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Correlation between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease: A Cross-Sectional Study

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the important health issues with high prevalence worldwide. However, there is no approved medication for that. As one of the indicators of metabolic syndrome, uric acid might play a role in the pathogenesis of NAFLD. In this study, we aimed to determine the correlation between serum uric acid level, liver enzymes, and ultrasonographic grading of NAFLD.

Methods: This cross-sectional study included patients aged 18-65 with NAFLD. Patients with other metabolic disorders and a history of using alcohol or medications that alter uric acid levels were excluded. The patients' serum uric acid, alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and ultrasonographic grading of NAFLD at baseline, third month, and sixth month were collected.

Results: Of the 3000 patients, 500 patients met the eligibility criteria. The results showed that there is a significant positive relationship between ALT and serum uric acid level at the first (P= 0.01), third (P=0.01), and sixth month (P=0.01). Furthermore, there was a significant positive correlation between AST and serum uric acid level at the sixth month (P= 0.001). The comparison of 249 patients' ultrasonographic grading showed no significant correlation with serum uric acid levels.

Conclusion: To conclude, the serum uric acid level significantly correlates with ALT and AST over six months but not with the ultrasonographic grading. Further studies are required to determine the role of uric acid-lowering agents in the treatment of NAFLD.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is among the most common reasons for chronic hepatic disorders, with a high prevalence affecting approximately 24% of individuals worldwide. NAFLD is associated with the accumulation of excessive fat in the hepatocytes in the absence of alcohol consumption. This disorder is generally asymptomatic; however, some patients might experience fatigue and right upper quadrant pain (1-3).

As the disease progressed to higher stages, the level of the liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) usually increased (4). Various imaging methods such as ultrasound, computerized tomography scan, and magnetic resonance imaging recognize changes in the liver (5). Although the liver biopsy is the gold standard for identifying NAFLD, it cannot be

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used in all patients due to the high cost and invasiveness (6-8). Ultrasound is a simple and non-invasive technique that can be a practical method for detecting liver changes (9). Based on ultrasound results, NAFLD is classified into four stages (10).

The prevalence of NAFLD is significantly high among individuals with cardiovascular diseases, dyslipidemia, type 2 diabetes, and abdominal obesity; this highlights the role of metabolic syndrome in NAFLD pathogenesis. Therefore, NAFLD can be mentioned as a hepatic indicator of metabolic syndrome (11-13).

Uric acid, the finished product of purine nucleotide metabolism, has inflammatory properties and is related to several disorders such as gout, diabetes, and nephrolithiasis (14).

According to several studies, serum uric acid levels increased in metabolic syndrome. Moreover, uric acid might contribute to fat accumulation in the liver through the induction of insulin resistance (15, 16). In this regard, the relation between NAFLD and serum uric acid has been under consideration over recent years. Notably, this can be an opening for a new treatment modality since there is no approved treatment for NAFLD (15, 17-19). Thus, this study aimed to evaluate the correlation between the serum uric acid level and NAFLD indicators in the Iranian population. Considering the correlation between ultrasonographic grading of NAFLD and cardiovascular disease risk, the effective pharmacotherapy that could improve the ultrasonographic grading might decrease these risks as well (20).

To the best of our knowledge, this cross-sectional study is the first investigation that focused on the association between uric acid and the ultrasonographic grading of NAFLD.

Methods

The study process was confirmed by the ethics committee of Tabriz University of Medical Sciences with the identifier: TBZMED.REC.1396.1111. Informed consent was obtained from each patient included in the study. The study protocol conforms to the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee.

Patients with normal average weight (body mass index 18.5 to 24.9 kg/m2) aged 18-65 years with an approved diagnosis of NAFLD entered the study. The diagnosis of NAFLD was according to the results of ultrasound and laboratory data (ALT and AST) confirmed by a specialist. The study's exclusion criteria were chronic disorders, such as malignancy, chronic kidney disease and heart failure, pregnancy, breastfeeding, alcohol consumption, and history of using medications that alter serum uric acid levels, such as allopurinol and uricosuric agents. Also, patients did not have other metabolic syndromes, including obesity or comorbidities like polycystic ovarian syndrome and type 2 diabetes.

This retrospective cross-sectional study was accompanied in Imam Reza Hospital from August 22, 2016, to August 21, 2017. Data including serum uric acid, ALT, AST, and ultrasonographic grade at baseline, third month, and sixth month were collected according to the inclusion and exclusion criteria.

Data were analyzed using SPSS-24 (SPSS Inc., Chicago, IL). Continuous data were reported as mean ± standard deviation (SD). The normal distribution of data was confirmed by the Kolmogorov-Smirnov test. The chi-square test was conducted for the comparison of categorical variables. The Pearson test and logistic regression were conducted to analyze the relationship between serum uric acid level, liver enzymes, and ultrasonographic grading of NAFLD. P-values lower than 0.05 were assumed to be statistically significant.

Results

Of the 3000 enrolled patients, 500 patients met the eligibility criteria for analysis. 42.4 % of the patients were men. The mean (SD) ages of men and females were 47.3 (10.7) and 46.5 (9.6) years old, respectively.

The mean ± SDs for the levels (U/L) of ALT and AST were decreased over six months; 27.6 ± 14.1 versus 21.9 ± 19.3 for AST and 32.8 ± 20 versus 25.3 ± 21.5 for ALT at the first and sixth months, respectively. Also, the mean ± SD for the serum uric acid level (mg/dl) was decreased from 5.5 ± 2.9 to 4.1 ± 2.9 over six months (Table 1).

The results of correlation analysis between serum uric acid and liver enzymes showed that there is a significant positive relationship between ALT and serum uric acid level at first ($R = 0.133$, $P = 0.01$), third ($R = 0.141$, $P = 0.01$), and sixth months ($R = 0.615$, $P = 0.01$). Furthermore, there was a positive correlation between AST and serum uric acid levels in the sixth month, which was statistically significant ($P = 0.001$, $R = 0.5$). However, there was no meaningful relationship between them during the first and third months (Table 2). The statistically significant positive correlation between sixth-month ALT and AST with serum uric acid levels persisted after adjusting for sex and age ($P = 0.001$).

Of the 500 patients, the ultrasonographic grade of 249 patients was evaluated at baseline (221 patients had grade 1 and 28 patients had grade 2 and 3 NAFLD). The analysis of the correlation between ultrasonographic grading and sex showed no significant association ($P = 0.1$ for grade 1, $P = 0.4$ for grade 2, and $P = 0.2$ for grade 3). The P-values for comparing first, third, and sixth-month uric acid levels with ultrasonographic grading of NAFLD were 0.9, 0.3, and 0.7, respectively, which showed no significant correlation between ultrasonographic grading and serum uric acid levels.

Table 1. Mean levels of serum uric acid and liver enzymes at first, third, and sixth month

Variable	First month	Third month	Sixth month
Uric acid (mg/dl)	5.5 ± 2.9	5.3 ±1.3	4.1 ± 2.9
AST (U/L)	27.6 ± 14.1	26.2 ± 12.1	21.9 ± 19.3
ALT (U/L)	32.8 ± 20	31.1 ± 18.1	25.3 ± 21.5

Data are expressed as mean ± SD.
ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; SD, Standard deviation

Table 2. The correlation between serum uric acid and liver enzymes at first, third, and sixth month

	Uricacid1	Uricacid2	Uricacid3
ALT1	R = 0.133**	R = 0.057	R = 0.088
ALT2	R = 0.093*	R = 0.141**	R = 0.066
ALT3	R = 0.037	R = 0.117**	R = 0.615**
AST1	R = 0.072	R = 0.005	R = 0.005
AST2	R = 0.012	R = 0.055	R = 0.030
AST3	R = 0.013	R = 0.088*	R = 0.574**

baseline, 2 third month, 3 sixth month; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; R Pearson correlation 1
*P-value = 0.05, **P-value = 0.01

Discussion

It is necessary to study different pathological aspects regarding the high prevalence of NAFLD, its association with several disorders, and the lack of approved medication for treatment. Also, finding the potential mechanisms and underlying risk factors is substantial for the management of this disorder. Considering the potential role of uric acid in the pathophysiology of NAFLD, the xanthine oxidase inhibitors as uric acid lowering agents can be regarded as beneficial medications for the management of the disease (2, 15). Thus, additional studies are required to assess the relationship between uric acid and NAFLD.

In the current cross-sectional study, we highlighted an association between ALT and serum uric acid levels during a 6-month period. However, no significant relation between serum uric acid level and ultrasonographic grading was observed. In addition, according to our results, over half of the study population were women. In a meta-analysis conducted by Moghaddasifar et al., it has been indicated that NAFLD has a greater prevalence among men in the Iranian population (21). Of note, in this study, the serum uric acid and aminotransferases levels were in the normal range because most of the patients had grade 1 NAFLD, according to the ultrasonographic results. In addition, the function of the liver cannot be evaluated by enzymes, and aminotransferases only show temporary and acute liver injury (22).

In a meta-analysis of 28446 patients with NAFLD conducted by Gong et al., it has been shown that there is a correlation between hyperuricemia and NAFLD in both male and female patients. The results have revealed that among the individuals with hyperuricemia, the risk of NAFLD was significantly higher than individuals with no hyperuricemia (relative risk [RR] = 1.79, 95% confidence interval [CI] 1.55-2.07, P<0.001). Unlike our study, this study did not clarify the correlation between ultrasonographic grading, liver enzymes, and serum uric acid level. Also, several sources of heterogeneity were observed among the included studies (23).

Lonardo et al., in a case-control study on 120 patients, showed that the risk of NAFLD was increased with elevation of fasting insulin log (RR = 16.18, 95% CI 5.37-48.77) and serum uric acid (RR = 9.14, 95% CI 3.48-24.00) levels based on logistic regression analysis. This study aimed to assess only the potential biochemical predictors of NAFLD, and unlike our study, the effect of serum uric acid levels on ultrasonographic grading was not evaluated (24).

In 2011, a cohort of 5741 Korean men by Ryu et al., evaluated the link between uric acid level and fatty liver incidence. Under-study participants aged between 30 to 59 years old were healthy, and baseline data showed no evidence and a risk factor for fatty liver disease. The follow-up from

2002 to 2008 revealed that after adjusting for body mass index and other cardiometabolic factors, higher serum uric acid level was related to the greater incidence of fatty liver. However, this study just considered the Korean population and men, limiting the results' interpretation (25).

The relation between NAFLD and hyperuricemia has been revealed in Xu et al., study. The data showed that xanthine oxidase has a mediator role between hyperuricemia and NAFLD (26). Furthermore, a study conducted by Petta et al., showed an association between hyperuricemia and the severity of hepatic damage and steatosis grade. This study included 166 patients with biopsy-confirmed NAFLD, performed during the last six months before entering the study (27). The relation between serum uric acid level and liver histology was investigated by Sertoglu et al., In this study, 242 men with histologically assessed NAFLD (140 with simple steatosis and 102 with non-alcoholic steatohepatitis were entered. The results showed that in patients with non-alcoholic steatohepatitis, the serum uric acid levels were significantly higher in comparison to those suffering from simple steatosis (28).

The results of our study showed that hepatic enzymes (ALT and AST) are increased in the early stages of NAFLD, and their levels may decrease in the late stages of the disease. The ALT serum concentration is usually higher than the AST level in patients with NAFLD. It illustrates the importance of ALT as a specific liver enzyme for diagnosing liver disorders. The findings of our study are consistent with the mentioned studies. A similar result was reported in a prospective observational study by Xu et al. They found that elevated serum uric acid level as an independent issue increases the possibility of NAFLD (29). Sirota et al., showed an association between high serum uric acid and NAFLD after adjustment for metabolic syndrome factors. Also, they showed a significant correlation between serum uric acid and liver ultrasound grade (30). According to these findings, monitoring the efficacy of pharmacotherapy of NAFLD can be based on the serum uric acid levels since it is correlated with the ultrasonographic grading and the level of liver enzymes. Also, there is an association between ultrasonographic grading of NAFLD and cardiovascular disease risk. Hence, the effective pharmacotherapy that could improve the ultrasonographic grading might decrease these risks as well. Therefore, the use of drugs that reduce serum uric acid level might play a role in the pharmacotherapy of NAFLD. Although our study revealed no relationship between serum uric acid and hepatic ultrasound grade, further investigations are required.

The current study had some limitations. First, the population and the follow-up period of the study might be limited. Therefore, studies with more sample size and long follow-up period are suggested for future studies. Second, we could not extrapolate our results to patients with concomitant metabolic disorders, for example, obesity and type 2 diabetes. Third, although we adjusted the results for sex and age, other confounding factors may also exist.

To conclude, there was a strong association between serum uric acid level and liver enzymes (ALT and AST) after six months, which can be assumed as an independent index for evaluating NAFLD. However, ultrasonographic grading did not correlate with serum uric acid levels, which requires further studies.

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