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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

High-sensitivity C-reactive protein as a serum predictor of nonalcoholic fatty liver disease based on the Akaike Information Criterion scoring system in the general Japanese population

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Abstract
Background High-sensitivity C-reactive protein (hs-CRP) has been developed and used as a marker to predict coronary vascular diseases in metabolic syndrome (MS). We investigated whether serum hs-CRP concentration was associated with nonalcoholic fatty liver disease (NAFLD) based on the Akaike Information Criterion (AIC) scoring system, using patients from the human dry dock program.
Methods From 2004 to 2005, 1254 subjects visited our human dry dock annual checkup program. We excluded from this study individuals with markers of viral hepatitis and those whose alcohol consumption was more than 20 g/week. Finally, 230 subjects (93 men and 137 women) were investigated. Serum hs-CRP concentrations were measured using a highly sensitive latex agglutination assay system. The AIC scoring system with the CATDAP-20 program was introduced to evaluate the parameters that are present frequently in NAFLD.
Results NAFLD was diagnosed by ultrasound sonography in 35.4% of the men and 18.9% of the women. High serum hs-CRP concentrations were observed in women with NAFLD (normal: NAFLD = 0.45:1.47 mg/l, $P < 0.05$). Body mass index (BMI), waist circumference, and body weight had the three lowest AIC score ($P = 4.5e^{-19}$ to $2.6e^{-16}$). hs-CRP was the third lowest variable among the serum markers associated with NAFLD ($P = 2.3e^{-6}$) In addition, the hs-CRP concentration was correlated strongly with triglyceride values in females with NAFLD and with fasting blood glucose, HbA1c, and waist/hip ratio in males with NAFLD ($P < 0.05$).
Conclusions The serum hs-CRP concentration was a strong predictor for NAFLD with a low AIC score and correlated with serum markers that indicated lipid and glucose metabolism.

Keywords High sensitivity C-reactive protein (hs-CRP) · Nonalcoholic fatty liver disease (NAFLD) · Metabolic syndrome (MS) · Akaike Information Criterion (AIC) · Multiple logistic analysis · CATegorical Data Analysis Program (CATDAP-20)

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Introduction

Lifestyle-related diseases are becoming more common in Japan in parallel with the increase in the consumption of fatty foods and alcoholic beverages [1, 2]. Thirty percent of the Japanese population is obese, which is defined according to Japanese criteria as a body mass index (BMI) greater than 25 [3]. Recently, the joint committees of eight Japanese medical societies, including the Japanese Society of Internal Medicine (JSIM), recommended new criteria for metabolic syndrome (MS)[4] by making minor modifications of

previous criteria [5, 6]. We used the new criteria to define MS in this study. Because the prevalence rate of fatty liver (FL) is now almost 30% [2], it is predicted that the prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) will increase.

C-reactive protein (CRP) has been reported to play an important role in the development of atherosclerosis, resulting in a high risk of cardiovascular diseases [7, 8]. The newly established high-sensitivity CRP (hs-CRP) assays can identify more subtle changes in the systemic inflammatory process that are related to insulin resistance and MS. Although the serum concentration of hs-CRP is affected by various factors such as race, age, gender, smoking, and alcohol intake [9–11], serum hs-CRP has been shown to be involved in the pathogenesis and to be an early predictor of coronary vascular diseases in patients with MS [12–15].

NAFLD and MS have common clinical characteristics, such as obesity, dyslipidemia, and, especially, the presence of insulin resistance [16–19]. Accumulating reports of the clinical relationship between NAFLD and MS suggest that NAFLD is the hepatic manifestation of MS [20–23]. Attention has been focused on differentiation of NAFLD and NASH because NASH is manifested by fat deposition in hepatocytes, leading to liver degeneration and finally progressing to liver cirrhosis [24]. In addition, patients with NASH may be at high risk for hepatocellular carcinoma [25, 26].

Recent evidence indicated that serum CRP elevation is an independent risk factor for NAFLD [27, 28]. The association of NAFLD and carotid atherosclerosis suggests that both diseases have common pathogenetic features, such as circulating inflammatory markers derived from visceral adipose tissues [29]. Although several studies analyzed the relationship between serum hs-CRP concentrations and NAFLD, using multiple logistic analysis, the results were conflicting and the value of serum hs-CRP for prediction of NAFLD was controversial [30–33]. One study has reported the association of the serum hs-CRP concentration and NAFLD using multiple logistic regression analysis [28].

Multiple logistic regression analysis, however, is limited because variables selected in this analysis are not reliable for explaining the model well. When we analyze variables using a logistic regression model, we categorize variables into two groups: one is lower and the other higher than the normal range, or, in the case of age, one is below and the other above 65 years. That is, we analyze only two cross-contingency tables using a logistic regression model. However, it is possible to categorize variables by different points, and there are many types of categorization. In the case of age, subjects could be categorized into paired groups whether they are above or below 65, 62, or 55 years, and so on, and then each group categorized by different points is analyzed using the logistic regression model. Up to now, it has been impossible to determine which variables are reliable to explain the model by arranging paired groups with categorization at numerous points. However, we need to select variables based on numerous contingency tables before subjecting them to logistic regression analysis. To overcome this limitation and select reliable variables, the CATDAP-20 (CATegorical Data Analysis Program) was developed by the Center for Engineering and Technical Support in Japan, using the Akaike information criterion (AIC) [34, 35]. This program is able to select reliable variables by automatically analyzing all the cases of categorization in variables. In effect, this program calculates all the cases of contingency tables and thus can determine the predictors associated strongly with diseases. Therefore, we used the AIC scoring system to evaluate the predictive ability of the clinical variables for NAFLD and MS. The AIC gives statistical significance for the balance of adaptation and complexity of a model and quantifies the relative goodness of fit for various variables. The preferred model is that with the lowest AIC value: the lower the AIC, the better the model. In this study, we addressed the question whether the serum hs-CRP concentration was associated with or was a risk factor for NAFLD using categorical data based on the AIC scoring system.

Subjects and methods

Study subjects

We examined data on 1254 subjects who visited our human dry dock annual checkup program at the Department of General Medicine, International Medical Center of Japan, Tokyo, Japan, from September 2004 to November 2005. This type of annual checkup program is very common in Japan and promotes the early detection of malignant or chronic diseases. Written informed consent was obtained from all study subjects before the examination. We excluded subjects who were positive for hepatitis B surface antigen (HBsAg) or hepatitis C antibody (third generation). Because a small intake of alcohol may improve NAFLD, we excluded subjects who habitually drank alcohol more than once a week or had an alcohol intake of more than 20 g/week to eliminate completely the effects of alcohol intake. For this reason, a relatively small number of subjects were enrolled in the present study. Finally, data on 230 subjects (93 men and 127 women) were analyzed in this study.

Weight was measured to the nearest 0.1 kg with the subject in an upright position. BMI was calculated by

dividing weight (kg) by height squared (m^2). Waist circumference was measured at the end of normal expiration from the narrowest point between the rib cage and the iliac crest, and hip circumference measurement was taken at the iliac crest to the nearest 0.1 cm.

Fatty change was defined by ultrasound sonography (US) with findings of high hepatorenal echo contrast, bright liver, or attenuation of ultrasound in a deep area of the liver [36]. These findings were determined by well-trained examiners. We categorized subjects as those with a normal liver (group A), those with FL and a normal liver function (group B), and those with FL and an elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) level (group C).

Definition of metabolic syndrome (MS) and biochemical analysis

We adopted the MS criteria proposed by the joint committee of eight Japanese medical societies including the JSIM. Men and women whose waist circumference was more than 85 or 90 cm, respectively, and who had the following values were defined as having MS: (1) high-density lipoprotein cholesterol (HDL-C) <40 mg/l, or triglyceride (TG) ≥150 mg/l, or medicated for dyslipidemia; (2) fasting glucose ≥110 mg/l or medicated for diabetes; and (3) blood pressure ≥130/85 mmHg or medicated for hypertension.

Plasma concentration of glucose, total cholesterol (TC), TG, high-density lipoprotein (HDL) cholesterol (HDL-C), uric acid (UA), total protein, albumin, AST, ALT, γ-glutamyl transpeptidase (γ-GTP), and platelet count were measured with an autoanalyzer at a central laboratory. hs-CRP was measured by latex agglutination assay.

Statistical analysis

Subjects were categorized into three groups as already described.

All continuous variables were shown by the mean value ± SD. Correlation coefficients were determined by simple linear regression analysis conducted using KaleidaGraph 3.6J software (Synergy Software, Reading, PA, USA). Analysis of variance was applied to the comparison of the three groups, followed by *F* test for confirmation of statistical significance. To assess direct comparison of the variables associated with NAFLD, multivariate logistic regression analysis was performed in those with NAFLD (groups B and C) and those with normal liver (group A). Adjusted odds ratio and 95% confidence intervals (CIs) were calculated. The relationships between hs-CRP and other relevant covariates were determined by standardized correlation coefficients. AIC scores were measured by fort run-program CATDAP-02 (CATegorical Data Analysis Program), and then the statistical association was determined by χ^2 test. CATDAP-02 is a program for selection of variables that explain well the structure of categorical data, developed by the Center for Engineering and Technical Support in Japan. Continuous variables were categorized into four to five intervals and then analyzed by CATDAP-02. All statistical analyses were conducted with the SPSS statistical package (Chicago, IL, USA). All recorded *P* values were two-sided. A *P* value <0.05 was considered statistically significant.

Results

Basic characteristics of NAFLD

Based on our US findings, 33 men (35.4%) and 24 women (18.9%) were diagnosed with NAFLD (groups B and C; Table 1). The average age of male subjects in group C was lower than in the other groups, whereas female subjects in group C were older than those in group A. These differences in the distribution of NAFLD suggested that menopause has an effect on the initiation of NAFLD in women [37].

The average BMI, body weight, and waist circumference increased according to the severity of NAFLD, with a statistically significant difference among groups. NAFLD was found to have a relationship with ALT-dominant liver dysfunction as reported previously [38]. The average ALT and γ-GTP concentrations were highest in group C in men and women. TG concentrations were elevated also, whereas the average HDL-C concentrations decreased in order from groups A to C in men. Most data obtained from female subjects were similar to those from male subjects, although, interestingly, the average fasting blood sugar (FBS) and HbA1c concentrations were increased in order from groups A to C in women. In contrast, in men these factors did not correlate with the severity of NAFLD; specifically, the average FBS and HbA1c values in group C were lower than in group B.

The hs-CRP concentrations also were increased in accordance with the severity of NAFLD in order from groups A to C with a statistically significant difference in females. When comparing the hs-CRP concentrations between those with and without NAFLD, the average hs-CRP was significantly higher in female subjects in groups B and C (1.47 ± 2.0) than in group A (0.45 ± 0.5, $P < 0.05$), while there was no significant difference between these groups in male subjects (normal: NAFLD = 0.81 ± 1.1:1.12 ± 1.5, $P = 0.3$).

Because it was reported that the hs-CRP concentration was affected by smoking [9], we compared this value in

Table 1 Baseline clinical characteristics of study participants and unadjusted association of variables with the presence of nonalcoholic fatty liver disease (NAFLD)[a]

	Male[b]				Female[b]			
	A	B	C	*P*	A	B	C	*P*
Number of examinees	60	15	18		113	19	5	
Age (years)	58.1 ± 14.8*	55.8 ± 11.6	50.6 ± 13.2		55.9 ± 13.5	62.8 ± 8.6	56.2 ± 6.1	
Body weight (kg)	61.8 ± 8.7	72.4 ± 6.0	76.5 ± 8.8	<0.01	49.7 ± 6.0	59.0 ± 6.5	72.4 ± 21.0	<0.01
BMI (18.5–25) kg/m^2	22.1 ± 2.8	25.0 ± 2.5	26.4 ± 3.1	<0.01	20.7 ± 2.4	25.2 ± 2.5	27.8 ± 5.2	<0.01
Waist circumference (cm)	76.1 ± 8.0	87.0 ± 5.5	87.2 ± 9.6	<0.01	69.3 ± 9.6	82.3 ± 11.6	91.5 ± 11.2	<0.01
Hip circumference (cm)	87.6 ± 5.9	92.4 ± 2.7	94.5 ± 5.6	<0.01	86.6 ± 5.1	92.5 ± 6.5	100.8 ± 13.2	<0.01
W/H ratio	0.87 ± 0.1	0.94 ± 0.1	0.92 ± 0.1		0.80 ± 0.1	0.89 ± 0.1	0.98 ± 0.06	<0.01
hs-CRP (<3) mg/l	0.8 ± 1.1	1.1 ± 1.5	1.1 ± 1.4		0.5 ± 0.5	1.0 ± 0.9	3.3 ± 3.3	<0.01
Systolic blood pressure (mmHg)	120.2 ± 18.4	123.3 ± 11.0	124.1 ± 16.8		115.5 ± 15.8	125.5 ± 14.1	132.4 ± 20.1	<0.01
Diastolic blood pressure (mmHg)	76.5 ± 10.7	80.8 ± 5.0	78.1 ± 10.6		72.2 ± 8.8	76.8 ± 6.6	81.2 ± 13.5	<0.05
TC (140–219) mg/dl	206.0 ± 34.6	206.8 ± 33.3	200 ± 38.9		207.8 ± 32.7	226.2 ± 31.4	221 ± 17.3	
TG (38–149) mg/dl	100.7 ± 37.4	167.0 ± 82.6	178.6 ± 89.7	<0.01	83.2 ± 42.1	141.9 ± 61.0	129.4 ± 13.6	
HDL-C (41–84) mg/dl	58.9 ± 15.6	49.0 ± 9.0	42.7 ± 7.5	<0.01	68.9 ± 16.0	55.2 ± 10.8	54.6 ± 7.9	<0.01
UA (2.5–7.0) mg/dl	5.9 ± 1.0	5.7 ± 0.9	6.7 ± 1.8		4.5 ± 1.0	5.1 ± 0.9	4.5 ± 1.0	
FBS (<110) mg/dl	96.2 ± 12.3	127.0 ± 58.7	102.7 ± 13.3		93.1 ± 13.7	108.7 ± 52.2	127.8 ± 20.5	<0.01
HbA1c (4.3–5.8) %	5.3 ± 0.5	6.1 ± 1.7	5.2 ± 0.4		5.2 ± 0.5	5.6 ± 1.7	6.0 ± 0.7	<0.01
TP (6.0–8.0) g/dl	7.2 ± 0.4	7.1 ± 0.3	7.1 ± 0.3		7.2 ± 0.3	7.3 ± 0.3	7.3 ± 0.2	
Alb (3.5–5.0) g/dl	4.5 ± 0.3	4.5 ± 0.2	4.5 ± 0.2		4.5 ± 0.2	4.5 ± 0.3	4.5 ± 0.1	
AST (0–35) U/l	21.3 ± 4.1	20.4 ± 4.6	30.2 ± 7.8	<0.01	20.7 ± 4.5	21.0 ± 2.6	25.8 ± 4.7	<0.05
ALT (0–30) U/l	19.7 ± 5.3	22.4 ± 4.2	50.6 ± 20.6	<0.01	16.3 ± 4.5	19.8 ± 4.9	32.6 ± 5.9	<0.01
γ-GTP (0–75) U/l	25.7 ± 13.3	33.8 ± 12.7	54.3 ± 26.1	<0.01	19.0 ± 9.7	24.0 ± 12.1	38.4 ± 21.8	<0.01
Plt (15–35 × 10**)/U/l	22.5 ± 5.0	22.0 ± 5.5	20.7 ± 4.8		22.8 ± 5.5	25.3 ± 7.4	25.5 ± 4.7	
Smoker	32	11	16		18	3	0	
MS	0**	3	4	<0.05	0	2	1	<0.01

W/H ratio ratio of waist circumference to hip circumference

hs-CRP high-sensitivity C-reactive protein

*$\chi \pm$ SD (all such values)

**χ^2 test for categorical variables

[a] NAFLD was diagnosed by ultrasound sonography. ANOVA was applied to the comparison of continuous variables in the categorized three groups, followed by the F-test for confirmation of the statistical association

[b] Participants were categorized as follows: those with a normal liver (group A), those with FL and a normal transaminase level (group B), and those with FL and an elevated transaminase level (group C)

smokers and nonsmokers with NAFLD. In women, the average hs-CRP concentrations were 0.74 ± 0.5 in nonsmokers and 1.13 ± 0.5 in smokers, but in men these values were 0.61 ± 0.5 in nonsmokers and 0.72 ± 0.5 in smokers, with no statistically significant difference between smokers and nonsmokers in either men or women.

Among the men, MS was diagnosed in 3 of 15 (20.0%) in group B, 4 of 18 (22.2%) in group C, but, in sharp contrast, in none (0 of 60, 0%) of group A, based on the Japanese criteria [3]. Also, in women MS was not observed in group A, but was observed in 2 of 19 (10.5%) of group B and 1 of 5 (20%) of group C subjects.

In subjects with NAFLD (groups B and C), 7 of 33 (21.1%) men and 3 of 24 (12.5%) women met the MS criteria of Japan with a statistically significant difference compared to group A subjects ($P < 0.01$). In addition, all 10 subjects with MS had NAFLD as a complication, and the presence of more than one of the diseases in the MS criteria was more common in those with NAFLD than in subjects with a normal liver (data not shown).

AIC score of NAFLD

As shown in Table 2, BMI, waist circumference, and body weight provided the three lowest AIC scores for the total subject group. TG, waist/hip (W/H) ratio, hip circumference, HDL-C, and hs-CRP followed these three variables. Among the biochemical markers, hs-CRP was the third

Table 2 Akaike information criterion (AIC) score for variables associated with prediction of NAFLD[a]

Factor	AIC	*P*
All subjects		
BMI	−78.0	$4.5e^{-19}$
Waist circumference	−68.8	$3.7e^{-17}$
Body weight	−66.0	$2.6e^{-16}$
TG	−51.4	$1.0e^{-12}$
W/H ratio	−50.2	$2.7e^{-12}$
Hip circumference	−47.8	$2.7e^{-12}$
HDL-C	−40.4	$5.5e^{-10}$
hs-CRP	−20.8	$2.3e^{-6}$
FBS	−18.3	$3.9e^{-6}$
Diastolic blood pressure	−13.4	$1.8e^{-4}$
Systolic blood pressure	−12.2	$2.2e^{-4}$
Male subjects		
Body weight	−35.3	
Hip circumference	−30.6	
BMI	−29.7	
Waist circumference	−28.8	
TG	−23.9	
W/H ratio	−20.4	
HDL-C	−18.6	
FBS	−9.3	
Smoking	−5.9	
Age	−4.5	
hs-CRP	−4.4	
Female subjects		
BMI	−42.3	
Body weight	−34.5	
Waist circumference	−28.7	
TG	−27.0	
Hip circumference	−22.7	
W/H ratio	−16.6	
hs-CRP	−16.0	
HDL-C	−15.2	
Diastolic blood pressure	−13.6	
Systolic blood pressure	−11.4	
TC	−10.5	

W/H ratio ratio of waist circumference to hip circumference

[a] Statistical association was determined by χ^2 test

best fit variable for prediction of NAFLD following a high concentration of TG and a low concentration of HDL-C, both of which are included in the MS criteria. *P* values determined by the χ^2 test for these 11 variables that had a low AIC score were less than 0.001, thus showing a statistically significant difference.

In female subjects, parameters included in the criteria for MS, such as waist circumference, TG, HDL-C, and blood pressure, were associated with NAFLD with a low AIC score. In addition, the AIC score was lower for hs-CRP than for HDL-C and blood pressure. In male subjects, other factors such as smoking and age were ranked highly as predictive markers for NAFLD with lower AIC scores than that of hs-CRP. Also, in males blood pressure was not included in the top ten variables for NAFLD. Hence, variables associated with NAFLD may differ between female and male subjects.

Table 3 Akaike information criterion (AIC) score for variables associated with development of nonalcoholic fatty liver disease (NAFLD)

	AIC
1. Body weight	−74.1
2. BMI	−68.3
3. Waist circumference	−59.7
4. Triglyceride	−54.3
5. Hip circumference	−48.7
6. HDL-C	−39.1
7. FBS	−26.3
8. hs-CRP	−17.5
9. Diastolic blood pressure	−17.0
10. Sex	−12.3

BMI body mass index, *HDL-C* high-density lipoprotein chlorophyll, *FBS* fasting blood sugar, *hs-CRP* high-sensitivity C-reactive protein

As the next step, we measured the AIC score to identify variables associated strongly with the development of NAFLD by comparing the three groups in order from groups A–C (Table 3). This analysis provided almost the same results as shown in Table 2, except for the gender difference. These data suggest that the risk factors presented here are strongly related to the presence of NAFLD, as well as prediction of its development.

AIC score in MS

To confirm the reliability of AIC analysis, we examined variables associated with MS (Table 4). Waist circumference, body weight, BMI, hip circumference, and NAFLD were ranked as the lowest five variables with almost the same AIC scores, suggesting that these variables had the same explanatory values in prediction of MS. FBS, γ-GTP, ALT, systolic blood pressure, and TG occupied the next highest ranking position in AIC analysis. These results indicate that AIC analysis is a good system for the selection of predictive markers for MS as well as for NAFLD. These variables are already included in criteria for MS or have been reported previously as good markers for MS. Because the AIC score of hs-CRP was much lower than that observed in MS (see Table 4), hs-CRP was much more useful in prediction of NAFLD than of MS.

Table 4 Akaike information criterion (AIC) score for variables associated with metabolic syndrome (MS)[a]

	AIC	*P*-value
1. Waist circumference	−29.5	$7.2e^{-10}$
2. Body weight	−26.4	$1.7e^{-7}$
3. BMI	−26.3	$1.4e^{-8}$
4. Hip circumference	−24.4	$8.6e^{-8}$
5. NAFLD	−24.4	$4.6e^{-7}$
6. FBS	−20.2	$2.3e^{-6}$
7. γ-GTP	−18.6	$1.4e^{-5}$
8. ALT	−14.2	$3.0e^{-5}$
9. Systolic blood pressure	−13.4	$1.6e^{-4}$
10. Triglyceride	−12.3	$2.4e^{-4}$
11. W/H ratio	−10.9	$5.4e^{-4}$
12. HbA1c	−10.9	$1.1e^{-4}$
13. HDL-C	−7.2	
14. hs-CRP	−6.8	
15. Diastolic blood pressure	−6.1	

W/H ratio ratio of waist circumference to hip circumference

[a] Statistical association determined by χ^2 test

Multivariate logistic regression analysis in NAFLD

Multivariate logistic regression analysis was performed to compare the efficacy of the AIC scoring system for determining variables associated with NAFLD (Table 5). The continuous variables were categorized into two groups according to the Japanese MS criteria or whether values were over the normal range, then the odds ratio, 95% CI, and *P* value were determined. hs-CRP concentrations were divided into four categories: <1.0, 1.0–3.0, 3.0–5.0, and >5.0 mg/l. These were the same as those used in AIC analysis.

As shown in Table 5, BMI, waist circumference, TG, FBS, and body weight exhibited a statistically significant difference when referred to those with NAFLD and subjects with normal liver, whereas there were no significant differences in W/H ratio, hip circumference, HDL-C, hs-CRP, and diastolic or systolic blood pressure, which were listed among the lowest 10 AIC score (see Table 2). Although multivariate logistic regression analysis has been applied to many studies to identify a good model, it did not reveal that body weight, W/H ratio, hip circumference, HDL-C, and hs-CRP were risk factors for NAFLD.

Correlation of hs-CRP with lipid, glucose metabolism, and W/H ratio

We determined the correlation coefficient between the serum hs-CRP concentrations and other variables by simple linear regression analysis (Fig. 1). Of particular note, serum hs-CRP concentrations correlated positively with TG ($R = 0.56$, $P < 0.01$) in female subjects with NAFLD, and with the W/H ratio ($R = 0.47$, $P < 0.01$), FBS ($R = 0.41$, $P = 0.03$), and HbA1c ($R = 0.45$, $P = 0.02$) values in male subjects with NAFLD.

Discussion

Studies of several lifestyle-related diseases have focused on the designation of MS because this syndrome contributes to lethal coronary and brain vascular diseases. On the other hand, NAFLD is one of the most common liver diseases worldwide, although the clinical outcome remains unknown. However, with the establishment of a nationwide general health checkup system in Japan, it is valuable and now possible to determine the clinical significance of NAFLD. We speculated that NAFLD could be included as a part of MS and have analyzed the clinical variables related to NAFLD or MS.

We categorized subjects into three groups and analyzed clinical markers associated with NAFLD (see Table 1). The severity of NAFLD increased in order from group A to group C, the last of which had elevations of AST, ALT, and γ-GTP. In addition, body weight, BMI, waist circumference, and hip circumference also increased in the order of the three groups, from groups A–C; inversely, HDL-C was decreased in the same order. These results suggested that severity of NAFLD was correlated with clinical markers that have been shown to be associated with MS, particularly in female subjects.

Because hs-CRP was shown recently to be involved in the pathogenesis of atherosclerosis and an early predictor of cardiovascular disease in patients with MS [12–15], we addressed the question of whether serum hs-CRP concentrations can be a marker for prediction of or onset of NAFLD. To validate this point, we analyzed variables by the AIC scoring system and multiple logistic regression analysis. The AIC was calculated as the χ^2 statistic of significant change for the extended model compared to a reference model minus two times the number of degrees of freedom [34, 35]. AIC is a measure of the goodness of fit for the balance of adaptation and complexity of a model. To determine the variables associated with NAFLD, we validated the AIC score for NAFLD (groups B and C) compared with that for subjects with normal liver (group A) after categorizing continuous variables into four to five groups (Table 2). The preferred model is that with the lowest AIC value.

We calculated the AIC scores of subjects with or without NAFLD (see Table 2). The three lowest AIC scores were obtained by physical measurements, so that the optimal variables for the model of NAFLD were derived

Table 5 Adjusted associations with the presence of nonalcoholic fatty liver disease (NAFLD) by multivariate logistic analysis[a]

Variable	Odds ratio	95% CI	*P* value
BMI (<25, ≥25)	0.189	0.057–0.631	<0.01
Waist circumference (male: <85, ≥85; female: <90, ≥90)	0.173	0.051–0.582	<0.01
BW (<53, ≥53)	0.229	0.059–0.892	0.0336
Triglyceride (<150, ≥150)	0.119	0.040–0.353	<0.01
W/H ratio (<0.845, ≥0.845)	1.805	0.587–5.548	0.3027
Hip circumference (<90, ≥90)	1.084	0.308–3.814	0.8994
HDL-C (<40, ≥40)	2.648	0.571–12.284	0.2135
FBS (<110, ≥110)	0.222	0.062–0.795	0.0208
hs-CRP	0.665	0.352–1.257	0.2097
1>			
≥1, 3>			
≥3, 5>			
≥5			
Systolic blood pressure (<130, ≥130)	1.426	0.416–4.883	0.5721
Diastolic blood pressure (<85, ≥85)	0.798	0.167–3.825	0.7781

W/H ratio ratio of waist circumference to hip circumference

[a] Multivariate logistic analysis was performed for variables associated with NAFLD, and compared in subjects with normal liver (group A) and subjects with NAFLD (groups B + C)

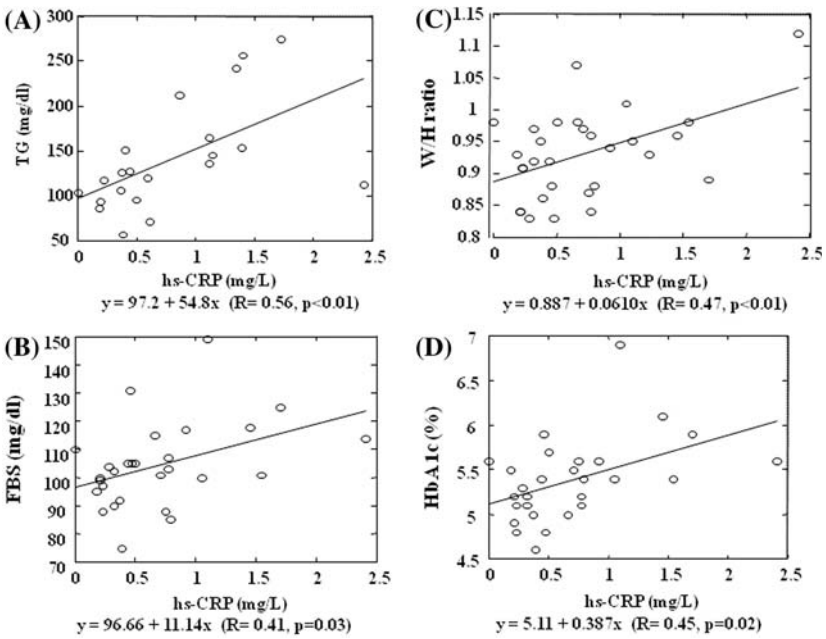

Fig. 1 Correlation coefficients determined by simple regression analysis between high-sensitivity C-reactive protein (hs-CRP) and variables. Triglyceride (**a**), fasting blood sugar (FBS) (**b**), waist circumference/hip circumference (W/H) ratio (**c**), and HbA1C (**d**) were correlated to hs-CRP with statistically significant difference ($R = 0.41$–0.56, $P = 0.03$ to <0.01)

from physical measurements rather than biochemical markers. hs-CRP had the eighth lowest AIC score, which was lower than that of FBS and blood pressure in all subjects. Among the biochemical markers, hs-CRP was the third best fit variable for prediction of NAFLD. The AIC system gives us the order of variables in reliability after analyzing cross-affecting factors. The absolute value of AIC score may represent the distance of variables, and hence −20.8 of hs-CRP is relatively far from −40.4 of HDL-C; in turn, it is near to the fourth place of FBS because of its closeness to −18.3 of FBS (see Table 2). NAFLD was correlated strongly with MS, and hs-CRP value was a good predictive variable for NAFLD, specifically in women (Table 2). When the AIC scores were calculated by comparing the three groups (A, B, and C), the tenth lowest AIC score was for gender difference (see Table 3). This result may support the idea that certain factors affect the progression from normal liver to NAFLD; in fact, menopause facilitated the appearance of NAFLD in women aged 50 years [37].

AIC analysis was a good system for the selection of predictive markers for MS as well as for NAFLD (see Table 4). As observed for NAFLD, waist circumference, body weight, and BMI yielded the three lowest AIC scores. Interestingly, NAFLD had the fifth lowest AIC score, which was lower than that of FBS, systolic blood pressure, TG, HbA1C, and HDL-C. In addition, all subjects with MS had NAFLD as a complication (data not shown). Hence, these results suggested that the presence of the same clinical entities for NAFLD and MS, or that NAFLD is a part of or a predictor of MS, as reported previously [20–23].

With the exception of one paper from Korea [28], there have been no reports of multiple logistic analysis showing that serum hs-CRP values were associated with NAFLD. The authors of that article reported that CRP and HOMA-IR were independent risk factors, although the odds ratio was low. In our study, multiple logistic analysis identified only BMI, waist circumference, TG, FBS, and body weight (BW) as clinical markers related to NAFLD, but did not indicate BW, W/H ratio, hip circumference, HDL-C, and hs-CRP (see Table 5). However, the AIC scoring system selected hs-CRP as the eighth lowest variable in NAFLD, which had a lower AIC score than that of FBS (see Table 2). Moreover, the serum hs-CRP concentrations were strongly correlated with serum markers of abnormal lipid or glucose metabolism (see Fig. 1a–d). Hence, hs-CRP could be a predictable marker for NAFLD.

In sharp contrast to the data from women, hs-CRP was relatively low in male subjects and did not increase from groups A–C. In male subjects, systolic and diastolic blood pressure also was not correlated to staging of NAFLD (see Table 1), and furthermore the AIC system did not identify blood pressure as a risk factor for NAFLD (see Table 2). We speculated that the hs-CRP level was related to staging of NAFLD in female subjects in accordance with an elevation of blood pressure because hs-CRP may represent endothelial damage to the arteries. In this study, male subjects did not exhibit such a circulatory affect. Interestingly, the gender difference was ranked at a higher position in the categorical variables (see Table 3), suggesting that development of NAFLD progressing in order from a normal liver to a fatty liver with an ALT elevation would be observed typically in female subjects in the general population of Japan.

A value greater than 3 mg/l for hs-CRP denoted proinflammatory effects in the microenvironment of the vascular wall [13]. In our study, subjects with a mean value of hs-CRP exceeding 3 mg/l were found only in group C women (data not shown). From these results, we speculated that, as observed in MS, vascular damage was present in NAFLD, particularly in female subjects, leading to acceleration of fat deposition in hepatocytes by various mechanisms. A positive correlation of high hs-CRP concentration with liver damage or NASH was shown [27, 28], although the relationship between the serum hs-CRP concentrations and the severity of histological changes in NAFLD is controversial [30–33].

Although NAFLD shares many of the features of MS, it has not been selected as one of the diseases within the definition of MS. Loria et al. postulated that NAFLD should be considered as a new entity of insulin resistance/metabolic-related liver disease [39], while Hamaguchi et al. [40] reported MS as a predictor of NAFLD. In our present data, variables having a lower AIC score in NAFLD were very similar to those in MS; thus, we propose that NAFLD could be included as a factor of the MS.

In conclusion, FL is not a disease of simple focal fat deposition in liver but a systemic disease, one within MS, because NAFLD had a high complication rate with more than one of the diseases in MS and a high hs-CRP concentration could be a serum predictor of NAFLD and MS.

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