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 Baoshan district, Shanghai, were included in the present study. The prevalence 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:XX-XX.)

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.⁶⁻¹² 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.¹³ Nevertheless, in another study including 101 patients with type 2 diabetes mellitus, NAFLD diagnosed by 1H-magnetic resonance spectroscopy is not associated with CIMT.¹⁴ 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...
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/height² (kg/m²). 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 \( \gamma \)-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 (mU/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 operator measured CIMT on the far wall of the right and left common ba-PWV was used for analysis. Among 8632 subjects, 716 subjects had self-reported history of cardiovascular disease or stroke.

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, \( \gamma \)-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 \( \chi^2 \) 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, high 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, BMI, 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 the associations between NAFLD and elevated CIMT or ba-PWV 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

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have a variety of cardiovascular risk factors, including components of metabolic syndrome.

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.

Previous studies have documented that NAFLD patients have a variety of cardiovascular risk factors, including obesity, hyperglycemia, and dyslipidemia. In 173 patients with biopsy-proven NAFLD who were followed for 13 years, CVD was the most frequent cause of death. 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. Compared with consistent results regarding the associations between CVD and NAFLD, those between subclinical atherosclerosis and NAFLD are inconsistent. McKimmin et al 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. 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. A meta-analysis including 3497 subjects confirmed that NAFLD diagnosed on ultrasonography is strongly associated with increased CIMT. 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. Among these methods, liver ultrasonography is the easiest to perform; however, it has been reported that presence of $>$33% fat on liver biopsy is optimal for radiological detection of steatosis, 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. However, some epidemiological

| 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                                        | Age, y                                        |
| 1.13 1.11–1.14 <0.0001                        | 1.13 1.13–1.14 <0.0001                        |
| Sex (male=1; female=2)                        | Sex (male=1; female=2)                        |
| 0.32 0.25–0.41 <0.0001                        | 0.32 0.18–0.55 0.0046                        |
| Current drinker                              | Current smoker                                |
| 1.30 0.80–2.12 0.29                          | 1.56 1.18–2.05 0.016                         |
| Current smoker                               | Regular exerciser                             |
| 0.90 0.81–1.21 0.01                          | 0.99 0.81–1.21 0.01                          |
| BMI, kg/m2                                    | LDL-C, mmol/L                                 |
| 1.02 0.98–1.06 0.01                          | 1.48 1.32–1.66 <0.0001                        |
| Central obesity                              | Central obesity                              |
| 0.97 0.74–1.28 0.01                          | 0.97 0.74–1.28 0.01                          |
| High FBG                                     | High TG                                      |
| 1.45 1.16–1.80 0.0009                        | 1.04 0.83–1.30 0.03                          |
| High TG                                      | Low HDL-C                                    |
| 1.91 1.63–2.24 <0.0001                       | 1.31 1.04–1.65 0.023                        |
| Low HDL-C                                    | HOMA-IR                                      |
| 0.66 0.51–0.86 0.0001                        | 1.01 1.00–1.02 0.10                          |
| HOMA-IR                                      | NAFLD                                        |
| 1.09 0.95–1.24 0.02                          | 1.32 1.03–1.68 0.029                        |

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.

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. Error bars represent SEs. 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.
This study was supported by grants from the Key Laboratory for Endocrine and Metabolic Diseases of Ministry of Health (1994DPI31044), the Sector Funds of Ministry of Health (201002002), the National Key New Drug Creation and Manufacturing Program of Ministry of Science and Technology (2012ZX09300006-001), the Creative Research Group of Ministry of Education (IRT0932), and the Major Project of Shanghai Committee of Science and Technology (09DZ1950200).

Disclosures
None.

References


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Arterioscler Thromb Vasc Biol. published online July 19, 2012;
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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