

The Metabolic Syndrome as a Predictor of Nonalcoholic Fatty Liver Disease

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Background: The frequent association of nonalcoholic fatty liver disease with components of the metabolic syndrome such as obesity, hyperglycemia, dyslipidemia, and hypertension is well known. However, no prospective study has examined the role of the metabolic syndrome in the development of this disease.

Objective: To characterize the longitudinal relationship between the metabolic syndrome and nonalcoholic fatty liver disease.

Design: A prospective observational study.

Setting: A medical health checkup program in a general hospital.

Participants: 4401 apparently healthy Japanese men and women, 21 to 80 years of age, with a mean body mass index (BMI) of 22.6 kg/m² (SD, 3.0).

Measurements: Alcohol intake was assessed by using a questionnaire. Biochemical tests for liver and metabolic function and abdominal ultrasonography were done. Modified criteria of the National Cholesterol Education Program Adult Treatment Panel III were used to characterize the metabolic syndrome.

Results: At baseline, 812 of 4401 (18%) participants had nonalcoholic fatty liver disease. During the mean follow-up period of 414 days (SD, 128), the authors observed 308 new cases (10%) of

nonalcoholic fatty liver disease among 3147 participants who were disease-free at baseline and who completed a second examination. Regression of nonalcoholic fatty liver disease was found in 113 (16%) of 704 participants who had the disease at baseline and who completed a second examination. Men and women who met the criteria for the metabolic syndrome at baseline were more likely to develop the disease during follow-up (adjusted odds ratio, 4.00 [95% CI, 2.63 to 6.08] and 11.20 [CI, 4.85 to 25.87], respectively). Nonalcoholic fatty liver disease was less likely to regress in those participants with the metabolic syndrome at baseline.

Limitations: Ultrasonography may lead to an incorrect diagnosis of nonalcoholic fatty liver disease in 10% to 30% of cases and cannot distinguish steatohepatitis from simple steatosis. Self-reported alcohol intake may cause bias. Because all of the participants were Japanese, generalizability to non-Japanese populations is uncertain.

Conclusions: The metabolic syndrome is a strong predictor of nonalcoholic fatty liver disease.

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Nonalcoholic fatty liver disease is increasingly recognized as a major cause of liver-related morbidity and mortality (1–3). Because of its potential to progress to cirrhosis and liver failure (4), interest in this disease is increasing among researchers and clinicians in the relevant basic and clinical science fields.

The pathologic picture of nonalcoholic fatty liver disease, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis, resembles that of alcohol-induced liver disease, but it occurs in patients who do not abuse alcohol (3). Nonalcoholic steatohepatitis that is characterized by hepatic steatosis and liver cell injury, hepatic inflammation, and fibrosis and necrosis is believed to be an intermediate stage of nonalcoholic fatty liver disease. (1) This disease is often associated with obesity (5), type 2 diabetes mellitus (6, 7), dyslipidemia (8), and hypertension (9). Each of these abnormalities carries a cardiovascular disease risk, and together they are often categorized as the insulin resistance syndrome or the metabolic syndrome (10). The third report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III [ATP III]) (11) recommended the use of 5 variables for diagnosing the metabolic syndrome, namely waist circumference, serum triglyceride level, serum

high-density lipoprotein (HDL) cholesterol level, blood pressure, and fasting plasma glucose level. As stated above, the frequent association of nonalcoholic fatty liver disease with individual components of the metabolic syndrome is now well known. However, it is unknown whether the risk for this disease is increased in patients with the metabolic syndrome. This is important because the metabolic syndrome is an emerging problem worldwide and its prevalence is likely increasing (12).

The current study was designed first to evaluate the cross-sectional relationship between the metabolic syndrome, defined by the modified ATP III criteria, and the prevalence of nonalcoholic fatty liver disease in Japanese persons. Second, and more important, we addressed longi-

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Context

The metabolic syndrome is often present in patients with nonalcoholic fatty liver disease (NAFLD), but no one knows whether it precedes NAFLD.

Content

At baseline, 812 members of a cohort of 4401 apparently healthy Japanese adults had NAFLD on abdominal ultrasonography. In 1 year, the authors identified 308 new cases, and NAFLD had resolved in 113 participants. Participants with the metabolic syndrome were much more likely to develop NAFLD and were less likely to experience disease resolution.

Limitations

Abdominal ultrasonography is not a perfect gold standard test for NAFLD.

Implication

The metabolic syndrome appears to predispose people to develop NAFLD.

—The Editors

tudinal aspects of the disease and its development and regression and tried to clarify the role of the metabolic syndrome in its pathogenesis. Despite serious concern about a possible future epidemic of this disease in the Asia-Pacific region (13), information regarding a possible association with the metabolic syndrome in Asia is very limited; our study may have special clinical relevance for people who live in this part of the world.

METHODS**Study Participants**

We designed a prospective cohort study to investigate the role of the metabolic syndrome in the pathogenesis of nonalcoholic fatty liver disease in participants in a medical health checkup program at Murakami Memorial Hospital, Gifu, Japan. Each participant had abdominal ultrasonography. The purpose of the medical health checkup program is to promote public health through early detection of chronic diseases and their risk factors. Medical service of this kind, known as “a human dock,” is very popular in Japan. The center at which the checkups were performed was founded in 1994 and currently evaluates more than 8000 examinees annually. Of these examinees, 60% repeatedly have annual or biannual examinations and 40% are newly registered examinees. Most of the participants were employees of various companies and local governmental organizations in Gifu, Japan, and their spouses. These companies and organizations recruit employees each year according to a contract with our center. The cost of the medical examination was largely paid for by the employers. Fewer than 10% of the participants individually registered

for the program and paid for it themselves, and they are citizens of local communities. Because many participants were expected to have repeated examinations, we took advantage of this opportunity to conduct a follow-up study on nonalcoholic fatty liver disease by using abdominal ultrasonography. The ethics committee of Murakami Memorial Hospital approved the study. All participants who were examined in the health checkup programs between January and December 2001 were invited to enroll in 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, habits regarding smoking, and habits regarding alcohol consumption, were surveyed by using a self-administered questionnaire. When the participants had difficulty completing the questionnaire, trained nurses provided assistance. 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. Habits regarding alcohol consumption were evaluated by asking the participants about the amount and type of alcoholic beverages consumed per week, then estimating the mean ethanol intake per day. The diagnosis of fatty liver was based on the results of abdominal ultrasonography, which was done by trained technicians. All ultrasonographic images were stored in the image server. One gastroenterologist reviewed the images 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) (14), the participants were required to have hepatorenal contrast and liver brightness to be given a diagnosis of nonalcoholic fatty liver disease. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of the participant's height in meters. The ATP III proposed the following 5 abnormalities to define the metabolic syndrome: 1) abdominal obesity (abdominal circumference > 102 cm for men and > 88 cm for women); 2) elevated serum triglyceride level (≥ 1.70 mmol/L [≥ 150 mg/dL]); 3) decreased HDL cholesterol level (<1.04 mmol/L [<40 mg/dL] for men and <1.30 mmol/L [<50 mg/dL] for women); 4) elevated blood pressure (systolic and diastolic blood pressure $\geq 130/85$ mm Hg); and 5) an elevated fasting glucose level (≥ 6.11 mmol/L [≥ 110 mg/dL]). Because waist measurements were not available for the entire study sample, we substituted a BMI of 25 kg/m² or greater for all participants as an index of obesity. A BMI of 25 kg/m² or greater has been proposed as a cutoff for the diagnosis of obesity in Asian people (15). Individuals with

3 or more of the 5 abnormalities were considered to have the metabolic syndrome.

Exclusion criteria were an alcohol intake of more than 20 g/d, known liver disease, or current use of medication. Regarding liver disease, participants who tested positive 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 (16).

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. Because the incidence rate of nonalcoholic fatty liver disease was unknown, a formal sample size estimate was not made a priori. Participants with and without follow-up visits were compared to determine the appropriateness of an analysis based on participants with complete data only. Two groups of participants were compared by using the unpaired *t*-test and the chi-square test. Logistic regression was used to analyze associations between the development and regression of nonalcoholic fatty liver disease and the metabolic syndrome while controlling for potential confounders. The potential confounders were selected from clinical variables, which were different between participants with and without the disease at baseline. As will be described later, weight change was also selected as a confounder because the development and regression of nonalcoholic fatty liver disease generally occurred with weight changes. Unadjusted and adjusted odds ratios and 95% CIs were calculated. Data are expressed as means and SDs for continuous variables.

Role of the Funding Source

No funding was received for this study.

RESULTS

Between January and December 2001, we invited 8056 participants in the health checkup program to enroll in the study. A total of 6654 Japanese participants (4601 men and 2053 women) gave informed consent to be included in the study. We excluded 290 participants (216 men and 74 women) who had known liver disease. In addition, 1657 participants (1577 men and 80 women) who consumed more than 20 g of ethanol per day and 306 participants (236 men and 70 women) who were currently receiving medication were excluded. As a result, there were 4401 participants (2572 men and 1829 women). Mean age and BMI were 47.6 years (SD, 8.8) (range, 21 to 80 years) and 22.6 kg/m² (SD, 3.0) (range, 14.2 to 38.1 kg/m²), respectively.

By the end of June 2003, 3876 of 4401 participants (2271 men and 1605 women) had completed the second examinations. For those who had two checkups during the follow-up period, the data obtained at the most recent examination were used. Twenty-five participants who began to take medication during the follow-up period were excluded from the follow-up analysis. There were 3851 participants (2248 men and 1603 women) available for the follow-up analysis of nonalcoholic fatty liver disease. The interval between the baseline and follow-up examinations was 414 days (SD, 128).

A total of 525 participants were lost to the follow-up analyses. At the time of writing, we did not have any data

Table 1. Baseline Characteristics of the Study Participants and Unadjusted Associations with the Presence of Nonalcoholic Fatty Liver Disease*

Variable	Men (n = 2572)			Women (n = 1829)		
	Normal US Results	NAFLD on US	<i>P</i> Value†	Normal US Results	NAFLD on US	<i>P</i> Value‡
Participants, <i>n</i>	1938	634		1651	178	
Mean age (SD), <i>y</i>	48.1 (9.0)	47.9 (8.4)	0.66	46.6 (8.8)	51.0 (7.7)	<0.001
Mean BMI (SD) kg/m ²	22.5 (2.5)	25.6 (2.8)	<0.001	21.3 (2.5)	25.7 (3.7)	<0.001
Mean Brinkman index (SD)§	357 (420)	359 (398)	0.90	22 (96)	23 (106)	0.85
Light drinkers, <i>n</i> (%)	1513 (78)	464 (73)	0.013	775 (47)	73 (41)	0.13
Participants who met each of 5 criteria of the metabolic syndrome, <i>n</i> (%)						
Increased BMI	292 (15)	342 (54)	<0.001	121 (7)	93 (52)	<0.001
Elevated fasting glucose level	187 (10)	179 (28)	<0.001	52 (3)	29 (16)	<0.001
Elevated blood pressure	453 (23)	261 (41)	<0.001	229 (14)	69 (39)	<0.001
Decreased HDL cholesterol level	564 (29)	324 (51)	<0.001	394 (24)	99 (56)	<0.001
Elevated triglyceride level	315 (16)	264 (42)	<0.001	67 (4)	36 (20)	<0.001
Participants who met ≥ 3 criteria of the metabolic syndrome, <i>n</i> (%)	163 (8)	252 (40)	<0.001	46 (3)	47 (26)	<0.001

* This summary is based on the 4401 study participants with baseline data. BMI = body mass index; HDL = high-density lipoprotein; NAFLD = nonalcoholic fatty liver disease; US = abdominal ultrasonography.

† *P* value = normal US results vs. NAFLD in men.

‡ *P* value = normal US results vs. NAFLD in women.

§ The Brinkman index is the number of cigarettes per day multiplied by years of smoking. A higher value indicates increased smoking-associated health hazard.

Table 2. The Relationship between the Metabolic Syndrome and the Development and Regression of Nonalcoholic Fatty Liver Disease*

Variable	Normal US Results at Both Baseline and Follow-up	Normal US Results at Baseline and NAFLD at Follow-up	P Value†	NAFLD at Baseline and Follow-up	NAFLD at Baseline and Normal US Results at Follow-up	P Value‡
Men (n = 2248)						
Total, n	1453	241		478	76	
Mean age (SD), y	47.7 (9.0)	48.3 (8.2)	0.38	47.5 (8.2)	47.9 (8.9)	0.72
Participants with each of 5 criteria of the metabolic syndrome at baseline, n (%)						
Increased BMI	176 (12)	70 (29)	<0.001	268 (56)	31 (41)	0.018
Elevated fasting glucose level	123 (8)	31 (13)	0.039	136 (28)	16 (21)	0.21
Elevated blood pressure	322 (22)	78 (32)	0.001	200 (42)	29 (38)	0.62
Decreased HDL cholesterol level	370 (25)	107 (44)	<0.001	243 (51)	34 (45)	0.39
Elevated triglyceride level	190 (13)	69 (29)	<0.001	197 (41)	31 (41)	1.00
Participants who met ≥ 3 criteria of the metabolic syndrome at baseline, n (%)	100 (7)	43 (18)	<0.001	194 (41)	23 (30)	0.100
Mean weight change (SD), kg	0.1 (2.2)	1.7 (1.7)	<0.001	0.1 (2.1)	-2.5 (3.2)	<0.001
Women (n = 1603)						
Total, n	1386	67		113	37	
Age (SD), y	46.3 (8.7)	50.0 (7.3)	<0.001	50.9 (7.1)	49.4 (9.0)	0.30
Participants with each of 5 criteria of the metabolic syndrome at baseline, n (%)						
Increased BMI	88 (6)	18 (27)	<0.001	66 (58)	11 (30)	0.004
Elevated fasting glucose level	39 (3)	9 (13)	<0.001	20 (18)	5 (14)	0.62
Elevated blood pressure	180 (13)	20 (30)	<0.001	48 (42)	12 (32)	0.34
Decreased HDL cholesterol level	316 (23)	30 (45)	<0.001	67 (59)	14 (38)	0.036
Elevated triglyceride level	44 (3)	11 (16)	<0.001	18 (16)	5 (14)	1.00
Participants who met ≥ 3 criteria of the metabolic syndrome at baseline, n (%)	27 (2)	11 (16)	<0.001	33 (29)	4 (11)	0.028
Mean weight change (SD), kg	0.1 (1.7)	1.3 (1.4)	<0.001	-0.1 (1.8)	-2.3 (2.3)	<0.001

* This summary is based on the 3851 participants with follow-up data. BMI = body mass index; HDL = high-density lipoprotein; NAFLD = nonalcoholic fatty liver disease; US = ultrasonography.

† P value = normal US results at both baseline and follow-up vs. normal US results at baseline and NAFLD at follow-up.

‡ P value = NAFLD at both baseline and follow-up vs. NAFLD at baseline and normal US results at follow-up.

to examine the reasons why these participants did not have a second examination by the end of June 2003; however, we were able to confirm that 87 of these participants subsequently had a second examination. Although these 525 participants were slightly older than the rest of the participants (mean age, 49.5 years [SD, 9.7] vs. 47.4 years [SD, 8.7]), sex (percentage of men, 57% vs. 59%), nonalcoholic fatty liver disease at baseline (19% vs. 18%), and percentage who met at least 3 of the 5 criteria of the metabolic syndrome (13% vs. 11%) were not different between the 2 groups.

Baseline Characteristics of the Study Participants

Nonalcoholic fatty liver disease was diagnosed using abdominal ultrasonography in 812 participants (18%). A total of 3589 participants did not have the disease (Table 1). Men had a higher prevalence of the disease than did women (25% vs. 10%). Women who were older and, unexpectedly, men who did not consume alcohol were more likely to have the disease at baseline. More men and women with nonalcoholic fatty liver disease met each one of the 5 criteria of the metabolic syndrome compared with

participants without the disease. In unadjusted comparisons, the participants with nonalcoholic fatty liver disease had approximately a 5 to 9 times higher prevalence of the metabolic syndrome.

Development of Nonalcoholic Fatty Liver Disease

Of the 3147 healthy participants (1694 men and 1453 women) who were disease-free at the baseline examination and who had the follow-up examination, 10%—241 men (14%) and 67 women (5%)—received new diagnoses of nonalcoholic fatty liver disease at the follow-up examination (Table 2). Men had a higher incidence rate of nonalcoholic fatty liver disease than did women. The proportions of participants who met each one of the 5 criteria and the prevalence of the metabolic syndrome at baseline were higher in the participants with newly developed disease than in those who were disease-free at baseline and at the second examination. The disease generally occurred with weight gain (226 of 241 men [94%] and 59 of 67 women [88%]). A small mean weight change was observed in these participants during this short-term study: 1.7 kg (SD, 1.7)

(range, -5.7 to 9.4 kg) in men and 1.3 kg (SD, 1.4) (range, -2.3 to 5.7 kg) in women.

Men and women were separately analyzed by logistic regression to determine the associations between the development of nonalcoholic fatty liver disease and the metabolic syndrome while controlling for potential confounders (Table 3). In the multivariate models, weight change was included as a covariate to determine whether the relationship between the metabolic syndrome and nonalcoholic fatty liver disease was independent of weight change. Participants' ages and habits regarding alcohol consumption were incorporated into the analysis because these variables were associated with the disease at baseline. In men, the presence of the metabolic syndrome at baseline and weight gain during the follow-up period were independently associated with the development of nonalcoholic fatty liver disease. In women, in addition to the metabolic syndrome at baseline and weight gain, age was also associated with the development of the disease, and each of the 3 variables was independent of each other.

Regression of Nonalcoholic Fatty Liver Disease

Of 704 participants (554 men and 150 women) who initially had nonalcoholic fatty liver disease and completed the second examination, 478 men and 113 women persistently had the disease on follow-up (Table 2). Seventy-six men and 37 women ($n = 113$ [16%]) no longer had evidence of the disease. Therefore, the disease regressed during the follow-up period in 76 of 554 men (14%) and 37 of 150 women (25%) who had it at baseline. Disease regression was associated with weight loss in most of the participants (70 of 76 men [92%] and 33 of 37 women [89%]), although this loss was small. The mean weight changes were -2.5 kg (SD, 3.2) (range, -20.8 to 2.6 kg) in men and -2.3 kg (SD, 2.3) (range, -9.0 to 0.9 kg) in women.

In the unadjusted analyses, weight loss was the only variable that had a statistically significant association with disease regression in men (Table 4). In the multivariate regression analyses, weight loss and the presence of the metabolic syndrome were independently associated with disease regression. The results were the same in women.

DISCUSSION

We found that the metabolic syndrome is a strong risk factor for nonalcoholic fatty liver disease in apparently healthy Japanese men and women. As mentioned previously, many studies have shown the cross-sectional associations between the metabolic syndrome and this disease (5–9). A cross-sectional relationship alone does not prove a causal relation. Our study showed that participants with the metabolic syndrome, as defined by the modified ATP III criteria, have a 4 to 11 times higher risk for future nonalcoholic fatty liver disease. In addition, if nonalcoholic fatty liver disease and the metabolic syndrome coexist, disease regression is less likely.

In our study, we used a cutoff level of less than 20 g of ethanol consumption per day to define nonalcoholic persons. Although the ideal cutoff level is not known (3), less than 20 g of ethanol per day did not seem to increase the risk for the disease.

The effect of sex on the prevalence of nonalcoholic fatty liver disease has been variously reported (1–3). We found a higher incidence of the disease in men than in women in our study sample. The fact that age was a risk factor for the disease in women but not in men may suggest a role of estrogen. Estrogen has been reported to protect against hepatic steatosis in mice (17).

Because the metabolic syndrome was shown to be highly predictive of insulin resistance (18), our results are

Table 3. Unadjusted and Adjusted Associations between the Development of Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome

Variable	Unadjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)*	P Value
Men (n = 1694)				
Age	1.01 (0.99–1.02)	0.38	1.01 (0.99–1.03)	0.21
Presence of the metabolic syndrome at baseline	2.94 (1.99–4.33)	<0.001	4.00 (2.63–6.08)	<0.001
Light drinker (ethanol consumption, 0–20 g/d) or nondrinker (ethanol consumption, 0 g/d)	0.79 (0.58–1.08)	0.145	0.82 (0.59–1.15)	0.26
Weight gain	1.46 (1.36–1.58)	<0.001	1.51 (1.40–1.63)	<0.001
Women (n = 1453)				
Age	1.05 (1.02–1.08)	0.001	1.05 (1.02–1.08)	0.001
Presence of the metabolic syndrome at baseline	9.89 (4.67–20.94)	<0.001	11.20 (4.85–25.87)	<0.001
Light drinker (ethanol consumption, 0–20 g/d) or nondrinker (ethanol consumption, 0 g/d)	0.79 (0.48–1.31)	0.36	0.86 (0.51–1.45)	0.56
Weight gain	1.50 (1.30–1.74)	<0.001	1.62 (1.39–1.89)	<0.001

* Adjusted for all other variables in the table.

Table 4. Unadjusted and Adjusted Associations between the Regression of Nonalcoholic Fatty Liver Disease and the Metabolic Syndrome

Variable	Unadjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)*	P Value
Men (n = 554)				
Age	1.01 (0.98–1.04)	0.57	1.02 (0.99–1.06)	0.166
Presence of the metabolic syndrome at baseline	0.59 (0.35–1.00)	0.051	0.47 (0.26–0.85)	0.013
Light drinker (ethanol consumption, 0–20 g/d) or nondrinker (ethanol consumption, 0 g/d)	0.84 (0.49–1.44)	0.53	0.89 (0.48–1.63)	0.71
Weight loss	1.60 (1.40–1.82)	<0.001	1.64 (1.43–1.88)	<0.001
Women (n = 150)				
Age	0.97 (0.93–1.02)	0.24	1.02 (0.99–1.05)	0.21
Presence of the metabolic syndrome at baseline	0.40 (0.14–1.11)	0.077	0.47 (0.26–0.84)	0.011
Light drinker (ethanol consumption, 0–20 g/d) or nondrinker (ethanol consumption, 0 g/d)	1.28 (0.61–2.71)	0.51	0.90 (0.49–1.64)	0.73
Weight loss	1.80 (1.39–2.32)	<0.001	1.63 (1.43–1.87)	<0.001

* Adjusted for all other variables in the table.

consistent with the idea that insulin resistance plays a pivotal role in the pathophysiology of nonalcoholic fatty liver disease (1). Although the focus of our study was limited to hepatic steatosis because biopsy of the liver was not done, other investigators showed a possible role of the metabolic syndrome in the more advanced stage of nonalcoholic fatty liver disease. A recent study (19) reported a higher prevalence of the metabolic syndrome in patients with nonalcoholic steatohepatitis than in patients with hepatitis C who had comparable fibrosis. The prevalence of the metabolic syndrome was high in patients with biopsy-proven nonalcoholic steatohepatitis compared with patients with simple hepatic steatosis (20).

The metabolic syndrome is now proposed to reflect a failure of normal partitioning of surplus fat exclusively into adipose tissue (21, 22). The failure leads to ectopic fat storage in the liver, muscle, and pancreatic β cells, which in turn causes hepatic steatosis, dyslipidemia, hepatic and peripheral insulin resistance, and insulin secretory failure. Adipocytokines, such as leptin and adiponectin, are proposed to play a pivotal role in preventing ectopic accumulation of lipids (22). In this regard, it is interesting that hypoadiponectinemia has been seen in patients with the metabolic syndrome (23) and also in patients with nonalcoholic steatohepatitis (24). Administration of adiponectin alleviated nonalcoholic fatty liver disease in mice (25).

Our study has several limitations. First, although ultrasonography has relatively high sensitivity (82% to 94%) and specificity (66% to 95%) in detecting fatty liver (26–31), it may give an incorrect diagnosis in 10% to 30% of cases. Moreover, it cannot distinguish steatohepatitis from simple steatosis, nor does it distinguish between nonalcoholic fatty liver disease and alcohol-related liver disease. Second, self-reported information regarding alcohol intake is frequently subject to underreporting, and misreporting could be a source of bias. In our study, there was a clear dose–response relation between alcohol consumption and γ -glutamyltransferase, a biological marker of alcohol in-

take, in the total study sample before we excluded 1657 participants who consumed more than 20 g of alcohol per day ($r = 0.486$; $P < 0.001$). This suggests that misclassification of alcohol intake was minimal. Third, although age and BMI in our study sample were well in accord with those reported in a larger population-based national nutrition survey done in Japan (32), we cannot exclude the possibility that our sample contained more health-conscious people than the general population in Japan. Finally, although the prevalence of nonalcoholic fatty liver disease (18%) on ultrasonography in our study sample was comparable to that (16%) in nonobese people who did not consume alcohol in an Italian study (5), the generalizability of our study to non-Japanese populations is uncertain.

In conclusion, the development and regression of nonalcoholic fatty liver disease occur in a substantial proportion of apparently healthy people with rather modest weight changes. Patients with the metabolic syndrome have an increased risk for this disease.

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References

- Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002;346:1221-31. [PMID: 11961152]
- Sanyal AJ. AGA technical review on nonalcoholic fatty liver disease. *Gastroenterology*. 2002;123:1705-25. [PMID: 12404245]
- Neuschwander-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. *Hepatology*. 2003;37:1202-19. [PMID: 12717402]
- Teli MR, James OF, Burt AD, Bennett MK, Day CP. The natural history of nonalcoholic fatty liver: a follow-up study. *Hepatology*. 1995;22:1714-9. [PMID: 7489979]
- Bellentani S, Saccoccio G, Masutti F, Crocè LS, Brandi G, Sasso F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. *Ann Intern Med*. 2000;132:112-7. [PMID: 10644271]
- Akbar DH, Kawther AH. Nonalcoholic fatty liver disease in Saudi type 2 diabetic subjects attending a medical outpatient clinic: prevalence and general characteristics [Letter]. *Diabetes Care*. 2003;26:3351-2. [PMID: 14633828]
- Gupte P, Amarapurkar D, Agal S, Bajjal R, Kulshrestha P, Pramanik S, et al. Non-alcoholic steatohepatitis in type 2 diabetes mellitus. *J Gastroenterol Hepatol*. 2004;19:854-8. [PMID: 15242486]
- Assy N, Kaita K, Mymin D, Levy C, Rosser B, Minuk G. Fatty infiltration of liver in hyperlipidemic patients. *Dig Dis Sci*. 2000;45:1929-34. [PMID: 11117562]
- Donati G, Stagni B, Piscaglia F, Venturoli N, Morselli-Labate AM, Rasciti L, et al. Increased prevalence of fatty liver in arterial hypertensive patients with normal liver enzymes: role of insulin resistance. *Gut*. 2004;53:1020-3. [PMID: 15194655]
- Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595-607. [PMID: 3056758]
- Executive Summary of the Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-97. [PMID: 11368702]
- Ford ES, Giles WH, Mokdad AH. Increasing prevalence of the metabolic syndrome among U.S. adults. *Diabetes Care*. 2004;27:2444-9. [PMID: 15451914]
- Chitturi S, Farrell GC, George J. Non-alcoholic steatohepatitis in the Asia-Pacific region: future shock? *J Gastroenterol Hepatol*. 2004;19:368-74. [PMID: 15012772]
- Kojima S, Watanabe N, Numata M, Ogawa T, Matsuzaki S. Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background. *J Gastroenterol*. 2003;38:954-61. [PMID: 14614602]
- World Health Organization Western Pacific Region, International Association for the Study of Obesity/International Obesity Task Force. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment*. Melbourne, Australia: Health Communications Australia; 2000.
- McCullough AJ. The clinical features, diagnosis and natural history of nonalcoholic fatty liver disease. *Clin Liver Dis*. 2004;8:521-33, viii. [PMID: 15331061]
- Hewitt KN, Pratis K, Jones ME, Simpson ER. Estrogen replacement reverses the hepatic steatosis phenotype in the male aromatase knockout mouse. *Endocrinology*. 2004;145:1842-8. [PMID: 14684602]
- Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes*. 2004;53:1195-200. [PMID: 15111486]
- Chitturi S, Abeygunasekera S, Farrell GC, Holmes-Walker J, Hui JM, Fung C, et al. NASH and insulin resistance: insulin hypersecretion and specific association with the insulin resistance syndrome. *Hepatology*. 2002;35:373-9. [PMID: 11826411]
- Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, et al. Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. *Hepatology*. 2003;37:917-23. [PMID: 12668987]
- Lewis GF, Carpentier A, Adeli K, Giacca A. Disordered fat storage and mobilization in the pathogenesis of insulin resistance and type 2 diabetes. *Endocr Rev*. 2002;23:201-29. [PMID: 11943743]
- Unger RH. Minireview: weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology*. 2003;144:5159-65. [PMID: 12960011]
- Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, et al. Adiponectin as a biomarker of the metabolic syndrome. *Circ J*. 2004;68:975-81. [PMID: 15502375]
- Hui JM, Hodge A, Farrell GC, Kench JG, Kriketos A, George J. Beyond insulin resistance in NASH: TNF-alpha or adiponectin? *Hepatology*. 2004;40:46-54. [PMID: 15239085]
- Xu A, Wang Y, Keshaw H, Xu LY, Lam KS, Cooper GJ. The fat-derived hormone adiponectin alleviates alcoholic and nonalcoholic fatty liver diseases in mice. *J Clin Invest*. 2003;112:91-100. [PMID: 12840063]
- Savarymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *Br Med J (Clin Res Ed)*. 1986;292:13-5. [PMID: 3080046]
- Steinmaurer HJ, Jirak P, Walchshofer J, Clodi PH. [Accuracy of sonography in the diagnosis of diffuse liver parenchymal diseases—comparison of sonography and liver histology]. *Ultraschall Med*. 1984;5:98-103. [PMID: 6474150]
- Needleman L, Kurtz AB, Rifkin MD, Cooper HS, Pasto ME, Goldberg BB. Sonography of diffuse benign liver disease: accuracy of pattern recognition and grading. *AJR Am J Roentgenol*. 1986;146:1011-5. [PMID: 3515875]
- Joseph AE, Savarymuttu SH, al-Sam S, Cook MG, Maxwell JD. Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol*. 1991;43:26-31. [PMID: 1999069]
- Mendler MH, Bouillet P, Le Sidaner A, Lavoine E, Labrousse F, Sautereau D, et al. Dual-energy CT in the diagnosis and quantification of fatty liver: limited clinical value in comparison to ultrasound scan and single-energy CT, with special reference to iron overload. *J Hepatol*. 1998;28:785-94. [PMID: 9625313]
- Graif M, Yanuka M, Baraz M, Blank A, Moshkovitz M, Kessler A, et al. Quantitative estimation of attenuation in ultrasound video images: correlation with histology in diffuse liver disease. *Invest Radiol*. 2000;35:319-24. [PMID: 10803673]
- Yoshiike N, Matsumura Y, Zaman MM, Yamaguchi M. Descriptive epidemiology of body mass index in Japanese adults in a representative sample from the National Nutrition Survey 1990-1994. *Int J Obes Relat Metab Disord*. 1998;22:684-7. [PMID: 9705030]

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