LIVER

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Association of Nonalcoholic Fatty Liver Disease With Components of Metabolic Syndrome According to Body Mass Index in Korean Adults

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OBJECTIVES: **Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, and its prevalence is much higher in obese individuals. NAFLD is closely related to metabolic syndrome (MetS); however, most concepts about the relationship between NAFLD and MetS have emphasized obesity, although NAFLD is not a rare disease in the non-obese population. In the present study, we aim to determine the association between NAFLD and MetS and to compare this association between non-obese and obese individuals.**

METHODS: **A total of 29,994 adults who underwent routine comprehensive health evaluations, including abdominal ultrasonography, were selected. We calculated the adjusted prevalence ratios (PRs) for components of MetS (high blood pressure (BP), impaired fasting glucose, low high-density lipoprotein cholesterol (HDL-C), and high triglycerides (TG)) according to NAFLD in non-obese and obese patients.**

RESULTS: **NAFLD was found in 12.6% of non-obese subjects and 50.1% of obese subjects. NAFLD was associated with most components of MetS in both obese and non-obese subjects. However, non-obese NAFLD patients had significantly higher PRs for certain components of MetS than did obese patients, especially among women. Adjusted PRs (95% confidence interval) for components of MetS in non-obese women vs. obese women were as follows: (1) high BP: 1.41 (1.31–1.51) vs. 1.05 (0.89–1.22) (2) impaired fasting glucose: 2.04 (1.95–2.75) vs. 1.37 (1.21–1.53) (3) low HDL-C: 2.00 (1.92–2.08) vs. 1.40 (1.26–1.55), and (4) high TG: 3.36 (3.24–3.47) vs. 1.97 (1.76–2.17).**

CONCLUSIONS: **NAFLD was associated with risk for components of MetS, and the association was stronger in non-obese than in obese individuals, especially in women. Therefore, NAFLD should be considered a meaningful predictor of metabolic diseases in the non-obese population.**

Am J Gastroenterol 2012; 107:1852–1858; doi:10.1038/ajg.2012.314; published online 2 October 2012

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is characterized by fat deposits in the liver and resembles alcohol-induced liver injury; however, it occurs in patients without possible causes of liver disease (e.g., alcohol consumption, viral hepatitis, inherited liver disease, and medication use) (1). NAFLD encompasses a broad spectrum of conditions, ranging from fat accumulation in hepatocytes without inflammation or fibrosis (i.e., simple hepatic steatosis) to nonalcoholic steatohepatitis with inflammatory activity with or without fibrosis, which may progress to cirrhosis (2).

NAFLD is the most common cause of chronic liver disease in western countries (3), with a prevalence of 15–39%, although the incidence of NAFLD is increasing in both western and eastern countries (4–6). In Korea, NAFLD is present in 10–25% of the general population (7,8), and its prevalence is rising steadily due to the westernization of the diet, aging of society, reduced physical activity, etc (9).

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Received 4 March 2012; accepted 28 May 2012

Prevalence of NAFLD increases with increase in body mass index (BMI) (10). Previous studies have reported that the prevalence of NAFLD increased to ~60–70% in obese patients (3). However, liver histology analyses showed that ~15% of non-obese patients also have NAFLD and that 3% have steatohepatitis (11).

NAFLD is closely associated with central adiposity, type 2 diabetes mellitus, dyslipidemia, and insulin resistance, all of which are components of metabolic syndrome (MetS). Previously, most concepts about the relationship between NAFLD and MetS emphasized obesity, although NAFLD is not a rare disease in the non-obese population. Several studies have evaluated the clinical significance of NAFLD in non-obese patients. Kim *et al.* (12) have shown that NAFLD in the non-obese, non-diabetic population is closely associated with metabolic disorders. Sinn *et al.* (13) and Musso *et al.* (14) reported that NAFLD is an independent predictor of insulin resistance in non-obese adult Asians and Caucasians, respectively. However, few studies have compared metabolic abnormalities associated with NAFLD between non-obese and obese patients.

The aim of the present study was to evaluate the association between NAFLD and components of MetS in non-obese and obese patients.

METHODS

Study population

The study was performed retrospectively. We selected 29,994 patients aged ≥18 years from 59,771 subjects who presented for a routine health evaluation (including abdominal ultrasonography) at the Healthcare system, Gangnam Center of Seoul National University Hospital, Korea, between October 2003 and December 2010.

All subjects answered a questionnaire about their medical history, which included queries regarding liver disease, alcohol consumption, and smoking. Furthermore, all subjects were interviewed by a physician to verify answers and to gain more information about possible causes of liver disease.

In this study, we defined NAFLD as observation of fat accumulated in the liver upon abdominal ultrasonography. Subjects without possible causes of liver disease, such as hepatitis virus, excessive alcohol consumption, and autoimmune or genetic liver disease (1), were included in the study.

We excluded individuals from this study based on: (i) the presence of hepatitis B virus antigen or hepatitis C virus antibody ($n=3,411$); (ii) indication of chronic liver disease history on the questionnaire or chronic liver disease/liver cirrhosis signs upon abdominal ultrasonography ($n=131$); (iii) alcohol consumption of ≥40 g/week ($n=18,884$); and (iv) use of medications associated with fatty liver changes (109 subjects receiving steroid therapy and 1,051 subjects receiving hormone replacement therapy) ($n=1,160$). We also excluded individuals with elevated alpha-fetoprotein levels or no data on alpha-fetoprotein levels ($n=194$).

Of the remaining 35,803 individuals, 5,809 (16%) subjects who were taking medications for diabetes, hypertension, and hyperlipidemia were excluded. Finally, 29,994 individuals were included in the analysis.

This study was approved by the institutional review board at Seoul National University Hospital. Informed consent was exempted by the institutional review board because researchers only accessed the database for analysis, and personal information was not accessed.

Anthropometric and laboratory measures

Anthropometric measures, including blood pressure (BP), height, body weight, and waist circumference, were obtained with subjects wearing light hospital gowns. BP was measured twice on the same day in a sitting position using an automated device, and the mean value was used in the current study. Height and weight were measured after an overnight fast, and BMI was calculated as weight (kg)/height (m^2). Waist circumference was measured using a tape measure at the mid-point between the lower margin of the last palpable rib and the top of the iliac crest by a trained examiner and recorded to the nearest 0.1 cm. The percentage of whole body fat was measured with bioelectrical impedance.

Laboratory evaluation included assessment of fasting blood glucose (FBG), fasting insulin, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), measurements associated with liver function (aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase (γ-GT)), and hepatitis viral antigen/antibody. All of these measurements were obtained after an overnight fast of at least 12 h.

Hepatic ultrasonography

Ultrasonographic measurements were obtained using a Hepatic US (Acuson, Sequoia 512, Siemens, Mountain View, CA) by experienced radiologists who were blinded to the clinical presentation and laboratory findings of the subjects. Generally, fatty liver disease (hepatic steatosis) is defined as a diffuse increase in fine echoes in the liver parenchyma, as compared with the parenchyma of the kidney or spleen (15).

Components of MetS

According to the guidelines published by the International Diabetes Foundation in 2005, components of MetS are defined as follows (16): (i) abdominal obesity (waist circumference of ≥90 cm in men and ≥80 cm in Asian women); (ii) high BP (systolic, ≥130 mmHg; diastolic, ≥85 mm Hg); (iii) low HDL-C level (<40 mg/dl in men and <50 mg/dl in women); (iv) high TG level (≥150 mg/dl); and (v) high FBG level (≥100 mg/dl). Of these components, we evaluated the relationships between high BP, low HDL-C, high TG, and high FBG with NAFLD in obese and non-obese subjects.

In addition, we used the homeostasis model assessment of insulin resistance (HOMA-IR) to define insulin resistance. We calculated HOMA-IR by the following formula:

HOMA-IR = fasting serum glucose (mg/dl)×fasting insulin (μU/ml)/405 (17).

According to previous studies in the East and Asia, the thresholds for HOMA-IR were variable, ranging from 1.8 to 2.3 (18,19). In our study, we defined insulin resistance as HOMA-IR values of >2 (20).

Table 1. Basic characteristics of the study population (*N*=29,994)

	Normal/over-weight group (BMI<25)		Obese group (BMI≥25)	
	Without NAFLD (*N*=20,994)	With NAFLD (*N*=3,014)	Without NAFLD (*N*=3,011)	With NAFLD (*N*=3,025)
Sex (men)[a,b]	5,103 (24.4)	1,590 (52.8)	1,597 (53.0)	2,037 (67.3)
Age[a]	44.0 (11.2)	49.4 (10.4)	47.7 (11.7)	47.7 (11.1)
Anthropometric index				
BMI[a,b]	21.3 (2.0)	23.1 (1.3)	26.7 (1.6)	27.4 (2.1)
Waist[a,b]	78.4 (6.3)	84.5 (4.8)	91.2 (5.7)	93.4 (6.2)
Body fat percentage[a]	25.1 (5.3)	26.0 (5.4)	29.6 (6.1)	29.4 (6.0)
Current smoker[a,b]	1,964 (9.4)	516 (17.1)	505 (16.8)	723 (23.9)
Regular exercise[a,b]	10,496 (50.1)	1,578 (52.4)	1,603 (53.2)	1,389 (45.9)
Measures of liver function				
AST[a,b]	20.7 (8.9)	24.0 (8.9)	23.6 (11.0)	27.8 (14.5)
ALT[a,b]	18.3 (15.0)	28.3 (16.9)	26.4 (18.2)	38.2 (28.2)
γ-GT[a,b]	19.8 (20.9)	31.7 (31.7)	31.4 (32.0)	41.1 (35.2)
Components of MetS				
High blood pressure[a,b]	2,940 (14.0)	831 (27.6)	966 (32.1)	1,165 (38.5)
Impaired fasting glucose[a,b]	3,234 (15.4)	1,079 (35.8)	973 (32.3)	1,270 (42.0)
Low HDL cholesterol[a,b]	3,460 (16.5)	968 (32.1)	834 (27.7)	1,114 (36.8)
High triglycerides[a,b]	1,346 (6.4)	866 (28.7)	656 (21.8)	1,203 (39.8)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; γ-GT, γ-glutamyl transpeptidase; HDL, high-density lipoprotein; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease.

Data are presented as mean (s.d.) or number (%).

[a]Component with a *P* value of <0.05 in the normal/overweight group.

[b]Component with a *P* value of <0.05 in the obese group.

Statistical analysis

The basic characteristics of the study population are presented as mean±s.d. for continuous variables and as numbers with percentages for categorical variables. Statistical differences between groups were analyzed by the *t*-test or χ^2-test, respectively.

The study population was categorized into the normal or overweight group (BMI<25) or obese group (BMI≥25), as recommended by the World health organization Asia-Pacific guidelines (21). We showed adjusted means (95% confidence intervals) of the components of MetS according to study groups (four groups divided by obesity and NAFLD), and verified the differences between groups by analysis of covariance.

Furthermore, a logistic regression model was used to calculate crude and adjusted prevalence for each component of MetS among subjects with and without NAFLD. We presented these data as prevalence ratios (PRs) between the two groups using the following convention: (PR=probability in subjects with NAFLD/probability in subjects without NAFLD). We compared PRs between the obese group and non-obese group and also identified the interaction *P*-value for NAFLD and obesity to determine whether the relationships differ based on the presence of obesity.

Adjusted covariates are recorded below each table. Statistical analysis was performed using STATA version 10.0 (Stata Corporation, College Station, TX) software. Differences were considered statistically significant if *P*-values were <0.05.

RESULTS

Basic characteristics

Of 29,994 individuals, 6,039 (20. 1%) had NAFLD. NAFLD was present in 3,014 (12.6%) participants in the non-obese group and in 3,025 (50.1%) participants in the obese group.

The clinical characteristics of the study population, classified according to NAFLD status and BMI, are shown in **Table 1**. The mean age was 45.3 years. Normal or overweight subjects without NAFLD were younger than subjects with NAFLD in this group. There was no difference in the ages of obese subjects with or without NAFLD. Mean BMI and waist circumference values were higher in the NAFLD group than in the non-NAFLD group, irrespective of whether subjects were obese. Body fat percentages were higher in non-obese subjects with NAFLD than in those without NAFLD, but did not differ between obese subjects with and without NAFLD.

Table 2. Adjusted means of MetS components between groups with NAFLD and without NAFLD, stratified by sex and obesity

	Normal/over-weight group (BMI<25)		Obese group (BMI≥25)	
Men	**Without NAFLD (*N*=5,103)**	**With NAFLD (*N*=1,590)**	**Without NAFLD (*N*=1,597)**	**With NAFLD (*N*=2,037)**
SBP[a]	115.8 (115.4–116.2)	117.2 (116.5–117.9)	120.7 (120.0–121.3)	121.7 (121.1–122.3)
DBP[a,b]	75.9 (75.6–76.2)	77.3 (76.7–77.8)	79.2 (78.7–79.7)	80.2 (79.7–80.7)
FBG[a,b]	95.1 (94.6–95.5)	98.2 (97.4–99.0)	97.9 (97.2–98.7)	100.8 (100.1–101.5)
Triglycerides[a,b]	103.1 (101.3–104.8)	133.6 (130.4–136.7)	134.6 (130.0–139.3)	164.3 (160.2–168.4)
HDL cholesterol[a,b]	51.7 (51.4–52.0)	48.7 (48.1–49.2)	47.3 (46.9–47.8)	44.6 (44.2–45.0)
Basal insulin[a,b] (*N*=2,248)	7.59 (7.37–7.80)	8.93 (8.54–9.33)	9.71 (9.21–10.22)	11.74 (11.32–12.15)
HOMA-IR[a,b] (*N*=2,248)	1.78 (1.73–1.84)	2.12 (2.02–2.22)	2.36 (2.22–2.49)	2.90 (2.79–3.02)
Women	**Without NAFLD (*N*=15,841)**	**With NAFLD (*N*=1,424)**	**Without NAFLD (*N*=1,414)**	**With NAFLD (*N*=988)**
SBP[a]	108.8 (108.6–109.0)	112.1 (111.4–112.8)	119.5 (118.7–120.4)	120.5 (119.5–121.5)
DBP[a]	68.7 (68.5–68.9)	70.8 (70.2–71.3)	74.6 (74.0–75.2)	74.8 (74.1–75.6)
FBG[a,b]	90.0 (89.9–90.2)	95.0 (94.4–95.5)	95.8 (95.0–96.6)	99.0 (98.1–100.0)
Triglycerides[a,b]	78.5 (77.9–79.2)	111.4 (109.2–113.6)	106.7 (102.8–110.6)	124.7 (120.1–129.2)
HDL cholesterol[a,b]	61.3 (61.1–61.5)	55.0 (54.3–55.7)	54.8 (54.2–55.4)	51.9 (51.1–52.6)
Basal insulin[a,b] (*N*=4,901)	7.45 (7.28–7.61)	9.93 (9.39–10.47)	9.05 (8.54–9.57)	11.13 (10.56–11.70)
HOMA-IR[a,b] (*N*=4,901)	1.64 (1.60–1.68)	2.34 (2.21–2.47)	2.12 (1.98–2.27)	2.74 (2.58–2.90)

BMI, body mass index; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease; SBP, systolic blood pressure.

Data are presented as mean (s.d.).

Data adjusted for age, waist circumference, exercise, and smoking status (plus menopausal status for women).

[a]Component with a *P* value of <0.05 in the normal/overweight group.

[b]Component with a *P* value of <0.05 in the obese group.

The percentage of current smokers was higher among subjects with NAFLD in both the non-obese and obese groups. The percentage of subjects who regularly exercised was higher among obese subjects without NAFLD than among those with NAFLD. In the non-obese population, regular exercisers constituted a larger fraction of subjects with NAFLD than of subjects without NAFLD.

The laboratory values for aspartate aminotransferase, alanine aminotransferase, and γ-GT and prevalence of MetS components (high BP, high FBG, low HDL-C, and high TG) were significantly higher in the NAFLD group among both obese and non-obese subjects.

Associations between metabolic disorders and NAFLD

The adjusted means of the components of MetS in individuals with NAFLD, stratified by BMI and gender, are shown in **Table 2**.

In both the non-obese and obese groups, compared with men without NAFLD, men with NAFLD had higher diastolic BP, FBG, TG, basal insulin, and HOMA-IR and lower HDL-C. Systolic BP was higher among subjects with NAFLD than among those without NAFLD only in the non-obese group. For non-obese women, systolic and diastolic BPs were higher in subjects with NAFLD than in those without NAFLD, but there were no significant differences in the obese group; the other results were the same as those for men.

In **Table 3**, crude and adjusted PRs for each of the MetS components are shown. Results are stratified by BMI and gender. Most PRs and 95% confidence intervals are higher than "1", which implies that NAFLD is associated with higher risk of MetS components, regardless of sex and obesity status. An exception is observed in the PR for high BP in obese women. For women, PRs of high BP, high FBG, low HDL-C, and high TG were significantly higher in the non-obese group than in the obese group: (i) high BP: 1.41 (1.31–1.51) vs. 1.05 (0.89–1.22), (ii) high FBG: 2.04 (1.95–2.75) vs. 1.37 (1.21–1.53), (iii) low HDL-C: 2.00 (1.92–2.08) vs. 1.40 (1.26–1.55), (iv) high TG: 3.36 (3.24–3.47) vs. 1.97 (1.76–2.17), and (v) insulin resistance: 1.96 (1.82–2.11) vs. 1.66 (1.38–1.95). For men, the PR of high TG was significantly higher in the non-obese group than in the obese group: (i) high BP: 1.10 (1.01–1.19) vs. 1.15 (1.04–1.26), (ii) high FBG: 1.30 (1.21–1.39) vs. 1.19 (1.07–1.30), (iii) low HDL-cholesterol: 1.53 (1.43–1.64) vs. 1.35 (1.22–1.48), (iv) high TG: 2.16 (2.07–2.26) vs. 1.51 (1.39–1.63), and (v) insulin resistance: 1.58 (1.39–1.77) vs. 1.57 (1.34–1.80).

Table 3. Adjusted prevalence ratios of MetS components in the population with NAFLD stratified by obesity (*N*=29,994)

	Normal/over-weight group (BMI < 25)	Obese group (BMI≥25)	Interaction *P* value*
Men	(*N*=6,693)	(*N*=3,634)	
High BP			
Crude	1.26 (1.18–1.35)	1.17 (1.07–1.26)	0.47
Adjusted	1.10 (1.01–1.19)	1.15 (1.04–1.26)	
IFG			
Crude	1.44 (1.36–1.53)	1.19 (1.09–1.39)	0.19
Adjusted	1.30 (1.21–1.39)	1.19 (1.07–1.30)	
Low HDL cholesterol			
Crude	1.84 (1.74–1.94)	1.45 (1.34–1.55)	0.19
Adjusted	1.53 (1.43–1.64)	1.35 (1.22–1.48)	
High triglycerides			
Crude	2.66 (2.57–2.75)	1.55 (1.46–1.65)	<0.01
Adjusted	2.16 (2.07–2.26)	1.51 (1.39–1.63)	
Insulin resistance (*N*=2,248)			
Crude	1.94 (1.77–2.12)	1.50 (1.29–1.70)	0.65
Adjusted	1.58 (1.39–1.77)	1.57 (1.34–1.80)	
	(*N*=17,265)	**(*N*=2,402)**	
Women			
High BP			
Crude	2.22 (2.13–2.30)	1.15 (1.03–1.28)	0.01
Adjusted	1.41 (1.31–1.51)	1.05 (0.89–1.22)	
IFG			
Crude	2.81 (2.73–2.89)	1.44 (1.32–1.56)	<0.01
Adjusted	2.04 (1.95–2.13)	1.37 (1.21–1.53)	
Low HDL cholesterol			
Crude	2.38 (2.31–2.45)	1.40 (1.28–1.52)	<0.01
Adjusted	2.00 (1.92–2.08)	1.40 (1.26–1.55)	
High triglycerides			
Crude	5.16 (5.06–5.26)	2.09 (1.94–2.24)	<0.01
Adjusted	3.36 (3.24–3.47)	1.97 (1.76–2.17)	
Insulin resistance (*N*=4,901)			
Crude	2.19 (2.06–2.33)	1.48 (1.25–1.72)	0.40
Adjusted	1.96 (1.82–2.11)	1.66 (1.38–1.95)	

BMI, body mass index; BP, blood pressure; IFG, impaired fasting glucose; MetS, metabolic syndrome; NAFLD, nonalcoholic fatty liver disease.

Data adjusted for age, waist circumference, regular exercise, and smoking status (plus menopausal status for women).

* *P* value of interaction between NAFLD and BMI.

DISCUSSION

Our data indicated that NAFLD was associated with increased risk of MetS in the total study population, regardless of obesity status. However, the associations were more pronounced in the non-obese group than in the obese group, even though NAFLD is less common in non-obese subjects.

Previous studies have shown that compared with the general population, individuals with NAFLD appear to have higher risks of MetS and death from cardiovascular disease (22–24). However, most of these studies have focused on obese subjects.

Our study is comparable to other studies that have evaluated the clinical significance of NAFLD in a non-obese population. Sinn *et al.* (13) and Musso *et al.* (14) demonstrated that NAFLD is an independent predictor of insulin resistance in non-obese Asian and Caucasian adults, respectively. However, these studies examined only non-obese subjects, and differences in metabolic abnormalities observed between non-obese and obese subjects with NAFLD were not reported. Kim *et al.* (12) showed that NAFLD is closely associated with metabolic disorders in non-obese, non-diabetic Korean adults. In this study, non-obese subjects were defined as those with a BMI lower than a cutoff value of 30. For Asians, a BMI cutoff of 25 is widely accepted as the boundary between normal weight/overweight and obesity (21). Kim *et al.* reported that odds ratios for metabolic disorders in subjects with NAFLD compared with those without NAFLD in the BMI < 25 group were higher than that in the BMI≥25 group. Although this result is similar to the result of our study, the significance of these differences was not verified in the study by Kim *et al.* In addition, patients taking medications for hypertension, diabetes, and hyperlipidemia were included in the relatively small sample size in that study. We excluded these subjects because medication could affect the major variables analyzed in this study. In addition, subjects with chronic diseases might rapidly change their lifestyles; this could also affect the outcomes of the study.

Our study suggests that the association between NAFLD and MetS components may vary, depending on whether a patient is obese. One possible explanation for this result may be fat distribution, that is, the amount of visceral fat. It has been proposed that the visceral component of abdominal fat, which is associated with all components of MetS, is more directly related to NAFLD than is BMI (5,25). Differences in the amount of visceral fat between individuals with NAFLD and those without NAFLD may be greater in the non-obese group than in the obese group. These differences could lead to changes in the risk of MetS. Visceral fat is directly associated with MetS and is a key element in the genesis of hepatic steatosis (25). In addition, several studies on metabolically obese normal-weight subjects have demonstrated that a higher relative fat mass, lower lean body mass, tendency for greater central fat mass (26), and increased visceral fat is associated with MetS (27). In our study population, the waist circumference was markedly higher in subjects with NAFLD than in those without NAFLD, and the differences in waist circumferences were more significant in the non-obese group (78.4 vs. 84.5 cm) than in the obese group (91.2 vs. 93.4 cm). Although we adjusted for waist circumference to minimize the effect of abdominal fat, waist circumference does not exactly match visceral fat. We therefore could not rule out the effect of visceral fat, and further research with visceral fat data is necessary.

Another reason for the differences between non-obese and obese individuals may be lifestyle factors. MetS is closely associated with health-related lifestyles, such as smoking (28), diet pattern (29), and physical activity (30). Therefore, if non-obese subjects with NAFLD have poorer health behaviors than those of subjects without NAFLD, these behaviors probably contribute to the incidence of MetS. The data we used in this study are limited because information regarding lifestyle factors was obtained from a subject-reported questionnaire. However, the proportion of regular exercisers was higher in non-obese subjects with NAFLD than in those without NAFLD. This finding may result from the limitation of the cross-sectional design. Patients who were diagnosed with NAFLD previously may have changed their health behaviors. Nevertheless, this finding suggests that our primary result was only slightly affected by regular exercise and that other health behaviors, such as diet, are more important in non-obese subjects. Our data does not include information about diet pattern, which is a major source of increased liver fat accumulation and an important factor for MetS (29,31). This assertion is supported by a study reporting that among normal-weight adults, those who are metabolically obese have a higher intake of carbohydrates and lower intake of proteins than do those who are metabolically healthy (32).

In our study, differences in PRs for MetS components between non-obese and obese subjects were more significant in women than in men. This suggests that relative to non-obese men, non-obese women with NAFLD are at increased risk for metabolic disease. The reason for this finding is unclear. Previous studies have suggested that sex hormones are important mediators in the pathogenesis of NAFLD and MetS. Postmenopausal women (33) and breast cancer patients treated with tamoxifen (34) are at increased risk of developing NAFLD, and insulin resistance and NAFLD are more frequent in patients with polycystic ovary syndrome (35). Although we adjusted data with menopausal status, sex hormones such as estrogen may act as mediators between NAFLD and MetS in non-obese women. Actually, when stratified by mean age, the significance of difference in the PRs disappeared in some components of MetS (high BP and low HDL-C) in young women (data not shown). Further studies on this topic are required.

The present study has some limitations. The first and most important factor is that the NAFLD was not confirmed by liver biopsy. Ultrasound is known to be an operator-dependent procedure, so a diagnosis of hepatic steatosis may be dependent upon the operator. When fat content in the liver falls below 30%, ultrasound is less accurate for detection of steatosis (15,36). However, we divided our study population on the basis of presence or absence of NAFLD and did not grade by severity of steatosis. Several studies have shown that ultrasound is the least expensive modality for detecting NAFLD, with a high sensitivity of 100% (15,37). Second, this study population was restricted to subjects who underwent a routine medical check-up; therefore, the population is not representative of all the socio-demographic groups in the Korean population. Third, as mentioned above, the information about smoking history, alcohol consumption, and physical activity was based on a self-reported questionnaire and this has an inherent limitation for accuracy. However, we confirmed this information through a doctor's interview for every subject.

Our findings revealed that NAFLD is associated with risk of components of MetS and that the association is stronger in the non-obese population than in the obese population, especially in women. Therefore, NAFLD should be considered a more meaningful predictor of metabolic diseases in the non-obese population. These results can be attributed to the fact that non-obese subjects with NAFLD display several conditions such as increased visceral adiposity and poor health behaviors, including unhealthy diet patterns, which render these subjects susceptible to MetS. Further studies with data on hepatic histological outcomes, visceral fat, and diet pattern are required to confirm these findings.

CONFLICT OF INTEREST

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Specific author contributions: Seung-Won Oh and Young-Min Kwon were responsible for the initial plan, study design, statistical analysis, and conduct of the study. Young-Min Kwon, Seung-Won Oh, CheolMin Lee, and Hyuktae Kwon were responsible for data collection, data extraction, data interpretation, and manuscript drafting. Seung-sik Hwang and Goh Eun Chung were responsible for data interpretation and manuscript revision. All authors prepared and approved the paper for submission.

Financial support: This study was supported by grant no. 04-2010-0710 from the SNUH Research Fund.

Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Obesity has an important role in the development of nonalcoholic fatty liver disease (NAFLD) and prevalence of NAFLD increases with increase in body mass index (BMI); however, NAFLD is not a rare disease in the non-obese population.
- ✓ NAFLD is associated with central adiposity, type 2 diabetes mellitus, dyslipidemia, insulin resistance, and metabolic syndrome (MetS).

WHAT IS NEW HERE

- ✓ NAFLD was found in 12.6% of non-obese (BMI < 25) Asian subjects.
- ✓ NAFLD was associated with higher risk of MetS components, regardless of obesity status.
- ✓ The association between NAFLD and risk for components of MetS was stronger in non-obese than in obese individuals.

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