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Sex differences in the impact of nonalcoholic fatty liver disease on cardiovascular risk factors

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Abstract *Background and aims:* Information on sex differences in the association of nonalcoholic fatty liver disease (NAFLD) with cardiovascular disease (CVD) risk factors is scarce. We examined whether men exhibit greater differences in established CVD risk factors between NAFLD and non-NAFLD than women.
Methods and results: We conducted a cross-sectional analysis using a cohort of 10761 apparently healthy Chinese adults who underwent comprehensive health checkups including abdominal ultrasonography. In the setting of NAFLD and non-NAFLD, although men had significantly higher levels of atherogenic lipids as indicated by higher levels of triglyceride, triglyceride/HDL-cholesterol, and lower levels of HDL-cholesterol and worsen renal function as indicated by higher levels of creatinine and lower levels of estimated glomerular filtration rate (eGFR) than female counterparts, men with NAFLD showed greater relative differences in atherogenic lipids and deteriorated renal function than women with NAFLD when compared with their non-NAFLD counterparts. The interactions between sex and NAFLD on triglyceride, HDL-cholesterol, triglyceride/HDL-cholesterol, creatinine, and eGFR were statistically significant ($P < 0.05$). In the multivariate Logistic regression analyses, we observed a stronger association of TG with NAFLD and comparable associations of eGFR or HDL-C with NAFLD in men compared with women.
Conclusion: There was greater adverse influence of NAFLD per se on triglyceride, and triglyceride/HDL-cholesterol in men compared with women. The greater adverse influence of NAFLD per se on HDL-C and eGFR in men compared with women probably related to the gender differences in TG levels.

Background

Nonalcoholic fatty liver disease (NAFLD), which is characterized by significant lipid deposits in liver in patients with absence of excessive alcohol consumption, is an increasingly prevalent condition, affecting 15%–40% of the population worldwide [1,2]. NAFLD is strictly associated with metabolic disorders such as insulin resistance, diabetes, and dyslipidemia. The potential implications of NAFLD for metabolic disorders have triggered an interest in exploring the putative role of NAFLD in the development of incident cardiovascular disease (CVD) [3,4]. Although conflicting results regarding the outcomes have been observed, a series of studies have convinced that NAFLD forecasts an increased risk of CVD incidence [3] and heralds a higher risk of subclinical atherosclerosis [5,6].

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Moreover, accumulating data suggest that CVD is the leading cause of mortality in patients with a diagnosis of NAFLD [7].

Although men have a much higher CVD risk than women [8,9], female diabetic patients confer comparable or greater absolute risk of CVD than male diabetic patients [10,11]. Like diabetes, gender influences the risk for disease acquisition and progression in patients with NAFLD, with the prevalence of NAFLD and elevated transaminases more commonly noted in men [12,13]. Moreover, significant gender differences exist with regard to the association of NAFLD with subclinical atherosclerosis [4–6]. However, few studies have compared the established CVD risk factors including blood pressure (BP) levels, glucose concentrations, lipid profile, and renal function between men and women with or without NAFLD. Hence, we aimed to examine whether men exhibit greater differences in established CVD risk factors between NAFLD and non-NAFLD than women.

Methods

Study population

The study participants were Chinese employees and retired workers aged 20–100 years from the Wuhan Iron and Steel Company (WISCO). Full details of the study have been described elsewhere [14]. In WISCO, the Industrial Safety and Health Law requires employees and retired workers to receive periodic health evaluations at the WISCO General Hospital (Wuhan, China). The present cohort included all employees and retired workers who received a comprehensive health examination (including abdominal ultrasonography) at the Healthcare system, WISCO general Hospital, between June 2008 and December 2010 (n = 15,753). We got agreement for analyzing the data from the WISCO hospital.

All subjects were asked to complete a standard questionnaire that gathered information on alcohol consumption habits, histories of current and previous illness, and medical treatments. We excluded 3490 participants from this study, comprising 1271 with alcohol consumption in amounts >70 g/week for women (73) and >140 g/week for men (1,198), 857 participants with hepatitis B surface antigen (HBsAg) positivity, and 1758 missing information on age, sex, anthropometric assessment, test results for HBsAg, or liver ultrasound scans. In addition, to avoid the effects of differences in treatment of CVD risk factors between men and women on the results, 1493 participants with lipid-lowering medication use, BP-lowering medication use, uric acid (UA)-lowering medication use, and anti-diabetic medication use were also excluded. As some individuals met more than one exclusion criteria, the remaining available 10,761 participants (6901 men and 3860 women) were included in our data analysis. The fact that men accounted for 64.1% of total participants was in consistent with the proportion of male employees at WISCO. According to the Private Information Protection Law, information that might identify subjects was safeguarded by the Health Examination Center. This study was approved by the institutional review board of WISCO general Hospital. Because we only retrospectively accessed a de-identified database for purposes of analysis, informed consent requirement was exempted by the institutional review board.

Anthropometric and biochemical measurements

Anthropometric measurements, including weight, height, and BP were measured following standardized protocols from the World Health Organization (WHO). Body mass index (BMI) was calculated as weight (in kilograms) divided by the square of height (in meters). Participants' seated BP was measured twice for every 5 min on the right arm after 5 min of rest by trained nurses with a sphygmomanometer. The mean of the two readings was used in data analysis.

Overnight fasting (at least 8 h) blood samples were collected from the antecubital vein of each individual. Biochemical measurements, including assessment of fasting plasma glucose (FPG), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), alanine aminotransferase (ALT), uric acid (UA), creatinine (sCr), and hepatitis viral antigen/antibody were measured enzymatically on an autoanalyzer (Hitachi 7600, Ltd, Tokyo, Japan). All the blood measurements were followed the same protocol.

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study equation: eGFR = 186.3 × (sCr) - 1.154 × age - 0.203 × (0.742 if female) [15].

The triglycerides and glucose index (TyG) were calculated using the published formula [16]. The TyG index: Ln [TG (mg/dl) × FPG (mg/dl)/2].

Assessment of NAFLD

Ultrasound tests were performed by trained sonographers using a high-resolution, real-time scanner (model SSD-2000; Aloka Co., Ltd., Tokyo Japan). One experienced radiologists used standard criteria in evaluating the images for the presence or absence of hepatic fat [17]. Images were captured following a standard manner with patients in the supine position with the right arm raised above the head. Generally, the diagnosis of fatty liver was made on the basis of characteristic ultrasonographic features consistent with the presence of a diffuse increase of fine echoes in the liver parenchyma compared with the kidney or spleen parenchyma, vessel blurring, and narrowing of the lumen of the hepatic veins [18]. The kappa statistics for intra-observer reliability for the diagnosis of fatty liver was 0.81.

Statistical analysis

All statistical analyses were conducted using SPSS software (version 12.0 for windows; SPSS, Chicago, IL, USA). Each

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