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Low-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio as a useful marker for early-stage carotid atherosclerosis

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Abstract

A higher ratio of low-density lipoprotein cholesterol (LDL-C) to high-density lipoprotein cholesterol (HDL-C) is associated with a greater risk of cardiovascular events in patients with coronary heart disease. However, the role of this lipid index during early-stage atherosclerosis has not yet been established. This study investigated relationships between LDL-C/HDL-C ratio and carotid plaque score as assessed by ultrasonography in 825 subjects from the general population (527 men, 298 women; mean age, 60.5 years). To identify factors strongly associated with plaque score, stepwise multiple regression analysis was performed using various clinical variables including conventional lipid indices. In both sexes, increased LDL-C/HDL-C ratio was associated with increased plaque score (men: $\beta = 0.132$, $P = .001$; women: $\beta = 0.150$, $P = .012$). This association was maintained in men with normal LDL-C level (<140 mg/dL). The highest quartile of LDL-C/HDL-C ratio (>2.9 in men, >2.6 in women) showed significantly increased plaque score even when adjusted by factors included in the final model of stepwise analysis ($P = .007$ in men, $P = .033$ in women). No association was seen between LDL-C and plaque score in the multivariate-adjusted model. These findings indicate that increased LDL-C/HDL-C ratio may also be associated with initiation of atherosclerosis. Assessment of this lipid ratio may thus facilitate early management of atherosclerotic risks better rather than assessment of LDL-C alone.

1. Introduction

An increased level of low-density lipoprotein cholesterol (LDL-C) in the bloodstream is well established as a major risk factor for atherosclerotic cardiovascular disease [1-4]. Lowering LDL-C level reduces the risk of future cardiovascular events, and the clinical benefit depends on the magnitude of reduction in LDL-C levels [5,6]. Epidemiologic studies have also shown a negative relationship between serum high-density lipoprotein cholesterol (HDL-C) levels and risk of cardiovascular events [7,8]. In patients with coronary heart disease, reduced HDL-C level increases the risk of cardiovascular events even among patients with LDL-C levels of less than 70 mg/dL [9]. Several recent studies have suggested the significant relationships between LDL-C/HDL-C ratio and cardiovascular events [9-14]. Both increased LDL-C/HDL-C ratio and reduced LDL-C level are reportedly associated with inhibition of coronary atherosclerotic progression or regression in patients with coronary heart disease [15-17]. However, the role of LDL-C/HDL-C ratio in early-stage atherosclerosis has yet to be established.

Carotid ultrasonography is widely used for the noninvasive detection of atherosclerotic changes in the arterial wall. Because specific carotid ultrasound indices can accurately reflect various atherosclerotic risk factors [18,19], evaluation of intima-media thickness (IMT) and plaque formation has been used for estimating the extent of systemic atherosclerosis.

To assess whether serum LDL-C/HDL-C ratio represents a significant marker of early-stage atherosclerosis, the present study investigated associations between lipid profiles and carotid atherosclerosis, particularly plaque

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formation, in participants of a health checkup from the general population.

2. Population and methods

2.1. Study population

Study subjects comprised 825 consecutive individuals (mean age, 60.5 ± 9.8 years; range, 40-86 years; 527 men, 298 women) who visited the Iwate Health Service Association for a health checkup from April 2006 to February 2008. The majority of subjects participated periodically in annual mass health-screening programs in the community or physical checkups in the workplace. In the present study, all participants underwent a routine clinical examination including medical history, physical examination, and carotid ultrasonography. The study protocols were approved by our institutional ethics committee, and all participants provided written informed consent.

2.2. Measurements

Venous blood samples from the antecubital vein of subjects resting in the sitting position were collected after an overnight fast. Samples were collected into vacuum tubes containing EDTA or a serum separator gel. After sampling, tubes were immediately centrifuged at 1500*g* for 10 minutes. Aliquots of serum were stored at −20°C; and routine hematology and biochemistry tests, including total cholesterol (TC), LDL-C, HDL-C and triglyceride, were performed within a few days after blood sampling. Serum LDL-C concentration was measured by direct liquid assay with routine automated chemistry instruments. Hemoglobin A_{1c} (HbA_{1c}) was measured using ion-exchange high-performance liquid chromatography. A part of serum was stored at −80°C for measurement of fasting insulin (immunoreactive insulin; IRI) level. Insulin resistance was measured using the homeostasis model assessment of insulin resistance (HOMA-IR) (fasting blood glucose [in milligrams per deciliter] × IRI [in microunits per milliliter]/405). Estimated glomerular filtration rate (eGFR) was calculated using revised equations for Japanese from serum creatinine [20]. Some other lipid indices including atherogenic index ([TC − HDL-C]/HDL-C) and LDL-C/HDL-C ratio were calculated for analysis.

Systolic blood pressure (sBP) and diastolic blood pressure (dBP) were measured by trained nurses using an automatic digital sphygmomanometer placed on the upper arm at the height of the heart in a sitting position after the subject had rested for 10 minutes. The average value from 2 measurements was used for the present analysis. Waist circumference was measured midway between the lower rib margin and iliac crest with the subject standing. Body mass index was calculated as body weight (in kilograms) divided by square of the height (in meters). *Smoking index* was defined as the product of packs per day and years of smoking (pack-years).

2.3. Carotid ultrasonography

Carotid ultrasound examination was performed using an SSD-5500 (ALOKA, Tokyo, Japan) or Power Vision 6000 (Toshiba Medical Systems, Tochigi, Japan) scanner equipped with a 7.5-MHz linear array imaging probe. The common carotid artery, carotid bulb, and internal and external carotid arteries on both sides were carefully scanned under B-mode imaging from multiple directions. In the common carotid artery at 1.0, 2.0, and 3.0 cm proximal to the beginning of the carotid bulb, IMT of the far wall was measured on the maximally zoomed image. *Intima-media thickness* was defined as the distance between the leading edge of the lumen-intima and the leading edge of the media-adventitia echo. Mean value of the 3 points was calculated for each side. *Plaque* was defined as a regional intimal thickening greater than 1.3 mm in height or double the adjacent IMT height. *Plaque score* was defined as the sum of maximum heights of each plaque located in the whole extracranial portion of both carotid arteries [21].

2.4. Statistics

Comparisons of demographic data between men and women were performed using the unpaired *t* test. To assess the significance of the impact of cardiovascular risk factors on increased carotid plaque score, simple regression analysis and forward stepwise multiple regression analysis were performed. The final model was determined using $P_{in} < .05$ and $P_{out} > .10$. Standardized coefficient (β) and *P* values are presented. Analysis of covariance was used to assess the associations of quartile ranges of lipid indices with carotid plaque score in models adjusted by atherosclerotic risk factors in the final model of stepwise regression analysis. Values of $P < .05$ were considered statistically significant. All analyses were performed using SPSS version 11.0 statistical software (Chicago, IL). Values in tables are expressed as mean ± standard deviation. Estimated values of plaque score in the multivariate-adjusted model are expressed as mean ± 90% confidence intervals in Fig. 1.

3. Results

Clinical characteristics of male and female subjects are shown in Table 1. Although no significant differences were noted in HbA_{1c}, HOMA-IR, or IRI, all other cardiovascular risk factors were significantly higher in men than in women. The HDL-C levels were lower in men than in women. However, the LDL-C levels were higher in women than in men.

To investigate factors associated with carotid atherosclerotic change, simple regression analysis used carotid plaque score and various clinical indices for total subjects. As a result, significant associations with plaque score were found for age, sBP, dBP, sex, fasting glucose, HbA_{1c}, uric acid, smoking index, eGFR, HDL-C, atherogenic index, TC/

Table 1
Clinical characteristics of male and female subjects

	Male (n = 527)	Female (n = 298)	*P*
Age, y	60.5 ± 10.1	60.6 ± 8.7	NS
sBP, mm Hg	124 ± 15	119 ± 16	<.001
dBP, mm Hg	74 ± 10	69 ± 11	<.001
Fasting blood glucose, mg/dL	106 ± 21	98 ± 15	<.001
HbA_{1c}, %	5.5 ± 0.7	5.6 ± 0.6	NS
eGFR, mL min^{-1} 1.73 m^{-2}	71.3 ± 14.1	74.6 ± 14.7	.001
Uric acid, mg/dL	6.0 ± 1.3	4.5 ± 1.0	<.001
LDL-C, mg/dL	122 ± 30	132 ± 34	<.001
HDL-C, mg/dL	55 ± 14	66 ± 15	<.001
Triglyceride, mg/dL	131 ± 100	95 ± 48	<.001
Body mass index, kg/m^2	24.6 ± 2.9	23.6 ± 4.0	<.001
Waist circumference, cm	88.7 ± 7.9	84.9 ± 10.4	<.001
Smoking index, pack-years	382 ± 426	14 ± 75	<.001
HOMA-IR	1.8 ± 1.4	1.8 ± 1.8	NS
Fasting insulin, ng/mL	6.9 ± 4.6	7.1 ± 5.4	NS
Carotid plaque score, mm	1.1 ± 1.6	0.4 ± 0.8	<.001

HDL-C ratio, and LDL-C/HDL-C ratio. Low-density lipoprotein cholesterol alone did not show a significant association with plaque score (Table 2). Subsequently, stepwise multiple regression analysis was performed separately by sex using all of the factors listed in Table 2. In men, significant associations with plaque score were found for age, sBP, dBP, smoking index, and LDL-C/HDL-C ratio. In women, age, uric acid, and LDL-C/HDL-C ratio were significantly associated with plaque score (Table 3).

Furthermore, comparison of carotid plaque score by quartiles (Q) of LDL-C/HDL-C ratio was performed. When values were adjusted by factors in the final model of multiple stepwise regression analysis (Table 3) in each sex, estimated plaque score was increased in Q4 levels of LDL-C/HDL-C ratio in both sexes (Q1 = 0.93, Q2 = 1.01, Q3 = 0.89, Q4 = 1.45, *P* for trend = .007 in men; Q1 = 0.40, Q2 = 0.43, Q3 = 0.28, Q4 = 0.71, *P* for trend = .033 in women). The Q4 range for LDL-C/HDL-C ratio was greater than 2.9 in men and greater than 2.6 in women (Fig. 1). To test the impact of antihypertensive treatment (n = 167 in men, n = 67 in women) and lipid-lowering therapy (n = 67 in men, n = 47 in women), the same analysis was performed with additional adjustment according to use of these medications. Similar results were obtained in both men (*P* for trend = .006) and women (*P* for trend = .029) (figure not shown).

In subjects with LDL-C less than 140 mg/dL, stepwise multiple regression analysis was performed separately by sex using all of the factors listed in Table 2, except sex. In men (n = 384), age, smoking index, sBP, and LDL-C/HDL-C ratio were significantly associated with plaque score (β = 0.12, *P* = .009 for LDL-C/HDL-C ratio). In women (n = 177), a significant association with plaque score was found only for age (β = 0.27, *P* < .001), not for LDL-C/HDL-C ratio (β = 0.04, *P* = .63).

Table 2
Factors associated with carotid plaque score (simple regression analysis)

	Coefficient	*P*
Age, y	0.353	<.001
sBP, mm Hg	0.230	<.001
dBP, mm Hg	0.073	.019
Sex	−0.206	<.001
Fasting blood glucose, mg/dL	0.069	.025
HbA_{1c}, %	0.098	.003
Waist circumference, cm	0.041	.13
Body mass index, kg/m^2	0.015	.67
Uric acid, mg/dL	0.150	<.001
Smoking index, pack-years	0.217	<.001
eGFR, mL min^{-1} 1.73 m^{-2}	0.071	.022
Fasting insulin, ng/mL	0.006	.43
Triglyceride, mg/dL	−0.005	.45
HDL-C, mg/dL	−0.135	<.001
LDL-C, mg/dL	0.027	.22
HOMA-IR	0.024	.49
Atherogenic index	0.138	<.001
TC/HDL-C ratio	0.138	<.001
LDL-C/HDL-C ratio	0.137	<.001

Atherogenic index: (TC − HDL-C)/HDL-C.

Table 3
Factors associated with carotid plaque score (stepwise multiple regression analysis)

	Male		Female	
	Standardized coefficient (β)	*P*	Standardized coefficient (β)	*P*
Age	0.332	<.001	0.214	<.001
sBP	0.289	<.001	–	–
dBP	−0.140	.021	–	–
Smoking index	0.158	<.001	–	–
LDL-C/HDL-C ratio	0.132	.001	0.165	.004
Uric acid	–	–	0.122	.032

All factors shown in Table 2, except sex, were entered into stepwise regression analysis.

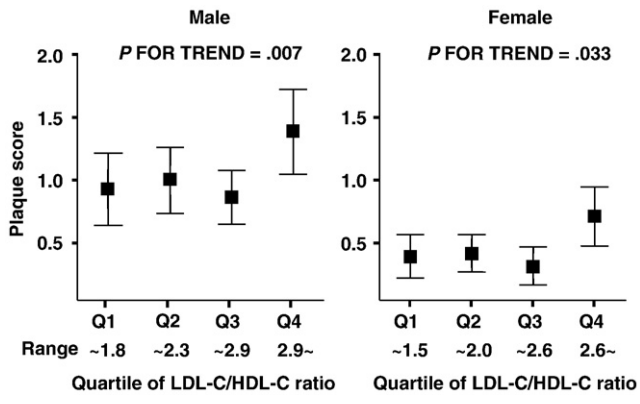

Fig. 1. Comparison of carotid plaque score by quartiles of LDL-C/HDL-C ratio. Values are adjusted by factors in the final model of multiple stepwise regression analysis (Table 3). Adjustments were performed using sex-specific factors associated with plaque score.

4. Discussion

This study demonstrated that LDL-C/HDL-C ratio represents an independent lipid index to reflect early-stage carotid atherosclerosis in apparently healthy men and women from the general population. This significant association was maintained in male subjects with normal levels of serum LDL-C.

Low-density lipoprotein cholesterol transports cholesterol from the liver to peripheral tissues and advances the foaming of macrophages via uptake within the arterial wall by LDL receptors in endothelium. Conversely, free cholesterol in macrophages is translocated into the extracellular space mediated by adenosine triphosphate–binding cassette transporter, subfamily A, member 1. High-density lipoprotein mediates the efflux of these with reverse transport to the liver and other lipoproteins. High-density lipoprotein also protects against atherosclerosis by inhibiting cytokine-induced expression of endothelial cell adhesion molecules [22,23]. According to these known mechanisms, the proportions of LDL-C and HDL-C concentrations in the bloodstream may be theoretically important to estimate the extent of lipid accumulation in the arterial wall or the severity of atherosclerotic intimal changes.

Kinosian et al [14] reported that, in the general population from the Framingham study, TC/HDL-C ratio or LDL-C/HDL-C ratio was superior to either TC level or LDL-C level for identifying people at greater risk of developing subsequent coronary heart disease events. Our study results obtained from the evaluation of carotid atherosclerosis, which has also been identified as a surrogate marker of cardiovascular events in a general population, support this prospective cohort analysis.

In a study investigating the correlation of carotid atherosclerotic plaque wall volumes with plasma lipid indices in patients with coronary heart disease, the correlation coefficient of LDL-C/HDL-C ratio was higher than those for LDL-C or HDL-C alone [24]. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels trial showed that, in patients with recent stroke or transient ischemic attack, baseline LDL-C/HDL-C ratio was associated with risk of recurrent stroke or first major cardiovascular events [25]. Nested case-control analysis from the Perindopril Protection Against Recurrent Stroke study revealed that LDL-C/HDL-C ratio was strongly associated with risk of myocardial infarction in patients with previous stroke or transient ischemic attack [26]. In subjects with cardiovascular disease, the usefulness of this lipid index has been suggested in the setting of secondary prevention.

Nicholls et al [17] reported a meta-analysis of data from 4 prospective randomized trials, in which patients with angiographic coronary disease underwent intravascular ultrasonography while receiving statin treatment for 18 or 24 months. In that analysis, higher LDL-C/HDL-C ratio (>2.0) in patients during treatment was associated with progression of coronary atheroma burden, whereas lower LDL-C/HDL-C ratio (<1.5) was linked to regression of the atheroma burden [17]. In our cross-sectional study, the quartile group with LDL-C/HDL-C ratio greater than 2.9 in men and the quartile group with ratio greater than 2.6 in women showed higher carotid plaque score. These threshold values were relatively higher than those in patients with coronary heart disease during statin therapy. This may be attributable to the fact that our study population comprised numerous low-risk participants.

Low-density lipoprotein cholesterol levels in the bloodstream have been unequivocally confirmed as a major risk factor for atherosclerotic diseases, and reducing LDL-C level contributes to a decrease in cardiovascular events [1-6]. However, no association between carotid atherosclerotic change and LDL-C alone was identified in the present study. Although the reason for this discrepancy is unknown, LDL-C may play little role in early-stage carotid atherosclerosis or initiation of plaque formation compared with HDL-C. In addition, subjects in this study included numerous healthy individuals; so baseline HDL-C levels may have been higher than those in patients with coronary heart disease. Obtaining an association with atherosclerosis may thus be difficult using LDL-C alone.

From the postulation that the balance of LDL-C and HDL-C is crucial for atherogenicity, a higher LDL-C/HDL-C ratio would also appear to be associated with extent of carotid atherosclerosis even in subjects with normal LDL-C levels. To verify this hypothesis in the present study, multiple regression analysis was similarly performed in subjects with LDL-C less than 140 mg/dL, as indicated in the results. In male subjects, a significant association between LDL-C/HDL-C ratio and carotid plaque score was maintained in the subgroup with normal LDL-C levels. This result emphasizes the concept that LDL-C/HDL-C ratio may offer a definitive marker for atherosclerosis compared with LDL-C alone, and evaluation of this lipid index may contribute to lipid management for reducing atherosclerotic cardiovascular events even in a general population. Conversely, because mean LDL-C/HDL-C ratio in women with normal LDL-C level was low (1.6) and the distribution of this lipid ratio was narrow, the association of LDL-C/HDL-C ratio with plaque score may not have been detected. The statistical power of the present study may therefore have been insufficient in women, and an investigation with a larger number of female subjects is thus needed.

Several limitations in the study design and interpretation of the results must be considered. First, this cross-sectional study did not assess changes in plaque score over a 2-point interval. Thus, target LDL-C/HDL-C for management as a primary preventive strategy in early-stage atherosclerosis cannot be established from the present results. Second, some patients in this study were receiving oral antiatherogenic medications such as antihypertensive drugs, statins, and antiplatelet agents. The influences of these agents on our results were not quantified. However, because similar results were obtained when adjusted by antihypertensive treatment

and lipid-lowering therapy, the effects of these medications may have been negligible in the present study population.

In conclusion, serum LDL-C/HDL-C ratio offers an index associated with increased carotid plaque score independent of other risk factors of atherosclerosis and may represent a useful marker for evaluating the extent of atherosclerosis even in the early stages in the general population compared with LDL-C alone.

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