Original Article

A Proposal for the Optimal Management Target for Serum Non-High-Density Lipoprotein Cholesterol Level in Low-Risk Japanese Workers

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Aim: The Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases 2012 (JAS Guidelines 2012) indicate that the management target for serum non-high-density lipoprotein cholesterol (non-HDL) level is 30 mg/dL higher than that for low-density lipoprotein cholesterol (LDL) level. However, it remains unclear whether this value is applicable to subjects at a low risk of cardiovascular disease. This study aimed to propose the optimal management target for serum non-HDL level in low-risk Japanese subjects.

Methods: Among 20,909 subjects who underwent annual medical checkup at a Japanese company in 2008, we analyzed the data of 17,023 subjects (14,352 men, mean age 37.8 ± 8.6 years) in risk category I according to the JAS Guidelines 2012. The correlation between LDL and non-HDL levels was examined.

Results: A strong correlation was found between LDL and non-HDL levels ($r=0.95$, $p<0.001$). The following regression equation for calculation of non-HDL was obtained from linear regression analysis: non-HDL (mg/dL) = $1.09 \times \text{LDL (mg/dL)} + 7.79$. According to this equation, the optimal management target for non-HDL level corresponding to that for LDL level (160 mg/dL) was 180 mg/dL. A multiple logistic regression analysis revealed that age, obesity, habitual alcohol intake, and current smoking were significantly associated with non-HDL ≥ 180 mg/dL.

Conclusions: The management target for non-HDL level is recommended to be set at 20 mg/dL higher than that for the LDL level (i.e., 180 mg/dL) in low-risk Japanese subjects.

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Key words: Non-high-density lipoprotein cholesterol, Japanese, Management target, Risk factors

Introduction

Large-scale cohort studies have shown that the incidence of cardiovascular disease (CVD) increases with greater low-density lipoprotein cholesterol (LDL) levels¹⁻³. Furthermore, the efficacy of LDL-lowering therapy via HMG-CoA reductase inhibitors

(statins) has been confirmed as a primary prevention of CVD in patients with hypercholesterolemia^{4, 5}. Therefore, the Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases 2012 (JAS Guidelines 2012) have recommended using LDL as the primary lipid management target for the prevention of CVD⁶. However, in a previous meta-analysis⁷, the use of statins for the primary prevention of CVD events have resulted in a reduced risk of up to approximately 20%. These findings indicate the existence of substantial residual risk. Research has indicated remnant lipoproteins, i.e., intermediate metabolites of chylomicron and very-low-density lipoprotein, as major sources of

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Fig. 1. Enrollment of study subjects. Categories I, II, and III are based on the risk categories shown by the JAS Guidelines 2012.

JAS Guidelines 2012, Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases 2012; HDLC, high-density lipoprotein cholesterol

such residual risk because they are considered to be atherogenic⁸⁾. In clinical settings, a simple and comprehensive evaluation of atherogenic lipoprotein profile is the measurement of non-high-density lipoprotein cholesterol (non-HDLC) because it represents the summation of atherogenic lipoproteins including low-density and remnant lipoproteins. The utility of measuring non-HDLC has, in fact, been indicated in several studies, which showed that non-HDLC is a good^{3, 9-13)} or even better¹⁴⁻¹⁷⁾ predictor of coronary artery disease (CAD) than LDLC.

Currently, LDLC level is preferably calculated using the Friedewald equation⁶⁾ because direct measurement of LDLC is not necessarily accurate¹⁸⁾. However, this equation yields inaccurate results if blood is collected without a fasting state or if the

serum triglycerides (TG) level is ≥400 mg/dL. Notably, community-based health checkup programs in Japan, such as the “specific health checkups” initiated by the Japanese government in 2008, accept blood sampling in a non-fasting state. As such, the JAS Guidelines 2012 have recommended using non-HDLC level as a secondary management target. In the JAS Guidelines 2012, the management target for the non-HDLC level is set at 30 mg/dL higher than that for the LDLC level, according to a statement in the US National Cholesterol Education Program Adult Treatment Panel III¹⁹⁾ and the results of previous hospital-based studies in Japan focused on patients with dyslipidemia^{20, 21)}. However, it remains unclear whether this management target for non-HDLC level is applicable to non-hospital-based Japanese subjects

Fig. 2. Distribution of subjects in each 5-year age group by sex

at low risk of CVD. Thus, this study aimed to propose the optimal management target for the non-HDLc level in this population.

Methods

Study Subjects

We analyzed the data of regular employees of a precision instrument company who underwent an annual medical checkup in Japan in 2008. The enrollment of the study subjects is summarized in **Fig. 1**. Among the 20,909 subjects in the overall study population, we excluded those who had a serum TG level ≥ 400 mg/dL ($n=218$), were receiving medications for dyslipidemia ($n=659$), and had a history of CVD ($n=116$) or malignancy ($n=183$). Furthermore, we excluded subjects without all the information required for the present analysis ($n=924$). Next, we classified subjects into low-risk category (risk category I) or other categories according to the JAS Guidelines 2012, and excluded those who were not in risk category I ($n=1,786$). The methodology of the risk classification procedure from the JAS guidelines 2012 is described elsewhere⁶. Briefly, subjects were assigned to risk category I when the following criteria were fulfilled: (1) a 10-year absolute risk of death from CAD

Table 1. Baseline characteristics of study subjects

N	17,023
Men (%)	14,352 (84.3)
Age, years	37.8 $\pm$ 8.6
Current smoking, n (%)	4,479 (26.3)
Habitual alcohol intake, n (%)	2,507 (14.7)
BMI, kg/m ²	22.5 $\pm$ 3.0
Obesity, n (%)	2,987 (17.5)
Systolic BP, mmHg	115.7 $\pm$ 13.5
Diastolic BP, mmHg	70.1 $\pm$ 10.6
Hypertension, n (%)	1,216 (7.1)
Fasting plasma glucose, mg/dL	88.6 $\pm$ 7.2
HbA1c, %	5.3 $\pm$ 0.3
TC, mg/dL	194.9 $\pm$ 32.2
LDLC, mg/dL	113.4 $\pm$ 29.2
HDLc, mg/dL	63.1 $\pm$ 13.9
Non-HDLc, mg/dL	131.8 $\pm$ 33.5
TG, mg/dL	
mean $\pm$ SD	91.8 $\pm$ 53.4
median (interquartile range)	77 (55, 112)

BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglycerides.

Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or reported use of antihypertensive medication.

Fig. 3. A scatter plot for the correlation and the linear regression equation between LDL-C and non-HDL-C levels in all subjects

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol

<0.5% based on the NIPPON DATA80 risk assessment chart and (2) no low-HDL cholesterolemia, family history of premature CAD, impaired glucose tolerance, or chronic kidney disease. However, we could not exclude subjects with chronic kidney disease from risk category I because the database we utilized lacked information on renal function. Ultimately, the data of 17,023 subjects (age range 18–59 years, 14,352 men) were analyzed in this study. The distribution of subjects in each 5-year age group by sex is shown in **Fig. 2**. This study was approved by the Ethics Committee of Nippon Medical School (Tokyo, Japan) and was conducted according to the principles of the Declaration of Helsinki.

Data Collection and Definition

Height and weight were measured without shoes and wearing light indoor clothing to determine body mass index (BMI; kg/m^2), calculated as body weight (kg) divided by the square of height (m). Blood pressure was measured by trained technicians using a standardized protocol with the subjects in a seated position after a rest period of at least 5 min. Venous blood

samples were collected from each subject after overnight fasting. Serum levels of TG, total cholesterol (TC), HDL-C, and plasma glucose were measured using automated measurement devices. The serum LDL-C level was calculated using the Friedewald equation²²). A self-reported questionnaire was used to collect data regarding the subjects' smoking habits, frequency of alcohol intake, family history of CVD, and medical information including prescribed drugs. Smoking habit was classified as currently smoking or not. Habitual alcohol intake was defined as alcohol intake of ≥ 6 days per week. Obesity was defined as $\text{BMI} \geq 25 \text{ kg}/\text{m}^2$ according to the Japan Society for the Study of Obesity²³). Hypertension was defined as systolic blood pressure $\geq 140 \text{ mmHg}$, diastolic blood pressure $\geq 90 \text{ mmHg}$, or reported use of antihypertensive medication. Impaired fasting glucose was defined as fasting blood glucose $\geq 110 \text{ mg}/\text{dL}$. Diabetes mellitus was defined as a fasting blood glucose $\geq 126 \text{ mg}/\text{dL}$, $\text{HbA1c} \geq 6.5\%$, or reported use of glucose-lowering medication including insulin injection.

Table 2. Characteristics of study subjects with and without high non-HDL-C (≥ 180 mg/dL)

	non HDL-C		<i>p</i>
	< 180	≥ 180	
N	15,605	1,418	–
Men, n (%)	13,079 (83.8)	1,273 (89.8)	< 0.001
Age, years	37.5 $\pm$ 8.7	41.1 $\pm$ 6.7	< 0.001
Current smoking, n (%)	4,035 (25.9)	444 (31.4)	< 0.001
Habitual alcohol intake, n (%)	2,311 (14.8)	196 (13.8)	0.283
BMI, kg/m ²	22.3 $\pm$ 2.9	24.7 $\pm$ 3.3	< 0.001
Obesity, n (%)	2,424 (15.5)	563 (39.7)	< 0.001
Systolic BP, mmHg	115.2 $\pm$ 13.4	120.6 $\pm$ 13.9	< 0.001
Diastolic BP, mmHg	69.7 $\pm$ 10.5	74.8 $\pm$ 10.6	< 0.001
Hypertension, n (%)	1,040 (6.7)	176 (12.4)	< 0.001
Fasting plasma glucose, mg/dL	88.3 $\pm$ 7.1	91.0 $\pm$ 7.3	< 0.001
HbA1c, %	5.2 $\pm$ 0.3	5.4 $\pm$ 0.3	< 0.001
TC, mg/dL	189.4 $\pm$ 27.0	255.4 $\pm$ 20.8	< 0.001
LDLC, mg/dL	108.4 $\pm$ 24.1	169.0 $\pm$ 21.3	< 0.001
HDLC, mg/dL	63.8 $\pm$ 14.0	55.3 $\pm$ 10.6	< 0.001
Non-HDLC, mg/dL	125.6 $\pm$ 27.1	200.1 $\pm$ 18.7	< 0.001
TG, mg/dL			
mean $\pm$ SD	86.0 $\pm$ 47.2	155.5 $\pm$ 72.0	< 0.001
median (interquartile range)	74 (54, 104)	141 (103, 192)	< 0.001

BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglycerides.

Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or reported use of antihypertensive medication.

Statistical Analysis

IBM SPSS for Windows, version 21 (IBM Japan, Tokyo, Japan), was used for all statistical analyses. Continuous variables with or without a skewed distribution were expressed as the median (interquartile range) or the mean $\pm$ SD, respectively. Categorical variables were expressed as percentages of the total. Between-group comparisons were conducted using Student's *t*-test or the Mann–Whitney *U*-test, as appropriate. Pearson's product–moment correlation coefficient was calculated between the LDLC and non-HDLC levels. Linear regression analysis was conducted between the LDLC and non-HDLC levels to identify the optimal management target. A multiple logistic regression analysis was performed to examine the independent determinants of high non-HDLC. Explanatory variables used in the analysis were age, sex, obesity, hypertension, current smoking, and habitual alcohol intake. A *p* < 0.05 was considered significant.

Results

Characteristics

The baseline characteristics of the study subjects

are shown in **Table 1**. The mean LDLC and non-HDLC levels were 113.4 mg/dL and 131.8 mg/dL, respectively. The mean and median TG levels were 91.8 mg/dL and 77.0 mg/dL, respectively. None of the subjects had either impaired fasting glucose/diabetes or a family history of CVD, indicating that they were all considered to be risk category I.

A New Proposal for the Management Target Value of Non-HDLC

A very strong correlation was observed between LDLC and non-HDLC levels ($r=0.95$, $p<0.001$, **Fig. 3**). The following regression equation for the calculation of non-HDLC was obtained from a linear regression analysis (**Fig. 3**):

$$\text{non-HDLC (mg/dL)} = 1.09 \times \text{LDLC (mg/dL)} + 7.79$$

The JAS Guidelines 2012 indicate that the management target for LDLC in risk category I is 160 mg/dL⁵⁾. Using the aforementioned equation, the non-HDLC level corresponding to an LDLC level of 160 mg/dL was calculated as 182.2 mg/dL. Therefore, our proposal for the management target for non-HDLC level in individuals of risk category I was 180 mg/dL,

Table 3. Multiple logistic regression analysis for determinants of non-HDL-C ≥ 180 mg/dL and LDL-C ≥ 160 mg/dL

	non-HDL-C ≥ 180 mg/dL		LDL-C ≥ 160 mg/dL	
	OR	95% CI	OR	95% CI
Age (1-year increase)	1.05	1.04-1.06	1.05	1.04-1.06
Sex (men/women)	1.64	1.37-1.97	0.92	0.77-1.10
Obesity (yes/no)	3.11	2.76-3.50	2.49	2.17-2.85
Hypertension (yes/no)	1.14	0.95-1.37	1.00	0.81-1.24
Current smoking (yes/no)	1.25	1.11-1.41	1.20	1.05-1.38
Habitual alcohol intake (yes/no)	0.66	0.56-0.77	0.60	0.50-0.73

BMI, body mass index; BP, blood pressure; OR, odds ratio; CI, confidence interval; HDLC, high-density lipoprotein cholesterol.

Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or use of antihypertensive medication.

Table 4. Characteristics of study subjects stratified by sex

	Men	Women	<i>p</i>
N	14,352	2,671	—
Age, years	37.7 $\pm$ 8.6	38.2 $\pm$ 8.3	0.007
Current smoking, n (%)	4,104 (28.6)	375 (14.0)	<0.001
Habitual alcohol intake, n (%)	2,368 (16.5)	139 (5.2)	<0.001
BMI, kg/m ²	22.7 $\pm$ 2.9	21.3 $\pm$ 3.4	<0.001
Obesity, n (%)	2,657 (18.5)	330 (12.4)	<0.001
Systolic BP, mmHg	116.8 $\pm$ 13.0	109.3 $\pm$ 14.5	<0.001
Diastolic BP, mmHg	71.0 $\pm$ 10.3	65.4 $\pm$ 10.9	<0.001
Hypertension, n (%)	1,095 (7.6)	121 (4.5)	<0.001
Fasting plasma glucose, mg/dL	88.9 $\pm$ 7.2	86.4 $\pm$ 6.7	<0.001
HbA1c, %	5.3 $\pm$ 0.3	5.3 $\pm$ 0.3	0.505
TC, mg/dL	195.1 $\pm$ 32.0	193.8 $\pm$ 33.2	0.068
LDLC, mg/dL	114.3 $\pm$ 29.0	108.9 $\pm$ 29.9	<0.001
HDLC, mg/dL	61.4 $\pm$ 13.3	72.0 $\pm$ 14.1	<0.001
Non-HDL-C, mg/dL	133.6 $\pm$ 33.4	121.9 $\pm$ 32.6	<0.001
TG, mg/dL			
mean $\pm$ SD	96.7 $\pm$ 54.9	64.9 $\pm$ 32.4	<0.001
median (interquartile range)	82 (59, 118)	57 (44, 76)	<0.001

BMI, body mass index; BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; TG, triglycerides.

Obesity was defined as BMI ≥ 25 kg/m². Hypertension was defined as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg, or reported use of anti-hypertensive medication.

i.e., 20 mg/dL higher than the LDL-C level.

Factors Associated with High Non-HDL-C

The characteristics of subjects with and without high non-HDL-C level (≥ 180 mg/dL) are shown in **Table 2**. Subjects with high non-HDL-C level were older and had a higher prevalence of current smoking, obesity, and hypertension. They had higher fasting blood glucose, TC, LDL-C, and TG levels and lower HDLC levels compared with those without high non-HDL-C levels. In a multiple logistic regression analysis,

age, obesity, and current smoking were positively associated with high non-HDL-C, whereas habitual alcohol intake was inversely associated with it (**Table 3**). When multiple logistic regression analysis was conducted to determine the factors associated with high LDL-C (≥ 160 mg/dL), similar results were obtained, except for sex (**Table 3**).

Stratified Analysis by Sex

Subjects' characteristics, stratified by sex, are shown in **Table 4**. Compared with women, men were

Fig. 4. Scatter plots for the correlation and linear regression equation of LDLC and non-HDLc levels in men (A) and women (B). LDLC, low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol.

younger and had a higher prevalence of current smoking, habitual alcohol intake, obesity, and hypertension. Although higher fasting blood glucose, LDLc, non-HDLc, and TG levels and lower HDLc levels were observed in men, TC level was not significantly different between men and women.

Similar to the findings of overall analysis, a strong correlation was found between LDLc and non-HDLc in both men ($r=0.90$, $p<0.001$) and women ($r=0.97$, $p<0.001$), as shown in **Fig. 4A** and **B**. The regression equations for calculating non-HDLc in men and women were as follows.

Men: non-HDLc (mg/dL) = $1.09 \times \text{LDLC (mg/dL)} + 8.95$

Women: non-HDLc (mg/dL) = $1.07 \times \text{LDLC (mg/dL)} + 4.92$

According to these equations, the non-HDLc level corresponding to an LDLc level of 160 mg/dL was calculated as 183.4 mg/dL in men and 176.1 mg/dL in women.

Discussion

In the present study of a Japanese population at a low-risk of CVD, the recommended management target for non-HDLc level was found to be 180 mg/dL,

or 20 mg/dL higher than that for the LDLc level. The JAS Guidelines 2012 suggest that the management target for the non-HDLc level is 190 mg/dL (i.e., 30 mg higher than that for the LDLc level) for risk category I⁽⁶⁾. This cutoff was based on the results of previous studies in Japan^{20, 21)}, which showed that the LDLc level of 160 mg/dL corresponded to a non-HDLc level of 189 mg/dL using a linear regression equation²¹⁾. However, importantly, the subjects in those studies were not from the general population, but were patients in a hospital or outpatient clinic. Therefore, it remained unclear whether the value would be applicable to the general population. To the best of our knowledge, this is the first study to propose the optimal management target for non-HDLc level in a large population of low-risk Japanese subjects.

Multiple logistic regression analysis revealed that age, obesity, and current smoking were positively associated with non-HDLc ≥ 180 mg/dL. Similar findings were obtained when examining the factors associated with LDLc ≥ 160 mg/dL. These results suggest that modifiable risk factors may contribute to increases in not only LDLc levels but also non-HDLc levels, thereby further supporting our proposal of 180 mg/dL as the optimal management target for non-HDLc level. Previous epidemiological surveys in Japan have

shown that non-HDLc level increases with age between 20's and 50's²⁴⁾. Obesity and smoking have been reported to be inversely associated with HDLc level^{25, 26)}, which would result in a higher non-HDLc level. Besides, habitual alcohol intake was inversely associated with a non-HDLc ≥ 180 mg/dL. This is likely because alcohol intake decreases the removal of circulating HDLc by increasing lipolysis of TG-rich particles and reduces cholesterol ester transfer protein activity^{27, 28)}, thereby increasing HDLc levels and decreasing non-HDLc levels. Collectively, the findings of our multiple logistic regression analysis are in line with previous observations.

The recommended management targets for LDLc and non-HDLc levels in risk category I in the JAS Guidelines 2012 are 160 mg/dL and 190 mg/dL, respectively. However, because an LDLc level of 160 mg/dL corresponded to a non-HDLc level of approximately 182 mg/dL in our study, it is clear that most subjects with non-HDLc levels between 182 and 190 mg/dL had an LDLc level ≥ 160 mg/dL. These results indicate that subjects with non-HDLc levels of between 182 and 190 mg/dL would be inappropriately evaluated if the target of the JAS Guidelines 2012 was followed. Accordingly, we recommend that the management target for non-HDLc level should be 180 mg/dL in subjects of risk category I.

The stratified analysis by sex indicated that the non-HDLc level corresponding to an LDLc level of 160 mg/dL was calculated as approximately 176 mg/dL in women and 183 mg/dL in men. This discrepancy could be potentially explained by the difference in the number of women and men in our study. Moreover, the clinical and socioeconomic characteristics of women in this study may differ from those of the Japanese general population because all women in this study were regular employees²⁹⁾. The JAS Guidelines 2012 does not set the lipid management targets by sex. Therefore, we recommend the same management target for non-HDLc (180 mg/dL) for both sexes in this study.

Limitations

First, serum lipid levels were measured in a single day. Therefore, intra-individual variation in lipid profiles was not considered in this study. Second, the JAS Guidelines 2012 recommend that non-HDLc level should be used only when blood is collected without fasting or the TG level is ≥ 400 mg/dL. However, this study excluded subjects with TG ≥ 400 mg/dL to calculate the LDLc level using the Friedewald equation. Third, as noted in the methods section, the informa-

tion on renal function was not available in this study, suggesting that a certain number of subjects were not correctly included in risk category I. Fourth, the study was conducted using data obtained from the working-age population in a single company. Therefore, it is uncertain whether the results of this study are applicable to other settings such as the elderly and community-based populations. In particular, non-HDLc levels have been reported to decrease over 60's²⁴⁾, suggesting that further studies targeting elderly individuals should be conducted to validate our present findings. Finally, this study was a cross-sectional investigation; therefore, the causal relationship between non-HDLc and future risk of CVD was not elucidated.

Conclusions

This study demonstrated that the management target for the non-HDLc level was recommended to be 180 mg/dL in Japanese subjects at low risk of CVD. Further longitudinal study is anticipated to clarify whether our recommended management target for non-HDLc is appropriate for primary prevention of CVD in a low-risk Japanese population.

Conflict of Interest

None.

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