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Advanced fibrosis associates with atherosclerosis in subjects with nonalcoholic fatty liver disease

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ABSTRACT

Objective: Nonalcoholic fatty liver (NAFLD) with advanced fibrosis usually has a deteriorated prognosis, which was mainly attributed to cardiovascular cause. We investigated whether advanced fibrosis assessed by noninvasive fibrosis markers was associated with subclinical atherosclerosis in NAFLD patients.

Methods: A total of 2550 participants with ultrasound confirmed NAFLD from a community based population study were included in the present analysis. NAFLD fibrosis score (NFS) derived from available parameters was calculated to assess severity of fibrosis of the NAFLD patients. The NAFLD patients with a NFS > 0.676 indicated of presence of advanced fibrosis. The carotid intima-media thickness (CIMT), carotid plaques and brachial-ankle pulse wave velocity (ba-PWV) were used as the indicators of early atherosclerosis.

Results: NAFLD patients with advanced fibrosis had higher CIMT and ba-PWV, compared with those without fibrosis (CIMT: 0.65 versus 0.57 mm; ba-PWV: 1884 versus 1535 cm/s, both $p < 0.0001$). Participants with advanced fibrosis were more likely to have higher homeostasis model assessment of insulin resistance index (HOMA_IR, 3.28 versus 2.45, $p < 0.0001$). After adjusting the confounders, participants with advanced fibrosis associated with 1.98-folds increased risk for elevated CIMT, 2.28-folds increased risk for present carotid plaque and 2.68-folds increased risk for arterial stiffness, respectively, as compared to participants without fibrosis. After further adjustment for HOMA_IR, the positive associations did not appreciably change.

Conclusion: Advanced fibrosis indicated by NFS was positively associated with CIMT, presence of carotid plaque and arterial stiffness in the NAFLD patients, independent of conventional cardiometabolic risk factors and insulin resistance.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) indicates a spectrum of liver diseases that encompass simple steatosis, fatty infiltration plus inflammation (NASH), fibrosis and ultimately cirrhosis. With an increase presence of NAFLD global widely, it has posed great burden on public health. Fatty liver has been considered as a risk factor of cardiovascular events, and currently the grade of NAFLD determines the progressive cardiovascular risk [1,2]. Simple steatosis is fairly benign and reversed [3,4], however, NAFLD progressing to NASH or advance fibrosis has a deteriorated prognosis [5]. The gold standard to confirm presence and severity of NAFLD fibrosis depends on the utilization of liver biopsy, which was not

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universally accepted by patients in clinic practice.

Recently, a growing number of studies were performed trying to explore the clinic value of the non-invasive scores for NAFLD fibrosis [6]. NAFLD fibrosis score (NFS) has been validated in 13 studies with more than 3000 patients [7], and it incorporates age, body mass index (BMI), hyperglycemia, blood platelet count, serum albumin and aspartate aminotransferase/alanine aminotransferase ratio (AST/ALT), which presents great accuracy for diagnosis of advanced fibrosis [8]. This score has been recommended to be applied in clinical practice with 97% specificity for confirming advanced fibrosis at the cut-off point of 0.676 [9]. Results derived from the National Health and Nutrition Examination Survey (NHANES) have shown that advanced fibrosis determined by non-invasive fibrosis panels is a significant predictor of mortality caused by cardiovascular disease (CVD) in patients with NAFLD, independent of other known risk factors [10]. To our best knowledge, studies exploring the association between NAFLD fibrosis and subclinical arterial vascular disease in community-based ultrasonography-confirmed NAFLD patients are limited. This study aims to evaluate the association of advanced fibrosis assessed by NFS with markers of subclinical arterial vascular disease such as carotid intima-media thickness (CIMT), presence of carotid plaques and arterial stiffness measured by brachial-ankle pulse wave velocity (ba-PWV).

2. Patients and methods

2.1. Subjects and study design

The participants were from a community-based cross-sectional survey, which was conducted in Jiading district, Shanghai, China, from March to August, 2010. The details of the study, including design, sampling extracting, eligibility criteria, items detected, information collected, have been described elsewhere [11]. A total of 10,375 inhabitants aged 40 years or older were recruited to take part in this survey. All participants were undergone abdominal ultrasonic examination. Of those, participants with a history of known liver disease such as viral or autoimmune hepatitis, liver cancer, or cirrhosis (n = 975), or participants abusing alcohol (alcohol consumption ≥140 g/week in men or ≥70 g/week in women, n = 863) were excluded. Further excluding those participants with missing information of atherosclerosis parameters such as CIMT or ba-PWV (n = 101), or NFS parameters including BMI, ALT, AST, blood platelet count, serum albumin and glucose levels (n = 155), a total of 8281 participants remained. Among them, 2550 participants suffered from NAFLD determined by hepatic ultrasonic examination and were ultimately included in the present analysis.

The study protocol was approved by the Institutional Review Board of the Ruijin Hospital, the Shanghai Jiao Tong University School of Medicine. All participants gave their written consents.

2.2. Clinical and laboratory evaluation

A standard questionnaire was performed to obtain the information on demographic characteristics, lifestyles, history of diseases and medication usage with face-to-face interviews by trained investigators. Participants' body weight and height were obtained in light clothes and bare feet to the nearest 0.1 kg and 0.1 cm, respectively. BMI was calculated according to weight in kilograms divided by square of height in meters. Waist circumference (WC) was measured at the level of the umbilicus with the patient in a standing position. Blood pressure was obtained on the non-dominant arm at a seated position with an automated electronic sphygmomanometer (OMRON Model HEM-752 FUZZY' Omron Co., Dalian, China) three times consecutively with 1-min interval, after at least 10-min rest. The average values of the three readings were used. Regular consume of cigarettes in the past 6 months was defined as current smoker. In line with it, regular consume of alcohol in the past 6 months was defined as current drinker. Fasting venous blood samples were collected after at least 10-h fast. Serum fasting triglycerides (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), ALT, AST, gamma-glutamyl transpeptidase (GGT) and serum albumin were measured on the autoanalyser (Modular E170, Roche). White blood cell (WBC), platelet count (PLT), and hemoglobin were measured on an automated cell counter (Hematology analyzer 120, ABX, France). A 75 g oral glucose tolerance test (OGTT) was conducted to collect two points (0 and 2 h) blood samples. Fasting blood glucose (FBG) and 2-h post-load glucose levels were measured by glucose oxidase method on an autoanalyser (Modular P800, Roche). Serum insulin was measured by using an electrochemiluminescence assay (Modular E170, Roche). The homeostasis model assessment of insulin resistance index (HOMA_IR) was calculated as fasting insulin (μIU/ml) × fasting glucose (mmol/L)/22.5.

According to 1999 World Health Organization (WHO) criteria, diabetes mellitus was defined as FBG levels of 7.0 mmol/L or higher, or a 2-h post-load glucose levels of 11.1 mmol/L or higher, or taking antidiabetic medications or insulin injection. Impaired fasting glycemia was defined as FBG between 6.1 mmol/L and 7.0 mmol/L, and 2-h post-load glucose levels less than 7.8 mmol/L. Hypertension was defined as systolic blood pressure of 140 mmHg or higher, or diastolic blood pressure of 90 mmHg or higher, or using antihypertensive drugs. Prior CVD referred to a self-reported history of myocardial infarction, coronary heart disease and stroke.

2.3. NAFLD and advanced fibrosis

Hepatic ultrasonic examination was performed by two specialists on ultrasonography who were blind to other data with a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Italy) equipped with a 3.5-MHz probe. Definition of NAFLD was based on the presence of at least two of the following three abnormal findings according to 2010 Chinese Guidelines on Diagnosis and Treatment of NAFLD [12]: diffusely increased echogenicity of the liver relative to the kidney, ultrasound beam attenuation, and poor visualization of intrahepatic structures, and the above caused by other than alcohol abuse and known liver disease.

In patients with NAFLD, NFS was used to assess severity of fibrosis. NFS was calculated according to the published formula: NFS = −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × impaired fasting glycemia or diabetes (yes = 1, no = 0) + 0.99 × AST/ALT − 0.013 × platelet count (×10^9/L) − 0.66 × serum albumin (g/dL) [8]. Two cut-off points were select to categorize participants with NAFLD into three groups: those with high NFS (NFS > 0.676), intermediate NFS (NFS: −1.455 ~ 0.676), and low NFS (NFS < −1.455). Patients with high NFS have 97% specificity to identify the presence of advanced fibrosis, whereas patients with low NFS have 90% sensitivity to exclude advanced fibrosis [8].

2.4. Subclinical atherosclerosis panels

CIMT and carotid plaque were measured using a high-resolution B-mode tomographic ultrasound system (Esaote Biomedica SpA, Italy), with a linear 7.5-MHz transducer by one experienced sonographer. The operator measured CIMT on the far wall of the common carotid arteries, 1.5 cm proximal to the bifurcation. The distance from the leading edge of the first echogenic line to that of the second echogenic line at the end of diastole was taken for CIMT.