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Original Articles

Assessment of LDL Particle Size by Triglyceride/HDL-Cholesterol Ratio in Non-diabetic, Healthy Subjects without Prominent Hyperlipidemia

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Small, dense low-density lipoprotein (LDL) is an atherogenic lipoprotein because of its susceptibility to oxidative modification. However, evaluating LDL size requires highly sophisticated techniques. We investigated potentially convenient biochemical parameters for assessing the presence of small, dense LDL. Thirty-nine male subjects, who had been involved in a work-site health promotion program, were recruited. Subjects were divided into two groups: normal LDL size (> 25.5 nm, Normal LDL group) and small LDL (≤ 25.5 nm, Small LDL group). Significant negative correlations were observed between LDL size and both triglyceride (TG) ($p < 0.001$) and remnant-like particle cholesterol concentrations ($p < 0.01$), while there was a significant positive correlation between LDL size and the high density lipoprotein cholesterol (HDL-C) concentration ($p < 0.01$). The TG concentration was a negative and the HDL-C concentration a positive independent variable predicting LDL size in multiple regression analysis ($p < 0.0001$). Seventy-five percent of the Small LDL group had TG/HDL-C ratios higher than 0.9 using mmol/L or 2.0 using mg/dL, while only 25% of the normal LDL group had ratios above the levels ($p = 0.0013$). A combined parameter, the TG/HDL-C ratio, is beneficial for assessing the presence of small LDL. ***J Atheroscler Thromb, 2003; 10: 186–191.***

Key words: Small, dense LDL, Remnant-like particle cholesterol, High density lipoprotein cholesterol, Triglyceride

Introduction

Clinical management of hyperlipidemia is crucial to prevent coronary heart disease (CHD) (1,2). There is a consensus that the diagnosis and management of hyperlipidemia for prevention of CHD should be based on low-density lipoprotein (LDL) cholesterol. However, a definite association between LDL and CHD has yet to be established, while the serum triglyceride (TG) level and CHD are clearly associated. Metabolic syndromes, such as elevation of TG, decreased high-density cholesterol (HDL-C), high blood pressure, and insulin resistance, were secondary targets of risk-reduction therapy in a recent National Cholesterol Education Program, the Adult Treatment Panel III (2). In the metabolic syndrome, hypertriglyceridemia is associated with low HDL-C, small, dense LDL, remnant-like particles (RLP) and intermediate density lipoprotein. In particular, small, dense LDL, also called LDL subclass pattern B, which has a major peak at a particle diameter of less than 25.5 nm, is associated with a three-fold increase in the risk of myocardial infarction (3). About 70% of Japanese men with CHD reportedly have the pattern B LDL subclass (4). Small, dense LDL and RLP are considered to promote atherosclerosis via increased entry into and retention in the arterial wall (5), because of a low affinity for LDL receptors (6,7) and susceptibility to oxidative modification (8,9). However, it is difficult to ascertain LDL particle size, if subjects with predominantly small LDL have TG and/or HDL-C concentrations within the normal range. In addition, it is not possible to measure LDL particle size with polyacryl-

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Table 1. LDL particle size and subject characteristics.

		All subjects	Normal LDL group	Small LDL group
Number		39	23	16
LDL-size	(nm)	25.5 ± 0.6	26.0 ± 0.3	24.9 ± 0.4***
Age		39.6 ± 6.3	39.5 ± 6.1	39.5 ± 6.8
Height	(cm)	171.9 ± 5.6	172.2 ± 5.6	171.5 ± 5.7
Weight	(kg)	75.7 ± 6.7	77.6 ± 6.4	73.1 ± 6.2*
BMI		25.6 ± 1.7	26.1 ± 1.5	24.8 ± 1.7*
Umbilical circumference	(cm)	90.4 ± 6.4	92.3 ± 6.3	89.0 ± 5.4

Values are presented as the Means ± S.D.
BMI: body mass index
*: $p < 0.05$, ***: $p < 0.0001$

amide gel electrophoresis in general medical examinations for a large number of subjects.

Thus, a simple means of assessing LDL particle size is desired to evaluate individual risks for atherosclerosis. In the present study, we investigated a potentially convenient biochemical parameter for assessing LDL particle size.

Methods

Subjects

Thirty-nine male subjects, who had been involved in a work-site health promotion program at a trading corporation in Tokyo, were recruited. The subjects were excluded if they were being treated with any medications or had impaired glucose tolerance or diabetes mellitus.

Physical and biochemical examinations

Body mass indices (BMI; in kg/m^2) were calculated using body weight and height measurements. Umbilical circumferences were determined using a tape measure, with the subject in a standing posture.

Fasting blood samples, collected by clean venipuncture, were allowed to clot at room temperature for 2-4 hours and then centrifuged at 3000 × g for 10 min at room temperature. Plasma samples were collected in tubes containing sodium fluoride for measuring glucose. Serum and plasma samples thus separated were transferred into 1.5 ml tubes and stored at – 80°C until use.

Serum total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (γ-GTP), total cholesterol, HDL-C, TG and fasting plasma glucose (FPG) concentrations were determined using a HITACHI 7450 auto analyzer.

Insulin and leptin were measured using a immunoradiometric assay (INSULIN · RIABEAD(II), DAINABOT Co., Ltd. Tokyo, Japan) and a HUMAN LEPTIN RIA KIT (LINCO Research Inc., Missouri, USA), respectively. RLP-C was measured by the method of Nakajima *et al.* (10). LDL-cholesterol (LDL-C) was calculated using Friedewald's formula; total cholesterol – (HDL-C) – TG/5. LDL particle size was determined by the method of Krauss *et al.*, using polyacrylamide gel electrophoresis (11). The homeostasis model assessment (HOMA-R) was calculated according to FPG (mmol/L) × Insulin (μU/mL)/22.5.

Subjects were divided into two groups: normal LDL size (Normal LDL) and small LDL (small LDL). LDL particle sizes were greater or less than 25.5 nm, respectively (3).

Statistical analysis

Statview J 5.0 (SAS Institute Inc, USA) was used for statistical analysis. Data are presented as means +/– SDs. For the continuous variables, Student's test (for parametric variables) and the Mann-Whitney U test (for non-parametric variables) were used. Spearman correlation coefficients were used to analyze the relationships between LDL particle size and clinical parameters. Multiple regression function using backward elimination was employed to determine the significance of factors affecting LDL particle size. Explanatory variables for LDL particle size were age and biochemical parameters. Differences in proportions were evaluated using Fisher's exact test. A value of $p < 0.05$ was considered statistically significant.

Results

Characteristics of subjects and LDL particle size are shown in Table 1. For all subjects, the mean age was 39.6 ± 6.3 years (Mean ± SD), BMI was 25.6 ± 2.4 and umbilical circumference was 90.4 ± 6.4 cm. According to the consensus assessment of the Japan Society for the Study of Obesity, 14 subjects (35.9%) were classified as "Obese I" as they had a BMI higher than 25, and 31 subjects (79.5%) as having abdominal obesity based on an umbilical circumference exceeding 85 cm (12). Sixteen subjects (41%) had predominantly small LDL with an LDL particle diameter below 25.5 nm, while LDL particles were 26.0 ± 0.3 nm in the Normal group and 24.9 ± 0.4 nm in the Small LDL group ($p < 0.0001$). BMI was lower in the Small LDL group than in the Normal group ($p < 0.05$).

Biochemical data are presented in Table 2. Japanese Guidelines for Hyperlipidemias in Adults define the diagnostic criteria for serum TG and HDL-C as 1.7 mmol/L

Table 2. Clinical parameters.

		All subjects	Normal LDL group	Small LDL group
Number		39	23	16
Total protein	(g/L)	73 ± 3	73 ± 3	73 ± 3
Albumin	(g/L)	47 ± 2	47 ± 2	47 ± 3
AST	(IU/L)	25 ± 8	27 ± 8	22 ± 7
ALT	(IU/L)	34 ± 20	34 ± 21	25 ± 16**
γ-GTP	(IU/L)	60 ± 41	55 ± 25	66 ± 58
Fasting plasma glucose	(mmol/L)	4.9 ± 0.4	4.9 ± 0.4	4.9 ± 0.4
	(mg/dL)	(88 ± 7)	(88 ± 7)	(88 ± 7)
Insulin	(uU/mL)	7.3 ± 3.0	7.7 ± 3.3	6.8 ± 2.4
HOMA-R		1.6 ± 0.7	1.7 ± 0.8	1.5 ± 0.5
Total Cholesterol	(mmol/L)	5.22 ± 0.92	5.19 ± 0.84	5.25 ± 1.04
	(mg/dL)	(202 ± 36)	(201 ± 32)	(203 ± 40)
RLP-Cholesterol	(mmol/L)	0.12 ± 0.06	0.10 ± 0.04	0.14 ± 0.08*
	(mg/dL)	(4.6 ± 0.2)	(3.9 ± 1.5)	(5.4 ± 3.1)
LDL-Cholesterol	(mmol/L)	3.25 ± 0.81	3.24 ± 0.77	3.26 ± 0.91
	(mg/dL)	(126 ± 31)	(125 ± 30)	(126 ± 35)
HDL-Cholesterol	(mmol/L)	1.40 ± 0.27	1.48 ± 0.28	1.28 ± 0.20*
	(mg/dL)	(54 ± 10)	(57 ± 11)	(49 ± 8)
Triglyceride	(mmol/L)	1.24 ± 0.60	1.03 ± 0.41	1.54 ± 0.71**
	(mg/dL)	(110 ± 53)	(91 ± 36)	(136 ± 63)
Leptin	(ng/mL)	4.15 ± 1.52	4.10 ± 1.41	4.22 ± 1.71

AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, HOMA-R: homeostasis model assessment, RLP-Cholesterol: remnant-like particle cholesterol, LDL-Cholesterol: low-density lipoprotein cholesterol, HDL-Cholesterol: high-density lipoprotein cholesterol

Values are presented as Means ± S.D.

Differences are significant between the normal LDL and small LDL groups.

*: $p < 0.05$, **: $p < 0.01$.

Table 3. Significant correlations between LDL size and clinical parameters.

	LDL-size	Probability
RLP-Cholesterol	$r = -0.476$	0.0022
HDL-Cholesterol	$r = 0.486$	0.0017
Triglyceride	$r = -0.545$	0.0003
Triglyceride/HDL-Cholesterol	$r = -0.644$	0.0001

$n = 39$

RLP-Cholesterol: remnant-like particle cholesterol

HDL-Cholesterol: high density lipoprotein cholesterol

(150 mg/dL) and 1.03 mmol/L (40mg/dL), respectively. TG and RLP-C concentrations were distributed from min. 0.37 mmol/L to max. 2.94 mmol/L, and min. 0.05 mmol/L to max. 0.30 mmol/L, respectively. TG and RLP-C concentrations were higher in the Small LDL group than in the Normal group (TG: $p < 0.01$, RLP-C: $p < 0.05$). HDL-C was 1.40 ± 0.27 mmol/L (min. 0.96 mmol/L and max. 2.15 mmol/L). HDL-C was lower in the Small LDL group than in the Normal group (HDL-C: $p < 0.05$).

Significant correlations were recognized between LDL particle size and biochemical parameters, as shown in Table 3. Significant negative correlations were observed between LDL particle size and both the TG ($r = -0.545$, $p = 0.003$) and the RLP-C concentration ($r = -0.476$, $p = 0.0022$), while there was a significant positive correlation between LDL particle size and the HDL-C concentration ($r = 0.486$, $p = 0.0017$). However, as shown as Figures 1A and 1B, among the Small LDL subjects there were only 5 with hypertriglyceridemia (31.3%), and only 3 low HDL-C subjects (18.8%) according to the aforementioned diagnostic criteria. There were 2 subjects (12.5%) who had not only hypertriglyceridemia but also a low HDL-C concentration.

Table 4 shows multiple correlation coefficient values expressing LDL particle size by age and biochemical parameters. The TG concentration was a negative and the HDL-C concentration a positive independent variable predicting LDL particle size (Adjusted $R^2 = 0.401$, $p < 0.0001$).

Figure 1C shows a significant correlation between LDL particle size and the TG/HDL-C ratio, based on the following equation:

LDL particle size (nm) = 26.262 – 0.776 (TG mmol/L)/HDL-C (mmol/L)).

(LDL particle size (nm) = 26.265 – 0.34 (TG (mg/dL)/

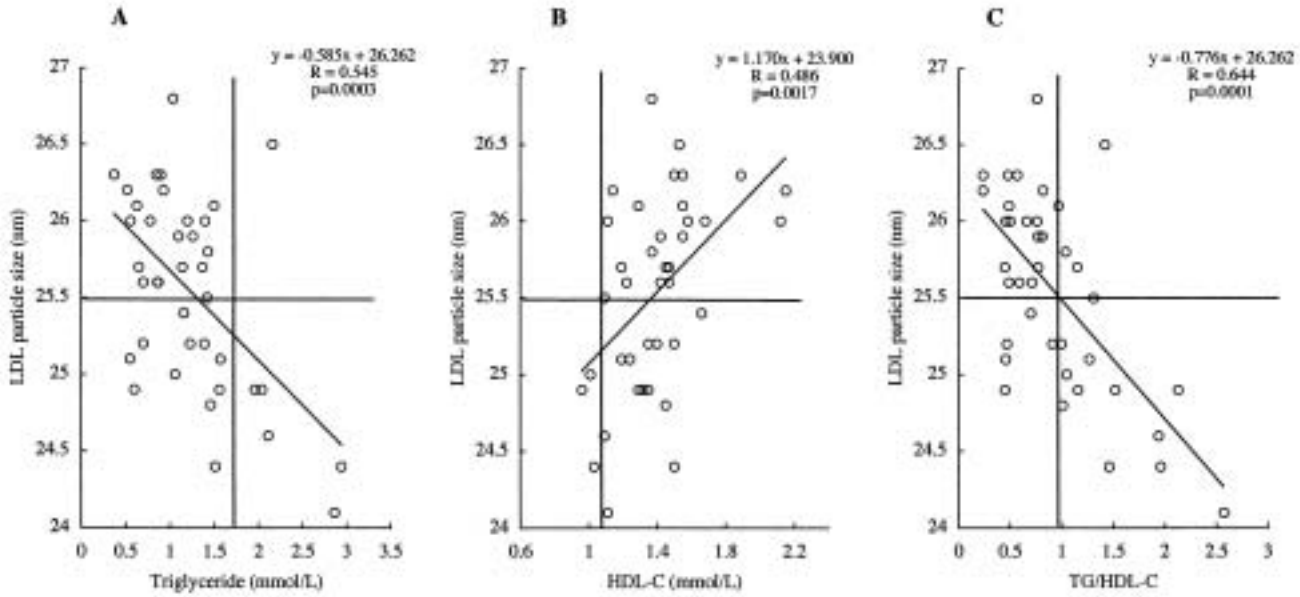

Figure 1. Simple correlations among LDL particle size, serum lipids and combined parameters.
A: Triglyceride; the Japanese diagnostic cut-off level for hypertriglyceridemia is 1.7 mmol/L.
B: HDL-cholesterol; the Japanese diagnostic cut-off level for low HDL-cholesterolemia is 1.03 mmol/L.
C: Combined parameter; the Triglyceride/HDL-cholesterol ratio.

Table 4. Coefficient values on multiple regression analysis for LDL particle size.

Variable	Standardized partial regression coefficient
Intercept	24.87
HDL-Cholesterol	0.378
Triglyceride	–0.456

$n = 39$, Adj. $r = 0.657$, Adj. $r2 = 0.401$, $p < 0.0001$
HDL-Cholesterol: high density lipoprotein cholesterol

HDL-C (mg/dL))

In the small LDL group, 12 of 16 subjects (75.0%) had TG/HDL-C ratios higher than 0.9 using mmol/L as the practical unit (2.0 when using mg/dL), while only 5 subjects (25%) in the normal LDL particle size group had ratios above 0.9 ($p = 0.0013$) (Figure 1C.).

In five persons in whom LDL particles were predominantly larger than 25.5 nm, however, the TG/HDL-C ratio was higher than 0.9.

Discussion

Although hypertriglyceridemia has been regarded as a risk factor for CHD, there is some controversy over whether it is an independent risk factor or not because of its association with a relatively low HDL-C concentration, which is recognized as a strong risk factor for CHD. However, based on the results of a meta-analysis, TG and HDL-C concentrations are both independent risk factors for CHD (13). On the other hand, a large number of epidemiological studies have identified small, dense LDL as an independent risk factor for CHD (3,6,14), which is often associated with both hypertriglyceridemia and low HDL-C.

The results of the present study support those of previous reports, as TG and RLP-C concentrations were higher and the HDL-C concentration was lower in the Small LDL group than in the Normal group. In addition, the TG concentration was a negative and the HDL-C level a positive independent predictor of LDL particle size in multiple regression analysis.

Lahdenpera *et al*. reported the serum TG concentration to be the major determinant of LDL size, regardless of whether coronary artery disease was present, in non-insulin dependent diabetic patients (15). In a study of the general population in Sweden, by Fagerberg *et al*., LDL peak particle size was independently associated with circulating log TG and log HDL-C, which together explained 67% of the variability in LDL particle size. In their study, log TG and log HDL-C explained 54% and 39% of the variation (from the beta-coefficient value) in LDL particle size (16). However, in our study, TG and

HDL-C concentrations together explained 40% of the variability in LDL particle size, while separately they explained 46% and 38% of this variation, respectively. The lower predictive value in our study might be attributable to our subjects having a lower BMI, umbilical circumference and TG concentration, as well as a higher HDL-C concentration, than the Swedish subjects. On the other hand, based on the present study, we divided the 75% of subjects who had small LDL into groups with LDL particle sizes less than 25.5 nm, using not only the two independent parameters of TG and HDL-C concentration, but also the TG/HDL-C ratio (larger than 0.9). Fagerberg *et al*. did not assess the relation between the TG/HDL-C ratio and LDL particle size, despite recognizing the importance of both the TG and the HDL-C concentration, because the aim of their study was to clarify the effect of insulin sensitivity on LDL peak particle size. On the other hand, Jeppesen *et al*. showed, in the Copenhagen Male Study, the two lipid ratios (log total cholesterol/log HDL-C and log TG/log HDL-C) to be the strongest predictors of the incidence of ischemic heart disease (17), and suggested a strategy for prevention of ischemic heart disease which involved lowering TG and increasing HDL-C levels (18). We aimed to detect an intact clinically measurable parameter which would facilitate evaluation of peak LDL particle size, without using sophisticated parameters such as the natural logarithms of biochemical data. A combined parameter, i.e. the TG/HDL-C ratio, facilitates assessment of the quality and presence of abnormal lipoproteins in small LDL, which suggest a high risk of developing atherosclerosis.

Most previous reports have shown a negative correlation between waist-to-hip ratio and small LDL particle size, and small, dense LDL are reported to be more abundant in subjects with than in those without abdominal obesity (19,20). About 80% of our subjects were slightly obese, based on umbilical circumference. However, those whose LDL particles were predominantly less than 25.5 nm in diameter and in whom the TG/HDL-C ratio was less than 0.9, generally had a low BMI and umbilical circumference, normal liver function parameters, and low levels of lipid and glucose metabolic parameters as compared with other small LDL group subjects.

Other determinants of LDL particle size are reported to include age, sex, pregnancy, and genetic factors influencing lipoprotein lipase, cholesterol ester transfer protein and phospholipids transfer protein (21) and hepatic lipase activity (22). Further study is necessary to determine the optimal cut-off levels for those parameters using a large number of subjects.

Furthermore, not only a reduction in the TG concentration but also an increase in the HDL-C concentration, especially with exercise and the relative restriction of fat and oil and/or carbohydrate consumption, is believed to effectively increase LDL particle size (23-25). Therapies including medication, aimed at improving the LDL subclass pattern, should be implemented to lower the risk of atherosclerosis (26, 27). The combined parameter, the TG/HDL-C ratio, is anticipated to be beneficial for assessing the effects of various therapies aimed at preventing small LDL formation.

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