Original Article

Significance of Serum High-Density Lipoprotein Cholesterol Levels for Diagnosis of Coronary Stenosis as Determined by MDCT in Patients with Suspected Coronary Artery Disease

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Aim: Since we previously reported that lower levels of HDL-C may be most useful for predicting coronary artery disease (CAD) as assessed by multi-detector row computed tomography (MDCT), we sought to confirm, among the levels of LDL-C, HDL-C, non-HDL-C (total cholesterol minus HDL-C) and the ratio of LDL-C to HDL-C (LDL-C/HDL-C), which is most closely related to the presence of CAD.

Methods and Results: The subjects consisted of 506 consecutive patients with suspected CAD who underwent MDCT with (+) or without (-) statin treatment. The levels of LDL-C in the statin (-) group were similar in categories I, II and III according to the Japan Atherosclerosis Society (JAS) Guidelines 2007, whereas the levels of HDL-C significantly decreased and LDL-C/HDL-C significantly increased as the category number increased. In the statin (-) group, the prevalence of CAD in categories I, II and III was 0, 16 and 33%, respectively ($p=0.0018$ for trend), in patients with good control of LDL-C levels according to the Guidelines. Multivariate logistic regression analysis was performed to examine the association between the presence of CAD and 11 possible factors. Age and HDL-C in the statin (-) group, and HDL-C in the statin (+) group were identified as significant independent variables that correlated with the presence of CAD. Receiver-operating characteristic curve analysis in the statin (-) and statin (+) groups showed a higher area under the curve for HDL-C than for LDL-C, non-HDL-C or LDL-C/HDL-C. In particular, the cut-off levels of HDL-C with the greatest sensitivity and specificity for the diagnosis of CAD in the statin (+) group were 55 mg/dL (sensitivity 0.816, specificity 0.510).

Conclusions: HDL-C levels are most closely associated with the presence of CAD. In particular, we need to perform coronary CT for suspected CAD patients with lower HDL-C levels under statin treatment.

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Key words; High-density lipoprotein cholesterol, Coronary artery disease, Multi-detector row computed tomography

Introduction

Many previous studies have revealed that serum levels of low- and high-density lipoprotein cholesterol (LDL-C and HDL-C, respectively) are the major pre-

dictors of atherosclerotic coronary artery disease (CAD)^{1, 2)}. Multi-detector row computed tomography (MDCT) has become more widely available in many general hospitals, and enables the accurate non-invasive assessment of coronary artery stenosis³⁾ and calcification⁴⁾, and plaque imaging⁵⁾ for CAD diagnosis. In addition, we previously reported that lower levels of HDL-C may be most useful for predicting CAD as assessed by MDCT, independent of metabolic factors such as adiponectin, visceral fat area or present medication⁶⁾. Lower levels of HDL-C may also be an indicator of, and provide additional information regarding

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the severity of, CAD compared to other lipidemic factors⁷⁾.

The level of LDL-C or HDL-C is an independent risk factor for CAD. Although lower values for the ratio of LDL-C to HDL-C (LDL-C/HDL-C) in addition to a greater percentage increase in HDL-C and lower levels of LDL-C in patients during treatment with statins have been associated with the regression of atheroma⁸⁾, few reports have discussed whether LDL-C/HDL-C or non-HDL-C (total cholesterol minus HDL-C) is a risk factor^{9, 10)}; therefore, we determined, among the levels of LDL-C, HDL-C, non-HDL-C and LDL-C/HDL-C, which is most closely related to the presence of CAD.

Methods

Study Subjects

Five hundred six consecutive subjects who were clinically suspected of having CAD or who had at least one cardiac risk factor were enrolled in this study. All subjects underwent MDCT coronary angiography between July 2006 and August 2008. We excluded patients with anti-lipidemic therapy, except for statins, from the present study. Patients with Cr > 2.0 mg/dL and contrast-induced allergy did not undergo MDCT. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital, and all subjects gave their informed consent to participate.

Evaluation of Coronary Stenosis Using MDCT

We evaluated coronary stenosis using MDCT as previously described¹¹⁾. Briefly, all patients were scanned by 64-MDCT on an Aquilion 64 (TOSHIBA, Tokyo, Japan). The use of beta-blockers and nitroglycerin before scanning was left to the physician's discretion. A 70-mL bolus of contrast media (Omnipaque, 350 mg iodine/mL; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was injected at a flow rate of 3.6 mL/sec, followed by 35 mL contrast agent and 30 mL saline solution, each at a flow rate of 1.8 mL/sec, with a dual injector. The region of interest was placed within the ascending aorta, and the scan was started when the CT density reached 100 Hounsfield Units higher than the baseline CT density. The scan was performed between the tracheal bifurcation and diaphragm with the following parameters: collimation width 0.5 mm, rotation speed 0.4 sec/rotation, tube voltage 135 kV, and effective tube current 360 mA.

All segments were assessed according to the 15-segment American Heart Association (AHA) coronary artery model¹²⁾. Since 85 (16.8%) patients had at least one unevaluable segment on MDCT because of

severe calcification and motion artifacts, they could not be evaluated by MDCT. Overall, 15 coronary artery segments of 506 patients (total 7,590) were assessed. Of these 7,590 segments, 109 (1.4%) and 232 (3.1%) segments could not be evaluated by MDCT because of severe calcification and motion artifacts, respectively; thus, we used 7,249 segments (95.5%) for analysis. Any narrowing of the normal contrast-enhanced lumen to < 50% that could be identified in multiplanar reconstructions or cross-sectional images was defined as significant stenosis in CAD.

Evaluation of CAD Risk Factors

Body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), serum levels of total cholesterol (TC) triglycerides (TG), HDL-C, LDL-C, LDL-C/HDL-C, non HDL-C (TC minus HDL-C), uric acid (UA), fasting glucose, hemoglobin A1c (HbA1c), smoking status (current versus non-smokers), family history [myocardial infarction (MI), angina pectoris or sudden death], and medication use were collected as CAD factors in all patients.

BMI was calculated as weight (kg)/height (m)². BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 minutes of rest. All blood samples were drawn in the morning after the patients had fasted overnight. The characteristics of patients were obtained from medical records with regard to the history of hypertension (HT), dyslipidemia (DL), diabetes mellitus (DM), and history of smoking. Patients who had a current SBP/DBP ≥ 140/90 mmHg or who were receiving antihypertensive therapy were considered to have HT. Patients with LDL-C ≥ 140 mg/dL, TG ≥ 150 mg/dL, and/or HDL-C < 40 mg/dL or who were receiving lipid-lowering therapy, were considered to have DL¹³⁾. DM was defined using the American Diabetes Association criteria¹⁴⁾ or by the administration of a glucose-lowering drug. Hyperuricemia (HU) was defined as a serum uric acid level of ≥ 7.0 mg/dL or the administration of uric acid-lowering drugs.

Diagnostic Criteria for Metabolic Syndrome (MetS)

MetS was diagnosed by the modified guidelines¹⁵⁾: visceral fat area (VFA) ≥ 100 cm² and the presence of two or more of the following: high BP (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or taking an anti-hypertensive drug), DL (TG ≥ 150 mg/dL or 40 mg/dL > HDL-C) or high fasting glucose (fasting glucose ≥ 110 mg/dL or taking a glucose-lowering drug). Subjects were classified according to the number of these components of MetS. For the measure-

Table 1. Patient Characteristics

Age, yrs	64 ± 11	DM, %	43
Sex (male), %	54	HbA1c, %	6.7 ± 2.0
Family history, %	15	Fasting glucose, mg/dL	125 ± 52
Smoking, %	32	HU, %	14
BMI, kg/m ²	24 ± 4	Uric acid, mg/dL	5.3 ± 1.5
HT, %	69	Medication use, %	
SBP, mmHg	136 ± 20	ARB/ACEI	39
DBP, mmHg	79 ± 11	CCB	40
DL, %	60	Statin	30
TG, mg/dL	130 ± 73	SFA, cm ²	156 ± 77
HDL-C, mg/dL	55 ± 17	VFA, cm ²	122 ± 63
LDL-C, mg/dL	119 ± 33	WC, cm	91 ± 11
LDL-C/HDL-C	2.4 ± 1.0	CAD, %	28
Non HDL-C	146 ± 37	MetS, %	35

Continuous variables are expressed as the mean ± SD. BMI, body mass index; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure; DL, dyslipidemia; TG, triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LDL-C/HDL-C, a ratio of LDL-C to HDL-C; Non HDL-C, total cholesterol minus HDL-C; DM, diabetes mellitus; HU, hyperuricemia; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; SFA, subcutaneous fat area; VFA, visceral fat area; WC, waist circumference; CAD, coronary artery disease; MetS, metabolic syndrome.

ment of the visceral fat area (VFA), subcutaneous fat area (SFA), and waist circumference, CT scan was performed. These values were measured from CT cross-sectional scans at the level of the umbilicus using software (Fat Scan; N2 System, Hyogo, Japan).

Statistical Analysis

Statistical analysis was performed using Excel 2003 (SSRI, Tokyo, Japan) and Stat View statistical software package (Stat View 5; SAS Institute Inc., Cary, NC, USA) at Fukuoka University (Fukuoka, Japan). Data are shown as the mean ± standard deviation (SD). Categorical and continuous variables were compared between groups by chi-square analysis and analysis of variance followed by Fisher's PLSD, respectively. Receiver-operating characteristic (ROC) curve analysis was used to determine the cut-off of HDL-C, LDL-C, LDL-C/HDL-C, and non-HDL-C to distinguish between the presence and absence of CAD at the highest possible sensitivity and specificity levels. Multivariate analysis was performed by logistic regression analysis for independent variables that were related to the presence or absence of CAD. A value of $p < 0.05$ was considered significant.

Results

Patient Characteristics

Table 1 shows the clinical characteristics of the

506 patients, who consisted of 273 (54%) men and 233 (46%) women. The prevalence of HT, DL and DM was 69%, 60% and 43%, respectively. The mean age was 64 ± 11 years, BMI was 24 ± 4 kg/m², and VFA was 122 ± 63 cm². In addition, the percentage use of angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme inhibitor (ACEI), calcium channel blocker (CCB), and statin was 39%, 40% and 30%, respectively.

Lipid Profile and Prevalence of CAD with or without Statin Treatment in Each Category

As shown in Table 2, we analyzed lipidemic parameters and the prevalence of the presence of CAD with or without statin treatment [statin (+) group or statin (−) group] in categories I (low-risk group), II (intermediate-risk group) and III (high-risk group) according to the Japan Atherosclerosis Society (JAS) Guidelines 2007¹⁰. The levels of LDL-C and non-HDL-C in the statin (−) group were similar in categories I, II and III, whereas the levels of HDL-C significantly decreased ($p < 0.0001$ for trend) and LDL-C/HDL-C and TG significantly increased as the category number increased ($p = 0.0003$ and $p = 0.0007$ for trend, respectively). In addition, the prevalence of CAD in categories I, II and III was 0, 16 and 33%, respectively ($p = 0.002$ for trend) in patients with good control of LDL-C levels according to the JAS Guidelines 2007. In the statin (+) group, none of the

Table 2. Lipid profile and prevalence of CAD with (+) or without (–) statin treatment in each category

Category	Statin (–) group				Statin (+) group	
	I (n=8)	II (n=160)	III (n=186)	p value for trend	II (n=51)	III (n=101)
LDL-C, mg/dL	115 ± 38	122 ± 34	115 ± 31	0.202	119 ± 45	147 ± 31 *
HDL-C, mg/dL	74 ± 30	61 ± 17	50 ± 15 *	<0.0001	58 ± 12	52 ± 16 *
TG, mg/dL	82 ± 46	112 ± 68	140 ± 82 *	0.0007	119 ± 45	147 ± 67 *
LDL-C/HDL-C	1.6 ± 0.5	2.0 ± 0.8	2.3 ± 1.0 *	0.0003	2.1 ± 1.0	2.8 ± 1.1 *
Non HDL-C	137 ± 49	147 ± 37	144 ± 36	0.622	143 ± 34	152 ± 38
VFA,	73 ± 62	101 ± 60	133 ± 63 *	<0.0001	112 ± 39	139 ± 66 *
MetS, %	0	8	54 *	<0.0001	18	54 *
CAD, %						
All	0	17	35	0.0002	25	36
Good	0	16	33	0.002	25	34
Poor	0	22	60	0.009	29	43

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride; LDL-C/HDL-C, a ratio of LDL-C to HDL-C; Non HDL-C, total cholesterol minus HDL-C; CAD, coronary artery disease. % CAD in all patients (All), patients with good control (Good) and poor control (Poor) in LDL-C levels according to the JAS Guidelines 2007. * $p < 0.05$ vs. group I and/or II.

patients were in category I. Patients in category III showed significantly higher levels of LDL-C, TG and LDL-C/HDL-C and lower levels of HDL-C than those in category II, and 36% of the patients in category III had CAD, whereas there was no difference in the levels of non-HDL-C between category II and III.

Lipid Profile with or without Statin Treatment in the Presence or Absence of CAD

Fig. 1 shows lipid profiles in the presence or absence of CAD in statin (–) and statin (+) groups. There were no differences in the levels of LDL-C between the presence and absence of CAD in statin (–) and (+) groups. Patients with CAD in statin (–) and (+) groups had significantly lower levels of HDL-C and higher levels of LDL-C/HDL-C, while there were no differences in the levels of non-HDL-C between the presence and absence of CAD in statin (–) and statin (+) groups (data not shown).

LDL-C Levels and the Prevalence of CAD According to HDL-C Levels

As shown in **Fig. 2**, we divided the patients in statin (–) and (+) groups into four groups according to HDL-C levels (<40 mg/dL, 40–49, 50–59, ≥60) because Mabuchi *et al.* reported that each 10 mg/dL increase in HDL-C concentration reduced the risk of CAD by 28.3%¹⁶⁾. There were no differences in LDL-C levels among the 4 categories in statin (–) and (+) groups. The presence of CAD significantly increased as HDL-C levels decreased in statin (–) and

(+) groups. The prevalence of CAD among the 4 categories in the statin (–) group was 38, 29, 25 and 18%, respectively ($p = 0.0002$ for trend). The statin (+) group also showed a significant trend ($p = 0.002$).

Comparison of Parameters with Regard to the Presence of CAD

Since LDL-C/HDL-C levels were significantly associated with both HDL-C [statin (–) group, $r = -0.675$, $p < 0.0001$; statin (+) group, $r = -0.679$, $p < 0.0001$] and LDL-C levels [statin (–) group, $r = 0.694$, $p < 0.0001$; statin (+) group, $r = 0.693$, $p < 0.0001$], and since non-HDL-C levels were significantly associated with LDL-C [statin (–) group, $r = 0.896$, $p < 0.0001$; statin (+) group, $r = 0.913$, $p < 0.0001$], we excluded LDL-C/HDL-C and non-HDL-C from multivariate logistic regression analysis. Analysis was performed to examine the association between the presence of CAD and 11 possible factors, as determined in **Table 3**. Age ($p = 0.0003$) and HDL-C ($p = 0.039$) in the statin (–) group and HDL-C ($p = 0.0007$) in the statin (+) group were identified as significant independent variables that correlated with the presence of CAD. The presence of CAD was not associated with LDL-C in statin (–) ($p = 0.203$) and statin (+) ($p = 0.757$) groups.

Cut-Off Value of HDL-C for Diagnosis of CAD

ROC curve analysis in statin (–) and statin (+) groups showed a higher area under the curve for HDL-C (0.598 and 0.671, respectively) than for

Fig. 1. Serum levels of LDL-C (a), HDL-C (b), TG (c) and LDL/HDL (d) in statin (-) and statin (+) groups. Open and closed bars indicate CAD (-) and CAD (+). N.S., not significant. * $p < 0.05$ vs. CAD (-).

LDL-C (0.453 and 0.514, respectively), LDL-C/HDL-C (0.388 and 0.398, respectively) or non-HDL-C (0.439 and 0.483, respectively) (**Fig. 3**), indicating that HDL-C levels may be a more useful lipidemic marker than LDL-C, LDL-C/HDL-C or non-HDL-C levels. The cut-off levels of HDL-C with the greatest sensitivity and specificity for the diagnosis of CAD in the statin (-) and statin (+) groups were 43 mg/dL (sensitivity 0.391, specificity 0.785) and 55 mg/dL (sensitivity 0.816, specificity 0.510), respectively.

Discussion

In the present study, the presence of CAD significantly increased as HDL-C levels decreased in statin (-) and (+) groups. In addition, age and HDL-C in the statin (-) group and HDL-C in the statin (+) group were identified as significant independent factors that correlated with the presence of CAD. Finally, ROC analysis indicated that HDL-C levels may be a more useful lipidemic marker than LDL-C, LDL-C/HDL-C or non-HDL-C levels for predicting CAD in

statin (-) and (+) groups.

The 11 factors in **Table 3**, except for TG, are independent risk factors for CAD^{11, 17}. Although there is reportedly an association between the TG level and morbidity of CAD^{18, 19}, this issue remains controversial. In this study, age and HDL-C in the statin (-) group, and HDL-C in the statin (+) group were identified as independent risk factors for CAD. Age is a risk factor for the progression of atherosclerosis²⁰ and was an independent risk factor in the statin (-) group. The mortality and morbidity rates of CAD increased after age 45 years in males and 55 years in females²¹. Although the average age in this study (64 ± 11 years) was higher than these ages, age was not an independent risk factor in the statin (+) group. Statin treatment contributes to enhanced endothelial nitric oxide synthase (eNOS) expression and NO release²², and has anti-proliferation and anti-inflammatory activity through the downregulation of adhesion molecules and chemokines^{23, 24}. Since these effects may induce an anti-aging effect on the vasculature, statin treatment may inhibit the adverse effect of aging-induced CAD, and lower levels of HDL-C may become the

Fig. 2. LDL-C levels and the prevalence of CAD according to HDL-C levels. Patients in the a) statin (-) and b) statin (+) groups were divided into 4 groups according to HDL-C levels (<40 mg/dL, 40-49 mg/dL, 50-59 mg/dL, ≥60 mg/dL). N.S., not significant.

Table 3. Comparison of parameters with regard to the presence of CAD

	Statin (-) group		Statin (+) group	
	OR (95% CI)	<i>p</i> value	OR (95% CI)	<i>p</i> value
Age	1.05 (1.02-1.09)	0.0003	1.00 (0.96-1.05)	0.894
Smoking	1.63 (0.92-2.90)	0.095	0.50 (0.20-1.23)	0.132
Family	1.07 (0.50-2.30)	0.859	1.16 (0.42-3.19)	0.780
SBP	1.02 (0.99-1.04)	0.057	1.02 (0.99-1.05)	0.232
DBP	1.00 (0.97-1.04)	0.897	0.99 (0.94-1.05)	0.798
HbA1c	1.09 (0.87-1.36)	0.445	1.04 (0.83-1.31)	0.713
Fasting blood glucose	1.00 (0.99-1.01)	0.557	1.00 (0.99-1.01)	0.724
Visceral fat area	1.00 (1.00-1.00)	0.824	1.00 (0.99-1.01)	0.635
LDL-C	1.01 (1.00-1.01)	0.203	1.00 (0.99-1.01)	0.757
HDL-C	0.98 (0.960-0.999)	0.039	0.94 (0.91-0.98)	0.0007
TG	1.00 (1.00-1.01)	0.356	1.00 (0.99-1.01)	0.988

CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic BP; HbA1c, hemoglobin A1c; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglyceride. OR, odds ratio; CI, confidence interval.

strongest risk factor in the statin (+) group.

The level of LDL-C was not a main risk factor for CAD in either the statin (-) or statin (+) group in this study. Statin treatment reduces the level of LDL-C by about 30% from the baseline^{25, 26}. As shown in **Fig. 1**, there were no differences in the level of LDL-C between the presence and absence of CAD in statin (-)

and statin (+) groups. When the level of LDL-C is reduced to around 120 mg/dL by statins, HDL-C may appear to become a stronger risk factor for CAD than LDL-C because the HDL-C level in CAD (+) is significantly lower than in CAD (-) (**Fig. 1**). Since the LDL/HDL ratio in the CAD (-) group was 2.1, aggressive statin treatment is needed to reach this ratio.

Fig. 3. Receiver-operating characteristic (ROC) curve for HDL-C (black lines), LDL-C (gray lines), non-HDL-C (gray dotted lines), and LDL-C/HDL-C (black dotted lines) levels for the diagnosis of CAD in a) statin (-) and b) statin (+) groups.

When the LDL/HDL ratio was >2.0 during statin treatment, the atheroma volume increased (+1.2%), and LDL/HDL <1.5 showed the regression of atheroma (-0.3%)⁸⁾. Even if a patient reaches an LDL/HDL ratio of 2.1, such a patient may develop CAD in the near future.

In the statin (-) group, the LDL-C level was about 120 mg/dL in categories I, II and III. Nonetheless, 16% and 33% of patients with good control of LDL-C levels according to the JAS Guidelines 2007 in categories II and III in the statin (-) group had CAD, respectively. In primary prevention, although patients in categories II and III without statins need to have improved HDL function, there are currently only a few therapeutic strategies for improving this function, such as the use of statins and cholesterol ester transfer protein inhibitor. The increases in HDL-C levels in REVERSAL²⁷⁾, CAMELOT²⁸⁾ and ACTIVATE²⁹⁾ were 1.9, 1.7 and 1.2 mg/dL, respectively, and these increments may not be enough to prevent CAD. Only rosuvastatin increased the HDL-C level by 5.7 mg/dL in ASTEROID³⁰⁾. Significant increases in HDL-C may regress atherosclerosis. Alternatively, a further reduction of LDL-C levels may be needed.

There are several limitations of this study. First, although the subjects in this study were clinically suspected of having CAD, over half of the subjects were considered to not have CAD by MDCT. Second, although coronary stenosis with severe coronary calcification was not evaluated using MDCT, recent studies have shown that both the sensitivity and specificity

of MDCT for the identification of significant coronary stenosis were approximately 95%, compared with invasive coronary angiography³¹⁾. In this study, we could evaluate 95.5% of all segments. Third, this study was cross-sectional. Although it takes a long time for coronary atherosclerosis to progress, we only analyzed the prevalence, the control situation, and the medications presently used to treat HT, DM and DL, and we did not have data on the duration of these diseases and medications.

In conclusion, age and HDL-C in the statin (-) group and HDL-C in the statin (+) group were identified as significant independent factors that correlated with the presence of CAD. In particular, we need to perform coronary CT for suspected CAD patients with lower levels of serum HDL-C under statin treatment.

Conflict of Interest

The authors declare no conflict of interest.

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