Relationship between serum uric acid level and nonalcoholic fatty liver disease in type 2 diabetes patients

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**Abstract**

This study aimed to investigate the association between serum uric acid (SUA) level and nonalcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes (T2DM). T2DM patients hospitalized in the Department of Hepatology, Yantai Qishan Hospital, between April 2012 and December 2018 were classified into the NAFLD group and the non-NAFLD group. Clinical data, glucose and lipid metabolism biomarkers, and liver and kidney function parameters were retrospectively collected.

Five hundred eighty-three T2DM patients met the inclusion and exclusion criteria; 227 patients were included in the non-NAFLD group and 356 patients were included in the NAFLD group. Multiple linear regression analyses showed that SUA was positively correlated with body mass index \((P = .003)\), triglycerides \((P = .009)\), aspartate aminotransferase \((P = .036)\), and alanine aminotransferase \((P = .038)\) and negatively correlated with estimated glomerular filtration rate \((P < .001)\) in T2DM patients. Multivariate regression analyses demonstrated that after adjusting for confounding factors, the SUA tertile was still significantly associated with NAFLD occurrence in T2DM patients \((P = .008)\). With reference to SUA tertile I, the odds ratios for NAFLD in the SUA tertile II and tertile III groups were 1.729 (95% confidence interval [CI]: 1.086–2.753) and 2.315 (95% CI: 1.272–4.213), respectively.

The level of SUA in T2DM patients was associated with the occurrence of NAFLD. Elevated SUA was associated with a significantly increased prevalence of NAFLD. The SUA level was an independent risk factor for NAFLD occurrence in patients with T2DM.

**Abbreviations:** 2hPG = 2-h plasma glucose, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, FC-P = fasting C-peptide, FINS = fasting insulin, FPG = fasting plasma glucose, GGТ = glutamyl transpeptidase, HbA1c = glycosylated hemoglobin A1C, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = Homeostatic model assessment for insulin resistance, HUA = hyperuricemia, IR = insulin resistance, LDL-C = low-density lipoprotein cholesterol, MS = metabolic syndrome, NAFL = non-alcoholic simple fatty liver, NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, OR = odds ratio, SBP = systolic blood pressure, Scr = creatinine, SUA = serum uric acidT2DM = type 2 diabetes, TC = cholesterol, TG = triglyceride, WHR = waist-to-hip ratio.

**Keywords:** insulin resistance, nonalcoholic fatty liver disease, serum uric acid, type 2 diabetes

**1. Introduction**

Nonalcoholic fatty liver disease (NAFLD) refers to pathological changes characterized by diffuse steatosis and lipid accumulation in hepatocytes in individuals without a history of alcohol consumption equivalent to <140 g/week for men or <70 g/week for women after eliminating other identified causes.\(^{[1]}\) According to whether the lesion is combined with an inflammatory reaction and/or fibrosis, NAFLD could be classified into the nonalcoholic simple fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), and NASH-related cirrhosis.\(^{[2]}\) NAFLD is a common cause of abnormal liver function and chronic liver diseases, and NAFLD affects 20% to 30% of the general population in Western developed countries.\(^{[3]}\) Recently, NAFLD has become the second most common chronic hepatic disease in China, ranking only after hepatitis virus B, and the development of cirrhosis in NASH patients is as high as 15% to 25% within 10 to 15 years.\(^{[4]}\) Potential risk factors for NAFLD include a high-fat, high-calorie dietary pattern; lifestyles with more sitting and less physical activity; metabolic syndrome (MS) and its main components (obesity, hypertension, dyslipidemia, and hyperglycemia); and insulin resistance (IR).\(^{[5]}\)

Uric acid is the end metabolite of purine in the body.\(^{[6]}\) In recent years, the incidence of hyperuricemia (HUA) has increased rapidly. HUA has been confirmed to be associated with IR, MS, and its related components, such as diabetes, hypertension, obesity, hyperlipidemia, and nonalcoholic fatty liver. Previous studies have confirmed that HUA is also one of the important components of MS, and HUA may trigger IR and maybe an independent risk factor for MS.\(^{[7,8]}\)
Many studies have clarified that the serum uric acid (SUA) level is closely related to NAFLD. Li et al. confirmed that ultrasound-diagnosed NAFLD patients had obviously higher SUA levels than controls, that SUA levels were associated with NAFLD, and that elevated SUA levels were an independent risk factor for NAFLD. Petta et al. demonstrated that the degree of SUA elevation was independently associated with the severity of liver tissue damage in NAFLD patients. Hwang et al. showed that elevated SUA, even within the normal range, was also independently associated with NAFLD occurrence. A prospective observational study also found that elevated SUA levels could independently predict an increased risk for incident NAFLD. In contrast, some studies have shown that the SUA level was not associated with NAFLD occurrence. Thus, the association between SUA level and NAFLD is still uncertain, and few studies have been conducted on T2DM patients. Herein, we explored the relationship between SUA levels and NAFLD in T2DM patients.

2. Patients and methods

2.1. Patients

We enrolled T2DM patients who were hospitalized in the Department of Hepatology, Yantai Qishan Hospital between April 2012 and December 2018. Diet intake was based on the standard meals for all T2DM patients provided by the hospital. Patients received liver examination through color Doppler ultrasonography with a 3.5-MHz probe (Toshiba, Tokyo, Japan). T2DM was diagnosed according to the 1999 World Health Organization diagnostic criteria. Patients with 1 of the following conditions were excluded: 1) type 1 diabetes, gestational diabetes, or acute complications of diabetes; 2) viral hepatitis, liver fat deposition caused by autoimmune liver disease, liver cirrhosis, or other causes; 3) acute and chronic urinary tract infection, acute and chronic nephritis, primary nephropathy, diabetic nephropathy stage V, and other severe kidney diseases; 4) current oral administration of drugs that affect uric acid metabolism; 5) acute infectious diseases, congestive heart failure (New York heart association class > 2), or inadequate hepatic, pulmonary, and renal function; and 6) medical history of hyperuricemia or gout.

The diagnostic criteria for NAFLD were in accordance with the 2010 Guidelines for the Diagnosis and Treatment of Nonalcoholic Fatty Liver Diseases: no history of excessive alcohol consumption (>140 g/week for males and >70 g/week for females) and histological changes in liver biopsy consistent with the pathological diagnostic criteria for fatty liver disease. Considering that liver histology diagnosis is difficult to obtain, NAFLD was defined as liver imaging manifestation meeting the diagnostic criterion for diffuse fatty liver (the presence of at least 2 of the following 3 abnormal findings: diffuse hyperechogenicity of the liver relative to the kidneys, attenuation of the ultrasound beam, and poor visualization of intrahepatic architectural details), with no other explanation. Patients with T2DM were classified into the NAFLD group and the non-NAFLD group. This study was approved by the Ethics Committee of Yantai Qishan Hospital, and the requirement for informed consent was waived by the Ethics Committee due to the retrospective design.

2.2. Data collection

The baseline data, including age, sex, smoking and alcohol consumption history, T2DM duration, complications (viral or autoimmune hepatitis, hypertension, tumor, primary kidney, etc), and usage of statins or antihypertensive drugs were collected from the medical records. Physical examinations were performed and clinical data were collected, including height, weight, waist circumference, waist-to-hip ratio, systolic blood pressure (SBP), and diastolic blood pressure. Venous blood samples were obtained for the detection of SUA, creatinine, triglycerides (TGs), cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, glycosylated hemoglobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and glutamyl transpeptidase. Fasting plasma glucose (FPG), plasma glucose 2h after a 75 g oral glucose load, fasting insulin (FINS), and fasting C-peptide (FC-P) were also recorded. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration formula (15). A homeostasis model was performed to evaluate IR: Homeostatic model assessment for insulin resistance (HOMA-IR) = FINS (mIU/L) × FPG (mmol/L)/22.5.

2.3. Statistical analysis

The distributions of continuous variables were analyzed by the Kolmogorov–Smirnov test. Normally distributed data are shown as the mean ± standard deviation and were compared by Student t test. Non-normally distributed data are indicated as the median (interquartile range) and were analyzed using the Mann–Whitney U test. Categorical variables are shown as frequencies and were analyzed using the chi-square test or Fisher exact test if appropriate. Pearson correlation analyses and multiple linear regression analyses (stepwise) were performed to explore the correlation between SUA level and other clinical characteristics (such as age, disease duration of T2DM, body mass index (BMI), blood pressure, glucose and lipid metabolism parameters, biochemical results of liver and kidney function, etc.). Multivariate regression analyses, including 3 calibration models, were performed to analyze factors independently associated with the occurrence of NAFLD in patients with T2DM (entered method), and the corresponding odds ratio (OR) and 95% confidence interval (CI) were calculated. Model I was adjusted for age, sex, T2DM duration, BMI, SBP, alcohol consumption history, and eGFR; Model II was adjusted for TGs, HbA1c, HOMA-IR, usage of statins, or antihypertensive drugs in addition to the factors adjusted in Model I. Model III was adjusted for FC-P, HDL-C, AST, and ALT in addition to the factors adjusted in Model II. The SUA tertiles were defined as follows: SUA tertile I: <278 μmol/L; SUA tertile II: 278–354 μmol/L; and SUA tertile III: >354 μmol/L. All analyses were performed by SPSS 20.0 (IBM, Armonk, NY, USA). A two-sided P-value <0.05 was considered significant.

3. Results

3.1. Demographic and clinical characteristics of the T2DM patients

Five hundred eighty-three patients who met the inclusion and exclusion criteria were classified into the non-NAFLD group (n = 227) and the NAFLD group (n = 356). Patients with NAFLD had a shorter T2DM duration (P < .001), lower levels of HDL-C (P < .001), and higher levels of BMI (P < .001), waist circumference (P < .001), waist-to-hip ratio (P < .001), diastolic blood pressure (P = .002), cholesterol (P = .002), TGs (P < .001), ALT (P < .001), AST (P < .001), glutamyl transpeptidase (P < .001), eGFR (P = .031), 2-h plasma glucose (P = .013), FINS (P < .001),
occurrence in T2DM patients

3.3. Relationship between SUA tertile and NAFLD

T2DM patients. The results are illustrated in Table 2.

independently and negatively correlated with eGFR (P < .001). Multiple linear regression analyses (stepwise) revealed that SUA was independently and positively correlated with BMI (P = .003), TGS (P = .009), AST (P = .036), and ALT (P = .038) and independently and negatively correlated with eGFR (P < .001) in T2DM patients. The results are illustrated in Table 2.

3.3. Relationship between SUA tertile and NAFLD occurrence in T2DM patients

Comparisons of NAFLD occurrence in T2DM patients classified according to SUA tertile are shown in Figure 1. The results showed that the prevalence of NAFLD gradually increased as

and HOMA-IR (P < .001) than those without NAFLD. It is worth noting that the SUA level in the non-NAFLD group was significantly higher than that in the non-NAFLD group (342 ± 88 vs 295 ± 93 μmol/L, P < .001). The baseline data of the 2 groups are presented in Table 1.

3.2. Correlation analyses between SUA and other metabolic risk factors

Pearson correlation analyses showed that the SUA level was positively correlated with BMI (P < .001), TGS (P < .001), HOMA-IR (P = .041), AST (P = .002), and ALT (P = .008) but negatively correlated with HDL-C (P = .027) and eGFR levels (P < .001). Multiple linear regression analyses (stepwise) revealed that SUA was independently and positively correlated with BMI (P = .003), TGS (P = .009), AST (P = .036), and ALT (P = .038) and independently and negatively correlated with eGFR (P < .001) in T2DM patients. The results are illustrated in Table 2.

3.3. Relationship between SUA tertile and NAFLD occurrence in T2DM patients

Comparisons of NAFLD occurrence in T2DM patients classified according to SUA tertile are shown in Figure 1. The results showed that the prevalence of NAFLD gradually increased as
non-NAFLD group ($P < .001$). Multiple linear regression analyses indicated that SUA was positively and independently correlated with BMI, TGs, AST, and ALT and negatively and independently correlated with eGFR in T2DM patients. Logistic regression analyses demonstrated that after adjusting for confounding factors, the SUA tertiles were still significantly associated with the occurrence of NAFLD. Using SUA tertile I as the reference, the OR for NAFLD in SUA tertile II and SUA tertile III were 1.729 (95% CI: 1.086–2.753) and 2.315 (95% CI: 1.272–4.213), respectively.

The results of our study also suggested that the SUA level was an independent risk factor for the comorbidity of NAFLD in T2DM patients, which was in line with the result of a meta-analysis.[13] Many previous studies, including cross-sectional surveys and prospective studies, have established the viewpoint that SUA levels are increased in NAFLD patients and are an independent risk factor for NAFLD occurrence. The occurrence of NAFLD in 583 T2DM patients in this study was 61.6%, which was close to the previous pooled prevalence of NAFLD in T2DM patients in a meta-analysis (59.7%, 95% CI: 54.3–64.9).[13]

Table 3

| SUA tertile I | SUA tertile II | SUA tertile III |
|---------------|---------------|-----------------|
| OR (95% CI)   | P for trend   | P for trend     |
| Model I       | 1.835 (1.115–3.021) | 2.663 (1.221–2.173) | <.001 |
| Model II      | 1.629 (1.084–2.440) | 2.571 (1.378–4.797) | .018 |
| Model III     | 1.729 (1.086–2.753) | 2.315 (1.272–4.213) | .006 |

The data was presented as an OR value and a 95% CI compared to the tertile I group. T2DM without NAFLD patients were defined as 0, and T2DM with NAFLD patients were defined as 1.

Model I: Adjust for age, gender, T2DM duration, BMI, SBP, drinking history, and eGFR.
Model II: Adjust for TGs, HbA1c, HOMA-IR, usage of statin, or anti-hypertensive drugs on the basis of Model I.
Model III: Adjust for FC-P, HDL-C, AST, and ALT on the basis of Model II.

Figure 1. Prevalence of NAFLD in T2DM patients according to SUA tertile. SUA tertile I: <278 μmol/L; SUA tertile II: 278–354 μmol/L; SUA tertile III: >354 μmol/L; and $P$ for trend <.001. NAFLD = nonalcoholic fatty liver disease, SUA = serum uric acid, T2DM = type 2 diabetes.

highlighting the unmet requirement of identifying the risk factors for incidental NAFLD. Sung et al.[16] found that the SUA level was an independent predictor of NAFLD occurrence in obese children in Italy. Hayden and Tyagi[17] also found that uric acid had a strong oxidant effect in patients with MS and was associated with the occurrence of NAFLD. Lee et al.[18] conducted a study in 3768 healthy Koreans and found that HUA was an independent predictor of NAFLD, independent of MS, sex, BMI, fasting blood glucose, blood lipids, and other potential risk factors. A study of 10,732 nondiabetic US adults evaluated the relationship between HUA and ultrasound-diagnosed NAFLD and found that elevated SUA was significantly associated with the occurrence and severity of NAFLD.[19] A large cohort of 5741 healthy Korean males found that 1717 subjects (29.9%) developed ultrasound-diagnosed NAFLD during the 5-year follow-up period, and the hazard ratio of individuals with SUA ≥ 7.0 mg/dL was 1.29 (1.14–1.46) compared to those with SUA < 7.0 mg/dL.[20] These previous studies not only indicated that SUA evaluation could be applied to predict current or future NAFLD occurrence but also implied that SUA might contribute to the development of NAFLD.

In our study, the results from Pearson correlation analyses showed that the SUA level was positively correlated with BMI, TGs, HOMA-IR, AST, and ALT but negatively correlated with HDL-C and eGFR levels, which was broadly in line with a previous study of Chinese T2DM patients.[21,22] Obesity, increased TGs, and impaired IR are factors generally known to be associated with an increased risk of NAFLD occurrence.[23] suggesting the possibility that the correlation between SUA and NAFLD could be mediated, at least in part, through these potential factors.

Our study demonstrated the association between increased SUA (vs SUA tertile I) and elevated NAFLD occurrence in T2DM patients, which was in broad agreement with findings from previous studies.[21,24,25] Interestingly, after adjustment for numerous potential risk factors and metabolic factors, including age, sex, T2DM duration, BMI, SBP, alcohol consumption history, eGFR, TGs, HbA1c, HOMA-IR, usage of statins or antihypertensive drugs, FC-P, HDL-C, AS, and ALT, the clear trend toward the association between a higher SUA tertile and a higher occurrence rate of NAFLD in T2DM patients could still be noted, with significant differences detected. Therefore, an
independent association between SUA tertiles and NAFLD occurrence was indicated by our analysis.

This study also had some shortcomings. First, this was a single-center study with small sample size, the clinical applicability may be limited, and sex differences in the relationship between SUA tertiles and NAFLD occurrence were not further explored. Second, due to the cross-sectional study design, it was impossible to determine the causal relationship between SUA and NAFLD in T2DM patients. Therefore, the exact contribution to increased SUA levels attributed to the nature of NAFLD or obesity-related metabolic syndrome still could not be differentiated or concluded. Third, the sensitivity and specificity of liver ultrasonography for detecting mild hepatic steatosis were not as good as liver biopsy, which is considered the gold standard of NAFLD diagnosis. In addition, although the advantages of ultrasonography are its noninvasive-ness and wide application, NAFLD severity was not graded in this survey, and the correlation between SUA and the severity of hepatic steatosis should be explored in future studies.

5. Conclusion

The SUA level in T2DM patients was significantly associated with NAFLD occurrence. With elevated SUA levels, the prevalence of NAFLD was obviously increased. Elevated SUA levels were an independent risk factor for NAFLD occurrence in patients with T2DM.

Author contributions

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