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Relationship Between N-AFLD and Serum Uric Acid Levels in Non-Diabetic and Non-Obese Adults

Diyabetik Olmayan ve Obez Olmayan Yetişkinlerde N-AFLD ile Serum Ürik Asit Düzeyleri Arasındaki İlişki

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ABSTRACT

Objective: Many studies are interested in the association between non-alcoholic fatty liver disease (N-AFLD) and other parameters. Our study evaluated the association between serum uric acid (SrUA) levels and N-AFLD in non-diabetic non-obese adults.

Methods: In this study, 50 patients and 50 control subjects were enrolled to investigate the association between SrUA and N-AFLD in adults. The Kruskal-Wallis test was used to compare SrUA values according to ultrasonographic liver fat levels.

Results: A statistically significant difference was found between the N-AFLD and control subjects according to the mean SrUA level ($p<0.001$). In the N-AFLD group, a positive relationship was found between SrUA levels and homeostasis model assessment of insulin resistance values ($r=0.35$, $p<0.001$).

Conclusion: In this study, an important positive relationship was detected between SrUA levels and N-AFLD and insulin resistance.

Keywords: N-AFLD, non-diabetic, non-obese, serum uric acid, HOMA-IR, metabolic syndrome

ÖZ

Amaç: Birçok çalışma non-alkolik yağlı karaciğer hastalığı (NAYKH) ile diğer parametreler arasındaki ilişkiyi ortaya koymaktadır. Çalışmamız diyabetik ve obez olmayan yetişkinlerde serum ürik asit (SrUA) ile NAYKH arasındaki ilişkiyi değerlendirmektedir.

Yöntemler: Bu çalışmaya yetişkinlerde SrUA ile NAYKH arasındaki ilişkiyi göstermek için 50 hasta ve 50 kontrol grubu dahil edildi. SrUA değerlerinin ultrasonografik karaciğer yağ düzeylerine göre karşılaştırılmasında Kruskal-Wallis testi kullanıldı.

Bulgular: Ortalama SrUA düzeyine göre NAYKH grubu ile kontrol grubu arasında istatistiksel olarak önemli bir fark bulundu ($p<0,001$). NAYKH grubunda SrUA düzeyi ile insülin direnci değerlerinin homeostaz modeli değerlendirmesi arasında pozitif ilişki bulundu ($r=0,35$, $p<0,001$).

Sonuç: Bu çalışmada SrUA düzeyleri ile NAYKH ve insülin direnci arasında pozitif yönde önemli bir ilişki tespit edilmiştir.

Anahtar Sözcükler: N-AFLD, diyabetik olmayan, obez olmayan, serum ürik asit, HOMA-IR, metabolik sendrom

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INTRODUCTION

Non-alcoholic fatty liver disease (N-AFLD), which is associated with metabolic syndrome (MSy), is a pathological finding in the liver. Triglyceride (TG), which causes hepatic fat deposition, is called N-AFLD when other reasons for steatosis are excluded. The incidence in Western countries is estimated to be between 20% and 30% (1). Although N-AFLD does not progress to more severe liver diseases in most cases, 20-30% of patients with N-AFLD have histological findings such as fibrosis and necroinflammation, which are indicators of non-alcoholic steatohepatitis.

N-AFLD includes clinical variability, starting with simple steatosis and progressing to fibrosis and cirrhosis that may cause hepatocellular carcinoma (2,3). N-AFLD, which is accepted as a metabolic disorder, is related to insulin resistance (IR) and MSy. Similar to N-AFLD, serum uric acid (SrUA) is associated with both cardiovascular diseases and MSY (4). Some studies have shown that SrUA is remarkably related to N-AFLD and that a high SrUA quantity is an independent risk factor for N-AFLD (5-9). The underlying mechanisms have not yet been elucidated. Although obesity is one of the prominent risk factors for N-AFLD, N-AFLD can be seen in people who are not obese. N-AFLD can be reflected as a primary indicator of metabolic disorders and the main response to cryptogenic liver disease in the non-obese population.

This study aimed to hypothesize the correlation between SrUA levels and non-obese non-diabetic N-AFLD.

MATERIALS AND METHODS

Fifty patients who were admitted to the Kırıkkale University Faculty of Medicine Research and Application Hospital, Clinic of Gastroenterology between 2010 and 2011 were enrolled in this study. The control group comprised 50 individuals who were referred to the same outpatient clinics with various complaints.

The exclusion criteria wereas follows: Cases over 70 years and less than 18 years of age, with weekly alcohol consumption >40 g, diagnosed diabetes mellitus (DM) or newly diagnosed DM, diagnosed with acute or chronic viral hepatitis in the serological and histopathological examination, those with hereditary disease (Wilson's disease, hemochromatosis, α1-antitrypsin deficiency, etc.), primary biliary cirrhosis, and autoimmune hepatitis serology positive cases, who use drugs for any reason, those with acute or chronic disease, previously jejunoileal bypass or small bowel resection, malignant disease, smoking history, cases with total parenteral nutrition, and pregnancy history were excluded from the study. Ethics committee approval was obtained from the Kırıkkale University Faculty of Medicine Local Ethics Committee (approval number: 2010/0028, dated 07.06.2010).

Height, weight, and waist circumference were calculated, and body mass indexes (BMI) were calculated using the formula (kg)/height2 (m^2). Patients with a BMI of 30 or higher were considered obese. Patients who drank more than 40 g of alcohol per week were excluded by performing detailed anamnesis. Ultrasonography was performed for the diagnosis of N-AFLD, and ultrasound was performed by a radiologist who was not aware of the purpose of the study or laboratory data.

Laboratory procedures were performed in the Kırıkkale University Faculty of Medicine Research and Application Hospital biochemistry laboratory, and ultrasonographic evaluation was performed in the radiology department. The waist circumference of the patients was measured while they were hungry and measured from the middle of the distance between the iliac crest and the lower rib. The blood pressures of the patients were measured with an ideal sphygmomanometer from the right arm in the sitting position after 20-30 min of rest. The American Hypertension Society recommendations were followed in blood pressure measurements. Blood samples were taken after 12 h of fasting; fasting blood glucose (FBG), total cholesterol (TC), TG, high-density lipoprotein (HDL), fasting serum insulin, and uric acid levels were evaluated. The low-density lipoprotein (LDL) level was calculated using the Friedewald formula [LDL = TC (VLDL + HDL); VLDL = TG/5]. The homeostasis model assessment of insulin resistance (HOMA-IR)-formula was used to determine IR. The HOMA-IR index was calculated according to the following formula: FBG (mmol/L) fasting insulin (μIU/L)/22.5.

Statistical Analysis

Statistical analysis was performed using the Statistical Analysis Software (SPSS) 17 (Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. Age, biochemical parameters, hip circumference, waist circumference, BMI, and blood pressure measurements were compared using Student's t-test. The Kruskal-Wallis test was used to compare SrUA values according to ultrasonographic liver fat levels. For qualitative variables (gender, etc.), the chi-square test was used for comparison. Analysis results: for qualitative variables, the percentage and frequency were expressed as mean ± standard deviation for continuous variables. P<0.05 was considered statistically significant in all analyses.

RESULTS

Fifty patients with N-AFLD and 50 subjects with no fatty liver disease-totaling 100 cases-were enrolled in the study. The median age of the N-AFLD group was 45.6±8.3 years, and that of the control group was 37.0±15.0 years. Both groups consisted of 22 male and 28 female patients. The BMI was 25.86±1.57 in the N-AFLD group and 24.30±2.95 in the control group, and a statistically significant difference was found between the two subjects according to BMI (Table 1). According to hip circumference, TC, LDL, TG, FBG, and diastolic and systolic blood pressure values, no statistically significant difference was found between the two subjects (Table 1). Waist circumference was found to be higher in the N-AFLD subject than in the control subject, and this difference was found to be statistically significant (p=0.014). TG and HOMA-IR levels were found to be statistically significant (Table 1). In the N-AFLD subject than in the control subject, HDL levels were found to be lower (p=0.047). The mean SrUA level was 5.28±1.15 mg/dL in the N-AFLD subject and 4.16±0.82 mg/dL in the control subject (Figure 1). A statistically significant difference was found between the N-AFLD and control subjects according to the mean SrUA level (p<0.001) (Table 1).

In the N-AFLD group, no relationship was found between SrUA level and FBG (r=-0.066, p=0.648), TC (r=-0.043, p=0.764), LDL (r=-0.166, p=0.249), HDL (r=-0.162, p=0.261), TG (r=0.212, p=0.139) levels, age (r=0.028, p=0.844), waist (r=0.075, p=0.603), and hip (r=0.086,

p=0.551) circumference measurements. The mean HOMA-IR value was 3.21±1.03 in the N-AFLD subject and 1.54±0.48 mg/dL in the control subject (Figure 2). A positive relationship was found between the SrUA level and HOMA-IR values (r=0.35, p<0.001).

Table 1. Comparison of clinical, laboratory, and demographic data of non-obese non-diabetic N-AFLD patients and controls

		N-AFLD	Control	p
(n)		50	50	
Age (years)		45.64±8.39	37.04±15.03	**0.001***
Gender	Male	22 (%44)	22 (%44)	1**
	Female	28 (%56)	28 (%56)	
BMI (kg/m^2)		25.86±1.57	24.30±2.95	**0.001***
Waist circumference (cm)		87.80±5.73	84.60±6.77	**0.014***
Hip circumference (cm)		98.16±4.73	99.12±5.94	0.374*
SBP (mmHg)		118.80±7.46	118.20±7.19	0.683*
DBP (mmHg)		74.40±6.44	72.80±7.57	0.258*
FBG (mg/dL)		89.86±6.44	89.04±6.82	0.538*
TC (mg/dL)		172.8±24.6	178.8±27.9	0.258*
TG (mg/dL)		125.8±33.9	111.4±43.6	0.069*
LDL (mg/dL)		103.4±22.3	102.4±24.3	0.834*
HDL (mg/dL)		47.5±10.5	52.4±13.6	**0.047***
SrUA (mg/dL)		5.28±1.15	4.16±0.82	**<0.001***
HOMA-IR		3.21±1.03	1.54±0.48	**<0.001***

*: Student's t-test, **: Chi-square test, N-AFLD: Non-alcoholic fatty liver disease, SD: Standard deviation, BMI: Body mass index, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, FBG: Fasting blood glucose, TC: Total cholesterol, TG: Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SrUA: Serum uric acid, HOMA-IR: Homeostasis model assessment of insulin resistance

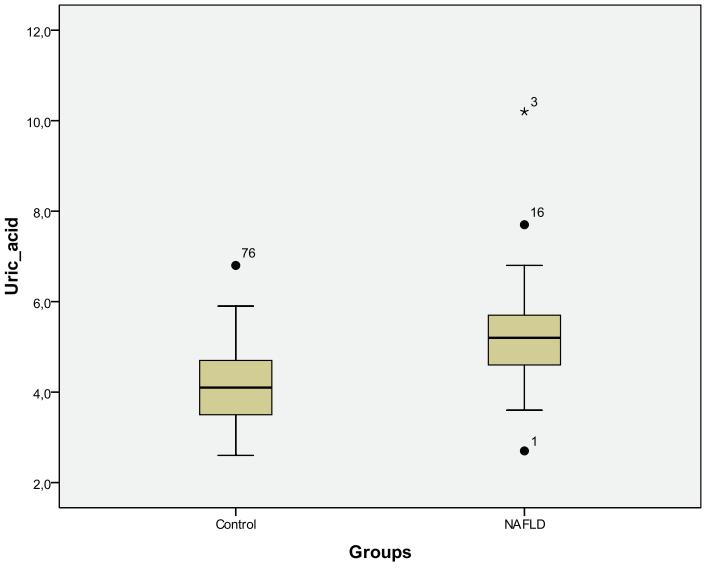

Figure 1. Uric acid levels in patients with N-AFLD and controls
N-AFLD: Non-alcoholic fatty liver disease

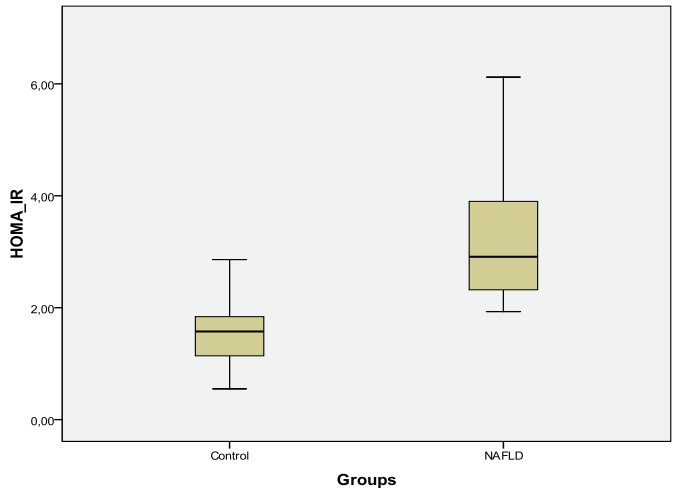

Figure 2. HOMA-IR levels in patients with N-AFLD and controls
HOMA-IR: Homeostasis model assessment of insulin resistance, N-AFLD: Non-alcoholic fatty liver disease

DISCUSSION

N-AFLD is a prominent etiological cause of chronic liver disease and cirrhosis. It is thought that many factors play a role in the progression of N-AFLD. N-AFLD is thought to be a manifestation of MSy in the liver because its correlation with MSy components such as HT, hyperlipidemia, central obesity, and type 2 DM is common.

SrUA is the final result of purine metabolism. Similar to N-AFLD, SrUA is related to obesity, HT, atherosclerosis, and IR (10). Studies have reported a correlation between SrUA and N-AFLD and that SrUA is an independent risk factor for N-AFLD (8,11,12). Hyperuricemia is correlated with N-AFLD independently of the initial metabolic risk factors. Because of clinical studies, the relationship between hyperuricemia and N-AFLD has been shown, and many underlying mechanisms have been suggested. SrAU level is strongly associated with IR as well as N-AFLD (13). Insulin facilitates renal tubular uric acid absorption (13). IR is one of the most prominent factors in the development of N-AFLD and Msy (14). After IR improves, SrUA levels decrease significantly, revealing that hyperuricemia is an important marker for IR (15). In addition, the increase in SrUA stimulates the release of inflammatory factors and may contribute to the increase of IR by causing oxidative stress (16). A high SrUA level may accelerate the development of IR by reducing cellular nitric oxide levels (4). Therefore, hyperuricemia and IR have a mutually causal relationship (4,17).

In this study, an important positive relationship was detected between SrUA levels, N-AFLD, and IR. The presence of IR in most patients with N-AFLD is a possible explanation for the relationship between SrUA levels and N-AFLD. Many researchers have noticed a significant correlation between IR and SrUA concentrations, which are major components of Msy (18-20). In our study, a positive relationship between SrUA values and IR was found in the N-AFLD group.

The circumference of the waist, which is an indicator of central obesity and is related to Msy and N-AFLD, appears to be more correlated with MS and N-AFLD than with the BMI (21). In our study, both BMI and waist circumference were remarkably lower in the

control group than in the N-AFLD group. However, no prominent correlation was observed with SrUA values. Recent studies using multivariate logistic regression analysis have shown an independent relationship between N-AFLD and SrUA levels (22,24). Our results were consistent with these findings. In addition, in the N-AFLD group, a positive relationship between SrUA concentrations and IR was found.

Study Limitations

There are some limitations to our study. First, it may not reflect the results of the general population because of the low number of patients and control groups and the fact that they consist of people who applied to a single center. Second, N-AFLD was not confirmed by liver biopsy. However, biopsy is invasive. Ultrasonography is a non-invasive, easily available method that qualitatively shows fatty liver disease; its specificity is 94% and its sensitivity is 84%.

CONCLUSION

Therefore, increased SrUA concentrations may be an important parameter in the presence of N-AFLD and IR. To understand the role of uric acid in the pathophysiology of N-AFLD, larger-scale, multicenter studies are required.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained from the Kırıkkale University Faculty of Medicine Local Ethics Committee (approval number: 2010/0028, dated 07.06.2010).

Informed Consent: It was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: G.P., F.Y., Design: G.P., Supervision: G.P., H.D., Resources: G.P., F.Y., Materials: G.P., Data Collection or Processing: G.P., F.Y., Analysis or Interpretation: G.P., H.D., Literature Search: G.P., F.Y., Writing: G.P., H.D., Critical Review: H.D., F.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

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