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Intrahepatic triglyceride content is independently associated with chronic kidney disease in obese adults: A cross-sectional study

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ABSTRACT

Background. Non-alcoholic fatty liver disease (NAFLD) and chronic kidney disease (CKD) are associated with some common critical cardio-metabolic risk factors. The aim of this study was to explore the association between intrahepatic triglyceride (IHTG) content and CKD in obese subjects.

Methods. A total of 1068 obese participants received anthropometric, biochemical measurements and hepatic ultrasonography. Of those, 485 participants received magnetic resonance spectroscopy (^{1}H-MRS) for the determination of IHTG content. CKD was defined as a urinary albumin:creatinine ratio (UACR) ≥ 30 mg/g and/or estimated glomerular filtration rate (eGFR) < 60 mL/min per 1.73 m^2.

Results. The prevalence of CKD was significantly higher in NAFLD subjects compared to subjects without NAFLD, while the prevalence of CKD was gradually increased as the IHTG content increased by quartiles (P for trend < 0.001). After adjustment for multivariate metabolic factors, the risk of abnormal albuminuria and CKD was increased by 68% [OR (95% CI): 1.68 (1.21–2.33), P < 0.01] and 54% [OR (95% CI): 1.54 (1.14–2.07), P < 0.01] respectively per one standard deviation (SD) increase in IHTG content. The association between IHTG content and CKD was not changed by conventional risk factors, including age, BMI and hypertension (all P < 0.05).

Conclusion. IHTG content is independently associated with CKD in obese adults.

Abbreviations: NAFLD, non-alcoholic fatty liver disease; IHTG, intrahepatic triglyceride; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TG, triglyceride; TC, total cholesterol; LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; UACR, urinary albumin:creatinine ratio; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) has emerged as a growing and worldwide public health problem. NAFLD is characterized by an increase in the accumulation of intrahepatic triglycerides and is recognized as an independent predictor of insulin resistance, metabolic syndrome, and cardiovascular disease (CVD) [1,2]. NAFLD also increases the risk for chronic kidney disease (CKD) [3].

CKD is a widespread health problem that affects up to 13% of adults in Western countries and bears a high morbidity and mortality rate [4]. CKD is defined by a sustained decline in the glomerular filtration rate (GFR) and/or by presence of structural/functional abnormalities in the kidneys through urinalysis, biopsy, or imaging, and associated with end-stage renal disease (ESRD) and cardiovascular diseases [5–7].

Accumulating evidence suggests that NAFLD and CKD share some critical cardio-metabolic risk factors [8–12]. It was reported that NAFLD was associated with an increase in the incidence of CKD [13–18]. However, the dose–response association between intra-hepatic triglyceride (IHTG) content and the presence of CKD has not been clearly delineated. Both CKD and NAFLD share with abdominal obesity and insulin resistance [8–12]. However, it is unclear whether this association of NAFLD and CKD is attributed to their shared cardiometabolic risk factors or whether NAFLD leads to the development of CKD independent of these factors. Therefore, an accurate assessment of abdominal visceral fat, intrahepatic fat, and insulin resistance would clarify the underlying links between NAFLD and CKD. The purpose of this cross-sectional study was to investigate the association between intrahepatic triglyceride content and the presence of CKD in obese adults.

2. Methods

2.1. Study Participants

This cross-sectional study investigated the association of both the presence and severity of NAFLD with the presence of CKD. We recruited participants from the Lianqian community, Xiamen, China from April 2011 to December 2013. The details of the study design and methods have been previously reported [19]. In brief, a total of 1068 adult subjects with a waist circumference greater than 90 cm for men and 80 cm for women were included. All participants received liver ultrasonography scanning and completed a uniform questionnaire including histories of diabetes, malignancy, cardiovascular disease, smoking status, alcohol consumption, and physical activity. The following participants were excluded: (1) those with any clinical evidence of cirrhosis, biliary obstructive diseases or other secondary chronic liver diseases (e.g. alcohol intake ≥ 140 g/week for men or 70 g/week for women currently or in the past 6 months, acute or chronic viral hepatitis, autoimmune hepatitis and/or the use of hepatotoxic medications, such as corticosteroids) and (2) those with established and newly diagnosed type 2 diabetes [20]. Of these, 485 participants were randomly selected to further receive magnetic resonance spectroscopy (^{1}H-MRS) for the measurement of IHTG content and computed tomography (CT) scanning for the measurement of abdominal fat area. There were no significant differences in terms of demographic or main laboratory variables between the 485 subjects and the whole sample of 1068 subjects (Table S1).

The study protocol was approved by the Human Research Ethical Committee of the First Xiamen Hospital. Written informed consent was obtained from each participant.

2.2. Clinical and Biochemical Measurements

Anthropometric measurements included height, weight, waist circumference, and blood pressure. Height and weight were measured after an overnight fast in a light gown and no shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. Waist circumference was measured at the level of the umbilicus. Blood pressure (BP) was assessed in triplicate using an electronic sphygmomanometer (OMRON). Body fat mass was determined using the HOLOGIC whole body DXA system (Hologic, Bedford, MA).

All blood samples were drawn in the morning after 12 hours of fasting. Plasma glucose, serum liver enzyme, creatinine, triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c) levels were determined on a Hitachi 7450 analyzer (Hitachi, Tokyo, Japan). Plasma glucose concentrations were measured using the glucose oxidase method. Serum TG, TC, LDL-c, and HDL-c were measured using enzymatic colorimetric assays. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by standard enzymatic methods. Serum gamma-glutamyltransferase (GGT) was measured by the Szasz-Persijn method. Serum insulin concentrations were measured using electrochemiluminescence immunoassay (Roche Elecsys Insulin Test, Roche Diagnostics, Mannheim, Germany). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the following formula: fasting serum insulin (FINS, mIU/L) × fasting plasma glucose (FPG, mmol/L)/22.5.

Metabolic syndrome was defined as waist circumference ≥90 cm in men or ≥80 cm in women plus two or more of the following: (a) low serum HDL-c (HDL-c <1.03 mmol/L in men or <1.29 mmol/L in women), (b) hypertriglyceridemia (TG ≥ 1.7 mmol/L), (c) hypertension (BP ≥ 130/85 mmHg or treatment of previously diagnosed hypertension), and (d) dysglycemia (FPG ≥ 5.6 mmol/L or previously diagnosed type 2 diabetes) according to the International Diabetes Federation (IDF) diagnostic criteria [21].

The estimated glomerular filtration rate (eGFR) in mL/min per 1.73 m^2 was calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [22]. The CKD-EPI equation, expressed as a single equation is GFR = 141 × min $(Scr/\kappa,1)^{\alpha}$ × max $(Scr/\kappa,1)^{-1.209}$ × 0.993^{Age} × 1.018 [if female], where Scr indicates serum creatinine (mg/dL), κ 0.7 for females and 0.9 for males, α −0.329 for females and −0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1. A first-voided early-morning spot urine sample was obtained for the measurement of urinary albumin and creatinine. Albuminuria was measured using an

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