.4 (34.0)	.276
Non-HDL-C (mg/dL)	156.3 (38.1)	159.4 (39.4)	.453
ApoA-I (mg/dL)	147.6 (22.0)	161.7 (27.4)	<.001
ApoB (mg/dL)	99.8 (23.0)	99.6 (22.6)	.933
Glucose (mg/dL)	101.9 (24.9)	95.4 (16.1)	<.001
HbA1C (%)	6.143 (0.894)	6.053 (0.739)	.517
HOMA-IR	1.646 (3.000)	1.193 (1.613)	.121
hsCRP (mg/L)	2.083 (4.830)	2.421 (4.661)	.162
Creatinine (mg/dL)	1.143 (0.202)	0.800 (0.123)	<.001
Cystatin C (mg/L)	0.819 (0.178)	0.702 (0.134)	<.001
Vitamin D (ng/mL)	23.992 (8.442)	19.899 (6.553)	<.001

All biochemical markers are expressed as the mean (standard deviation: SD), and subject numbers are presented as numbers (%).
VLDL, very-low-density lipoprotein; MID, intermediate-density lipoprotein midband; LDL, low density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; HbA1C, hemoglobin A1C; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein. *P*-value: male versus female.

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