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Obesity is more closely related with hepatic steatosis and fibrosis measured by transient elastography than metabolic health status

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ABSTRACT

Objective. The pathogenesis of non-alcoholic fatty liver disease (NAFLD) involves multiple concomitant events induced by obesity and metabolic health condition. This study aimed to assess the risk of NAFLD according to metabolic health and obesity status using transient elastography (TE).

Materials and Methods. A total of 2198 asymptomatic adults without chronic liver disease and who underwent a medical health check-up were recruited. Subjects were categorized into four groups according to metabolic health and obesity statuses: metabolically healthy non-obese (MHNO); metabolically unhealthy non-obese (MUNO); metabolically healthy obese (MHO); and metabolically unhealthy obese (MUO). Hepatic steatosis was defined as controlled attenuation parameter (CAP) ≥238 dB/m, and significant liver fibrosis was defined as liver stiffness measurement (LSM) >7.0 kPa, as defined by TE.

Results. Compared with MHNO group, the odds ratios (ORs) [95% confidence interval (CI)] for hepatic steatosis were 2.94 [2.32–3.71], 4.62 [3.52–6.07], and 12.02 [9.08–15.92] in the MUNO, MHO, and MUO groups, respectively ($P < 0.001$) in crude model. Regarding liver fibrosis, there was no significant difference in the ORs in MUNO group (ORs: 0.95 [95% CI, 0.33–2.78], P value = 0.929), whereas there was a significant increase in the ORs in MHO group compared with MHNO group (ORs: 4.32 [95% CI, 1.73–10.76], $P = 0.002$) in the fully adjusted model.

Abbreviations: NAFLD, nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; MHNO, metabolically healthy non-obese; MUNO, metabolically unhealthy non-obese; MHO, metabolically healthy obese; MUO, metabolically unhealthy obese; DM, diabetes mellitus; TE, transient elastography; CAP, controlled attenuation parameter; LSM, liver stiffness measurement; ALT, alanine aminotransferase; LDL-C, lower-density lipoprotein cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyceride; IQR, interquartile range.

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Conclusion. Our results show that MHO was associated with both liver steatosis and fibrosis assessed by transient elastography. Our results suggest that a healthy metabolic profile does not protect obese adults from hepatic steatosis or fibrosis, indicating that obesity itself might contribute to liver fibrosis.

1. Introduction

Obesity and metabolic syndrome are worldwide epidemics [1,2] that have led to the increased prevalence of chronic metabolic disorders, such as type 2 diabetes (T2D), non-alcoholic fatty liver disease (NALFD), and cardiovascular disease [3,4]. Several recent studies, however, have shown that obesity and MS could independently contribute to the development of chronic metabolic diseases [5,6] and even chronic kidney diseases [7]. Beyond the clinical relevance of obesity and metabolic syndrome, the concept of being metabolically healthy or unhealthy, rooted from the characteristics of metabolic syndrome, has recently gained popularity after adopting the notion that an individual can exhibit an obese phenotype in the absence of any metabolic abnormalities and vice versa [8]. Although many studies have investigated the clinical relevance of metabolically healthy obese (MHO), metabolically unhealthy non-obese (MUNO), and metabolically unhealthy obese (MUO) statuses with various biomarkers [9,10] and diseases, such as T2D, atherosclerosis, chronic kidney disease, [11–13] which are risk factors of cardiovascular events, the influence of metabolic status on NAFLD is not well-established.

NAFLD, a histological spectrum ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and liver cirrhosis, is a condition in which lipid droplets accumulate in the hepatocytes of patients who do not consume excessive alcohol [14]; and the rate of NAFLD is expected to increase as obesity rate increases, populations become older, and physical activity levels decrease [15]. There is growing evidence regarding the increasing prevalence of NAFLD [16], as well as serious complications and mortality of NAFLD and its large burden on public healthcare systems [17]. Among the categories of NAFLD, NASH and liver fibrosis are well known to progress to liver cirrhosis. Furthermore, the rate of progression to cirrhosis over 10 years is more often estimated as 1/4 to 1/3 of adults with NASH [18]. To relive the burden of NAFLD on public healthcare, optimal strategies for identifying risk factors and preventing the progression of NAFLD should be established. In fact, obesity is a well-known risk factor of hepatic steatosis and fibrosis. However, it is unclear whether the impacts of obesity on hepatic steatosis and liver fibrosis are independent of metabolic abnormalities such as hyperglycemia, high blood pressure, and dyslipidemia, as these metabolic abnormalities are often associated with obesity.

Although liver biopsy has been regarded as the gold standard for detecting NASH and liver fibrosis, it is innately invasive and can lead to mortality, misdiagnosis due to interpretational variability, and sampling errors due to uneven fibrosis distribution within the liver parenchyma [19]. Recently, controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) using transient elastography (TE) has emerged as a promising, non-invasive tool for assessing hepatic steatosis and the degree of liver fibrosis. This technique is non-invasive, accurate, reproducible, convenient, and useful for serial measurement.

Therefore, to better understand the relationship between metabolic health/obesity status and NAFLD, we investigated the effects of MHO/MUNO/MUO status on hepatic steatosis and fibrosis examined by TE in patients without known liver disease [20].

2. Methods

2.1. Study Subjects

The study population consisted of subjects who underwent comprehensive health examinations and tests, including a TE examination, at Severance Checkup (Center for health promotion and personalized medicine), between April 2013 and August 2014 as one part of routine clinical cares to find medical problems before they manifest as a disease. During this period, 2521 subjects participated (Fig. 1). Participants were excluded for the following reasons: unreliable LSM values (n = 15), alcohol intake >140 g/week for men and 70 g/week for women (n = 93), and positive serologic markers for hepatitis B (n = 86) or C (n = 29). Of all study participants who met the inclusion criteria, 2198 subjects aged 20 years or older were recruited for the present study. Participants were stratified into four groups according to metabolic health and obesity status. All subjects completed a questionnaire about medical and/or surgical history, current alcohol consumption, and smoking status. All subjects provided written informed consent. This study was approved by the institutional review board of Severance Hospital and this study was carried out in accordance with the ethical standards of the Helsinki Declaration.

2.2. Definitions of Metabolic Health and Obesity Status

Obesity was defined according to Asia-Pacific body mass index (BMI) criteria (non-obese <25 kg/m^2 and obese ≥25 kg/m^2) as defined by the World Health Organization Western Pacific Region (WHO-WPR) [21]. We used standard operating protocols to measure ATP-III components to define a metabolically healthy state [22]. The waist circumference criterion was not used because of its collinearity with BMI. Participants who met fewer than two of the following four criteria were considered as being metabolically healthy according to the modified Wildman criteria [23]: (1) a systolic blood pressure ≥130 mmHg and/or a diastolic blood pressure ≥85 mmHg or on antihypertensive treatment; (2) triglyceride ≥150 mg/dL; (3) fasting glucose ≥100 mg/dL or on antidiabetic treatment; and (4) high-density lipoprotein cholesterol <40 mg/dL in men and <50 mg/dL in women. According to these criteria, study participants were categorized into four groups: (1) MHNO: BMI <25 kg/m^2 and <2 metabolic risk factors; (2) MUNO: BMI <25 kg/m^2 and ⩾2