

Metabolic Significance of Nonalcoholic Fatty Liver Disease in Nonobese, Nondiabetic Adults

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Background: Obesity and type 2 diabetes are well-known risk factors for the development of nonalcoholic fatty liver disease (NAFLD). However, NAFLD is not rare in nonobese, nondiabetic adults. The aim of this study was to evaluate the metabolic significance of NAFLD in nonobese, nondiabetic adults.

Methods: This study examined 768 nonobese (body mass index [BMI] [calculated as weight in kilograms divided by the square of height in meters], ≥ 18.5 and < 30) (460 normal-weight and 308 overweight subjects), nondiabetic individuals older than 30 years who participated in a medical checkup. All the subjects had negative serologic findings for hepatitis B and C viruses and had an alcohol intake less than 140 g/wk. A standard interview, anthropometrics, a biochemical study, and abdominal ultrasonography were conducted.

Results: The prevalence of NAFLD in the enrolled subjects was 23.4%. In the normal-weight (BMI, ≥ 18.5 and

< 25) and overweight (BMI, ≥ 25 and < 30) groups, NAFLD was a significant predictor of insulin resistance and other metabolic disorders, including hypertriglyceridemia and hyperuricemia. The odds ratio of the metabolic disorders in subjects with NAFLD compared with those without NAFLD in the normal-weight group was higher than that in the overweight group. Multiple logistic regression analysis showed that sex, waist circumference, triglyceride level, and insulin resistance were independently associated with NAFLD in the normal-weight group.

Conclusions: Nonalcoholic fatty liver disease is closely associated with metabolic disorders, even in nonobese, nondiabetic subjects. Nonalcoholic fatty liver disease can be considered an early predictor of metabolic disorders, particularly in the normal-weight population.

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NONALCOHOLIC FATTY liver disease (NAFLD) describes a clinicopathologic condition that is characterized by significant lipid deposition in the hepatocytes of the liver parenchyma in patients with no history of excessive alcohol consumption. The spectrum of this disease is broad, ranging from a simple steatosis to nonalcoholic steatohepatitis, fibrosis, and cirrhosis.¹⁻³

Nonalcoholic fatty liver disease has attracted a great deal of attention since the report by Leevy⁴ described 270 patients with NAFLD in 1962. However, the clinical implications of this condition are still under investigation. Nonalcoholic fatty liver disease is the most common liver disease in Western countries, and it is becoming increasingly prevalent in Asian-Pacific regions because of the increasing westernization of the lifestyle, such as a high-fat and high-calorie diet, less physical activity, and increasing incidence of central obesity and type 2 diabetes.⁵

It has been reported that NAFLD is related to obesity,^{6,7} diabetes mellitus,^{6,8,9} and

dyslipidemia.⁸⁻¹⁰ However, NAFLD has been found in individuals without such risk factors.⁹ Recent studies have suggested that hyperinsulinemia and insulin resistance may play a role in the pathogenesis of NAFLD.¹¹ It has now been proposed that NAFLD is associated with a metabolic syndrome.^{12,13}

Obesity and diabetes are well-known risk factors for the development of a fatty liver,⁸ and few studies have examined NAFLD in nonobese, nondiabetic populations. Although Asians are less obese than Western people, the prevalence of NAFLD and metabolic syndrome is not lower than that in Western people.¹⁴

Therefore, the aims of this study were to evaluate the metabolic significance of NAFLD in nonobese, nondiabetic adults and to assess the independent factors associated with NAFLD.

METHODS

STUDY POPULATION

From April 1 to June 30, 2001, 932 individuals 30 years and older who received a medical

checkup in the Korea Association of Health Promotion Center in Seoul, Korea, underwent screening.

The exclusion criteria were as follows: (1) alcoholic intake of 140 g/wk or more¹⁵; (2) National Institutes of Health–defined body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) obesity (BMI, ≥ 30) or underweight (BMI, < 18.5)¹⁶ according to the National Institutes of Health–defined cutoff point; (3) a history of diabetes mellitus or fasting hyperglycemia according to the American Diabetes Association criteria (> 126 mg/dL [7.0 mmol/L])¹⁷; (4) a positive serologic finding for hepatitis B or C virus; (5) the presence of autoantibodies indicative of autoimmune hepatitis; (6) a history of another known liver disease; (7) a malignancy; (8) previous gastrointestinal tract surgery; and (9) ingestion of drugs known to produce hepatic steatosis, including corticosteroids, high-dose estrogens, methotrexate, tetracycline hydrochloride, amiodarone, or tamoxifen citrate in the previous 6 months.

Finally, 768 subjects were enrolled in this study. The Ethics Committee of Yonsei University College of Medicine, Seoul, approved this study, and informed consent was obtained from each subject.

All participants were interviewed to obtain their history of diabetes mellitus, hypertension, myocardial infarction, cerebrovascular accident, etc, as well as alcohol consumption and smoking. Their height, weight and waist and hip circumferences were measured to the nearest half-centimeter or half-kilogram. The waist circumference was measured at the midpoint between the lower border of the rib cage and the iliac crest, whereas the hip circumference was obtained at the widest point between the hip and buttock.

The blood pressure was measured using a standard mercury sphygmomanometer after the subject had been seated for at least 10 minutes. The percentage of whole body fat was measured by means of a bioelectrical impedance analysis method (Inbody 2.0; Biospace Co, Ltd, Seoul, Korea).

The laboratory evaluation included measurement of the aspartate aminotransferase, alanine aminotransferase, fasting blood glucose, fasting insulin, total cholesterol, high-density lipoprotein cholesterol (HDL-C), triglyceride, and uric acid levels. The low-density lipoprotein cholesterol level was calculated using the equation by Friedewald et al.¹⁸ The level of fasting blood glucose was determined by calculating the mean of the repeated checked value. The index of insulin resistance was calculated according to the homeostasis model assessment method (HOMA_{IR}),¹⁹ as follows:

$$\text{Fasting Insulin Level} \times \text{Fasting Glucose Level} / 22.5.$$

Similarly, the index of insulin secretion (HOMA _{β -cell function}) was calculated as

$$(20 \times \text{Fasting Insulin Level}) / (\text{Fasting Glucose Level} - 3.5).$$

For both formulas, insulin was measured as microunits per milliliter; glucose, as millimoles per liter.

One experienced radiologist performed abdominal ultrasonography, and the presence of fatty liver was defined as an increased echogenicity of the hepatic parenchyma with an attenuation of the portal vein or diaphragm echogenicity.²⁰

DEFINITION OF METABOLIC VARIABLES

The nonobese subjects were classified into the normal-weight (BMI, ≥ 18.5 and < 25) and the overweight (BMI, ≥ 25 and < 30) groups,¹⁶ and the subjects with and without NAFLD were compared within each BMI category.

Men and women with waist circumference values of at least 90 and 80 cm, respectively, were considered to have central obesity, according to the World Health Organization perspective

on the western Pacific region for Asians.²¹ Hypertension was defined as a systolic blood pressure of 140 mm Hg or greater, a diastolic blood pressure of 90 mm Hg or greater, or the use of antihypertensive medication, according to the guidelines of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.²² Impaired fasting glucose level was defined as a fasting plasma glucose level of 110 mg/dL or greater (≥ 6.1 mmol/L) but less than 126 mg/dL (< 7.0 mmol/L). The presence of insulin resistance was defined as the highest quartile of the HOMA_{IR}.²³ Hypertriglyceridemia and low HDL-C level were defined according to the Adult Treatment Panel III of the National Cholesterol Education Program guidelines (triglyceride level, ≥ 150 mg/dL [≥ 1.7 mmol/L]; HDL-C level, < 40 mg/dL [< 1.0 mmol/L] in men or < 50 mg/dL [< 1.3 mmol/L] in women).²⁴ Hyperuricemia was defined as a uric acid level of 6.7 mg/dL or greater (≥ 400 $\mu\text{mol/L}$).¹²

STATISTICAL ANALYSIS

The difference between groups with and without NAFLD was compared using an unpaired *t* test. The χ^2 test or Fisher exact test was used to compare the prevalence data. The odds ratio was calculated for 2 \times 2 cross tables and is expressed with the 95% confidence interval. Logistic regression analysis was used to examine the independent factor on NAFLD. A 1-way analysis of variance (ANOVA) was used to assess the prevalence of a fatty liver according to the BMI, body fat, waist circumference, triglyceride level, and HOMA_{IR} quartile groups. When found to be significant, a post hoc (Scheffé method) multiple comparison was used to establish the differences between the groups. The statistical analyses were performed using the SPSS version 11.0 software package (SPSS Inc, Chicago, Ill). *P* values of less than .05 were considered significant.

RESULTS

CLINICAL CHARACTERISTICS OF SUBJECTS

The prevalence of a fatty liver was 23.4% in all the subjects and was higher in the overweight group than in the normal-weight group (34.4% vs 16.1%; $P < .001$).

In the clinical and laboratory data of all the enrolled subjects, there were significant differences between the subjects with and without NAFLD in the variables, including the BMI, body fat, waist circumference, lipid profile, HOMA_{IR}, and HOMA _{β -cell function} (**Table 1**).

The characteristics of the subjects according to the BMI are shown in **Table 2**. In the normal-weight group, there were significant differences between the subjects with and without NAFLD in terms of sex; BMI; waist circumference; waist-hip ratio; levels of total cholesterol, triglycerides, HDL-C, uric acid, fasting blood glucose, insulin, aspartate aminotransferase, and alanine aminotransferase; HOMA_{IR}; and HOMA _{β -cell function}. In the overweight group, a comparison between subjects with and without NAFLD showed a similar tendency to that in the normal-weight group (Table 2).

There were no significant differences between the normal-weight group with NAFLD and the overweight group without NAFLD in terms of the metabolic variables such as waist-hip ratio, blood pressure, lipid profiles, levels of fasting blood glucose and insulin, HOMA_{IR}, and HOMA _{β -cell function} (Table 2).

Table 1. Clinical and Laboratory Characteristics of the Subjects*

Characteristic	Total (n = 768)	NAFLD Absent (n = 588)	NAFLD Present (n = 180)	P Value†
Male, %	46.0	41.5	60.0	<.001
Age, y	51.7 ± 10.0	51.3 ± 10.0	53.2 ± 9.8	.03
BMI	24.3 ± 2.4	23.9 ± 2.3	25.6 ± 2.3	<.001
Body fat, %	27.0 ± 6.5	26.8 ± 6.4	27.9 ± 6.7	.04
Waist circumference, cm	83.2 ± 7.2	81.7 ± 7.0	87.8 ± 5.9	<.001
WHR	0.86 ± 0.05	0.85 ± 0.05	0.88 ± 0.04	<.001
SBP, mm Hg	130.0 ± 18.7	128.6 ± 18.6	134.1 ± 18.6	.001
DBP, mm Hg	79.8 ± 12.4	79.1 ± 12.4	82.1 ± 11.9	.004
FBG level, mg/dL	92.5 ± 9.2	91.7 ± 8.6	95.3 ± 10.2	<.001
Insulin level, μU/mL	10.7 ± 42.9	9.9 ± 5.6	13.2 ± 6.3	<.001
TC level, mg/dL	201.9 ± 33.4	199.4 ± 33.2	210.2 ± 32.9	<.001
HDL-C level, mg/dL	47.5 ± 12.4	48.7 ± 12.6	43.5 ± 10.8	<.001
LDL-C level, mg/dL	124.4 ± 30.6	122.9 ± 30.7	129.4 ± 29.6	.02
TG level, mg/dL	161.6 ± 119.3	147.6 ± 111.6	207.2 ± 131.7	<.001
Uric acid level, mg/dL	5.0 ± 1.4	4.8 ± 1.3	5.5 ± 1.4	<.001
HOMA _{IR}	2.47 ± 1.46	2.28 ± 1.38	3.12 ± 1.52	<.001
HOMA _{β-cell function}	140.5 ± 87.4	133.9 ± 82.8	162.3 ± 98.2	<.001
AST level, mU/mL	22.3 ± 6.8	21.6 ± 6.2	24.6 ± 8.1	<.001
ALT level, mU/mL	24.2 ± 14.1	21.6 ± 10.9	32.9 ± 19.1	<.001

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL-C, high-density lipoprotein cholesterol; HOMA_{β-cell function}, index of insulin secretion calculated according to the homeostasis model assessment (HOMA) method; HOMA_{IR}, index of insulin resistance calculated according to the HOMA method; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WHR, waist-hip ratio.

SI conversion factors: To convert FBG to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; TC, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and uric acid to micromoles per liter, multiply by 59.48.

*Unless otherwise indicated, data are expressed as mean ± SD.

†Calculated by comparison of subjects with and without NAFLD. Significant values appear in boldface type.

METABOLIC ABNORMALITIES OF NAFLD BY BMI

The prevalence and odds ratios of the metabolic disorders according to the presence of NAFLD are shown in **Table 3** and **Table 4**, respectively. In the normal-weight group, the prevalence of hypertriglyceridemia, hyperuricemia, central obesity, and insulin resistance was higher in the subjects with a fatty liver than in those without one. However, in the overweight group, there was no difference in the prevalence of central obesity between the subjects with and without a fatty liver (Table 3).

In both the normal-weight and overweight groups, NAFLD was a significant predictor of insulin resistance and other metabolic abnormalities, including triglyceridemia and hyperuricemia. The odds ratios in the normal-weight group were higher than those in the overweight group (Table 4).

MULTIPLE LOGISTIC REGRESSION ANALYSIS OF THE CLINICAL AND LABORATORY FACTORS ASSOCIATED WITH NAFLD

According to multiple logistic regression analysis, age and BMI were independently associated with NAFLD in the overweight group, but not in the normal-weight group. In the normal-weight group, sex, waist circumference, triglyceride level, and logarithm HOMA_{IR} were independently associated with NAFLD (**Table 5**).

PREVALENCE OF NAFLD BY BMI, WAIST CIRCUMFERENCE, TRIGLYCERIDE LEVEL, AND HOMA_{IR} QUARTILE GROUPS

The **Figure** shows the prevalence of NAFLD according to the quartiles of the factors associated with NAFLD. In the prevalence of NAFLD according to BMI quartiles, there were significant differences in both the normal-weight and overweight groups according to the ANOVA results, although not every quartile group showed a significant difference (Figure, A). However, the prevalence of NAFLD according to the body fat quartiles did not show any significant difference among the quartile groups according to ANOVA (data not shown). In terms of the waist circumference and triglyceride quartiles, the prevalence of NAFLD was significantly higher in the upper quartile groups in both the normal-weight and overweight groups (Figure, B and C). In the analysis according to the HOMA_{IR} quartiles, the prevalence of NAFLD was higher in the upper quartile groups (Figure, D).

COMMENT

Recently, an increasing number of studies have examined the significance of NAFLD, as NAFLD is increasingly prevalent and understood as a feature of the metabolic syndrome.²⁵ In the general population studies, screening with ultrasonography²⁶⁻²⁹ or computed tomography³⁰ has indicated a prevalence ranging from

Table 2. Clinical and Laboratory Characteristics of the Subjects According to BMI*

Characteristic	Normal-Weight Subjects (n = 460)			Overweight Subjects (n = 308)		
	NAFLD Absent (n = 386)	NAFLD Present (n = 74)	P Value†	NAFLD Absent (n = 202)	NAFLD Present (n = 106)	P Value‡
Male, %	42.2	64.9	<.001	40.1‡	56.6	.006
Age, y	51.0 ± 10.1	51.6 ± 9.7	.66	51.9 ± 9.7	54.3 ± 9.8	.04
BMI	22.6 ± 1.6	23.4 ± 1.3	<.001	26.5 ± 1.2‡	27.1 ± 1.3§	<.001
Body fat, %	24.9 ± 5.9	25.7 ± 6.8	.34	30.3 ± 5.9‡	29.6 ± 6.2§	.38
Waist circumference, cm	78.6 ± 5.7	83.9 ± 4.8	<.001	87.6 ± 5.2‡	90.6 ± 4.9§	<.001
WHR	0.84 ± 0.05	0.87 ± 0.04	<.001	0.87 ± 0.05	0.89 ± 0.04§	.002
SBP, mm Hg	126.7 ± 18.4	129.8 ± 19.6	.19	132.2 ± 18.5	137.0 ± 17.2§	.03
DBP, mm Hg	77.8 ± 12.0	79.4 ± 12.5	.28	81.7 ± 12.8	84.0 ± 11.2§	.11
FBG level, mg/dL	91.3 ± 8.4	93.9 ± 10.4	.02	92.4 ± 9.1	96.2 ± 10.1	.001
Insulin level, µU/mL	9.2 ± 4.7	11.5 ± 4.3	<.001	11.5 ± 6.9	14.5 ± 7.2§	<.001
TC level, mg/dL	197.8 ± 32.3	208.8 ± 34.3	.008	202.5 ± 34.7	211.2 ± 32.0	.03
HDL-C level, mg/dL	50.0 ± 12.5	44.1 ± 11.2	<.001	46.1 ± 12.2	43.1 ± 10.6	.03
LDL-C level, mg/dL	122.1 ± 29.5	127.5 ± 29.8	.16	124.3 ± 33.1	130.8 ± 29.5	.10
TG level, mg/dL	130.0 ± 76.7	194.6 ± 102.3	<.001	181.5 ± 153.3	216.1 ± 148.6	.06
Uric acid level, mg/dL	4.8 ± 1.3	5.6 ± 1.4	<.001	4.9 ± 1.3‡	5.5 ± 1.4	.001
HOMA _{IR}	2.08 ± 1.12	2.66 ± 1.02	<.001	2.66 ± 1.72	3.44 ± 1.72§	<.001
HOMA _{3-cell function}	125.3 ± 73.5	146.7 ± 72.2	.02	150.3 ± 96.3	173.2 ± 111.9	.06
AST level, mU/mL	21.7 ± 6.5	23.5 ± 7.7	.04	21.3 ± 5.5‡	25.4 ± 8.4	<.001
ALT level, mU/mL	20.9 ± 11.1	31.9 ± 19.0	<.001	22.8 ± 10.3‡	33.6 ± 19.2	<.001

Abbreviations: See Table 1.

SI conversion factors: To convert FBG to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; TC, HDL-C, and LDL-C to millimoles per liter, multiply by 0.0259; triglycerides to millimoles per liter, multiply by 0.0113; and uric acid to micromoles per liter, multiply by 59.48.

*The normal-weight group had BMI of at least 18.5 and less than 25; overweight group, BMI of at least 25 and less than 30. Unless otherwise indicated, data are expressed as mean ± SD.

†Calculated by comparison of subjects with and without NAFLD within each BMI group. Significant values appear in boldface type.

‡For comparison of normal-weight subjects with NAFLD and overweight subjects without NAFLD, *P* < .05.

§For comparison of normal-weight and overweight subjects with NAFLD, *P* < .05.

Table 3. Prevalence of Metabolic Disorders*

Disorder	Total			Normal-Weight Subjects			Overweight Subjects		
	NAFLD Absent	NAFLD Present	P Value†	NAFLD Absent	NAFLD Present	P Value‡	NAFLD Absent	NAFLD Present	P Value‡
Hypertension	31.0	43.3	.002	27.0	35.1	.16	38.6	49.1	.08
IFG	4.1	10.6	.002	3.4	8.1	.06	5.4	12.3	.03
Hypertriglyceridemia	33.6	58.9	<.001	30.1	60.8	<.001	40.5	57.5	.004
Low HDL-C level	42.3	50.8	.045	37.7	45.9	.18	51.2	54.4	.61
Hyperuricemia	9.4	21.1	<.001	8.5	23.0	<.001	10.9	19.8	.03
Insulin resistance‡	19.0	45.0	<.001	20.2	50.0	<.001	16.8	40.6	<.001
Central obesity§	41.7	63.3	<.001	21.2	35.1	.01	80.7	83.0	.62

Abbreviations: HDL-C, high-density lipoprotein cholesterol; IFG, impaired fasting glucose level; NAFLD, nonalcoholic fatty liver disease.

*Definitions of normal-weight and overweight groups: see Table 2. Data are expressed as number (percentage) of subjects.

†Calculated by comparisons of subjects with and without NAFLD. Significant values appear in boldface type.

‡Defined as the highest quartile of the index of insulin resistance calculated according to the homeostasis assessment method.

§Defined as >90 cm and >80 cm in waist circumference for men and women, respectively.

13% to 23%. In the present study, the prevalence of NAFLD in nondiabetic, nonobese adults was 23.4% (16.1% in the normal-weight group and 34.4% in the overweight group). Although the subjects in this study were nondiabetic, nonobese adults, the prevalence of NAFLD was higher than that in other reports in which the subjects were obtained from the general population. This suggests that lifestyle or genetic factors besides obesity, diabetes mellitus, and dyslipidemia may be a

part of the risk factors for NAFLD. A recent study suggests that the fatty liver group had much greater carbohydrate intake than the control group and that the restriction of carbohydrates might contribute to the recovery of a fatty liver.³¹ Koreans have a higher carbohydrate intake than white subjects,^{32,33} and the high prevalence of NAFLD can be partially ascribed to the increased intake of a higher percentage of carbohydrates in the regular diet.

Table 4. Odds Ratios of the Metabolic Disorders in the Subjects With NAFLD Compared With the Control Group*

Disorder	Total	Normal-Weight Group	Overweight Group
Hypertension	1.70 (1.21-2.40)†	1.46 (0.86-2.48)	1.53 (0.95-2.46)
IFG	2.77 (1.48-5.19)†	2.53 (0.93-6.89)	2.43 (1.05-5.62)†
Hypertriglyceridemia	2.83 (2.01-3.99)†	3.61 (2.16-6.04)†	1.99 (1.24-3.21)
Low HDL-C level	1.41 (1.01-1.97)†	1.41 (0.85-2.32)	1.13 (0.70-1.81)
Hyperuricemia	2.59 (1.65-4.08)†	3.19 (1.67-6.10)†	2.02 (1.05-3.88)†
Insulin resistance‡	3.48 (2.43-4.98)†	3.95 (2.35-6.64)†	3.37 (1.98-5.76)†
Central obesity‡	2.42 (1.71-3.41)†	2.01 (1.18-3.43)†	1.17 (0.63-2.17)

Abbreviations: See Table 3.

*Definitions of normal-weight and overweight groups: see Table 2. Data are expressed as odds ratios (95% confidence intervals). Significant values appear in boldface type.

† $P < .05$.

‡Definitions: see Table 3.

In the present study, the diagnosis of NAFLD was based on the exclusion of the known etiologic factors responsible for liver disease and ultrasound examination results, but the diagnosis was not confirmed by liver biopsy results. In a prospective study comparing ultrasound scanning with histological examination results, Saverymuttu et al³⁴ showed that ultrasound examinations can accurately identify a steatosis with a sensitivity of 94% and a specificity of 84%. Although ultrasonography has some limitations in distinguishing a fatty liver from other liver diseases, the present study used ultrasonography to examine subjects in sufficient numbers, using a noninvasive method.

Diabetes and obesity are well-known risk factors for the development of NAFLD, but the causality of them to NAFLD is unclear. They may play an important role as confounding factors. Therefore, the significance of NAFLD, excluding diabetes and obesity, was investigated in this study.

Recent studies^{11,12,35} have suggested that insulin resistance might be a primary phenomenon adding to obesity- and diabetes-associated insulin resistance in NAFLD. However, previous studies lacked an appreciation of NAFLD as a risk factor for metabolic disorders and did not evaluate NAFLD by comparing a normal-weight with an overweight group. This study assessed the NAFLD from the viewpoint of metabolic disorders, dividing the subjects on the basis of BMI. The results showed that NAFLD is a significant predictor of insulin resistance, and insulin resistance was found to be an independent factor associated with NAFLD on multiple logistic regression analysis in both the normal-weight and overweight groups. Not only was insulin resistance more prevalent in the subjects with NAFLD in both groups, also other metabolic disorders such as hypertriglyceridemia and hyperuricemia also were more prevalent.

The relationship between obesity and NAFLD is well known. However, it has been proposed that the waist-hip ratio or the waist circumference, which reflects central obesity, is more related to NAFLD than BMI is.^{12,36} In contrast to the overweight group, the BMI was not an independent risk factor for NAFLD in the normal-weight group in the present study. However, patients with NAFLD showed an increased central obesity, even in the presence of a normal weight, and waist circumference was an independent risk factor for NAFLD, particularly in the

Table 5. Multiple Logistic Regression Analysis of the Factors Associated With NAFLD*

Factor	Total		Normal-Weight Group		Overweight Group	
	β	P Value†	β	P Value†	β	P Value†
Sex	0.96	.02	1.12	.046	-0.03	.96
Age	0.01	.22	0.001	.94	0.04	.01
BMI	0.01	.85	-0.12	.37	0.59	<.001
Body fat	0.06	.049	0.10	.09	-0.07	.22
Waist circumference	0.07	.003	0.13	.001	0.02	.52
TG level	0.001	.11	0.004	.01	0.001	.46
HDL-C level	-0.02	.04	-0.02	.24	-0.02	.11
SBP	0.01	.38	0.003	.86	0.02	.26
DBP	-0.01	.51	-0.01	.70	-0.01	.61
Logarithm HOMA _{IR}	2.35	<.001	1.74	.03	2.86	<.001

Abbreviations: see Table 1.

*Definitions of normal-weight and overweight groups: see Table 2.

†Significant values appear in boldface type.

normal-weight group. In addition, we found significant differences in the normal-weight and overweight groups in the prevalence of NAFLD according to the waist circumference quartiles by ANOVA. A previous study reported that a central body fat distribution determined by the waist-hip and waist-height ratios and the skinfold thickness predicted a fatty liver only in women.³⁷ However, in this study, when the data were analyzed in men and women separately, the waist circumference was found to be an independent factor in normal-weight men and women (data not shown).

In Asians, an impairment of early-phase insulin secretion plays an important role in the pathogenesis of type 2 diabetes,³⁸ and overall obesity is relatively uncommon. Asians have a higher proportion of visceral fat and a lower lean body mass than do white subjects with the same BMI.^{15,39} Central obesity is the key factor that contributes to insulin resistance,⁵ and an increased visceral adiposity might be relevant in the pathogenesis of NAFLD.¹² Visceral adipose tissue is more resistant to insulin, exhibits a greater lipolysis, and produces more free fatty acid than does adipose tissue in other sites.⁴⁰ The increased availability of a substrate for lipogenesis and

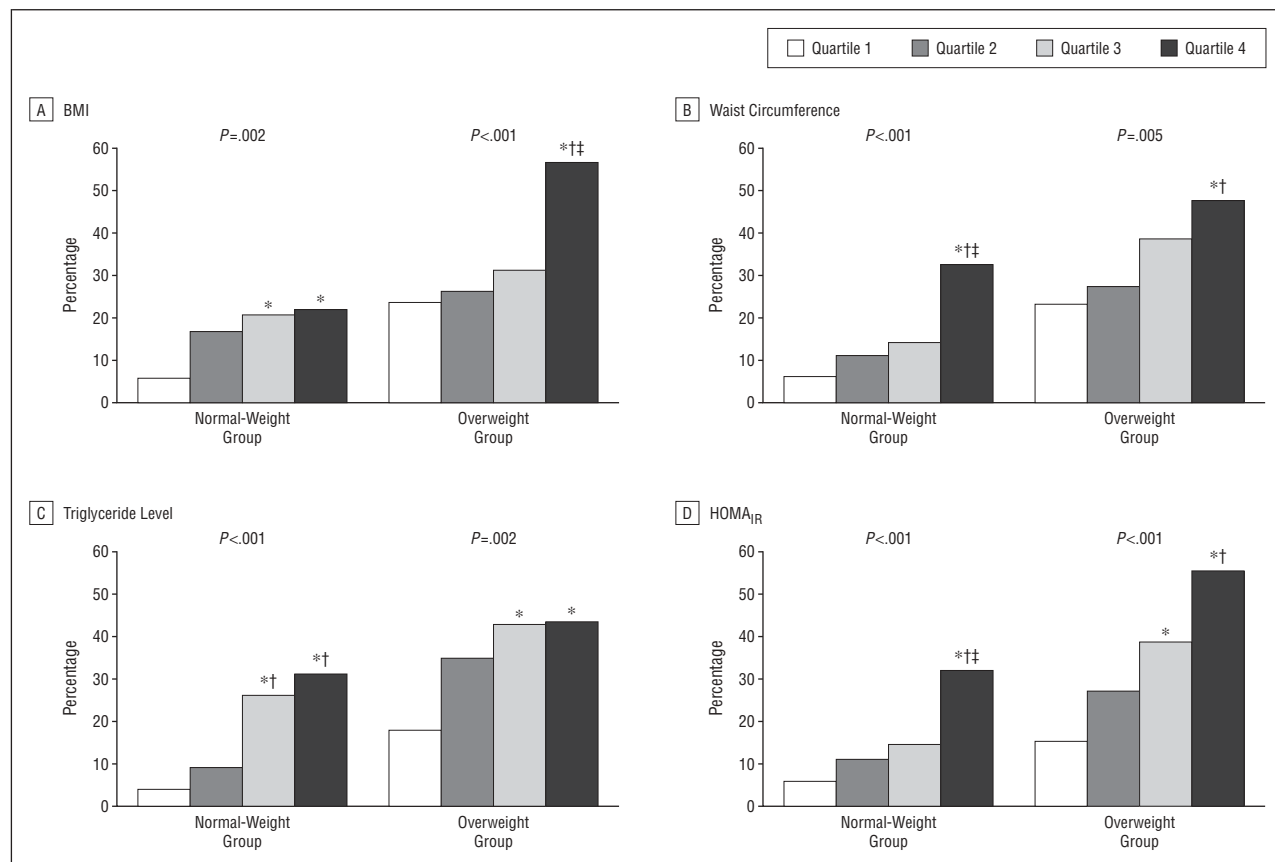


Figure. Prevalence of nonalcoholic fatty liver disease (NAFLD) according to the quartiles of body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters) (A), waist circumference (B), triglyceride level (C), and homeostasis model assessment method of the index of insulin resistance (HOMA_{1R}) (D). The *P* value was calculated using 1-way analysis of variance. Asterisk indicates *P* < .05 vs quartile 1; dagger, *P* < .05 vs quartile 2; double dagger, *P* < .05 vs quartile 3, based on the post hoc multiple comparison between quartile groups. The normal-weight group has a BMI of at least 18.5 and less than 25; the overweight group, BMI of at least 25 and less than 30.

the relative hyperinsulinemia in insulin resistance status promote lipogenesis in the liver.⁴¹ The high prevalence of NAFLD in this study can be attributed to the relatively increased visceral fat depot in Asians, in addition to the high carbohydrate intake.

Our results found no difference between the normal-weight subjects with NAFLD and the overweight subjects without NAFLD in terms of the metabolic variables such as the waist-hip ratio, HOMA_{1R}, HOMA_{β-cell} function, and levels of fasting glucose, insulin, total cholesterol, HDL-C, and triglycerides. From the metabolic point of view, this finding suggests that normal-weight subjects with fatty liver are comparable to overweight subjects, although they have an apparently normal weight.

Moreover, in the normal-weight group, the odds ratios of insulin resistance and metabolic disorders such as hypertriglyceridemia, hyperuricemia, and central obesity in subjects with NAFLD compared with those without NAFLD were higher than the odds ratios in the overweight group. This suggests that NAFLD can be considered to be a more meaningful predictor of metabolic disorders, particularly in the normal-weight population.

The pathogenesis of NAFLD is still under active investigation. The “2-hits hypothesis” by Day and James⁴² suggests that the first hit involves the accumulation of excess fat in the hepatic parenchyma. This step has been linked to insulin resistance. The second hit is generally attrib-

uted to oxidative stress that causes the peroxidation of lipids in the hepatocyte membrane, which can initiate fibrosis via the proinflammatory cytokines and activated stellate cells. Lipid peroxidation and the generation of free radicals can also directly and adversely affect the hepatocytes, resulting in cell death and hepatic necrosis.

Considerable interest has been generated recently in nonalcoholic steatohepatitis, because the prevalence of cirrhosis was significantly higher among patients with nonalcoholic steatohepatitis than among patients with a steatosis alone.³ The limitation of this study was the lack of a histological confirmation of a diagnosis of nonalcoholic steatohepatitis.⁴³ Therefore, this study could not define the association between the histological significance and the metabolic abnormalities.

CONCLUSIONS

In summary, our study resulted in the following findings. First, NAFLD was a significant predictor of insulin resistance and metabolic disorders, and it may be an indicator of metabolic disorders even in nonobese, nondiabetic people. Second, the significance of central obesity was more meaningful for NAFLD in the normal-weight group than in the overweight group, and this suggests that visceral adiposity rather than the overall

amount of body fat is important, particularly in normal-weight people. Third, insulin resistance and central obesity were independently associated with NAFLD in normal-weight subjects, and this might have therapeutic implications. Insulin-sensitizing drugs or a reduction in central obesity through a nutritional regimen and exercise might reverse a fatty liver. Therefore, there is a need for further clinical studies. In conclusion, NAFLD is closely associated with metabolic disorders, regardless of obesity or diabetes, and can be considered an early predictor of metabolic disorders, particularly in the normal-weight population.

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REFERENCES

- Ludvig J, Viggiano TR, McGill DB, Oh BJ. Nonalcoholic steatohepatitis: Mayo Clinic experiences with a hitherto unnamed disease. *Mayo Clin Proc.* 1980;55:434-438.
- Schaffner F, Thaler H. Nonalcoholic fatty liver disease. *Prog Liver Dis.* 1986;8:283-298.
- Matteoni CA, Younossi ZM, Gramlich T, Boparai N, Liu YC, McCullough AJ. Non-alcoholic fatty liver disease: a spectrum of clinical and pathological severity. *Gastroenterology.* 1999;116:1413-1419.
- Leevy CM. Fatty liver: a study of 270 patients with biopsy proven fatty liver and review of the literature. *Medicine (Baltimore).* 1962;41:249-276.
- Farrell GC. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? *J Gastroenterol Hepatol.* 2003;18:124-138.
- Wanless IR, Lentz JS. Fatty liver hepatitis (steatohepatitis) and obesity: an autopsy study with analysis of risk factors. *Hepatology.* 1990;12:1106-1110.
- Eriksson S, Eriksson KF, Bondesson L. Nonalcoholic steatohepatitis in obesity: a reversible condition. *Acta Med Scand.* 1986;220:83-88.
- Powell EE, Cooksley WG, Hanson R, Searle J, Halliday JW, Powell LW. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. *Hepatology.* 1990;11:74-80.
- Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology.* 1994;107:1103-1109.
- Diehl AM, Goodman Z, Ishak KG. Alcoholic liver disease in nonalcoholics: a clinical and histologic comparison with alcohol-induced liver injury. *Gastroenterology.* 1988;95:1056-1062.
- Marchesini G, Brizi M, Morselli-Labate AM, et al. Association of nonalcoholic fatty liver disease to insulin resistance. *Am J Med.* 1999;107:450-455.
- Marchesini G, Brizi M, Bianchi G, et al. Nonalcoholic fatty liver disease: a feature of the metabolic syndrome. *Diabetes.* 2001;50:1844-1850.
- Cortez-Pinto H, Camilo ME, Baptista A, De Oliveira AG, De Moura MC. Non-alcoholic fatty liver: another feature of the metabolic syndrome? *Clin Nutr.* 1999;18:353-358.
- Das UN. Metabolic syndrome X is common in South Asians, but why and how? *Nutrition.* 2002;18:774-776.
- Coates RA, Halliday ML, Rankin JG, Feinman SV, Fisher MM. Risk of fatty liver infiltration or cirrhosis of the liver in relation to ethanol consumption: a case-control study. *Clin Invest Med.* 1986;9:26-32.
- National Institutes of Health National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—the evidence report. *Obes Res.* 1998;6(suppl 2):51S-210S.
- Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care.* 1997;20:1183-1197.
- Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem.* 1972;18:499-502.
- Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β -cell function from plasma fasting glucose and insulin concentrations in man. *Diabetologia.* 1985;28:412-419.
- Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *BMJ.* 1986;292:13-15.
- Steering Committee of the Western Pacific Region of the World Health Organization International Association for the Study of Obesity, and International Obesity Task Force. *The Asia-Pacific Perspective: Redefining Obesity and Its Treatment.* Melbourne, Australia: Health Communications Australia Pty Ltd; 2000: 15-21.
- Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report *JAMA.* 2003;289:2560-2572 [published correction appears in *JAMA.* 2003;290:197].
- Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications, part 1: diagnosis and classification of diabetes mellitus, provisional report of a WHO consultation. *Diabet Med.* 1998;15:539-553.
- Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. 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;285:2486-2497.
- Falck-Ytter Y, Younossi ZM, Marchesini G, McCullough AJ. Clinical features and natural history of nonalcoholic steatosis syndromes. *Semin Liver Dis.* 2001;21:17-26.
- Araujo LM, De Oliveira DA, Nunes DS. Liver and biliary ultrasonography in diabetic and non-diabetic obese women. *Diabetes Metab.* 1998;24:458-462.
- Lonardo A, Bellini M, Tartoni P, Tondelli E. The bright liver syndrome: prevalence and determinants of a "bright" liver echopattern. *Ital J Gastroenterol Hepatol.* 1997;29:351-356.
- Ballentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in northern Italy. *Ann Intern Med.* 2000;132:112-117.
- Pares A, Tresserras R, Nunez I, et al. Prevalence and factors associated to the presence of fatty liver in apparently healthy adult men [in Spanish]. *Med Clin (Barc).* 2000;114:561-565.
- el-Hassan AY, Ibrahim EM, al-Mulhim FA, Nabhan AA, Chammam MY. Fatty infiltration of the liver: analysis of prevalence, radiological and clinical features and influence on patient management. *Br J Radiol.* 1992;65:774-778.
- Okita M, Hayashi M, Sasagawa T, et al. Effect of a moderately energy-restricted diet on obese patients with fatty liver. *Nutrition.* 2001;17:542-547.
- Shim JE, Baek HY, Lee SY, et al. Assessment of vitamin A and E status in Korean rural adult population by dietary intake and serum levels. *Korean J Nutr.* 2001;34:213-221.
- Appel LJ, Moore TJ, Obarzanek E, et al; DASH Collaborative Research Group. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med.* 1997;336:1117-1124.
- Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. *BMJ.* 1986;292:13-15.
- Lee JH, Rhee PL, Lee JK, et al. Role of hyperinsulinemia and glucose intolerance in the pathogenesis of nonalcoholic fatty liver in patients with normal body weight. *Korean J Intern Med.* 1998;13:12-14.
- Omagari K, Kadokawa Y, Masuda J, et al. Fatty liver in non-alcoholic non-overweight Japanese adults: incidence and clinical characteristics. *J Gastroenterol Hepatol.* 2002;17:1098-1105.
- Lonardo A, Trande P. Are there any sex differences in fatty liver? a study of glucose metabolism and body fat distribution. *J Gastroenterol Hepatol.* 2000;15:775-782.
- Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. *Metabolism.* 2001;50:590-593.
- Dudeja V, Misra A, Pandey RM, Devina G, Kumar G, Vikram NK. BMI does not accurately predict overweight in Asian Indians in northern India. *Br J Nutr.* 2001;86:105-112.
- Kissebah AH, Krakower GR. Regional adiposity and morbidity. *Physiol Rev.* 1994;74:761-811.
- Haque M, Sanyal AJ. The metabolic abnormalities associated with non-alcoholic fatty liver disease. *Best Pract Res Clin Gastroenterol.* 2002;16:709-731.
- Day CP, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology.* 1998;114:842-845.
- Reid AE. Nonalcoholic steatohepatitis. *Gastroenterology.* 2001;121:710-723.