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Lipid phenotypes in patients with nonalcoholic fatty liver disease

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ABSTRACT

Objective. There has been conflicting evidence regarding the role of single lipid species in the pathogenesis of nonalcoholic fatty liver disease (NAFLD). We aimed to explore the associations between dyslipidemia phenotypes (combinations of lipid parameters) and the risk of NAFLD.

Methods. We conducted a cross-sectional analysis using a cohort of 9560 apparently healthy Chinese adults who underwent comprehensive health checkups including abdominal ultrasonography.

Results. Of 3709 participants with NAFLD, 41.8% were classified as normolipemia (NL), 3.8% as combined hyperlipidemia, 3.2% as hypercholesterolemia, 17.7% as dyslipidemia of metabolic syndrome (MetS), 10.2% as isolated low high-density lipoprotein cholesterol (HDL-C), and 23.3% as isolated hypertriglyceridemia. The multivariable-adjusted odds ratios (ORs) (with 95% confidence intervals) for NAFLD in those with combined hyperlipidemia, those with hypercholesterolemia, those with MetS dyslipidemia, those with low HDL-C, and those with hypertriglyceridemia compared with those with NL were 4.79 (3.19–7.20), 1.26 (0.94–1.69), 3.31 (2.74–3.99), 1.13 (0.95–1.34), and 2.63 (2.26–3.08), respectively. The associations between combined hyperlipidemia, MetS dyslipidemia, or hypertriglyceridemia and risk of NAFLD were consistently seen in various evaluated subgroups. The interactions between lipid phenotypes and sex, body mass index (BMI), blood pressure (BP), fasting plasma glucose (FPG), or uric acid (UA) were not significant for NAFLD (all $P > 0.05$).

Conclusions. There were diverse dyslipidemia phenotypes in patients with NAFLD. Combined hyperlipidemia, MetS dyslipidemia, and hypertriglyceridemia were strongly and independently associated with increased risk of NAFLD. Gender, BMI, BP, FPG, and UA status did not modify the associations between dyslipidemia phenotypes and NAFLD.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NL, normolipemia; MetS, metabolic syndrome; HDL-C, high-density lipoprotein cholesterol; OR, Odds ratio; BMI, body mass index; BP, blood pressure; FPG, fasting plasma glucose; UA, uric acid; CVD, cardiovascular disease; WHO, World Health Organization; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; ALT, alanine aminotransferase; SD, standard deviations; CI, confidence interval.

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1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is an increasingly prevalent condition, affecting 15%–40% of the population worldwide [1–3]. Emerging studies have established that NAFLD heralds an increased risk of subclinical atherosclerosis [4–6] as well as cardiovascular disease (CVD) [7]. Moreover, several longitudinal studies have unequivocally evidenced that CVD is the most common cause of mortality in those with a diagnosis of NAFLD [8,9]. Lipid abnormalities are one of the most important risk factors for CVD [10]. Although the characteristic dyslipidemic profile in patients with NAFLD is hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) [11], dyslipidemias may vary in phenotypic expression because lipid metabolism in NAFLD involves complex biological pathways. Recent evidence highlighted the central role of dysregulation of cholesterol homeostasis in the pathogenesis of NAFLD [12,13]. Hence, the conventional dyslipidemia phenotype (hypertriglyceridemia and low HDL-C) may be insufficient to demonstrate the complete dyslipidemia phenotypes in the setting of NAFLD. The 5 major dyslipidemia phenotypes (combined hyperlipidemia, hypercholesterolemia, dyslipidemia of metabolic syndrome [MetS], low HDL-C, and hypertriglyceridemia (Table 1)) have been shown to have strong and independent associations with incident CVD [14]. Given that CVD is the leading cause of death in those with NAFLD, and that dyslipidemias, which frequently occur in patients with NAFLD, play a critical role in CVD involvement, it is essential and reasonable to examine the dyslipidemia phenotypes in NAFLD patients in detail. Hence, we aimed to explore the dyslipidemia phenotypes in patients with NAFLD, and to determine whether there were independent associations between dyslipidemia phenotypes and NAFLD.

2. Methods

2.1. Study Population

The study participants were Chinese employees and retired workers from the Wuhan Iron and Steel Company (WISCO). Full details of the study have been described elsewhere [15]. The present cohort included participants free of known CVD who received a comprehensive health examination (including abdominal ultrasonography) at the Healthcare system, WISCO general Hospital, between June 2008 and December 2010 (n = 15,199). 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. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

All subjects were asked to complete a standard questionnaire that gathered information on cigarette smoking and alcohol consumption habits, histories of current and previous illness, and medical treatment. We excluded 5639 participants from this study, comprising 1271 with alcohol consumption in amounts >70 g/wk for women (73) and >140 g/wk for men (1198), 857 participants with hepatitis B surface antigen (HBsAg) positivity, and 1980 missing information on age, sex, anthropometric assessment, lipid measurements, test results for HBsAg, or liver ultrasound scans. In addition, to avoid the effects of lipid-lowering on all lipid parameters, 933 participants with lipid-lowering medication use were excluded. Furthermore, 1111 individuals with diabetes (defined according to the 2015 American Diabetes Association criteria [16]) were also excluded as diabetes has a strong independent relationship with increased levels of triglycerides (TG), decreased levels of HDL-C, and increased risk of NAFLD. As some individuals met more than one exclusion criteria, the remaining available 9560 participants (6022 men and 3538 women) were included in our data analysis. There were no statistically significant differences in the total sample vs the analytical sample in CVD risk factors (data not shown). The fact that men accounted for 63% of total participants was consistent with the proportion of male employees at WISCO.

Table 1 – Definition of lipid phenotypes.

	HDL-C (mg/dl)	LDL-C (mg/dl)	Triglycerides (mg/dl)
Normolipemia	>40 in men, >50 in women	<160	<150
Combined hyperlipidemia	No cutoff	≥160	≥150
Hypercholesterolemia	No cutoff	≥160	<150
Dyslipidemia of metabolic syndrome	≤40 in men, ≤50 in women	<160	≥150
Low HDL-C	≤40 in men, ≤50 in women	<160	<150
Hypertriglyceridemia	>40 in men, >50 in women	<160	≥150

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
Adapted from Paramsothy et al. [14].

2.2. Anthropometric and Biochemical Measurements

Anthropometric measurements, including weight, height, and systolic/diastolic blood pressure (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), TG, low-density lipoprotein cholesterol (LDL-C), HDL-C, alanine aminotransferase (ALT), uric acid (UA), hepatitis viral antigen/antibody, and creatinine (sCr) were measured on an autoanalyzer (Hitachi 7600, Ltd., Tokyo, Japan). All the blood measurements followed the same protocol. Estimated glomerular filtration rate (eGFR) was calculated using the formula: eGFR = 186.3 × (sCr) − 1.154 × age − 0.203 × (0.742 if female).