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Can levels of serum uric acid and HDL cholesterol effectively predict the presence of fatty liver in children with obesity?

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ABSTRACT

Aims: Our study aimed to evaluate the relationship between biochemical parameters such as high uric acid and low HDL levels and metabolic dysfunction-associated steatohepatitis (MDAS) in children with obesity.

Methods: The records of 81 obese children with a body mass index above two standard deviations for their age who underwent fasting lipids, liver enzymes, uric acid level, oral glucose tolerance tests (OGTT), and abdominal ultrasounds to assess fatty liver were reviewed retrospectively. The findings from physical examinations and results from laboratory and imaging tests were documented. The relationship between laboratory data and MDAS was examined.

Results: The study included 81 children, 27 males and 54 females. Fifty-six out of the total participants, accounting for 69.2%, were diagnosed with steatohepatitis. the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. HDL levels were significantly lower in MDAS children than in non-MDAS children (39.90±7.89 vs. 45.23±7.32, p=.005,). Moreover, the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. There was a statistical difference between the two groups (p<.001,).To assess the diagnostic performance of each marker and predictive model, we conducted a receiver operating characteristics (ROC) analysis. As individual predictors, SUA (AUC=0.729 [95% CI, 0.619–0.822], cut-off >6.89, sensitivity=37.5, specificity=100) and HDL (AUC=0.699 [95% CI, 0.587–0.796], cut-off ≤39.2, sensitivity=51.8, specificity=84) showed similar diagnostic performance in discriminating MDAS from non-MDAS patients.

Conclusion: Elevated SUA levels with low HDL levels may significantly predict MDAS.

Keywords: Uric acid, HDL, obesity, children, fatty liver

INTRODUCTION

Obesity is a significant factor in several endocrine diseases, including insulin resistance (IR), type 2 diabetes (T2D), hypertension, hyperuricemia, and metabolic syndrome. This significantly strains patients, families, and the public health system. Many cross-sectional studies have shown that obesity, as diagnosed by body-mass index (BMI), often leads to hyperuricemia.[1] Recent studies have found that hyperuricemia not only leads to gouty arthritis and nephropathy but may also be associated with IR, T2D, and cardiovascular morbid events.[1-3]

Metabolic dysfunction-associated steatohepatitis (MDAS) can be seen as a hepatic manifestation of metabolic syndrome in children and adolescents. The incidence of MDAS is increasing parallel to the increase in obesity, hyperlipidemia, and T2D mellitus. Uric acid is a product of purine metabolism due to protein catabolism. Its increased levels are associated with high consumption of purines (animal protein, meat, and seafood) and fructose (fruit, processed foods). High serum uric acid (SUA) levels play an essential role in the pathophysiology of arterial hypertension, renal failure, congestive heart failure, and T2D, and some studies have shown that it directly induces fat accumulation in hepatocytes.[3] In a large prospective cohort study of 2832 individuals in China, the authors found that high SUA levels were an independent risk factor for MDAS.[4] A large-scale population-based study in Western countries also found that hyperuricemia was significantly associated with MDAS.[5] In contrast, a recent cross-sectional study in children and adolescents in Brazil showed that SUA levels were associated with metabolic syndrome and puberty but not with MDAS.[6]

Our study aimed to evaluate SUA, HDL, and other laboratory parameters that may be associated with MDAS in obese children.

METHODS

The study was approved by the local ethics committee of Selçuk University Faculty of Medicine (Date: 08.10.2024, Decision No: 2024/509). All procedures were carried out in

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accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study analyzed the records of patients who visited the endocrinology clinic with concerns about excessive weight from November 2020 to May 2022. Eighty-one children aged ten years and over, with a BMI standard deviation score (BMI-SDS) ≥2, who underwent abdominal ultrasound to evaluate liver steatosis and who also underwent fasting lipids [included total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and triglycerides (TGs)]; fasting glucose, fasting insulin, SUA, and OGTT tests in our hospital were included in the study.

The patient's records documented height, weight, all anthropometric measurements, age, gender, laboratory, and clinical findings. The presence of acanthosis nigricans was evaluated in patients whose physical examinations were performed by a single pediatric endocrinologist. Pubertal status was assessed according to Tanner staging.[7]

The relationship between the presence and degree of MDAS in the patient's abdominal USG and SUA and other laboratory levels was evaluated. All subjects were divided into two groups (with or without MDAS) based on hepatic ultrasound examination results.

Statistical Analysis

All data processing and statistical analyses were performed using R language version 4.2.1. (www.r-project.org). A two-sided p-value<.05 was considered statistically significant. Patient characteristics were reported as mean±standard deviation (SD) or median with quartiles [1st quartile–3rd quartile] for numerical variables and frequency (n) with percentage (%) for categorical variables. Before statistical analyses, the Shapiro-Wilk normality test was used to check the conformity of the distributions of continuous variables to the normal distribution. In addition, Levene's test was used to assess the homogeneity of variances when comparing continuous variables between groups. Comparisons (univariate analysis) between groups were analyzed by student's t-test, Welch's t-test, Mann-Whitney U test for numerical data, and Chi-square test with Yates continuity correction for categorical data. The variables found to be significant in the univariate analysis were included in the multiple analysis. A multiple logistic regression analysis was performed to examine.

Logistic regression analysis with a stepwise backward elimination approach was used for model development. The predictive accuracy of the models was compared using receiver operating characteristic (ROC) curves. Multiple models considered covariates with a p-value of 0.10 or less significant.

In multiple models, sex was included as a covariate.

The odds ratio (OR) and 95% confidence interval (CI) of the risk factors.

RESULTS

The study included 81 children, 27 males and 54 females. Fifty-six out of the total participants, accounting for 69.2%, were diagnosed with steatohepatitis. The mean age of the whole cohort was 14.09±2.24 years; it was 13.93±2.36 years in the non-MDAS group and 14.17±2.20 years in the MDAS group. Based on the records of pubertal examination, only seven patients (7.4%) were found to be in the prepubertal period.

Compared with the non-MDAS children, MDAS children were more likely to be male and overweight and had higher biochemical indices, including serum levels of insulin, AST, ALT, and GGT (**Figure 1 A-E and H**). In addition, HDL levels were significantly lower in MDAS children than in non-MDAS children (39.90±7.89 vs. 45.23±7.32, p=.005, **Figure 1-G**). Moreover, the MDAS and non-MDAS subjects' SUA levels were 6.34±1.36 mg/dl and 5.26±1.09 mg/dl, respectively. There was a statistical difference between the two groups (p<.001, **Figure 1-F**). The clinical and biochemical characteristics of the study population are summarized in **Table**.

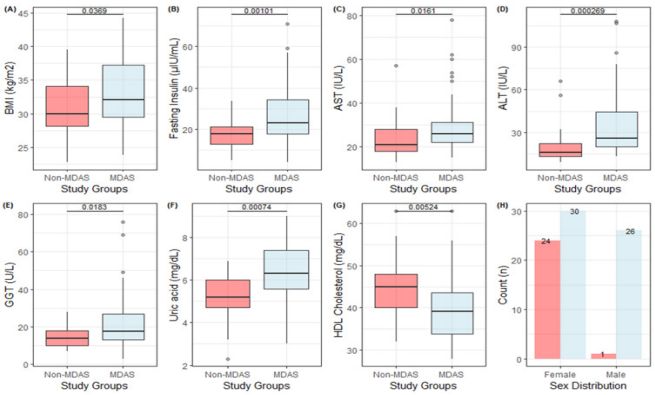

Figure 1. Boxplots compare (**A**) BMI, (**B**) fasting insulin, (**C**) AST, (**D**) ALT, (**E**) GGT, (**F**) uric acid, and (**G**) HDL cholesterol for children with MDAS and non-MDAS groups. The boxplots represent the data distribution; the horizontal line indicates the median. The sample's first and third quartiles are the box's lower and upper hinges. (H) The bar plot shows the sex distribution of the study groups
BMI: Body-mass index, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, HDL: High-density lipoprotein, MDAS: Metabolic dysfunction-associated steatohepatitis

Multiple logistic regression analyses of sex, BMI, ALT, AST, GGT, SUA, and HDL parameters identified only sex, uric acid, and HDL as significant independent predictors of MDAS.

To assess the diagnostic performance of each marker and predictive model, we conducted a ROC analysis (**Figure 2**). As individual predictors, SUA (AUC=0.729 [95% CI, 0.619–0.822], cut-off >6.89, sensitivity=37.5, specificity=100) and HDL (AUC=0.699 [95% CI, 0.587–0.796], cut-off ≤39.2, sensitivity=51.8, specificity=84) showed similar diagnostic performance in discriminating MDAS from non-MDAS patients (DeLong's test Z=0.403, p=.687). The predictive model, including sex as a confounding variable, had a superior diagnostic performance for the diagnosis of MDAS compared to SUA (DeLong's test Z=2.200, p=.028) and HDL (DeLong's test Z=2.465, p=.014) with an AUC of 0.833 [95% CI, 0.733–0.906].

DISCUSSION

MDAS is a complex disease that has become the most common chronic liver condition in both children and adults globally. Over the past few decades, the prevalence of MDAS has more than doubled.[8] With the rising obesity rates, these numbers are expected to increase even more.[9] In a meta-

Table. The clinical and biochemical characteristics of the study population

	Non-MDAS(n=25)	MDAS (n=56)	p-value
Age (months)	167.16±28.33	170.11±26.46	.652[1]
Sex (male/female)	1 (4%)/24 (96%)	26 (46.4%)/30 (53.6%)	<.001[2]
Weight (kg)	76.68±16.13	89.96±19.64	.004[1]
Weight SD	2.94±0.99	3.37±1.20	.128[1]
Height (cm)	156.98±10.60	162.96±11.75	.032[1]
Height SD	0.17±1.00	0.65±1.57	.099[3]
BMI (kg/m²)	30.82±4.48	33.31±5.05	.037[1]
BMI SD	2.68±0.65	2.90±0.69	.175[1]
Pubertal status	23 (92%)	52 (92.9%)	>.999[4]
Acanthosis nigricans	19 (76%)	41 (73.2%)	>.999[2]
Stria	12 (48%)	27 (48.2%)	>.999[2]
FBS (mg/dl)	86.68±10.94	88.04±12.70	.645[1]
Fasting insulin (µIU/ml)	18 (13–21.4)	23.2 (18–34.25)	.001[5]
PBS (mg/dl)	110 (90–125)	106 (89.25–125)	.595[5]
Post-prandial insulin (µIU/ml)	65.4 (54–87)	71.5 (44.15–117.25)	.775[5]
HbA1c (%)	5.50±0.54	5.68±0.73	.287[1]
AST (IU/L)	21 (18–28)	26 (22–31.25)	.016[5]
ALT (IU/L)	16 (13–22)	26 (20–44.5)	<.001[5]
GGT (U/L)	14 (10–18)	17.5 (13–27)	.018[5]
Uric acid (mg/dl)	5.26±1.09	6.34±1.36	<.001[1]
TSH (mIU/L)	1.8 (1.47–2.7)	2.6 (1.9–3.2)	.051[5]
fT4 (ng/dl)	1.04±0.22	1.09±0.20	.293[1]
Vitamin B-12 (pg/ml)	255 (183–302)	270.5 (217–374.5)	.269[5]
25 (OH) vitamin D (ng/ml)	12.4 (8.7–15)	12.25 (7.72–16.7)	.935[5]
TG (mg/dl)	116 (87–154)	120.5 (90.75–168.25)	.529[5]
Total cholesterol (mg/dl)	157.16±31.70	159.02±34.61	.820[1]
LDL cholesterol (mg/dl)	91.04±24.47	92.63±29.31	.814[1]
HDL cholesterol (mg/dl)	45.23±7.32	39.90±7.89	.005[1]
Haemoglobin (g/dl)	13.7 (13–14.2)	13.8 (13.05–14.45)	.649[5]
PTH (pg/ml)	51 (43–67)	53 (35.38–72)	.963[5]

[1] student's t-test; [2] Chi-square test with Yates continuity correction; [3] Welch's t-test; [4] Fisher's exact test; [5] Mann-Whitney U test.
Data were presented as mean±standard deviation or median with quartiles [1st quartile–3rd quartile], as appropriate for numerical data; categorical variables were also described as count (n) and percentage (%).
MDAS: Metabolic dysfunction-associated steatohepatitis, BMI: Body-mass index, FBG: Fasting blood sugar, PBS: Postprandial blood sugar (OGTT 2nd hour blood sugar), AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma glutamyl transferase, TSH: Thyroid stimulating hormone, fT4; Free thyroxine, TG; Triglyceride, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, PTH: Parathyroid hormone, SD: Standard deviation

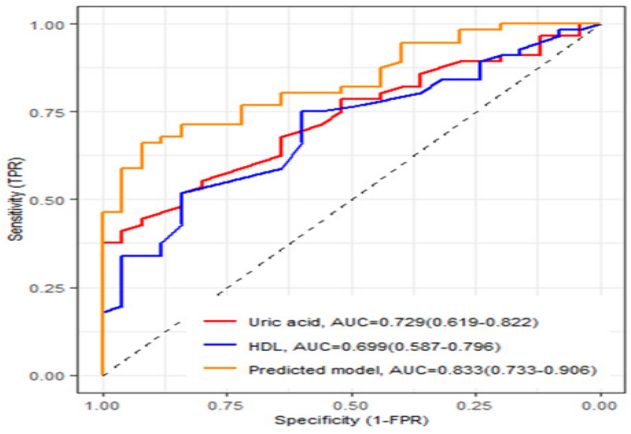

Figure 2. Receiver operating characteristics (ROC) curve of SUA, HDL, and the predictive model combining SUA and HDL, and adjusting for sex as a confounding variable to identify MDAS
HDL: High-density lipoprotein, MDAS: Metabolic dysfunction-associated steatohepatitis, SUA: High serum uric acid

analysis conducted by Anderson et al.[10], MDAS in children with obesity was estimated to be 34.2% (95% CI: 27.8–41.2%), compared to 7.6% (95% CI: 5.5–10.3%) in the general pediatric population. Our study found MDAS in 69.2% (56 participants) of the 81 children examined for obesity.

Dietary factors such as high fructose intake, consumption of high-glycemic index foods, and sugar-sweetened beverages play a crucial role in developing MDAS.[11] The fructose component of sugar and high-fructose corn syrup contributes to the formation of fatty liver by promoting the creation of new fat and inhibiting the breakdown of fatty acids.[12] The effects mentioned are linked to fructokinase's metabolism of fructose. This process leads to the conversion of nucleotides and the formation of uric acid. It also causes a decrease in adenosine triphosphate (ATP), which results in prooxidative and pro-inflammatory effects that worsen the formation of

fat in the liver.[13,14] A meta-analysis of 11 studies from various countries, including China, Korea, Japan, India, and the United States, found a significant association between SUA and MDAS. The risk of MDAS was almost doubled in the highest SUA group compared to the lowest group.[15] Similarly, this study found that patients with MDAS had higher SUA values than those without.

In the literature, some studies suggest that high SUA has a more significant impact on causing fatty liver in females than males. However, studies indicate that the predictive value of SUA levels is higher in males or similar in both genders.[4,15-17] In this study, the estimated model, including Gender as a confounding variable, had a superior diagnostic performance in men compared to SUA and HDL for MDAS diagnosis. The different results may stem from variations in sample sizes, populations, definitions of hyperuricemia, lifestyles, and dietary habits.

HDL is the primary vehicle for transporting cholesterol from peripheral cells to the liver for disposal and catabolism. However, during this intricate metabolic process, molecules other than lipids (such as hormones, vitamins, proteins, and miRNAs) are also known to be incorporated into HDL particles and transported to distant organs. This process may play a role in maintaining cardiovascular health.[18] Although the mechanism is unclear, a relationship between MDAS and low HDL levels has been described.[19] A large Mendelian randomization study found low HDL levels associated with MDAS.[20] Multiple sex-adjusted logistic regression analyses performed in this study showed that a higher risk of having MDAS was associated with higher SUA levels and lower HDL levels.

While liver biopsy remains the gold standard for diagnosing and staging MDAS, ultrasonography is the most widely used screening tool for hepatic steatosis in clinical practice.[21,22] New scoring systems have improved the reliability of ultrasonography in this disease.[23,24] The sensitivity of liver ultrasonography may vary depending on hepatic fat content. However, as previously mentioned, liver ultrasonography offers several advantages, including its noninvasiveness. It has also been reported that when performed correctly, it can detect liver fat content as low as 5% or more.[25] Fatty liver screening of obese children included in the study was performed using ultrasonography.

Limitations

Our study has some limitations. First, as mentioned above, our cross-sectional study design cannot establish causality between uric acid and MDAS. Instead, such data should be viewed as hypothesis-generating. Secondly, the fatty liver condition was assessed using ultrasound. Third, more direct and accurate visceral adiposity and IR measurements were unavailable in this study. Fourthly, this study focused exclusively on obese children and compared them based on the presence of DAS. A healthy control group was not included in the evaluation. Finally, we did not account for lifestyle or dietary factors, such as meat and fructose intake, which may contribute to increased uric acid levels and MDAS. Healthy lifestyle changes should be the primary approach, not just lowering uric acid levels.

CONCLUSION

As a result, pediatric MDAS is likely to continue progressing as a hidden epidemic in the coming years. To avoid a diagnosis of exclusion, reaching an international consensus on terminology and improving diagnostic methods is essential. We think that easily accessible and cost-effective methods such as SUA and HDL are practical parameters for MDAS prediction.

In addition, further studies are needed to better understand the relationship between SUA and MDAS and evaluate whether specific dietary or pharmacological strategies to reduce serum uric acid levels may benefit MDAS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the local ethics committee of Selçuk University Faculty of Medicine (Date: 08.10.2024, Decision No: 2024/509).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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