Nonalcoholic Fatty Liver Disease Is Associated With Atherosclerosis in Middle-Aged and Elderly Chinese

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Objective—To evaluate the associations between nonalcoholic fatty liver disease (NAFLD) and atherosclerosis.

Methods and Results—A total of 8632 participants aged ≥40 years from Jiading district, Shanghai, were included in the present study. The presence of NAFLD was evaluated by ultrasonography. Carotid intima-media thickness (CIMT) and brachial-ankle pulse wave velocity (ba-PWV) were measured in each participant. The prevalence of NAFLD was 30.0% in the total population, with 30.3% in men and 29.9% in women, respectively. Subjects with NAFLD had remarkably higher CIMT and ba-PWV compared with those without NAFLD (0.594±0.105 mm versus 0.578±0.109 mm, $P<0.0001$; 1665±424 cm/s versus 1558±430 cm/s, $P<0.0001$). Subjects with both NAFLD and metabolic syndrome had significantly higher CIMT and ba-PWV compared with those with neither or either of these 2 diseases after adjustment for age and sex (all $P<0.05$). Logistic regressions also revealed that NAFLD conferred 35% and 30% increased odds ratios of elevated CIMT and ba-PWV, independent of conventional risk factors and the presence of metabolic syndrome.

Conclusion—NAFLD was associated with elevated CIMT and ba-PWV, independent of conventional cardiovascular disease risk factors and metabolic syndrome. The effects of NAFLD and metabolic syndrome on atherosclerosis might not fully overlap. **(*Arterioscler Thromb Vasc Biol*. 2012;32:2321-2326.)**

Key Words: atherosclerosis ■ brachial-ankle pulse wave velocity ■ carotid intima-media thickness ■ metabolic syndrome ■ nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic histological abnormalities that range from simple hepatic steatosis to nonalcoholic steatohepatitis to liver fibrosis to cirrhosis.[1] The importance that liver contributes to the metabolism was discovered ≈1.5 centuries ago, but it is only recently that relationships between NAFLD and metabolic diseases gained attention.[2] It is reported that NAFLD affects ≈30% of the general population in Western countries.[3] A recent epidemiological study revealed that in a Chinese population, the prevalence of NAFLD is 23.3%,[4] which indicates that not only in the Western population, but also in the relatively leaner Chinese population, NAFLD is highly epidemic.

NAFLD is assumed to be the hepatic manifestation of the metabolic syndrome,[2] which arouses interest in investigating the association between NAFLD and atherosclerosis. Given the different methods used to diagnose NAFLD and different populations chosen to perform studies, results are inconsistent.[5–13] In some relatively small samples from the community population, ultrasonographically diagnosed NAFLD has been found to be independently associated with carotid atherosclerosis and arterial stiffness.[6,7] Biopsy-proven NAFLD patients had remarkably greater carotid intima-media thickness (CIMT) compared with that of age-, sex-, and body mass index (BMI)–matched healthy subjects in a case-control study.[8] Nevertheless, in another study including 101 patients with type 2 diabetes mellitus, NAFLD diagnosed by 1H-magnetic resonance spectroscopy is not associated with CIMT.[12] Therefore, the present study aimed to extensively investigate the association between ultrasonographically diagnosed NAFLD and atherosclerosis in a large middle-aged and elderly Chinese community population.

Methods

Population

From March 2010 to August 2010, a population-based cross-sectional survey was conducted in Jiading district, Shanghai, China. During the recruiting phase, a total of 10 569 inhabitants aged ≥40 years in these 10 communities were invited by telephone or door-to-door visit to participate in this study. From them, 10 375 residents

Received on: December 26, 2011; final version accepted on: June 21, 2012.

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Arterioscler Thromb Vasc Biol **is available at http://atvb.ahajournals.org** **DOI: 10.1161/ATVBAHA.112.252957**

signed the consent form and agreed to take part in the present study, with a participation rate of 98.2%. The protocol was approved by the Institutional Review Board of Ruijin Hospital affiliated with Shanghai Jiao-Tong University School of Medicine.

Clinical and Biochemical Measurements

Trained physicians collected detailed information about demography, medical history, and lifestyle, including smoking and drinking status and physical activities using standard questionnaires. Anthropometric measurements included body weight, body height, and waist circumference (WC). Body weight and height were measured in light clothes and bare feet to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated using the formula of weight/height^2 (kg/m^2). WC was measured at the level of the umbilicus in the late exhalation phase while the patient was standing. Blood pressure (BP) was measured on the nondominant arm in a seated position after a 10-minute rest, using an electronic BP monitor (OMRON Model HEM-752 FUZZY; Omron Company, Dalian, China). Three measurements were taken at 1-minute intervals, and the average was used for analysis.

Two-point (0 and 2 hours) oral glucose tolerance test with a 75-g glucose load was performed. Blood glucose was measured using the glucose oxidase method on an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Fasting serum insulin, triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, serum alanine aminotransferase, and γ-glutamyl transpeptidase were measured using chemiluminescence methods on the autoanalyzer (Modular E170; Roche). Serum insulin levels were measured using immunoradiometric assay (RIABEAD II; Abbott, Tokyo, Japan). The index of homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: HOMA-IR=fasting insulin concentrations (mIU/L)×fasting glucose concentrations (mmol/L)/22.5.

One trained sonographer performed CIMT measurements using a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Genoa, Italy), with a linear 7.5-MHz transducer. The operator measured CIMT on the far wall of the right and left common carotid arteries, 1.5 cm proximal to the bifurcation. The transducer was manipulated so that the lumen diameter was maximized in the longitudinal plane. CIMT was measured on-line at the end of diastole as the distance from the leading edge of the first echogenic line to that of the second echogenic line. The first and second lines represent the lumen–intimal interface and the collagen-contained upper layer of tunic adventitia, respectively. The greater value of the right and left common CIMT was used for analysis.

Brachial-ankle pulse wave velocity (ba-PWV) indicates brachial to ankle PWV. It was determined by Colin VP-1000 (Model BP203RPE II, form PWV/ABI) after participants had rested for 10 to 15 minutes. To determine the ba-PWV, pulse waves were measured simultaneously with cuffs placed on the right upper arm and the right ankle. The difference in the times of the start of the pulse waves was corrected for distance to obtain the ba-PWV. The greater value of the right and left ba-PWV was used for analysis.

Hepatic ultrasonographic examination was performed by 2 experienced ultrasonographists using high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA) with a 3.5-MHz probe.

After excluding subjects abusing alcohol (alcohol consumption ≥140 g/week in men and ≥70 g/week in women, n=980), or with viral or autoimmune hepatitis or hepatitis caused by drugs (n=424), or with missing data regarding hepatic ultrasonography (n=51) or components of metabolic syndrome (n=21) or CIMT (n=44) or ba-PWV (n=223), 8632 participants were included in the final analysis (Figure 1). Among 8632 subjects, 716 subjects had self-reported history of cardiovascular diseases (CVDs).

Definition

Metabolic syndrome was defined according to the US National Cholesterol Education Program Adult Treatment Panel III guidelines,[14] with modification as recommended in the latest American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement by adopting the Asian criteria for WC.[15] Metabolic syndrome was defined as having ≥3 of the following metabolic risk factors: (1) central obesity (WC ≥80 cm in women and ≥90 cm in men); (2) high TG (fasting serum TG ≥1.69 mmol/L); (3) low HDL-C (fasting serum HDL-C <1.29 mmol/L in women and <1.04 mmol/L in men); (4) high fasting blood glucose (fasting blood glucose ≥5.6 mmol/L or already taking antidiabetic treatment); and (5) high BP (BP ≥130/85 mm Hg or taking regular antihypertensive medications). Participants who engaged in light physical activity for 4 hours per week or more vigorous activity for >2 hours per week, or regular heavy exercise, or competitive sports several times per week were categorized as exercisers.[16] Prior CVD referred to a history of coronary heart disease or stroke.

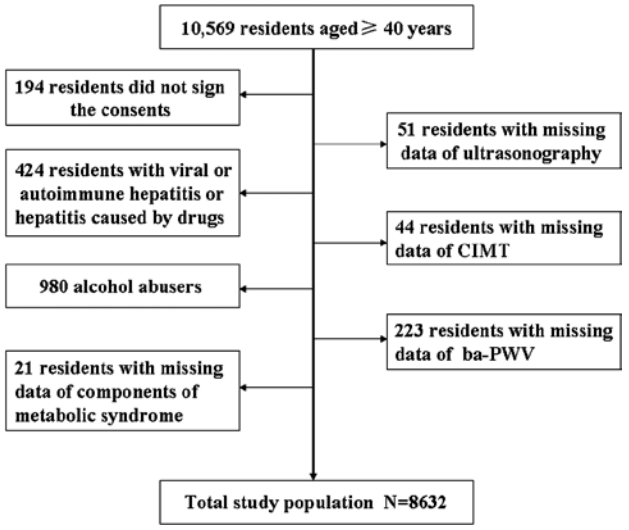

Figure 1. Flow chart of the recruitment and selection procedure of the study population.

Diagnosis of fatty liver by ultrasonography is based on the presence of at least 2 of 3 abnormal findings: diffusely increased echogenicity of the liver relative to the kidney, ultrasound beam attenuation, and poor visualization of intrahepatic structures.[17]

Subjects in the highest 5% of CIMT (≥0.8 mm) were classified as having elevated CIMT. Upper quartile of ba-PWV (≥1799 cm/s) was regarded as arterial stiffness.

Statistical Analysis

Statistical analysis was performed using SAS 9.1 (SAS Institute, Cary, NC). Variables were presented as mean±SD, median (interquartile ranges), or n (%). Fasting serum TG, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, and HOMA-IR were transformed logarithmically because of non-normal distributions. Means of continuous variables were compared using *t* test or 1-way ANOVA. The percentage difference between groups was compared using χ^2 tests. Treating CIMT and ba-PWV as dichotomous variables (using the upper 5% of CIMT and the upper 25% of ba-PWV as cut-off values), we used logistic regression to examine associations between clinical variables and CIMT or ba-PWV. Logistic regressions were also used to evaluate the association between NAFLD and elevated CIMT or arterial stiffness in 4 models. In model 1, covariates including age, sex, BMI, low-density lipoprotein, HOMA-IR score, regular exerciser, and smoking and drinking status were adjusted. In model 2, individual components of metabolic syndrome including central obesity, high TG, low HDL, high BP, and high fasting blood glucose were further adjusted based on model 1. In model 3, the presence of metabolic syndrome was further adjusted based on model 1. In model 4, prior CVD history was further adjusted based on model 3. The 2-tailed test was used, and $P<0.05$ was regarded as statistically significant.

Results

General Characteristics of the Population

NAFLD was found in 30.0% of the total population in our study, with the prevalence of 30.3% in men and 29.9% in women, respectively. Table 1 shows the general characteristics of the study population. Compared with subjects without NAFLD, those with NAFLD had significantly higher BMI, WC, blood glucose, HOMA-IR, BP, liver enzymes, and more atherogenic lipid profiles (all $P<0.0001$). In addition, remarkably higher ba-PWV and CIMT were found in subjects with NAFLD in comparison with those without NAFLD (all $P<0.0001$). Notably, compared with the participants without NAFLD, the proportion of those with prior CVD was higher in participants with NAFLD ($P=0.0002$). However, proportions of men, current smokers, and current drinkers did not differ significantly between the 2 groups (all $P>0.05$).

Associations Among CIMT, ba-PWV, and NAFLD

Treating CIMT and ba-PWV as dichotomous variables, multivariable regression analysis revealed that age, sex, low-density lipoprotein cholesterol, high fasting blood glucose, high BP, and the presence of NAFLD was independently related to both elevated CIMT and ba-PWV (Table 2). In addition, low HDL-C and current smokers were associated with elevated CIMT, whereas current drinkers, BMI, HOMA-IR, and high TG were associated with increased ba-PWV. The presence of NAFLD conferred 32% and 26% increased odds ratios of having elevated CIMT and ba-PWV, respectively.

We further analyzed CIMT and ba-PWV levels in subjects with either, neither, or both NAFLD and metabolic syndrome. After adjustments for age and sex, subjects with either or both of these 2 diseases had significantly higher CIMT compared with those without these 2 diseases (0.586±0.0033, 0.590±0.0024, 0.597±0.0021 versus 0.574±0.0014 mm, $P=0.0005$, <0.0001, and <0.0001, respectively; Figure 2A). No difference was detected between groups with either NAFLD or metabolic syndrome ($P=0.46$). However, significantly higher CIMT was found in the group with both NAFLD and metabolic syndrome in comparison with those with either NAFLD or metabolic syndrome ($P=0.0080$ and 0.021, respectively). Similar results were found regarding the association between ba-PWV levels and these 4 groups. Nevertheless, a much higher level of ba-PWV was also found in the group with only metabolic syndrome compared with the one with only NAFLD ($P=0.0001$, Figure 2B).

We further analyzed the associations between NAFLD and elevated CIMT or arterial stiffness in 4 different logistic regression models. After adjusting for the components of metabolic syndrome in addition to conventional cardiovascular risk factors, the associations between NAFLD and elevated CIMT or arterial stiffness remained significant, although the magnitude decreased (Table 3). No fundamental changes regarding these associations were found after adjusting for the presence of metabolic syndrome instead of components of metabolic syndrome (odds ratio, 1.35; 95% CI, 1.06–1.71; odds ratio, 1.30; 95% CI, 1.11–1.51). Further adjustments for prior CVD history barely affected the associations between NAFLD and elevated CIMT or arterial stiffness.

Table 1. General Characteristics of Subjects With and Without NAFLD

	Without NAFLD (n=6042)	With NAFLD (n=2590)	*P* Value
Age, y	58.5±10.0	58.5±8.8	0.92
Male, n (%)	1866 (30.9)	812 (31.4)	0.67
Current drinker, n (%)	128 (2.2)	71 (2.8)	0.083
Current smoker, n (%)	920 (15.9)	388 (15.5)	0.71
Regular exerciser, n (%)	3600 (59.9)	1603 (62.3)	0.043
BMI, kg/m^2	24.1±2.8	27.5±3.0	<0.0001
WC, cm	79.4±7.8	88.9±7.8	<0.0001
FBG, mmol/L	5.32±1.23	6.02±1.86	<0.0001
2h-BG, mmol/L	7.46±3.61	10.14±4.97	<0.0001
HOMA-IR	1.38 (0.95–1.96)	2.62 (1.85–3.88)	<0.0001
SBP, mm Hg	138±20	146±20	<0.0001
DBP, mm Hg	81±10	85±10	<0.0001
TG, mmol/L	1.22 (0.89–1.67)	1.85 (1.37–2.56)	<0.0001
TC, mmol/L	5.29±0.98	5.50±1.07	<0.0001
HDL-C, mmol/L	1.38±0.32	1.20±0.27	<0.0001
LDL-C, mmol/L	3.16±0.84	3.31±0.90	<0.0001
Uric acid, mmol/L	278±85	327±91	<0.0001
AST, IU/L	21 (18–25)	22 (19–27)	<0.0001
ALT, IU/L	16 (13–21)	23 (17–33)	<0.0001
GGT, IU/L	18 (13–26)	28 (20–42)	<0.0001
ba-PWV, cm/s	1558±430	1665±424	<0.0001
CIMT, mm	0.578±0.109	0.594±0.105	<0.0001
Central obesity, n (%)	2049 (33.9)	2036 (78.6)	<0.0001
IGR, n (%)	1564 (25.9)	923 (35.6)	<0.0001
Diabetes mellitus, n (%)	715 (11.8)	845 (32.6)	<0.0001
Hypertension, n (%)	3201 (53.0)	1918 (74.1)	<0.0001
High triglycerides, n (%)	1450 (24.0)	1499 (57.9)	<0.0001
Low HDL-C, n (%)	1810 (30.0)	1398 (54.0)	<0.0001
Metabolic syndrome, n (%)	1478 (24.5)	1824 (70.4)	<0.0001
Carotid plaque, n (%)	865 (14.3)	357 (13.8)	0.52
Prior CVD, n (%)	458 (7.6)	258 (10.0)	0.0002

Data are means±SD or median (interquartile ranges) or number (percentage) of subjects. Data were missing for current smoker (n=327), current drinker (n=304), regular exerciser (n=49), or carotid plaque (n=75). BMI indicates body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; 2h-BG, 2-hour blood glucose; HOMA-IR, the index of homeostasis model assessment of insulin resistance; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl transferase; ba-PWV, brachial ankle pulse wave velocity; CIMT, carotid intima-media thickness; CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; IGR, impaired glucose regulation. *P* values for comparisons between groups are based on ANOVA or χ^2 test.

Discussion

In the present study, CIMT and ba-PWV were significantly higher in NAFLD patients compared with those without NAFLD. NAFLD conferred 35% and 30% increased odds ratios of having elevated CIMT and ba-PWV, independent of conventional cardiovascular risk factors including components of metabolic syndrome.

Table 2. Association Among Elevated CIMT, Arterial Stiffness, and Clinical or Biochemical Variables

	Elevated CIMT			Arterial Stiffness		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age, y	1.13	1.11–1.14	<0.0001	1.13	1.13–1.14	<0.0001
Sex (male=1; female=2)	0.32	0.25–0.41	<0.0001	1.30	1.08–1.55	0.0046
Current drinker	1.30	0.80–2.12	0.29	0.60	0.38–0.94	0.024
Current smoker	1.56	1.18–2.05	0.016	0.97	0.77–1.22	0.80
Regular exerciser	0.99	0.81–1.21	0.91	1.09	0.95–1.24	0.22
BMI, kg/m^2	1.02	0.98–1.06	0.31	0.96	0.93–0.98	0.0011
LDL-C, mmol/L	1.48	1.32–1.66	<0.0001	1.08	1.00–1.17	0.042
Central obesity	0.97	0.74–1.28	0.84	1.07	0.90–1.27	0.46
High FBG	1.45	1.16–1.80	0.0009	1.91	1.63–2.24	<0.0001
High TG	1.04	0.83–1.30	0.73	1.39	1.20–1.60	<0.0001
High BP	1.61	1.15–2.24	0.0050	6.65	5.21–8.50	<0.0001
Low HDL-C	1.31	1.04–1.65	0.023	0.94	0.81–1.09	0.41
HOMA-IR	1.01	1.00–1.02	0.10	1.07	1.03–1.11	0.0007
NAFLD	1.32	1.03–1.68	0.029	1.26	1.08–1.48	0.0041

BMI indicates body mass index; FBG, fasting blood glucose; HOMA-IR, the index of homeostasis model assessment of insulin resistance; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; CIMT, carotid intima-media thickness; OR, odds ratio.

Previous studies have documented that NAFLD patients have a variety of cardiovascular risk factors, including obesity, hyperglycemia, and dyslipidemia.[18–21] In 173 patients with biopsy-proven NAFLD who were followed for 13 years, CVD was the most frequent cause of death.[21] In a population-based study including 4160 German individuals, increased risk of death from any cause and death from CVDs were observed in men with NAFLD after adjustments for a variety of confounders.[22] Compared with consistent results regarding the associations between CVD and NAFLD, those between subclinical atherosclerosis and NAFLD are inconsistent. McKimmie et al[13] demonstrated that fatty liver evaluated by computed tomography was not associated with CIMT in a population with high prevalence of type 2 diabetes mellitus. Similarly, in another study including 101 patients with type 2 diabetes mellitus, fatty liver diagnosed by 1H-magnetic resonance spectroscopy is not associated with CIMT.[12] Comparatively, in a case-control study, patients with biopsy-proven NAFLD had remarkably greater CIMT than control subjects; furthermore, the severity of liver histopathology of NAFLD patients is strongly associated with CIMT.[8] A meta-analysis including 3497 subjects confirmed that NAFLD diagnosed on ultrasonography is strongly associated with increased CIMT.[23] The main reason that accounts for inconsistency might be the difference in methodology of defining NAFLD. Although liver biopsy is considered the gold standard for diagnosis of NAFLD and quantification of liver fat, the invasive nature of the technique confines its clinical use. In comparison, imaging examinations including magnetic resonance spectroscopy, magnetic resonance image, computed tomography, or ultrasound are noninvasive and safer, but their sensitivity is limited.[24] Among these methods, liver ultrasonography is the easiest to perform;

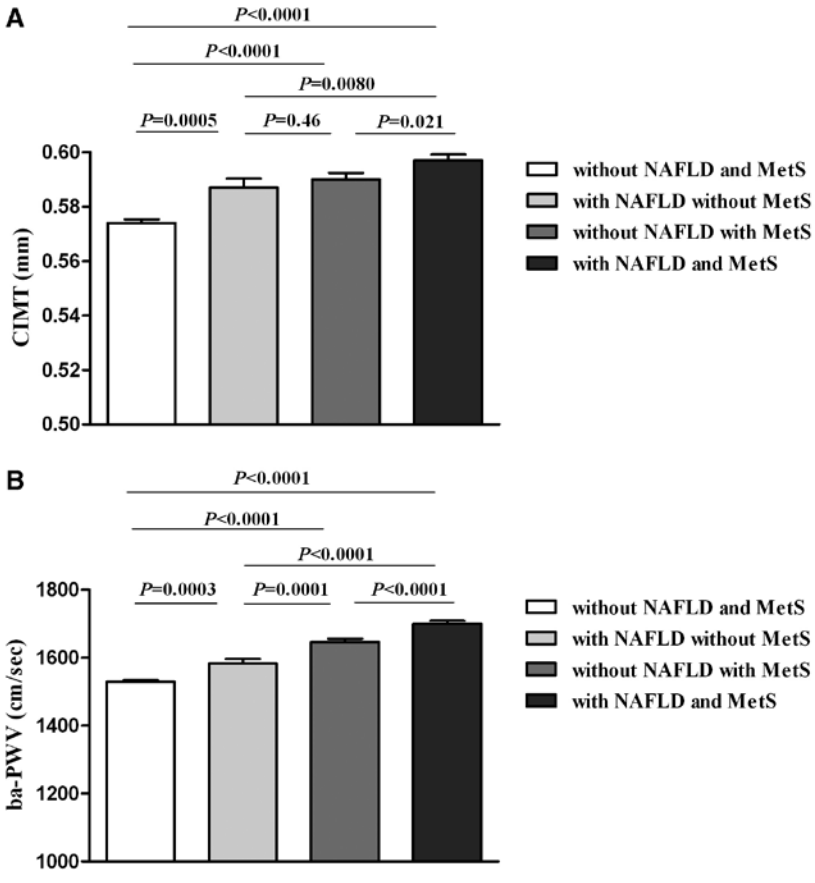

Figure 2. Carotid intima-media thickness (CIMT) and brachial-ankle pulse wave velocity (ba-PWV) in subjects with neither nonalcoholic fatty liver disease (NAFLD) nor metabolic syndrome (Mets), either NAFLD or Mets, and both NAFLD and Mets after adjustments for age and sex. **A**, CIMT levels in subject according to the presence of NAFLD or Mets. **B**, ba-PWV levels in subjects according to the presence of NAFLD or Mets. Number of subjects in each group are as follows: without NAFLD and Mets, n=4564; with NAFLD without Mets, n=766; with Mets without NAFLD, n=1478; with NAFLD and Mets, n=1824.

Table 3. Association Between NAFLD and Elevated CIMT or Arterial Stiffness in Different Logistic Regression Models

Elevated CIMT			Arterial Stiffness		
OR	95% CI	*P* Value	OR	95% CI	*P* Value
Model 1: adjusted for age, sex, BMI, LDL-C, HOMA-IR score, regular exerciser, and smoking and drinking status					
1.48	1.17–1.86	0.0010	1.50	1.29–1.75	<0.0001
Model 2: further adjusted for individual components of metabolic syndrome based on model 1					
1.32	1.03–1.68	0.029	1.26	1.08–1.48	0.0041
Model 3: further adjusted for the presence of metabolic syndrome based on model 1					
1.35	1.06–1.71	0.015	1.30	1.11–1.51	0.0011
Model 4: further adjusted for prior histories of cardiovascular diseases based on mode 3					
1.35	1.06–1.72	0.015	1.30	1.11–1.51	0.0011

BMI indicates body mass index; FBG, fasting blood glucose; HOMA-IR, the index of homeostasis model assessment of insulin resistance; LDL-C, low density lipoprotein cholesterol; NAFLD, nonalcoholic fatty liver disease; CIMT, carotid intima-media thickness; ba-PWV, brachial-ankle pulse wave velocity; OR, odds ratio.

however, it has been reported that presence of >33% fat on liver biopsy is optimal for radiological detection of steatosis,[25] which means that liver ultrasound can only detect moderate to severe fatty infiltration in liver. In other words, ultrasound-diagnosed NAFLD represents a more advanced or severe stage of NAFLD. Therefore, it might be not surprising to find the association between CIMT and ultrasound-diagnosed NAFLD rather than computed tomography– or magnetic resonance spectroscopy–diagnosed NAFLD.

Previous studies claimed that NAFLD was a new component of metabolic syndrome or merely the hepatic manifestation of metabolic syndrome.[2,26,27] However, some epidemiological data showed that not all subjects with metabolic syndrome will develop NAFLD and not all subjects with NAFLD were diagnosed with metabolic syndrome as well.[28,29] Therefore, whether the increased cardiovascular risk in NAFLD patients is simply an epiphenomenon conferred by metabolic syndrome is still in debate. Our study, along with some others,[6,7] demonstrated that the strong correlation between atherosclerosis and NAFLD was independent of insulin resistance and metabolic syndrome. Meanwhile, subjects with both NAFLD and metabolic syndrome had remarkably higher levels of CIMT and ba-PWV compared with those with either of these diseases, which imply that the effect on atherosclerosis of NAFLD or metabolic syndrome might not fully overlap. Additional factors besides metabolic syndrome and insulin resistance may also play a key role in the development of atherosclerosis in NAFLD patients, which requires further research.

Some limitations of the present study are also noteworthy. First, due to the cross-sectional nature of the present study, no causal relationships can be established. Large prospective studies are in urgent need to confirm the relationship between NAFLD and atherosclerosis. Second, the diagnosis of NAFLD in the present study was based on ultrasonographic examination, which means that NAFLD patients in our study were in at least moderate stage of the disease. Therefore, we failed to assess the association between mild-stage NAFLD and atherosclerosis in the present study.

In conclusion, the present study showed that NAFLD was associated with elevated CIMT and ba-PWV, independent of conventional CVD risk factors and the presence of metabolic syndrome. The study added more evidence to the notion that the risk of CVD increased in patients with NAFLD. Furthermore, the effects of NAFLD on atherosclerosis might not fully overlap.

Acknowledgments

We thank the field workers for their contribution and the participants for their cooperation.

Sources of Funding

This study was supported by grants from the Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health (1994DP131044), the Sector Funds of Ministry of Health (201002002), the National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09303006-001), the Creative Research Group of Ministry of Education (IRT0932), and the Major Project of Shanghai Committee of Science and Technology (09DZ1950200).

Disclosures

None.

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Arteriosclerosis, Thrombosis, and Vascular Biology

JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Arterioscler Thromb Vasc Biol. 2012;32:2321-2326; originally published online July 19, 2012;
doi: 10.1161/ATVBAHA.112.252957
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1079-5642. Online ISSN: 1524-4636