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Non-alcoholic fatty liver disease is associated with progression of arterial stiffness

N. Li [a,1], G.-w. Zhang [b,1], J.-r. Zhang [c], D. Jin [c], Y. Li [c,d], T. Liu [e], R.-t. Wang [c,*]

[a] Department of Cardiology, The Second Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, China
[b] Department of Cardio-Vascular Surgery, The First Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, China
[c] Department of Geriatrics, The Second Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, China
[d] International Physical Examination and Healthy Center, The Second Affiliated Hospital, Harbin Medical University, Harbin, Heilongjiang, China
[e] Division of Hypothalamic Research, Department of Internal Medicine, UT Southwestern Medical Center, Dallas, TX 75390, USA

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Abstract *Background and aims:* NAFLD is an independent risk factor for increased cardiovascular disease. Arterial stiffness is an index of subclinical atherosclerosis. The aims of this study were to examine prospectively the relationship between Non-alcoholic fatty liver disease (NAFLD) and the progression of arterial stiffness.
Methods and results: A prospective study of 728 men and 497 women free of hypertension, and diabetes at the baseline were conducted. The subjects were followed for 5 years. The progression rate of arterial stiffness was measured by calculating the increase in brachial-ankle pulse wave velocity (baPWV) the changes of the baPWV (adjusted for age) during the study period was significantly greater in the patients with NAFLD (172.4 ± 42.1 cm/s for men, 95.8 ± 36.7 cm/s for women) than in the subjects without NAFLD (70.3 ± 56.5 cm/s for men, 55.4 ± 42.2 cm/s for women). For the subjects with metabolic syndrome, after adjusting for multiple risk factors, NAFLD was a significant predictor of baPWV progression (for male, $\beta = 0.843$; $P < 0.001$; for female, $\beta = 0.575$; $P < 0.001$, respectively). In addition, results were unmodified in subjects without metabolic syndrome.
Conclusions: NAFLD was found to be an independent predictor of faster progression of baPWV even after adjusting other cardiovascular risk factors. These prospective data support a pathogenic role for NAFLD in the development of arterial stiffness.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver condition in the western countries, affecting 20–40% of the general population. A growing body of evidence suggests that NAFLD is an independent risk factor for increased cardiovascular disease (CVD). Moreover, studies showed a graded association between NAFLD severity and increased vascular risk [1]. Several studies have pointed out CVD as the leading cause of death in patients with NAFLD [2,3].

Abbreviations: NAFLD, non-alcoholic fatty liver disease; baPWV, brachial-ankle pulse wave velocity; CVD, cardiovascular disease; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyl transpeptidase; FPG, fasting plasma glucose.

* Corresponding author. Department of Geriatrics, The Second Affiliated Hospital, Harbin Medical University, No. 246 Xuefu ST, Nangang District, Harbin 150086, China. Tel.: +86 451 86605721; fax: +86 451 86605725.
E-mail address: ruitaowang@126.com (R.-t. Wang).
[1] N.L. and G.-w.Z. contributed equally to this work.

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Pulse wave velocity reflects the stiffness of central and peripheral muscular arteries and is widely used as an index of arterial stiffness and vascular damage. Brachial-ankle PWV (baPWV) measurement, a simple, noninvasive, and automated measurement method, is closely correlated with aortic pulse wave velocity [4]. Previous studies demonstrated that elevated baPWV is linked with metabolic syndrome, cardiovascular diseases, stroke, and renal disease, as well as elevated total mortality [5–8].

Cross-sectional studies revealed independent associations between NAFLD and faster progression of atherosclerosis [9–11]. However, no prospective study has been conducted to determine whether NAFLD might accelerate the progression of arterial stiffening. Therefore, the purpose of the study was to examine the relationship between NAFLD and the progression of arterial stiffness.

Methods

Study design

Our study is a prospective study which includes 2297 subjects who visited International Physical Examination and Healthy Center, Harbin, China, from January 2006 through December 2007. For the purpose of this study, we excluded 887 participants with meeting exclusion criteria at baseline, 113 participants with missing data on baPWV at baseline, and 72 participants not attending any follow-up visit after the baseline visit. The sample size for the eligible population was 1225. All patients underwent a physical examination, abdominal ultrasonography, and blood sampling. Risk factors and medical history were assessed with questionnaires. Subjects have been followed−up for 5 years on an annual basis. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of the Second Hospital of Harbin Medical University, China, and all individuals provided informed consent.

Clinical examination

Clinical data, including medical history, smoking status, alcohol consumption, physical activity, and medication use, were recorded for each participant. Cigarette smoking was defined as having smoked at least 100 cigarettes in one's lifetime. Alcohol drinking was defined as the consumption of at least 30 g of alcohol per week for 1 year or more. Regular leisure-time physical activity was defined as participation in moderate or vigorous activity for 30 min or more per day at least 3 days a week. The validity of the physical activity questionnaire is supported by objective measures of activity using accelerometry devices in 106 British adults from the general population [12]. All the subjects underwent physical examination which included anthropometric and blood pressure measurements, and an ultrasound scan of the liver. Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15-min rest. Systolic and diastolic blood pressures were measured twice on the same day and mean values were used in the analysis. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Biochemical analyses

Fasting venous blood samples were drawn for the analysis. The values included total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), and fasting plasma glucose (FPG). All assays were conducted at the Laboratory of Analytical Biochemistry at the Second Hospital of Harbin Medical University, Harbin, using a biochemical analyzer (Modular Analytics, Roche, Mannheim, Germany). All measurements were performed within 2 h of sampling.

An experienced ultrasonographist performed the abdominal ultrasonography using a sonography machine (Voluson E8, GE, America) with a 3.5-MHz probe at baseline and 5 years later. Hepatic steatosis was diagnosed by characteristic echo patterns, such as diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic structures [13].

Metabolic syndrome was defined by the presence of 3 or more of the following risk factors: obesity with BMI $\geq$ 25.0 kg/m^2; high TG $\geq$ 1.7 mmol/L; low HDL $<$ 1.04 mmol/L for men and $<$1.30 mmol/L for women; elevated systolic blood pressure (SBP) $\geq$ 130 mmHg or elevated diastolic blood pressure (DBP) $\geq$ 85 mmHg; and high FPG $\geq$ 6.1 mmol/L [14].

Measurement of baPWV

BaPWV was measured both at baseline and at the end of follow-up using an automatic device (model MB3000, M&B Electronic Instruments, Beijing, China). The subjects rested in the supine position for 5 min. The baPWV was automatically calculated according to the formula (L/PTT). *L* is the difference between the length from heart to ankle and the length from heart to brachium. PTT was the pulse transit time between the brachial and tibial arterial waveforms. Mean right and left baPWV value was calculated during analysis. The coefficients of variation were 2.3% for interobserver reproducibility and 3.7% for intraobserver reproducibility. All measurements were conducted by a single examiner who was blinded to the clinical data. The method has been validated previously [15,16].

Exclusion criteria

The exclusion criteria included: an alcohol intake of more than 20 g/day, viral or autoimmune liver disease, a prior history of taking medication that could cause steatosis, a prior history of any kind of liver disease, coronary heart disease, renal or hepatic failure, and medical treatment