Non-high-density cholesterol level as a predictor of maximum carotid intima-media thickness in Japanese subjects with type 2 diabetes: a comparison with low-density lipoprotein level

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Abstract

Aim To determine whether non-high-density lipoprotein cholesterol (non-HDL-C) level, in comparison with low-density lipoprotein cholesterol (LDL-C) level, is useful for predicting the values of various surrogate atherosclerosis markers in Japanese subjects with type 2 diabetes (T2DM).

Methods Data were retrieved from medical records of 265 subjects with T2DM who underwent laboratory tests to evaluate for atherosclerosis by using the following parameters: brachial-ankle pulse wave velocity, mean and maximum carotid intima-media thickness (mean CIMT and max-CIMT), and ankle-brachial index, with simultaneous fasting blood sampling for routine lipid parameters.

Results In a multiple stepwise regression analysis, non-HDL-C level, but not LDL-C level, positively correlated with max-CIMT (β coefficient = 0.14, $F = 6.84$). Stepwise logistic regression analysis revealed that a 0.26 mmol/L (10 mg/dL) increase in non-HDL-C level, but not LDL-C level, was significantly associated with high risk of max-CIMT (≥ 1.1 mm; odds ratio, 1.096; 95 % confidence interval, 1.003–1.202; $p = 0.046$). However, in a receiver operating characteristic curve (ROC) analysis, the addition of non-HDL-C level to the three significant independent variables obtained from the stepwise analyses did not significantly increased the area under the ROC curve (from 0.7789 to 0.7864, $p = 0.4343$).

Conclusions Non-HDL-C levels may be non-inferior to LDL-C level for the prediction of high-risk max-CIMT in Japanese subjects with T2DM.

Keywords Non-HDL cholesterol · LDL cholesterol · Maximum carotid intima-media thickness · Type 2 diabetes

Introduction

Although elevated low-density lipoprotein cholesterol (LDL-C) levels remain the main focus of therapy in the primary and secondary prevention of coronary heart disease, some triglyceride-rich lipoproteins are now widely recognized also to contribute to atherogenesis [1]. Non-high-density lipoprotein cholesterol (non-HDL-C), the level of which is calculated by subtracting HDL cholesterol level from the total cholesterol, contains all known and potential atherogenic lipid particles, all of which incorporate atherogenic apolipoprotein B. Therefore, non-HDL-C levels may be suitable as LDL-C levels in the prediction of the risk of cardiovascular diseases (CVD).

The recently revised Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic CVD recommend that non-HDL-C levels should be considered a secondary target of therapy in individuals with triglyceride levels >4.5 mmol/L (400 mg/dL) [2]. Non-HDL-C target levels are 30 points higher than the recommended LDL-C threshold levels [2]. In contrast to LDL-C levels, which are traditionally calculated by using the Friedewald formula [3] and require a fasting blood sample, non-HDL-C level can be measured in the non-fasting state, without involving any assumptions regarding lipoprotein composition [1, 2] and added expense.

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Non-HDL-C level has been shown to be a predictor of coronary heart disease and mortality in a number of prospective cohort studies that predominantly or exclusively enrolled CVD-free individuals [4–14] and exclusively enrolled individuals with prevalent coronary artery disease (CAD) [15]. In addition, several recent studies [4, 6, 7, 10, 13–15] have suggested that non-HDL-C level is superior to LDL-C level in terms of predictive value for CVD.

Particularly in patients with type 2 diabetes (T2DM), the role of the triglyceride-rich lipoproteins in non-HDL-C in the development of atherosclerosis will likely increase [16]. However, to our knowledge, few data validate the use of non-HDL-C level instead of LDL-C level as a predictor of cardiovascular outcome in patients with T2DM in Japan. The aim of this study was to determine whether non-HDL-C levels are more useful in predicting the values of various surrogate atherosclerosis markers than LDL-C levels in Japanese subjects with T2DM.

Materials and methods

Ethics statement

This study was conducted in accordance with Good Clinical Practice, International Conference on Harmonization guidelines, and applicable laws and regulations. The study protocol was approved by the ethics committee of Fukui-ken Saiseikai Hospital. All of the patients provided written informed consent before enrollment after receiving a full explanation of the study.

Subjects

This retrospective, cross-sectional study used data from the medical records of Japanese patients with T2DM from the Fukui-ken Saiseikai Hospital. The subjects underwent brachial-ankle pulse wave velocity (baPWV), carotid intima-media thickness (CIMT), and ankle-brachial index (ABI) tests to evaluate for atherosclerosis within 1 month from fasting blood sampling for routine lipid parameters. Subjects were eligible for enrollment in this study if the basic demographic data collected from their medical records included sex, age, body mass index (BMI), hemoglobin A1c level (HbA1c), current smoking status, estimated glomerular filtration rate (eGFR), systolic and diastolic blood pressure, and history of ischemic heart disease or ischemic stroke. For the subjects with T2DM, additional collected data included diabetes duration, oral hypoglycemic agents (OHAs) used, insulin or antihypertensive agents used, and presence of retinopathy. Subjects with type 1 diabetes, history of CVD, thyroid or

gastrointestinal diseases, fasting triglyceride levels ≥ 4.5 mmol/L (400 mg/dL), and receiving steroids or any lipid-lowering agents were excluded from this study.

Clinical and laboratory analyses

Blood samples for analysis of serum concentrations of total cholesterol, triglycerides, HDL-C, and HbA1c were collected from patients in the morning in the sitting position after overnight fasting. LDL-C level was calculated by using the Friedewald equation [3]. Non-HDL-C level was calculated by subtracting HDL-C level from total cholesterol level. All the blood tests were performed by using standard methods. Blood pressure (BP) was determined through the conventional cuff method by using a mercury sphygmomanometer after the subject had rested for at least 5 min.

Mean arterial pressure (MAP) was calculated by using the following formula: $\text{MAP} = [(2 \times \text{diastolic BP}) + \text{systolic BP}] / 3$. Hypertension was defined as a systolic BP ≥ 140 mmHg and/or a diastolic BP ≥ 90 mmHg, or current use of antihypertensive agents.

The principal investigator diagnosed T2DM in accordance with the standards of the Japan Diabetes Society. BMI was calculated as weight (in kg) divided by height squared (in m^2). eGFR was calculated by using the formula reported by Matsuo et al. [17]. Subjects who had smoked more than 100 cigarettes in their lifetime and smoked at least one cigarette daily for 6 months prior to undergoing the three laboratory tests to evaluate for atherosclerosis were defined as current smokers [18].

Measurement of CIMT

CIMT was measured by using an ultrasound device (Toshiba SSA-660A or Toshiba TUS-A400, Toshiba Medical Systems, Japan) equipped with a 7.5 MHz linear transducer. Scanning of the extracranial common carotid artery (CCA), carotid bulb (Bul), and internal carotid artery (ICA) in the neck was performed bilaterally in three different longitudinal projections and transverse projections, and the site of greatest thickness, including plaque lesions, was sought along the arterial walls. CIMT was measured as the distance between two parallel echogenic lines corresponding to the blood-intima and media-adventitial interface on the posterior wall of the artery. Three determinations of CIMT were conducted at the site of the thickest point and two adjacent points (located 1 cm upstream and 1 cm downstream from the thickest point). The mean CIMT from the three determinations was calculated. The greatest of the six mean CIMT values (three each from the left and right arteries) was used as the representative value for each individual. Max-CIMT refers to the greatest

CIMT value in the areas of the CCA, Bul, and ICA accessible for analysis [19].

Based on the published literature [20–22], arterial wall thickening was defined in our hospital as a max-CIMT ≥ 1.1 mm (the high-risk level of max-CIMT). Five experienced laboratory technicians conducted all the scans. To avoid inter-investigator variability, all the scans were electronically stored, sent to a central office, and analyzed in random order by a single investigator (I.I.) blinded to the clinical characteristics of the patients. The intra-investigator coefficients of variation of the mean and max-CIMT measurements were 4.7 and 5.4 %, respectively, for 250 consecutively replicated measurements (male 54 %; mean age 55 ± 8.3 years).

Measurement of PWV

baPWV was measured with the patient in the supine position by using Form PWV/ABI (Nippon Colin, Ltd, Komaki, Japan), as reported previously [23, 24]. Briefly, electrocardiogram electrodes were placed on both wrists, a microphone for detecting heart sounds was placed on the left edge of the sternum, and cuffs wrapped both the brachia and ankles. The cuffs were connected to a plethysmographic sensor that determines volume pulse form and an oscillometric pressure sensor that measures BP. Pulse volume waveforms were recorded by using a semiconductor pressure sensor, with the sample acquisition frequency for PWV set at 1,200 Hz. Volume waveforms for the brachium and ankle were stored, and the sampling time was 10 s, with automatic gain analysis and quality adjustment. Time interval between brachium and ankle was defined as the time interval between the wave front of the brachial waveform and that of the ankle waveform. The distance between the baPWV sampling points was calculated automatically based on the height of the subjects. A previously described equation was used [25]. Mean baPWV was defined as the mean of the right and left baPWVs.

Measurement of ABI

ABI was automatically calculated as the ratio of systolic BP in the leg to that in the arm on each side by using the device Form PWV/ABI. Subjects with an ABI < 0.9 on either or both sides were considered to have a peripheral artery disease. Mean ABI was defined as the mean value of the right and left ABIs.

Statistical analysis

Data were expressed as mean $\pm$ standard deviation values unless otherwise noted. To investigate whether non-HDL-C and/or LDL-C levels are independent determinants of

each of the three atherosclerosis markers of the other risk factors, we performed multiple stepwise linear regression analyses for all the subjects after including sex (male 1; female 0), age, BMI, HbA1c, eGFR ($\text{mL min}^{-1} 1.73 \text{ m}^{-2}$), mean BP (mmHg), current smoking (smoker 1; non-smoker 0), and non-HDL-C or LDL-C levels (mg/dL) as independent variables. The F value for the inclusion of the variables was set at 4.0.

Stepwise logistic regression and receiver operating characteristic (ROC) curve analyses were performed to investigate which cholesterol-related variable was a more useful predictor of the degree of atherosclerosis based on the surrogate atherosclerosis markers. For all the tests, a $p < 0.05$ was considered statistically significant. All the statistical analyses were performed with the JMP version 5.1 (SAS Institute Inc., Cary, NC, USA). In addition, we referenced the pages on the instructions on how to perform a ROC curve analysis by using multiple variables from the homepage of the statistical software JMP (SAS; http://www.jmp.com/japan/support/faq/stat_3703.shtml).

Results

Baseline characteristics of the study subjects

Table 1 summarizes baseline clinical characteristics of the study subjects. Abnormal lipid profiles (LDL-C level ≥ 3.1 mmol/L [120 mg/dL], triglyceride level ≥ 1.7 mmol/L [150 mg/dL], HDL-C level < 1.1 mmol/L [40 mg/dL], and non-HDL-C level ≥ 3.9 mmol/L [150 mg/dL]) were observed in 121 (45.6 %), 91 (34.3 %), 44 (16.6 %), and 122 (45.6 %) subjects, respectively. Among 69 subjects with hypertension, 54 (20.4 %) received antihypertensive medications, of whom 15 had monotherapy, 28 had dual therapy, and 10 had triple therapy.

Multiple stepwise linear regression analyses

The results of the multiple stepwise linear regression analyses showed that the mean-baPWV level was significantly related to age [β coefficient (β) = 0.537, F = 145.4] and MAP (β = 0.419, F = 88.3) as independent variables. Similarly, the mean ABI level was significantly related to age (β = -0.327 , F = 4.2). The mean CIMT level was significantly related to age (β = 0.459, F = 76.5), sex (β = 0.199, F = 14.4), and MAP (β = 0.172, F = 10.7). However, none of these three markers of atherosclerosis was significantly related to non-HDL-C or LDL-C levels (Table 2).

As shown in Table 3, max-CIMT was not significantly related to LDL-C level, but was significantly related to age (β = 0.464, F = 78.2), sex (β = 0.188, F = 12.8), and

Table 1 Baseline clinical characteristics of the study subjects

<i>n</i>	265
Sex (male/female)	140/125
Age (years)	56.9 ± 12.5
BMI (kg/m ²)	24.2 ± 4.5
Diabetes duration (years)	6.7 ± 3.9
HbA1c (%)	8.2 ± 2.2
Therapy (diet/OHA/insulin)	85/130/50
Total cholesterol (mg/dL)	212 ± 6.1
LDL-cholesterol (mg/dL)	131 ± 31
Triglycerides (mg/dL)	138 ± 88
HDL-cholesterol (mg/dL)	53.6 ± 15.5
Non-HDL-cholesterol (mg/dL)	159 ± 36
Current smoker (<i>n</i>)	32 (12 %)
eGFR [mL/(min·1.73 m ²)]	79.0 ± 20.0
Complications	
Retinopathy (<i>n</i>)	32 (12 %)
Hypertension (<i>n</i>)	69 (26 %)
Therapy (ARB/CCB/diuretics/others)	48/39/10/8
Ischemic heart disease (<i>n</i>)	12 (5 %)
Ischemic stroke (<i>n</i>)	21 (8 %)
Mean baPWV (m/s)	1505 ± 296
Mean ABI	1.11 ± 0.10
Mean CIMT (mm)	1.04 ± 0.23
Maximum CIMT (mm)	1.24 ± 0.29

BMI body mass index, *HbA1c* hemoglobin A1c, *OHA* oral hypoglycemic agents, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *eGFR* estimated glomerular filtration rate, *ARB* angiotensin 2 receptor blockers, *CCB* calcium channel blockers, *baPWV* brachial-ankle pulse wave velocity, *ABI* ankle-brachial index, *CIMT* carotid intima-media thickness. All values are means ± standard deviations or numbers of subjects with percentages in parentheses

MAP ($\beta = 0.175$, $F = 11.1$) when LDL-C level was used as an independent variable (model 1). However, max-CIMT was significantly related to age ($\beta = 0.490$, $F = 86.0$), sex ($\beta = 0.195$, $F = 14.1$), MAP ($\beta = 0.142$, $F = 6.9$), and non HDL-C level ($\beta = 0.141$, $F = 6.8$) when non HDL-C level was used as an independent variable (model 2).

Stepwise logistic regression analysis

After obtaining the aforementioned results, we performed a stepwise logistic regression analysis of the high-risk level of max-CIMT (≥ 1.1 mm) [20–22], which included the same confounding variables as in the multiple stepwise linear regression analyses. The analysis revealed that non-HDL-C level was significantly related to the high-risk value of max-CIMT [≥ 1.1 mm; odds ratio for max-CIMT, 1.096; 95 % confidence interval (CI), 1.003–1.202;

Table 2 Independent predictors of various surrogate markers of atherosclerosis (except max-CIMT) from the multiple stepwise linear regression analysis

	β coefficient	r^2
Mean baPWV (m/sec)		
Age (years)	0.537	0.318
Mean blood pressure (mmHg)	0.419	0.174
Total r^2		0.492
Mean ABI		
Age (years)	−0.327	0.015
Total r^2		0.015
Mean IMT (mm)		
Age (years)	0.459	0.222
Sex (male 1, female 0)	0.199	0.045
Mean blood pressure (mmHg)	0.172	0.029
Total r^2		0.296

BMI body mass index, *baPWV* brachial-ankle pulse wave velocity, *ABI* ankle-brachial index, *CIMT* carotid intima-media thickness

Table 3 Independent predictors of max-CIMT from the multiple stepwise linear regression analysis

	β coefficient	r^2
Model 1 ^a		
Age (years)	0.464	0.227
Sex (male 1, female 0)	0.188	0.040
Mean blood pressure (mmHg)	0.175	0.030
Total r^2		0.297
Model 2 ^b		
Age (years)	0.490	0.227
Sex (male 1, female 0)	0.195	0.040
Non-HDL-cholesterol (mg/dL)	0.141	0.030
Mean blood pressure (mmHg)	0.142	0.019
Total r^2		0.316

BMI body mass index, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *CIMT* carotid intima-media thickness

^a Analysis using age, sex, BMI, presence of diabetes mellitus, estimated glomerular filtration rate, mean blood pressure, current smoking, and LDL-cholesterol as dependent variables

^b Analysis using age, sex, BMI, presence of diabetes mellitus, estimated glomerular filtration rate, mean blood pressure, current smoking, and non-HDL-cholesterol as dependent variables

$p = 0.046$], although the LDL-C level was not significantly related to the high-risk value (Table 4).

ROC curve analysis

To establish whether the addition of non-HDL-C or LDL-C level (mg/dL) to the confounding variables could improve

Table 4 Stepwise logistic regression analysis of the relationship between various parameters and high risk of max-CIMT (≥ 1.1 mm) in subjects with type 2 diabetes

	Odds ratio	95 % Confidence interval	<i>p</i> Value
Model 1^a			
Age (years)	1.108	1.107–1.145	<0.0001
Sex (male 1, female 0)	2.150	1.161–4.027	0.0155
Model 2^b			
Age (years)	1.112	1.078–1.151	<0.0001
Sex (male 1, female 0)	2.102	1.135–3.932	0.0187
Non-HDL-cholesterol (per 10 mg/dL increase)	1.096	1.003–1.202	0.0461

CIMT carotid intima-media thickness, *BMI* body mass index, *HDL* high-density lipoprotein

^a Analysis using age, sex, BMI, estimated glomerular filtration rate, mean blood pressure, and LDL-cholesterol level (per 10 mg/dL increase) as dependent variables

^b Analysis using age, sex, BMI, estimated glomerular filtration rate, mean blood pressure, and non-HDL-cholesterol level (per 10 mg/dL increase) as dependent variables

the predictive ability of max-CIMT ≥ 1.1 mm, ROC curves were plotted for the three significant independent variables obtained in the multiple stepwise linear regression analyses, namely sex, age, and MAP, with and without the addition of non-HDL-C or LDL-C level for all the subjects. The analysis revealed that the area under the ROC curve (AUC) did not significantly increase after the addition of non-HDL-C or LDL-C level to the three confounding variables (0.7789, 95 % CI: 0.713–0.8323 with the confounding variables; 0.7864, 95 % CI: 0.7234–0.8382 with the confounding variables and non-HDL-C level, $p = 0.4343$; and 0.7840, 95 % CI: 0.7209–0.8361 with the five confounding variables and LDL-C level, $p = 0.4352$; Fig. 1).

Discussion

In the multiple stepwise regression analysis, we found that non-HDL-C level, but not LDL-C level, was positively correlated with max-CIMT only, whereas neither of these two lipid levels showed any significant correlations with all the other markers, including baPWV, mean-CIMT, and ABI. Using stepwise logistic regression analysis, a 0.26 mmol/L (10 mg/dL) increase in non-HDL-C level, but not in LDL-C level, was significantly associated with the high-risk level of max-CIMT (≥ 1.1 mm). These results indicate that non-HDL-C level may be non-inferior to LDL-C level for the prediction of the high-risk level of max-CIMT in Japanese subjects with T2DM. CIMT is a marker of early atherosclerosis and vascular remodeling

Fig. 1 Receiver operating characteristic (ROC) curve analyses for predicting the high-risk level of max-CIMT (≥ 1.1 mm). The ROC curves for the three significant independent variables obtained from the multiple stepwise regression analyses, with and without addition of non-HDL-C or LDL-C level for the subjects with T2DM. The ROC curves for the confounding variables without addition of non-HDL-C or LDL-C level are shown in *blue*. The ROC curves for the confounding variables with addition of LDL-C and non-HDL-C levels are shown in *red* and *green*, respectively

that can be assessed quickly, noninvasively, and at a low cost with high-resolution ultrasonography. It is considered a surrogate marker of atherosclerosis. Previous studies have established CIMT as one of the most reliable markers of systemic atherosclerosis, and many reports have shown that CIMT is associated with cardiovascular events and CAD [26–28].

In particular, several recent studies have reported that max-CIMT is a superior surrogate marker of atherosclerosis compared with mean CIMT. Irie et al. [29] reported that max-CIMT, but not mean-CIMT, was one of four independent predictors of coronary artery stenosis in asymptomatic T2DM patients, as assessed by performing coronary computed tomography angiography and multivariate logistic regression analysis. In addition, based on an ROC curve analysis, the AUC for max-CIMT (0.73; 95 % CI, 0.66–0.81; $p < 0.001$) was significantly higher than that for mean-CIMT (0.64; 95 % CI, 0.56–0.73; $p = 0.001$). Takiuchi et al. [30] found that max-CIMT had the highest correlation coefficient of the severity of target organ damage (retinal arteriosclerosis, microalbuminuria, and left ventricular hypertrophy) among all the carotid parameters, including conventional CIMT, max-CIMT, mean CIMT, and plaque score (the sum of all plaque thicknesses). In their more recent cross-sectional analysis

of 333 asymptomatic T2DM patients without a history of CAD, Irie et al. [31] found that max-CIMT is an independent predictor of the presence of severe CAD that requires treatment with revascularization and that the ability to predict severe CAD significantly increased when max-CIMT was added to the conventional coronary risk factors. Therefore, the authors suggested that max-CIMT could be one of the most appropriate screening parameters to identify high-risk individuals among subjects with T2DM.

In addition, the stepwise logistic regression analysis conducted in the present study revealed that a 0.26 mmol/L (10 mg/dL) increase in non-HDL-C level, but not LDL-C level, was significantly related to the high risk of max-CIMT. This indicates that non-HDL-C level may be more closely related to high risk of max-CIMT than LDL-C level in Japanese subjects with T2DM.

Some previous studies have investigated the relationships between LDL-C or non-HDL-C level and the risk of CVD in patients with diabetes. In 2004, Jiang et al. [32] reported that non-HDL-C and apoB levels were more potent predictors of CVD incidence among diabetic men than LDL-C level. Furthermore, in 2005, Liu and colleagues [33] reported that non-HDL-C level was a stronger predictor of CVD-related death in white diabetic individuals aged ≥ 30 years who had no CVD at baseline (12,660 men and 6,721 women) than LDL-C level.

The role of the triglyceride-rich lipoproteins in non-HDL-C in the development of atherosclerosis will likely increase as the population ages and becomes increasingly obese, insulin resistant, and hyperglycemic [16]. Insulin resistance, which increases with age and obesity, leads to a greater fatty acid flux to the liver, which is accompanied by an increased synthesis of very low-density lipoprotein (VLDL). Non-HDL-C is particularly elevated in patients with metabolic syndrome and T2DM [34, 35]. Therefore, our findings suggest that in comparison with the level of LDL-C, which does not account for the triglyceride-rich lipoproteins, non-HDL-C level is a more appropriate marker for identifying high-risk individuals among subjects with metabolic syndrome and T2DM.

Finally, the ROC curve analysis for predicting high risk of max-CIMT revealed that the AUC did not significantly increase after the addition of non-HDL-C or LDL-C level to the confounding variables, although a small increase in AUC was recognized after the addition of these lipid-related variables. A larger sample size with consecutive lipid samplings is needed to verify whether addition of non-HDL-C or LDL-C level significantly affects the AUC in Japanese subjects with T2DM.

Interestingly, our data revealed that none of the markers of atherosclerosis, except max-CIMT, was significantly related to non-HDL-C level. The reason that PWV and

mean CIMT were not significantly related to the lipid levels should be elucidated. A systematic review published in Hypertension [36] reported that only approximately 10 % of the studies on the correlation between serum LDL-C level and carotid-femoral PWV suggested a positive correlation in a multiple regression model. This suggests that at least in its early stages, aortic stiffening is not driven by an atherosclerotic process, but by an alternative pathology in which blood pressure, which develops to transfer the load to stiffer elements with greater tensile strength within the arterial wall (e.g., from elastin to collagen), is one of the most important factors [36, 37], which was also a potent influencing factor of mean-baPWV in our analysis, as shown in Table 2. Similarly, the reported relationships between cardiovascular risk factors, including serum lipids, CIMT, and plaques, were inconsistent and show differing patterns of association with each risk factor [38, 39]. Hayase et al. recently reported a significant relationship between LDL-C level and mean CIMT in current smokers ($p = 0.001$) but not in ex- or non-smokers (subjects who never smoked), in multivariate regression analyses for 448 healthy middle-aged Japanese men. This suggests that the impact of lipid levels on CIMT may be dependent on smoking status [40]. Therefore, the limited number of current smokers ($n = 32$) in our study might have obscured the relationship between CIMT and lipid levels, especially mean CIMT.

Study limitations

Our study has several limitations. First, it is a cross-sectional retrospective study with a relatively small number of subjects. In addition, outcome measures were not cardiovascular events, but surrogate markers, particularly max-CIMT. Second, a selection bias could be present because the study patients were selected based on the presence of T2DM without treatment with any lipid-lowering agents for the reason that the agents might complicate the statistical analysis using various lipid levels. However, in actual clinical settings, many subjects with T2DM and dyslipidemia received some lipid-lowering agents, mainly statin. Therefore, further study might be needed to clarify the relationship between non HDL-C or LDL-C levels and max CIMT under long-term use of lipid-lowering agents. In addition, we excluded subjects with triglycerides levels >4.5 mmol/L because we calculated the LDL-C level by using the Friedewald equation. Therefore, the suitability of non-HDL-C level for screening should be verified in a prospective study with a larger sample size by using true cardiovascular end points. Finally, all the participants were Japanese; therefore, our findings cannot be generalized to other races or ethnic groups.

Conclusions

Non-HDL-C level may be non-inferior to LDL-C level for the prediction of the high-risk level of max-CIMT in Japanese subjects with T2DM.

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Conflict of interest None of the authors has conflicts of interest to declare.

Human rights statement and informed consent All procedures conducted in this study were in accordance with the ethics committee of Fukui-ken Saiseikai Hospital and with the Helsinki Declaration of 1964 and later revision. Informed consent or substitute for it was obtained from all patients for being included in the study. Identifying information of patients of human subjects, including names, initials, addresses, admission dates, hospital numbers, or any other data that might identify patients were not included in our written descriptions.

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