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RAPID COMMUNICATION

Nonalcoholic fatty liver disease is a novel predictor of cardiovascular disease

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Abstract

AIM: To clarify whether nonalcoholic fatty liver disease (NAFLD) increases the risk of cardiovascular disease.

METHODS: We carried out a prospective observational study with a total of 1637 apparently healthy Japanese men and women who were recruited from a health check-up program. NAFLD was diagnosed by abdominal ultrasonography. The metabolic syndrome (MS) was defined according to the modified National Cholesterol Education Program (NCEP) ATP Ⅲ criteria. Five years after the baseline evaluations, the incidence of cardiovascular disease was assessed by a self-administered questionnaire.

RESULTS: Among 1221 participants available for outcome analyses, the incidence of cardiovascular disease was higher in 231 subjects with NAFLD at baseline (5 coronary heart disease, 6 ischemic stroke, and 1 cerebral hemorrhage) than 990 subjects without NAFLD (3 coronary heart disease, 6 ischemic stroke, and 1 cerebral hemorrhage). Multivariate analyses indicated that NAFLD was a predictor of cardiovascular disease independent of conventional risk factors (odds ratio 4.12, 95% CI, 1.58 to 10.75, P = 0.004). MS was also independently associated with cardiovascular events. But simultaneous inclusion of NAFLD and MS in a multivariate model revealed that NAFLD but not MS retained a statistically significant correlation with cardiovascular disease.

CONCLUSION: Although both of them were predictors of cardiovascular disease, NAFLD but not MS retained a statistically significant correlation with cardiovascular disease in a multivariate model. NAFLD is a strong predictor of cardiovascular disease and may play a central role in the cardiovascular risk of MS.

Key words: Nonalcoholic fatty liver disease; Metabolic syndrome; Coronary heart disease; Cardiovascular disease; Risk factors

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common clinical condition with histological features that resemble those of alcohol-induced liver injury, but occur in patients who do not abuse alcohol[1]. It is emerging as the most common chronic liver disease in Western countries and also in other parts of the world[2-4]. NAFLD encompasses a histological spectrum ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis[1]. The problem of NAFLD is not confined to its potential to cause serious liver related morbidity and mortality. It frequently occurs with features of the metabolic syndrome including obesity, type 2 diabetes mellitus[5,6], dyslipidemia[7] and hypertension[8]. In fact, the metabolic syndrome is a strong predictor of NAFLD[9]. Although the metabolic syndrome is a well-known precursor of cardiovascular disease[9-13], the potential cardiovascular risk of NAFLD itself has not been well investigated. Therefore, we designed a prospective observational study in apparently

healthy Japanese people to assess whether subjects with NAFLD have an increased risk of cardiovascular disease.

MATERIALS AND METHODS

Study subjects

In order to investigate whether non-alcoholic fatty liver disease is a predictor of cardiovascular disease, a prospective observational cohort study was carried out in a setting of a medical health checkup program at Murakami Memorial Hospital, Gifu, Japan. The purpose and details of the health checkup program were described previously[9]. Briefly, the center at which the checkups were performed was founded in 1994 and evaluated about 5000 examinees annually at the beginning of this study. Of these examinees, 60% repeatedly participated in the program annually or biennially and 40% were new registrants. Most of the participants were employees of various companies and local governmental organizations and their spouses. These companies and organizations recruit the participants each year from their employees according to a contract with our center. The cost of the medical examination was largely paid by the employers. The ethics committee of Murakami Memorial Hospital approved the study. Between January and December 1998, the center evaluated a total of 5409 participants. Among them, there were 3835 participants who had repeated the checkups on an annual or biennial basis. These repeaters who were thought to be suitable for a follow up at our center were invited to join the study.

Data collection and measurements

The health checkup programs included the following: urinalysis, blood cell counts, blood chemistry, measurements of hepatitis B antigen and hepatitis C antibody, electrocardiography, chest radiography, barium examination of the upper gastrointestinal tract, and abdominal ultrasonography. Medical history and lifestyle factors, including physical activity, smoking and alcohol consumption were surveyed by a self-administered questionnaire. Regarding medical history, participants were asked whether they had any past or current illness, and if so they were asked to indicate the doctor's diagnosis and the time of diagnosis, medication, and any surgical operations undergone. Smoking status was expressed by using the Brinkman index, which is calculated as the number of cigarettes smoked per day multiplied by the number of years that the participant smoked. We asked participants about the amount and type of alcoholic beverages consumed per week, and then estimated the mean ethanol intake per day. When the participants had difficulty completing the questionnaire, trained nurses provided assistance. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the participant's height in meters.

The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained technicians with Aloka SSD-650CL (Aloka Co., Ltd., Tokyo, Japan). All ultrasonographic images were stored as photocopies. One gastroenterologist reviewed the photocopies and made the diagnosis of fatty liver without reference to any of the participant's other individual data. Of 4 known criteria (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring)[9,14], the participants were required to have hepatorenal contrast and liver brightness to be given a diagnosis of NAFLD.

We used the criteria of National Cholesterol Education Program Adult Treatment Panel Ⅲ (NCEP ATP Ⅲ)[15] to characterize the metabolic syndrome. Because waist measurements were not available for the entire study sample, we substituted a BMI of 25 kg/m^2 or greater for all participants as an index of obesity. A BMI of 25 kg/m^2 or greater has been proposed as a cutoff for the diagnosis of obesity in Asian people[16]. Individuals with 3 or more of the 5 abnormalities were considered to have the metabolic syndrome.

We excluded participants who reported previous myocardial infarction, angina pectoris, ischemic stroke, cerebral hemorrhage or cancer. Additional exclusion criteria were known liver disease and an alcohol intake of more than 20 g/d. Regarding liver disease, participants with a positive test for hepatitis B antigen or hepatitis C antibody and those who reported a history of known liver disease, including viral, genetic, autoimmune, and drug-induced liver disease, were also excluded[9,17].

Follow up study

Between January 2003 and December 2004, the incidence of cardiovascular events among the study participants was assessed by a self-administered questionnaire when they visited the center for their health check-ups. To those who did not come back to our center during the period of the follow-up study we sent the questionnaire by mail. Cardiovascular diseases were defined to include coronary heart disease, ischemic stroke and cerebral hemorrhage. Coronary heart disease includes unstable angina, acute myocardial infarction and silent myocardial infarction. Stable angina pectoris were not counted. The participants who reported a doctor's diagnosis compatible with the above definition of cardiovascular disease or those who reported signs and symptoms indicative of cardiovascular disease were interviewed at the time of their visits or by phone. Thereby, we identified hospitals where the diagnosis of cardiovascular diseases was made. Through contacts with the hospitals the diagnosis of cardiovascular disease was confirmed. We counted only first-ever events in this study.

Statistical analysis

The SPSS statistical package, version 11.0.1 J (SPSS, Inc., Chicago, Illinois) was used for all statistical analyses, and a P value less than 0.05 was considered statistically significant. Two groups of participants were compared by the unpaired t-test and the chi-square test. Logistic regression was used to analyze correlations between the incidence of cardiovascular disease and NAFLD or the metabolic syndrome while controlling for conventional cardiovascular risk factors. Unadjusted and adjusted odds ratios and 95% CI were calculated. Data are expressed as means and SD for continuous variables.

Table 1 Baseline characteristics of the study participants (*n* = 1647)

Variables	Subjects without NAFLD (*n* = 1335)	Subjects with NAFLD (*n* = 312)	*P*
Asparate aminotransferase, U/L	17.4 ± 5.2	23.9 ± 11.2	< 0.001
Alanine aminotransferase, U/L	17.7 ± 9.6	38.8 ± 27.8	< 0.001
Gamma-glutamyltransferase, U/L	17.8 ± 18.2	34.0 ± 31.5	< 0.001
Men, *n* (%)	730 (54.7)	250 (80.1)	< 0.001
Age (yr)	47.8 ± 8.6	49.1 ± 8.7	0.017
The Brinkman index[1]	223.8 ± 359.3	358.6 ± 461.9	< 0.001
LDL-C, mmol/L	3.4 ± 0.8	3.7 ± 0.9	< 0.001
The metabolic syndrome, *n* (%)	87 (6.5)	119 (38.1)	< 0.001
BMI, kg/m^2	21.9 ± 2.6	25.1 ± 2.5	< 0.001
Fasting plasma glucose, mmol/L	5.1 ± 0.6	5.7 ± 1.3	< 0.001
Systolic blood pressure, mmHg	114.6 ± 16.2	123.7 ± 15.9	< 0.001
Diastolic blood pressure, mmHg	71.6 ± 10.2	77.8 ± 9.7	< 0.001
HDL-C, mmol/L	1.3 ± 0.3	1.0 ± 0.2	< 0.001
Triglycerides, mmol/L	1.2 ± 0.7	1.9 ± 1.0	< 0.001
C reactive protein, mg/dL	0.1 ± 0.4	0.2 ± 0.3	0.19

NAFLD: nonalcoholic fatty liver disease; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol. We applied unpaired *t*-test and the chi-square test to unpaired values between two groups. [1]The Brinkman index is the number of cigarettes per day multiplied by years of smoking. A higher value indicates increased smoking-associated health hazard.

RESULTS

Between January and December 1998, a total of 2429 participants (1680 men and 748 women) gave informed consent to be included in the study. Fifty subjects (44 men and 6 women) reported a previous history of myocardial infarction, angina pectoris, stroke, or cancer, and were excluded from the study. In addition, we excluded 108 subjects (80 men and 28 women) who had known liver disease, 531 subjects (510 men and 21 women) who consumed more than 20 g of ethanol per day, and 93 subjects (66 men and 27 women) who were taking medication concurrently. As a result, there were 1647 study subjects (980 men and 667 women). Mean age and BMI were 47.8 years (SD, 8.5) (range, 22 to 83 years) and 22.0 kg/m^2 (SD, 2.4) (range, 15.1 to 32.6 kg/m^2), respectively.

At baseline there were 312 subjects (18.9%) with NAFLD (Table 1). Mean age, BMI, and the Brinkman index were higher and systolic and diastolic blood pressures were also higher in the subjects with NAFLD. The NAFLD group included more men. The subjects with NAFLD had higher liver enzymes, fasting plasma glucose, LDL-cholesterol and triglycerides, and lower HDL-cholesterol than those without NAFLD. The metabolic syndrome was diagnosed in 206 of the 1647 study participants (12.5%), and the prevalence of the metabolic syndrome was higher in the subjects with NAFLD (38.1%) than those without (6.5%).

Incidence of cardiovascular disease

One thousand two hundred twenty one of 1647 participants (74.1%) completed the follow-up investigations. One thousand thirty three of them filled out the questionnaire at the time of their visits to our center and 188 subjects responded to the questionnaire mailed to them. Four hundred twenty six subjects did not send back the mailed questionnaire and were lost to the follow up analyses. Of 1221 participants available for follow up analyses, 231 subjects had NAFLD and 162 subjects had the metabolic syndrome at baseline. When the baseline characteristics were compared between the participants who completed and those who were lost to the follow-up study, there were more men among those who completed the follow-up than those who were lost to it (% of men, 61.3% *vs* 54.5%). LDL-cholesterol was slightly lower in the subjects who completed the follow-up than in those who did not complete it (3.4 ± 0.8 mg/dL *vs* 3.6 ± 0.9 mmol/L). The prevalence of NAFLD (18.9% *vs* 19.0%) or the metabolic syndrome (13.3% *vs* 10.3%) and the other parameters listed in Table 1 except for LDL-cholesterol were not different between the two groups.

Table 2 Univariate analyses of factors associated with cardiovascular disease among 1221 subjects

	Odds ratio (95% CI)	*P*
NAFLD	5.37 (2.29-12.58)	< 0.001
Gamma -glutamyltransferase, U/L	1.02 (1.01-1.03)	< 0.001
Age, 10 yr	2.30 (1.46-3.61)	< 0.001
Men	1.70 (0.66-4.38)	0.27
The Brinkman index, 100 index[1]	1.08 (1.00-1.17)	0.049
LDL-C, mmol/L	1.48 (0.89-2.46)	0.13
The metabolic syndrome	3.14 (1.26-7.83)	0.014
The components of metabolic syndrome		
BMI, kg/m^2	1.14 (1.00-1.31)	0.044
Fasting plasma glucose, mmol/L	1.42 (1.01-2.01)	0.046
Systolic blood pressure, 10 mmHg	1.72 (1.4-2.12)	< 0.001
Diastolic blood pressure, 10 mmHg	2.31 (1.57-3.39)	< 0.001
HDL-C, mmol/L	0.16 (0.03-0.84)	0.031
Triglycerides, mmol/L	1.61 (1.11-2.32)	0.012

NAFLD: nonalcoholic fatty liver disease; LDL-C: low dense lipoprotein cholesterol; HDL-C: high dense lipoprotein cholesterol. [1]The Brinkman index is the number of cigarettes per day multiplied by years of smoking. A higher value indicates increased smoking-associated health hazard.

During 7115 person-years of follow-up, we identified 22 events (1.8%) of nonfatal cardiovascular disease among 1221 subjects who completed the follow-up study: 8 events of coronary heart disease (7 events of acute coronary syndrome and 1 event of silent myocardial infarction), 12 events of ischemic stroke and 2 events of cerebral hemorrhage. A death due to carcinoma, the details of which were unknown, was reported from the family of a participant. There was no death due to cardiovascular disease (CVD) during the study period. In the 231 subjects with NAFLD, 12 events of cardiovascular disease occurred (5.2%), which comprised 5 events of coronary heart disease, 6 events of ischemic stroke and 1 event of cerebral hemorrhage. On the other hand, 10 events of CVD (1.0%) occurred in the 990 subjects without NAFLD, which comprised 3 events of coronary heart disease, 6 events of ischemic stroke and 1 event of cerebral hemorrhage. The incidence of cardiovascular disease was higher in the subjects with NAFLD than in those without ($P < 0.001$).

Table 3 Multivariate analyses of factors associated with cardiovascular disease among 1221 subjects (748 men and 473 women)

Total (n = 1221)	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
NAFLD	3.57 (1.47-8.67)	0.005	(-)	(-)	4.12 (1.58-10.75)	0.004
The metabolic syndrome	(-)	(-)	2.61 (1.03-6.60)	0.042	1.38 (0.49-3.86)	0.54
Age, 10 yr	1.61 (0.97-2.66)	0.064	2.08 (1.30-3.33)	0.002	2.12 (1.32-3.41)	0.002
The Brinkman index, 100 index[1]	1.06 (0.97-1.16)	0.18	1.05 (0.96-1.14)	0.28	1.03 (0.95-1.12)	0.48
Systolic blood pressure, 10 mmHg	1.60 (1.26-2.04)	< 0.001	(-)	(-)	(-)	(-)
LDL-C, mmol/L	1.19 (0.70-2.03)	0.52	1.35 (0.8-2.3)	0.26	1.24 (0.73-2.08)	0.43
Men (n = 748)	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
NAFLD	2.78 (0.98-7.89)	0.054	(-)	(-)	3.56 (1.16-10.95)	0.027
The metabolic syndrome	(-)	(-)	2.06 (0.70-6.11)	0.19	1.13 (0.34-3.78)	0.84
Age, 10 yr	1.59 (0.90-2.80)	0.11	1.90 (1.11-3.23)	0.019	1.96 (1.15-3.34)	0.014
The Brinkman index, 100 index[1]	1.07 (0.97-1.18)	0.19	1.05 (0.95-1.15)	0.35	1.04 (0.95-1.13)	0.44
Systolic blood pressure, 10 mmHg	1.51 (1.10-2.07)	0.011	(-)	(-)	(-)	(-)
LDL-C, mmol/L	1.42 (0.74-2.71)	0.29	1.53 (0.81-2.90)	0.19	1.42 (0.76-2.65)	0.27
Women (n = 473)	Model 1		Model 2		Model 3	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
NAFLD	14.33 (1.98-103.57)	0.008	(-)	(-)	7.32 (1.22-43.84)	0.029
The metabolic syndrome	(-)	(-)	4.59 (0.78-27.10)	0.093	2.86 (0.42-19.39)	0.28
Age, 10 yr	1.87 (0.60-5.78)	0.28	3.28 (1.09-9.86)	0.035	3.04 (0.99-9.31)	0.051
The Brinkman index, 100 index[1]	0.46 (0.03-6.76)	0.57	0.55 (0.04-7.63)	0.65	0.41 (0.03-6.44)	0.53
Systolic blood pressure, 10 mmHg	1.88 (1.23-2.86)	0.003	(-)	(-)	(-)	(-)
LDL-C, mmol/L	0.62 (0.21-1.85)	0.39	0.87 (0.30-2.52)	0.80	0.77 (0.27-2.16)	0.62

NAFLD: nonalcoholic fatty liver disease; LDL-C: low dense lipoprotein cholesterol. [1]The Brinkman index is the number of cigarettes per day multiplied by years of smoking. A higher value indicates increased smoking-associated health hazard.

Among 162 subjects with the metabolic syndrome, 7 events of CVD (4.3%) comprising 1 event of coronary heart disease and 6 events of ischemic stroke occurred, while 15 events of CVD (1.4%) comprising 7 events of nonfatal coronary heart disease, 6 events of ischemic stroke, and 2 events of cerebral hemorrhage occurred among 1059 subjects without the metabolic syndrome. The incidence was higher in the subjects with the metabolic syndrome than in those without (P = 0.019). Correlations of CVD events with NAFLD and the metabolic syndrome in addition to conventional CVD risk factors were first analyzed by univariate analyses (Table 2). NAFLD, gamma-glutamyltransferase, age, smoking (Brinkman index) and the metabolic syndrome showed statistically significant correlations with CVD. Each component of the metabolic syndrome also had a statistically significant correlation with CVD. Male gender and LDL-cholesterol were not correlated with CVD.

We constructed 3 models for multivariate analyses of the correlation of CVD events with NAFLD and other variables. Model 1 included NAFLD, age, smoking (Brinkman index), systolic blood pressure and LDL-cholesterol as independent variables. In model 2 the metabolic syndrome in place of NAFLD was selected as an independent variable. NAFLD as well as the metabolic syndrome was simultaneously included in model 3. Although gender was not correlated with CVD events in the univariate analyses, multivariate analyses were performed with subjects as a whole and men and women separately in order to examine a possible gender difference with respect to the relation between NAFLD and cardiovascular disease.

Analyses with subjects as a whole revealed that NAFLD and systolic blood pressure showed statistically significant correlations with CVD events in model 1. The respective odds ratios were 3.57 (95% CI, 1.47 to 8.67, P = 0.005) and 1.60 (95% CI, 1.26 to 2.04, P < 0.001) (Table 3). In model 2, the metabolic syndrome and age retained statistically significant correlations with CVD events. In a separate analysis, we replaced the metabolic syndrome with 5 components of the metabolic syndrome to evaluate the role of each component as a risk factor of CVD. In this analysis, only systolic blood pressure was correlated with CVD events. In model 3, NAFLD and age retained statistically significant correlation with CVD events and the metabolic syndrome lost an independent association with CVD events.

When men and women were separately analyzed, results were generally the same as described above. Although the correlation between NAFLD and CVD events appeared to be stronger in women than in men, a clear gender difference was not concluded. Some variables lost statistical significance, probably because a decrease in the number of CVD events weakened statistical power.

DISCUSSION

In this study, we found that NAFLD was a predictor of cardiovascular events among apparently healthy Japanese men and women. The association between NAFLD and future CVD events was independent of conventional cardiovascular risk factors.

Several previous studies demonstrated associations between NAFLD and intima-media thickness and/or

plaques of carotid artery that were used as measures of early atherosclerosis[18-20]. These were all cross-sectional studies in nature and it was difficult to determine a cause-effect relationship. Recently, Targher *et al*[21] reported in a prospective nested case-control study that NAFLD is a strong predictor of future cardiovascular events among type 2 diabetic patients. The subjects of their study were all patients with type 2 diabetes, which constitute a very high-risk population for cardiovascular disease. Therefore, it was uncertain whether the study could be extrapolated to the general population. We extended their study and showed that NAFLD can serve as a strong predictor of cardiovascular disease in apparently healthy people.

The metabolic syndrome defined by the modified National Cholesterol Education Program (NCEP ATP Ⅲ) criteria was also a predictor of CVD events in this study. Since an accumulating body of evidence suggests that there is a close association between the metabolic syndrome, which is a well-known atherogenic condition, and NAFLD, the mechanisms linking NAFLD with CVD events are at least partly mediated by the atherogenic abnormalities of the metabolic syndrome, that is, obesity, hyperglycemia, hypertriglyceridemia, low HDL-cholesterol and hypertension[15]. In fact, a correlation between the severity of liver histology of NAFLD and early carotid atherosclerosis was reported[19], while the association between liver histology and severity of the metabolic syndrome[22] has been noted as well. In a multivariate analysis based on the model that included NAFLD and the metabolic syndrome simultaneously as covariates, we found that NAFLD but not the metabolic syndrome retained an independent correlation with CVD events. This may suggest that NAFLD plays a central role in the pathway connecting the metabolic syndrome and cardiovascular diseases. The biological mechanism by which NAFLD promotes atherosclerosis is not known. Possible mechanistic pathways include increased oxidative stress, subclinical inflammation, an abnormal adipocytokine profile, endothelial dysfunction and lipid abnormalities[23].

Limitations of our study should be noted. First, although ultrasonography has a relatively high sensitivity (82%-94%) and specificity (66%-95%) in detecting fatty liver, it may give an incorrect diagnosis in 10%-30% of cases[24-28]. Moreover, it cannot distinguish steatohepatitis from simple steatosis. Second, our analysis is based on the incidence of self-reported cardiovascular disease. It is possible that selection biases could have masked a true association between NAFLD and cardiovascular disease. Finally, although the incidence rate of coronary heart disease in our study population was comparable to that of a much larger scale study reported recently from Japan[29], it was far lower than those reported in Western countries[13], and so the generalizability of our study to non-Japanese populations is uncertain.

In conclusion, our study confirms that NAFLD is a strong predictor of cardiovascular disease. The clinical implications of our study are twofold. Since ultrasonography of the liver is a non-invasive and easily applicable clinical test, it may be a useful tool for risk evaluation of cardiovascular disease. In patients with NAFLD, in addition to lifestyle modifications to reduce fat deposition, it may be important to explore the patients for risk factors of cardiovascular disease, and if found, treat them aggressively.

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