Low-density Lipoprotein Cholesterol is a Predictor of Metabolic Syndrome in a Japanese Health Screening Population

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Abstract

Objective Both increased serum levels of low-density lipoprotein cholesterol (LDLC) and metabolic syndrome (MetS) are associated with obesity and have been established to be risk factors of cardiovascular disease. However, studies on the relationship between LDLC and MetS have been limited.

Methods Cross-sectional (n=3,871) and longitudinal (n=2,558) associations between LDLC and MetS were examined in a Japanese health screening population.

Results The odds ratio (OR) [95% confidence interval (CI)] of coexisting MetS for each one SD increase in the LDLC level was 1.25 [1.12-1.40] ($p<0.001$) adjusted for body mass index (BMI) and other confounding covariates and 1.12 [0.97-1.28] ($p=0.119$) adjusted for numerical values of the components of MetS and other confounding covariates. The similarly adjusted ORs [95% CIs] for the highest quartile of LDLC (Q4) compared with the lowest quartile (Q1) were 1.76 [1.22-2.54] ($p=0.002$) and 1.46 (0.93-2.30) ($p=0.101$), respectively. The hazard ratio (HR) [95% CI] for developing MetS for each one SD increase in the LDLC level was 1.24 [1.10-1.40] ($p<0.001$) adjusted for BMI and other confounding covariates and 1.19 [1.05-1.34] ($p=0.006$) adjusted for the pre-existing dichotomous five components of MetS and other confounding covariates. The similarly adjusted HRs [95% CIs] for developing MetS for Q4 compared with Q1 were 1.71 [1.17-2.51] ($p=0.006$) and 1.61 [1.08-2.40] ($p=0.020$), respectively.

Conclusion The LDLC level is associated with coexisting MetS and functions as a predictor of the development of MetS, independent of BMI or the pre-existing components of MetS, in a Japanese health screening population.

Key words: LDL cholesterol, metabolic syndrome, cardiovascular disease, risk factor

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Introduction

Metabolic syndrome (MetS) (1-6) is a constellation of interrelated metabolic risk factors for cardiovascular disease (CVD). The International Diabetes Federation (IDF), National Heart, Lung, and Blood Institute, American Heart Association, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity jointly adopted the revised National Cholesterol Education Program criteria (5) as the harmonizing worldwide criteria for MetS in 2009 (6). MetS is a useful concept

in education and for investigating the complex interrelated pathophysiological mechanisms of CVD (8) although some professional societies have pointed out the limitations of MetS as a clinical and epidemiological tool (7, 8). A core underlining mechanism of MetS involves inflammatory changes in adipose tissue (9, 10) characterized by increased aggregation of activated macrophages into adipose tissue (11) induced by chronic energy overload and is related to many other complex pathophysiological mechanisms such as systemic and vascular inflammation (12), insulin resistance (13), and endothelial dysfunction (14). Meanwhile, an increased serum level of low-density lipoprotein cholesterol

Table 1. Baseline Data

	cross-sectional study	longitudinal study		p
		candidate subjects	follow-up subjects	
n (male%)	3,871 (62.9)	3,381 (61.1)	2,558 (62.8)	0.175
age	51.7 (9.7)	51.3 (9.7)	51.7 (9.4)	0.174
LDL cholesterol (mg/dL)	121.3 (29.5)	120.1 (28.9)	120.6 (28.3)	0.525
body mass index (kg/m ²)	22.7 (3.1)	22.2 (2.7)	22.2 (2.6)	0.557
waist circumference (cm)	82.4 (8.7)	80.9 (7.8)	81.1 (7.6)	0.376
systolic BP (mmHg)	118.8 (18.0)	116.5 (16.9)	116.8 (16.9)	0.535
diastolic BP (mmHg)	74.9 (11.2)	73.6 (10.6)	73.8 (10.6)	0.360
fasting glucose (mg/dL)	94.0 (14.7)	92.1 (12.6)	92.1 (12.0)	0.848
triglycerides (mg/dL)	108.9 (73.7)	98.0 (58.8)	98.3 (58.4)	0.809
HDL cholesterol (mg/dL)	61.1 (15.2)	62.8 (14.9)	62.8 (15.0)	0.947
metabolic syndrome	12.6			
abdominal obesity	30.2	22.7	22.8	0.947
high blood pressure	33.5	26.6	27.6	0.429
high fasting glucose	21.3	14.3	14.5	0.809
high triglycerides	18.0	11.4	11.5	0.952
high HDL cholesterol	8.3	4.6	4.6	0.987
antihypertensive medication	16.2	12.6	13.0	0.630
antidiabetic medication	2.8	1.7	1.6	0.967
antihyperlipidemic medication	9.9	8.9	9.4	0.549
stroke	1.6	1.5	1.5	0.968
coronary heart disease	3.2	2.7	2.7	0.914
current smoker	23.9	22.8	23.2	0.720
everyday drinker	38.4	37.8	38.3	0.739
physically active person	35.4	36.3	36.0	0.767

mean (SD) or %, BP: blood pressure

(LDLC) is an established risk factor for CVD (15) but is not included in the components of MetS, although both conditions are associated with obesity (16). The relationship between LDLC and MetS has not been sufficiently studied in Japan, where obesity is not prevalent. In the present study, the author investigated the cross-sectional and longitudinal associations between LDLC and MetS in a Japanese health screening population.

Materials and Methods

Subjects

The subjects of this cross-sectional study included 2,435 men and 1,436 women who visited our Medical Check-up Center for general health screening between April 2008 and March 2009 and provided their written informed consent. The participants were required to complete a questionnaire including questions about their history of coronary heart disease (CHD) and stroke, smoking and drinking status, level of physical activity and use of antihypertensive, antidiabetic, and antihyperlipidemic medications. Excluding subjects with MetS at baseline, 2,064 men and 1,317 women remained as candidate subjects for the longitudinal study. Among them, 1,606 men and 952 women revisited our center between April 2009 and March 2012 and were included in the longitudinal study. The study was approved by the ethics committee of Tachikawa Medical Center.

Measurements

Blood samples were obtained after an overnight fast to

measure the blood levels of routine medical check-up parameters, including fasting glucose, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL) and LDL. The chemical measurements were determined at BML Nagaoka (Nagaoka, Japan) using routine laboratory methods. The LDL levels were measured using a direct surfactant method with the Choletest-LDL (Sekisui Medical Inc., Tokyo, Japan). The average systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated from two measurements obtained with the subject in a sitting position after five minutes of rest. The body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference (WC) was measured at the level of the umbilicus in the standing position.

Statistical analysis

Definition of MetS and hyper-LDL cholesterolemia

Based on the presumption that visceral adipose tissue (VAT) exerts adverse effects on the mortality of patients with obesity and CVD, whereas subcutaneous abdominal adipose tissue exerts favorable effects in such patients, the concept of Japanese MetS (JMetS) was proposed in 2005 by several academic societies in Japan (17). However, this assumption is not accepted worldwide, and there is a report that VAT was not significantly associated with all-cause, obesity-related or CVD-related mortality after adjusting for BMI, a marker of general obesity, in a long-term follow-up study of Japanese Americans (18). It has been suggested that an increased amount of VAT does not directly cause meta-

Table 2. Prevalence of Metabolic Syndrome and Its Components by the Quartiles of LDL Cholesterol

	Q1	Q2	Q3	Q4	p for trend
LDL cholesterol (mg/dL)	19-101	102-120	121-139	140-307	
n (male%)	949 (62.6)	1003 (61.1)	941 (65.4)	978 (62.7)	
metabolic syndrome	8.1	11.9	12.4	18.0	<0.001
abdominal obesity	21.2	26.7	30.8	42.0	<0.001
high blood pressure	32.5	32.0	35.9	33.7	0.255
high fasting glucose	17.9	19.6	23.1	24.4	<0.001
high triglycerides	12.5	16.0	18.2	25.3	<0.001
low HDL cholesterol	7.2	7.5	7.9	10.8	0.004

Table 3. Odds Ratios of Metabolic Syndrome for Each 1 SD Increase in LDL Cholesterol, Hyper-LDL Cholesterol, and the Higher Quartiles of LDL Cholesterol Compared with the Lowest Quartile

	odds ratio (95% confidence interval)	p
Model 1		
each 1 SD increase	1.53 (1.38-1.69)	<0.001
hyper-LDL cholesterol	2.11 (1.70-2.62)	<0.001
the 2nd quartile	1.69 (1.22-2.35)	0.002
the 3rd quartile	1.82 (1.32-2.54)	<0.001
the 4th quartile	3.14 (2.28-4.33)	<0.001
Model 2		
each 1 SD increase	1.25 (1.12-1.40)	<0.001
hyper-LDL cholesterol	1.43 (1.12-1.82)	0.005
the 2nd quartile	1.39 (0.96-2.00)	0.080
the 3rd quartile	1.36 (0.94-1.96)	0.098
the 4th quartile	1.76 (1.22-2.54)	0.002
Model 3		
each 1 SD increase	1.12 (0.97-1.28)	0.119
hyper-LDL cholesterol	1.10 (0.82-1.48)	0.524
the 2nd quartile	1.63 (1.02-2.61)	0.043
the 3rd quartile	1.35 (0.87-2.11)	0.179
the 4th quartile	1.46 (0.93-2.30)	0.101

Model 1: adjusting for sex, age, smoking and drinking status, physical activity, histories of CHD and stroke, and use of antihypertensive, antihyperlipidemic, and antidiabetic medications, Model 2: adjusting for the covariates in Model 1 plus body mass index, Model 3: adjusting for the covariates in Model 1 plus waist circumference, systolic blood pressure, fasting plasma glucose, triglycerides, and HDL cholesterol

bolic dysfunction, as omentectomy does not have a significant ancillary impact on the components of MetS and does not induce important changes in inflammatory mediators in patients undergoing Roux-en-Y gastric bypass surgery (19). This journal is intended for both domestic readers and readers worldwide. Therefore, MetS was defined according to the above mentioned harmonizing worldwide criteria (6) as the coexistence of three or more components among the five components of MetS, in which the cutoff points for WC, blood pressure, fasting glucose, triglycerides, and HDLC are 90 cm in men and 80 cm in women for Japanese individuals according to the recommendation of the IDF (4), 130 mmHg for SBP and/or 85 mmHg for DBP, 100 mg/dL, 150 mg/dL, and 40 mg/dL in men and 50 mg/dL in women, respectively. Apart from the above criteria, subjects receiving antihypertensive medications were included in the high blood pressure group and those receiving antidiabetic medications were included in the high fasting glucose group;

however, those receiving antihyperlipidemic medications were not included in the high triglyceride or low HDLC group because detailed information about the drugs was not available. Hyper-LDL cholesterol (hyper-LDLC) was defined as an LDLC level of 140 mg/dL or higher.

Cross-sectional study

The prevalence of MetS and its components was calculated according to the quartile of the LDLC level. Odds ratios (ORs) for coexisting MetS were calculated for each one SD increase in the LDLC level, for hyper-LDLC and for the higher quartiles (Q2, Q3, and Q4) of LDLC compared with the lowest quartile (Q1), adjusted for age, smoking and drinking status, physical activity, history of CHD or stroke and the use of antihypertensive, antihyperlipidemic, and antidiabetic medications (Model 1), adjusted for the covariates in Model 1 plus BMI (Model 2) and further adjusted for the covariates in Model 1 plus WC, SBP, fasting glucose, triglycerides and HDLC (Model 3). DBP was not included in the covariates because SBP and DBP were found to be strongly correlated ($p=0.92$). Physical activity was defined as walking for one hour or longer per day or exercising for 30 minutes or longer twice or more per week.

Longitudinal study

The baseline data for all candidate subjects who did not have MetS at baseline and those of the follow-up subjects were compared to examine a selection bias.

The incidence of developing MetS and its components was calculated according to the quartile of the LDLC level. Subjects with the respective component of MetS at baseline were excluded when the incidence of each MetS component was calculated. Hazard ratios (HRs) for developing MetS were calculated for each one SD increase in the LDLC level, for hyper-LDLC, and for Q2, Q3, and Q4 compared with Q1 adjusted for Model 1, for Model 2, and for the covariates in Model 1 plus the pre-existing dichotomous five components of MetS (Model 4). The HRs for developing each MetS component were calculated for each one SD increase in the LDLC level adjusted for Model 1, for Model 2, and for the covariates in Model 1 plus the pre-existing dichotomous other four components of MetS (Model 5). The HRs for developing MetS were re-calculated excluding subjects who used antihyperlipidemic drugs, including statins,

Table 4. Incidence of Metabolic Syndrome and Its Components by the Quartile of LDL Cholesterol

	Q1	Q2	Q3	Q4	p for trend
LDL cholesterol (mg/dL)	33-101	102-119	120-138	139-272	
metabolic syndrome n (male%)	643 (62.8)	623 (61.3)	641 (64.6)	651 (62.4)	
incidence	6.5	7.7	10.1	14.3	<0.001
p values by log rank tests between each Kaplan-Meier survival curve for the quartiles of LDL cholesterol					
Q2	0.464				
Q3	0.017	0.096			
Q4	<0.001	<0.001	0.022		
abdominal obesity n (male%)	541 (68.4)	506 (70.2)	483 (73.5)	446 (74.4)	
incidence	5.9	6.3	9.1	10.1	0.005
high blood pressure n (male%)	454 (52.9)	454 (55.5)	444 (59.9)	501 (59.7)	
incidence	15.6	15.2	14.9	17.4	0.006
high fasting glucose n (male%)	555 (60.4)	544 (57.7)	536 (62.1)	552 (60.0)	
incidence	7.9	8.6	9.5	9.8	0.237
high triglycerides n (male%)	594 (60.3)	557 (58.5)	569 (61.3)	544 (57.5)	
incidence	6.9	7.7	10.5	15.6	<0.001
low HDL cholesterol n (male%)	617 (63.4)	601 (61.7)	616 (64.8)	607 (62.6)	
incidence	2.9	5.2	4.1	7.1	0.003

at baseline. The HRs for developing MetS with respect to longitudinal changes in LDLC, BMI and WC were also calculated.

Studies using calculated LDLC instead of directly measured LDLC

The same study was repeated using LDLC values calculated with the Friedewald equation instead of directly measured LDLC levels in subjects whose serum level of triglycerides was lower than 400 mg/dL.

The statistical analyses were performed using the Dr SPSS-2 software program (IBM Japan, Tokyo, Japan). p values lower than 0.05 were considered to be significant.

Results

Cross-sectional study

The baseline data of the subjects are presented in Table 1. The prevalence of MetS and its components stratified by the quartile of the LDLC level is shown in Table 2. A significant linear trend was observed in the prevalence of MetS, abdominal obesity, high fasting glucose, high triglycerides and low HDLC through the quartiles of the LDLC level.

The ORs for MetS for each one SD increase in the LDLC level, for hyper-LDHC and for Q2, Q3, and Q4 compared with Q1 are shown in Table 3. The OR [95% confidence interval (CI)] for MetS for each one SD increase in the LDLC level was 1.53 [1.38-1.69] ($p<0.001$) in Model 1, 1.25 [1.12-1.40] ($p<0.001$) in Model 2, and 1.12 [0.97-1.28] ($p=0.119$) in Model 3, that for hyper-LDLC was 2.11 [1.70-2.62] ($p<0.001$) in Model 1, 1.43 [1.12-1.82] ($p=0.005$) in Model 2, and 1.10 [0.82-1.48] ($p=0.524$) in Model 3, and that for Q4 compared with Q1 was 3.14 [2.28-4.33] ($p<0.001$) in Model 1, 1.76 [1.22-2.54] ($p=0.002$) in Model 2, and 1.46 [0.93-2.30] ($p=0.101$) in Model 3.

Longitudinal study

The baseline data of the candidate subjects for the longitudinal study and the actually followed subjects are presented in Table 1. There were no significant differences in the baseline data between the candidate subjects and the actually followed subjects.

The incidence of developing MetS and its components stratified by the quartile of the LDLC level and the p values according to the log-rank test between each Kaplan-Meier survival curve for MetS based on the quartile of the LDLC level are shown in Table 4. A significant linear trend was observed in the incidence of MetS, abdominal obesity, high blood pressure, high triglycerides and low HDLC through the quartiles of the LDLC level. Significant differences were seen between the Kaplan-Meier survival curves for MetS for Q1 and Q3, for Q1 and Q4, for Q2 and Q4, and for Q3 and Q4.

The HRs for MetS for each one SD increase in the LDLC level, for hyper-LDLC, and for Q2, Q3, and Q4 compared with Q1 are shown in Table 5. The HR [95% CI] for MetS for each one SD increase in the LDLC level was 1.42 [1.26-1.60] ($p<0.001$) in Model 1, 1.24 [1.10-1.40] ($p<0.001$) in Model 2, and 1.19 [1.05-1.34] ($p=0.006$) in Model 4, that for hyper-LDLC was 1.85 [1.42-2.41] ($p<0.001$) in Model 1, 1.42 [1.09-1.86] ($p=0.010$) in Model 2, and 1.39 [1.06-1.82] ($p=0.018$) in Model 4, and that for Q4 compared with Q1 was 2.40 [1.65-3.51] ($p<0.001$) in Model 1, 1.71 [1.17-2.51] ($p=0.006$) in Model 2, and 1.61 [1.08-2.40] ($p=0.020$) in Model 4. The HRs for developing MetS for each one SD increase in the LDLC level, for hyper-LDL cholesterolemia and for Q4 compared with Q1 are illustrated in Figure. The HRs for developing each component of MetS for each one SD increase in the LDLC level are presented in Table 6. The LDLC level was a significant predictor of abdominal obesity, high blood pressure, high triglycerides and low HDLC in Model 1, high blood pressure and high triglyc-

Table 5. Hazard Ratios of Metabolic Syndrome for Each 1 SD Increase in LDL Cholesterol, Hyper-LDL Cholesterolemia, and the Higher Quartiles of LDL Cholesterol Compared with the Lowest Quartile

	hazard ratio (95% confidence interval)	p
Model 1		
each 1 SD increase	1.42 (1.26-1.60)	<0.001
hyper-LDL cholesterolemia	1.85 (1.42-2.41)	<0.001
the 2nd quartile	1.26 (0.82-1.93)	0.290
the 3rd quartile	1.60 (1.08-2.38)	0.019
the 4th quartile	2.40 (1.65-3.51)	<0.001
Model 2		
each 1 SD increase	1.24 (1.10-1.40)	<0.001
hyper-LDL cholesterolemia	1.42 (1.09-1.86)	0.010
the 2nd quartile	1.14 (0.74-1.76)	0.542
the 3rd quartile	1.34 (0.90-2.00)	0.146
the 4th quartile	1.71 (1.17-2.51)	0.006
Model 4		
each 1 SD increase	1.19 (1.05-1.34)	0.006
hyper-LDL cholesterolemia	1.39 (1.06-1.82)	0.018
the 2nd quartile	1.20 (0.78-1.86)	0.409
the 3rd quartile	1.27 (0.85-1.91)	0.246
the 4th quartile	1.61 (1.08-2.40)	0.020

Model 1: adjusting for sex, age, smoking and drinking status, physical activity, histories of CHD and stroke, and use of antihypertensive, antihyperlipidemic, and antidiabetic medications, Model 2: adjusting for the covariates in Model 1 plus body mass index, Model 4: adjusting for the covariates in Model 1 plus the pre-existing five components of metabolic syndrome

Table 7. Hazard Ratios of Metabolic Syndrome for Each 1 SD Increase in LDL Cholesterol, Hyper-LDL Cholesterolemia, and the Higher Quartiles of LDL Cholesterol Compared with the Lowest Quartile in Subjects who Did Not Use Antihyperlipidemic Drugs at Baseline

	hazard ratio (95% confidence interval)	p
Model 1		
each 1 SD increase	1.35 (1.20-1.53)	<0.001
hyper-LDL cholesterolemia	1.74 (1.33-2.28)	<0.001
the 2nd quartile	1.64 (1.09-2.47)	0.018
the 3rd quartile	1.75 (1.15-2.64)	0.008
the 4th quartile	2.48 (1.67-3.70)	<0.001
Model 2		
each 1 SD increase	1.21 (1.07-1.37)	0.002
hyper-LDL cholesterolemia	1.34 (1.02-1.76)	0.034
the 2nd quartile	1.64 (1.08-2.49)	0.020
the 3rd quartile	1.63 (1.08-2.48)	0.021
the 4th quartile	1.87 (1.25-2.80)	0.002
Model 4		
each 1 SD increase	1.16 (1.03-1.32)	0.015
hyper-LDL cholesterolemia	1.32 (1.01-1.74)	0.043
the 2nd quartile	1.62 (1.07-2.46)	0.024
the 3rd quartile	1.42 (0.93-2.17)	0.106
the 4th quartile	1.76 (1.17-2.65)	0.007

Model 1: adjusting for sex, age, smoking and drinking status, physical activity, histories of CHD and stroke, and use of antihypertensive and antidiabetic medications, Model 2: adjusting for the covariates in Model 1 plus body mass index, Model 4: adjusting for the covariates in Model 1 plus the pre-existing five components of metabolic syndrome

erides in Model 2 and abdominal obesity and high triglycerides in Model 5.

The HRs for developing MetS in the subjects who did not use antihyperlipidemic drugs at baseline are shown in Table 7. The HR [95% CI] for MetS for each one SD increase

Table 6. Hazard Ratios of Each Component of Metabolic Syndrome for 1SD Increase in LDL Cholesterol

	hazard ratio (95% confidence interval)	p
Model 1		
abdominal obesity	1.32 (1.12-1.54)	<0.001
high blood pressure	1.31 (1.07-1.61)	0.009
high fasting glucose	1.10 (0.95-1.27)	0.221
high triglycerides	1.45 (1.29-1.64)	<0.001
low HDL cholesterol	1.29 (1.05-1.50)	0.011
Model 2		
abdominal obesity	1.16 (0.98-1.37)	0.093
high blood pressure	1.23 (1.00-1.52)	0.049
high fasting glucose	1.01 (0.87-1.18)	0.850
high triglycerides	1.35 (1.19-1.53)	<0.001
low HDL cholesterol	1.16 (0.96-1.39)	0.116
Model 5		
abdominal obesity	1.29 (1.09-1.51)	0.002
high blood pressure	1.20 (0.97-1.49)	0.096
high fasting glucose	1.05 (0.90-1.22)	0.566
high triglycerides	1.36 (1.20-1.54)	<0.001
low HDL cholesterol	1.14 (0.95-1.38)	0.162

Model 1: adjusting for sex, age, smoking and drinking status, physical activity, histories of CHD and stroke, and use of antihypertensive, antihyperlipidemic, and antidiabetic medications, Model 2: adjusting for the covariates in Model 1 plus body mass index, Model 5: adjusting for the covariates in Model 1 plus the pre-existing four components of metabolic syndrome

Table 8. Hazard Ratios of Metabolic Syndrome for Each 1 SD Logitudinal Changes in LDL Cholesterol, Body Mass Index and Waist Circumference

	hazard ratio (95% confidence interval)	p
Model 1		
changes in LDL cholesterol	0.89 (0.76-1.03)	0.123
changes in body mass index	2.92 (2.20-3.88)	<0.001
change in waist circumference	2.45 (1.82-3.30)	<0.001
Model 2		
changes in LDL cholesterol	0.93 (0.80-1.09)	0.397
changes in body mass index	2.88 (2.18-3.79)	<0.001
change in waist circumference	2.58 (1.94-3.44)	<0.001
Model 4		
changes in LDL cholesterol	0.97 (0.84-1.13)	0.694
changes in body mass index	3.34 (2.46-4.54)	<0.001
change in waist circumference	3.18 (2.39-4.24)	<0.001

Model 1: adjusting for sex, age, smoking and drinking status, physical activity, histories of CHD and stroke, and use of antihypertensive, antihyperlipidemic, and antidiabetic medications, Model 2: adjusting for the covariates in Model 1 plus body mass index for changes in LDL cholesterol and changes in waist circumference while the covariates in Model 1 plus waist circumference for changes in body mass index, Model 4: adjusting for the covariates in Model 1 plus the pre-existing five components of metabolic syndrome

in the LDLC level was 1.35 [1.20-1.53] ($p<0.001$) in Model 1, 1.21 [1.07-1.37] ($p=0.002$) in Model 2 and 1.16 [1.03-1.32] ($p=0.015$) in Model 4, that for hyper-LDL was 1.74 [1.33-2.28] ($p<0.001$) in Model 1, 1.34 [1.02-1.76] ($p=0.034$) in Model 2, and 1.32 [1.01-1.74] ($p=0.043$) in Model 4 and that for Q4 compared with Q1 was 2.48 [1.67-3.70] ($p<0.001$) in Model 1, 1.87 [1.25-2.80] ($p=0.002$) in Model 2 and 1.76 [1.17-2.65] ($p=0.007$) in Model 4. Therefore, the HRs were similar to those in Table 5, although slightly lower for each one SD increase in the LDLC level and for

Figure. Hazard ratios with 95% confidence intervals for developing metabolic syndrome for each one SD increase in the LDL cholesterol level (1 SD), for hyper-LDL cholesterolemia (HC), and for Q4 compared with Q1 (Q4). Model 1: adjusted for age, smoking and drinking status, physical activity, history of CHD or stroke and the use of antihypertensive, antihyperlipidemic, and antidiabetic medications; Model 2: adjusted for the covariates in Model 1 plus BMI; Model 4: adjusted for the covariates in Model 1 plus the pre-existing dichotomous five components of MetS.

hyper-LDL and slightly higher for Q4 compared with Q1 than those in Table 5.

The HRs for developing MetS with respect to longitudinal changes in the LDLC level, BMI and WC are presented in Table 8. The longitudinal changes in the LDLC level were not significantly associated with the development of MetS. However, the longitudinal changes in BMI and WC were strongly associated with the development of MetS as a matter of course.

Studies using calculated LDLC

The study results using the calculated LDLC levels instead of the measured LDLC levels in the subjects with a triglyceride level lower than 400 mg/dL are presented in Supplementary Tables s1-s6. The results were similar to those presented in Tables 1-6.

Discussion

The present study demonstrated that the LDLC level was associated with coexisting MetS and functioned as a predictor of the development of MetS, independent of BMI or the pre-existing components of MetS, in a Japanese health screening population.

Adipose tissue secretes many hormone-like substances and obesity is considered to be an endocrine and inflammatory disorder closely related to insulin resistance. The adipose expression of tumor necrosis factor- α plays a direct role in the development of obesity-linked insulin resistance (10). An increased number of crown-like structures consisting of activated macrophages surrounding enlarged

dead adipocytes has been shown to be a characteristic histological feature of adipose tissue disorders (11). MetS may be a systemic manifestation of adipose tissue disease (9) and is related to many other complex pathophysiological mechanisms such as systemic inflammation (12), insulin resistance (13), and endothelial dysfunction (14). Meanwhile, LDLC is associated with obesity (16), endothelial dysfunction, vascular inflammation, and atherosclerosis (20) and has been recognized to be an established risk factor for CVD (15).

Williams et al. (21) compared the associations between the level of apolipoprotein B (apoB) and LDLC and CVD risk factors in the Insulin Resistance Atherosclerosis Study and reported that subjects with an elevated apoB level with a normal LDLC level have higher associated CVD risks than those with an elevated LDLC level with a normal apoB level. After adjusting for the LDLC level, the correlation between the apoB level and CVD risk remained significant, whereas several correlations with the LDLC level became significant in the direction of lower risk after adjusting for the apoB level (21). Onat et al. (22) reported that the apoB level, which reflects the number of small dense LDL particles in plasma, is a significant predictor of MetS after adjusting for WC, C-reactive protein, and other confounding variables. Holvoet et al. (23) reported that a higher concentration of oxidized LDL is associated with an increased incidence of MetS after adjusting for the LDLC level and other confounding covariates, while the association between the LDLC level and incident MetS is not significant after adjusting for covariates including BMI, and there are no associations after further adjusting for the oxidized LDL level. In contrast, the present study demonstrated that the LDLC level is a predictor of MetS, independent of BMI or the pre-existing five components of MetS. The difference in results between the study by Holvoet et al. and the present study may be partially due to the differences in the ethnicity and age of the subjects and the length of the follow-up period. The association between the LDLC level and MetS may be stronger in Japan where obesity and insulin resistance are not as prevalent as in Western countries where these abnormalities are predominant.

Clinical implications

The present results suggest that an increase in the LDLC level is associated with the development of MetS, independent of obesity and the pre-existing components of MetS. Endothelial dysfunction and vascular inflammation can result from an increased LDLC level, which may be associated with increased levels of apoB (21), small, dense LDL (22) and oxidized LDL (23), may be involved in the causal mechanisms of MetS. The present results also suggest that risk of CVD caused by hyper-LDL cholesterolemia may be mediated in part by the development of MetS and that the beneficial effects of LDLC-lowering agents, such as statins, may be partially attributable to their ability to prevent the development of MetS.

Limitations

The subjects of the present study were not recruited from the general population, but rather from a health screening population. Detailed information regarding antihyperlipidemic drugs was not available, and the levels of apolipoproteins, sub-fractions of LDL and oxidized LDL were not measured. However, when the data were recalculated excluding subjects who used antihyperlipidemic drugs, including statins, the LDL-C level remained a significant predictor of MetS, as shown in Table 7. Despite these limitations, the present study demonstrated for the first time that the LDL-C level is a predictor of incident MetS, independent of obesity and the pre-existing five components of MetS.

The author states that he has no Conflict of Interest (COI).

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