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Association of serum uric acid level with non-alcoholic fatty liver disease: A cross-sectional study☆

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***Background/Aim*: Serum uric acid level has been suggested to be associated with factors that contribute to the metabolic syndrome. The aim of this study was to investigate the association of serum uric acid level with non-alcoholic fatty liver disease (NAFLD).**

***Methods*: A cross-sectional study was performed among the employees of Zhenhai Refining & Chemical Company Ltd., Ningbo, China.**

***Results*: The study included 8925 subjects (6008 men) with a mean age of 43 years. The prevalence rates of NAFLD and hyperuricemia were 11.78% and 14.71%, respectively. NAFLD patients had significantly higher serum uric acid levels than controls (370.3 ± 86.6 *vs.* 321.1 ± 82.6 μmol/L; $P < 0.001$). The prevalence rate of NAFLD was significantly higher in subjects with hyperuricemia than in those without hyperuricemia (24.75% *vs.* 9.54%; $P < 0.001$), and the prevalence rate increased with progressively higher serum uric acid levels (P value for trend < 0.001). Multiple regression analysis showed that hyperuricemia was associated with an increased risk of NAFLD (odds ratio [OR]: 1.291, 95% confidence interval [CI]: 1.067–1.564; $P < 0.001$).**

***Conclusion*: Serum uric acid level is significantly associated with NAFLD, and elevated serum uric acid level is an independent risk factor for NAFLD.**

***Keywords*: Non-alcoholic fatty liver disease; Uric acid; Association**

1. Introduction

Non-alcoholic fatty liver disease (NAFLD), ranging from simple steatosis to non-alcoholic steatohepatitis (NASH) and cirrhosis, is the most common liver disease in Western countries, with a prevalence of 20–30% in the general population [1,2]. NAFLD has also become a significant public health concern in developing countries [3,4]. The development of NAFLD is closely associated with obesity, type 2 diabetes mellitus, dyslipidemia and hypertension, which form a cluster of metabolic disorders that is now identified as metabolic syndrome [5,6]. For this reason, NAFLD has been regarded as a hepatic manifestation of metabolic syndrome [6].

Uric acid is the major end product of purine metabolism, and the level of serum uric acid (SUA) is

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Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GGT, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; MBP, mean blood pressure; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio; CI, confidence interval; PR%, prevalence rate; PR, prevalence ratio; SBP, systolic blood pressure; SD, standard deviation; SE, standard error; SUA, serum uric acid; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

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maintained by the balance between uric acid production and excretion [7]. Over the past few years, an association between SUA level and metabolic syndrome has been repeatedly demonstrated [8–10]. SUA levels are often increased in subjects with metabolic syndrome, and SUA levels increase as patients develop increasing numbers of metabolic syndrome-related disorders [8,9]. The association between SUA level and metabolic syndrome is also illustrated by the fact that the prevalence rate of metabolic syndrome shows a graded increase according to SUA level [10].

Although NAFLD is a hepatic manifestation of metabolic syndrome and an association between SUA level and metabolic syndrome has been well documented, the association between NAFLD and SUA level is controversial in the literature. Some studies have reported that NAFLD patients had higher SUA levels than controls [11,12], where as a recent study found that this association was not statistically significant [13]. These conflicting data may be the result of small sample sizes, differences in study populations, and differences in the definition of hyperuricemia. In addition to the uncertainty regarding an association between NAFLD and elevated SUA level, it is also unclear whether an elevated SUA level is a risk factor for NAFLD. Further clarifying the relationship between SUA level and NAFLD may have significant clinical implications for the prevention and treatment of NAFLD by modulating the SUA level.

Therefore, in this study, we conducted a cross-sectional survey to investigate the relationship between SUA level and NAFLD in the Chinese population.

2. Materials and methods

2.1. Study design and subjects

A cross-sectional study was conducted among the employees of Zhenhai Refining & Chemical Company Ltd. (Ningbo, China) to evaluate the relationship between the SUA level and NAFLD. The study initially enrolled all of the employees who were attending their annual health examination in the period between January 1, 2005 and December 31, 2005. Subjects meeting the following criteria were excluded: (1) those taking antihypertensive or antidiabetic agents, lipid-lowing agents, or hypouricemic agents; (2) those with alcohol consumption greater than 140 g/week for men and 70 g/week for women; (3) those with a history of other known causes of chronic liver disease such as viral hepatitis or autoimmune hepatitis, and those using hepatotoxic medications. A total of 8925 eligible subjects were enrolled (6008 male and 2917 female, with a mean age of 41.8 ± 13.4 years and 44.9 ± 12.2 years, respectively). The study protocol was approved by the Local Ethics Committee.

2.2. Clinical examination

Clinical examinations were administered in the morning after an overnight fast, and subjects were also instructed to refrain from exercise during the day prior to their examination. The examination consisted of a physical examination by a physician, a blood draw, a blood pressure measurement, anthropometry, and a health habit inventory.

Blood pressure was measured using an automated sphygmomanometer with the subject in a sitting position. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at the first and fifth Korotkoff phases, respectively. Mean blood pressure (MBP) was calculated as DBP plus the pulse pressure divided by three. Standing height and body weight were measured without shoes or outer clothing. Body mass index (BMI, kg/m^2), used as an index of body fat, was calculated as weight in kilograms divided by height in meters squared. Waist circumference (WC) was measured with the measuring tape positioned midway between the lowest rib and the superior border of the iliac crest as the patient exhaled normally [14].

2.3. Biochemical analyses

Fasting blood samples were obtained from an antecubital vein, and the samples were used for the analysis of biochemical values. The values included triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), γ-glutamyltransferase (GGT), urine acid, and fasting plasma glucose (FPG). All values were measured by an Olympus AU640 autoanalyzer (Olympus, Kobe, Japan) using standard methods.

2.4. Ultrasonography

Hepatic ultrasonic examination was performed in all subjects by a trained ultrasonographist who was unaware of the clinical and laboratory data, using a Toshiba Nemio 20 sonography machine (Toshiba, Tokyo, Japan) with a 3.5-MHz probe. Hepatic steatosis was diagnosed by characteristic echo patterns according to conventional criteria, such as the evidence of diffuse hyperechogenicity of the liver relative to the kidneys, ultrasound beam attenuation, and poor visualization of intrahepatic structures [15].

2.5. Definitions and statistical analyses

NAFLD was diagnosed by abdominal ultrasound following exclusion of alcohol consumption, viral, or autoimmune liver disease [16,17]. Hyperuricemia was defined as a SUA level >420 μmol/L in men and >360 μmol/L in women [18]. The diagnosis of metabolic syndrome was based on the definition recommended by the Asia-Pacific Working Party on NAFLD 2006 [19]; for a person to be defined as having metabolic syndrome they must have any three or more of the following: (1) central obesity: waist circumference >90 cm for male and >80 cm for female and/or BMI >25 kg/m^2 in both genders; (2) hypertriglyceridemia: triglycerides $\geqslant 1.7$ mmol/L; (3) low HDL-C: HDL-C <1.03 mmol/L for men and <1.29 mmol/L for women; (4) elevated blood pressure: blood pressure $\geqslant 130/85$ mmHg; (5) elevated fasting glucose: FPG $\geqslant 5.6$ mmol/L or previously diagnosed type 2 diabetes.

Statistical analyses were performed using the SPSS software package version 11.5 for Windows (SPSS Inc., Chicago, IL). Continuous variables are presented as the mean and standard deviation (SD) or the median and interquartile range (IQR), as appropriate. The Student's *t*-test or the Mann–Whitney *U* test was used for comparisons of continuous data, while the χ^2-test was used for comparisons of categorical variables. Linear regression analysis was used to determine the relationship between SUA level and prevalence of NAFLD and metabolic syndrome. Stepwise multiple regression analysis (Backward: Wald; Entry: 0.05, Removal: 0.10) was used to evaluate the risk factors for NAFLD. $P<0.05$ (2-tailed test) was considered statistically significant.

3. Results

3.1. Characteristics of study subjects

Of the 8925 enrolled subjects, 1051 (11.78%; 697 males and 354 females) fulfilled the diagnostic criteria