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Effects of Lipid Profiles and Vitamin D Levels on the Degree of Fatty Liver in Children with Non-Alcoholic Fatty Liver Disease

Non-Alkolik Yağlı Karaciğer Hastalığı Olan Çocuklarda Lipid Profilleri ve D Vitamini Düzeylerinin Yağlı Karaciğer Derecesi Üzerindeki Etkileri

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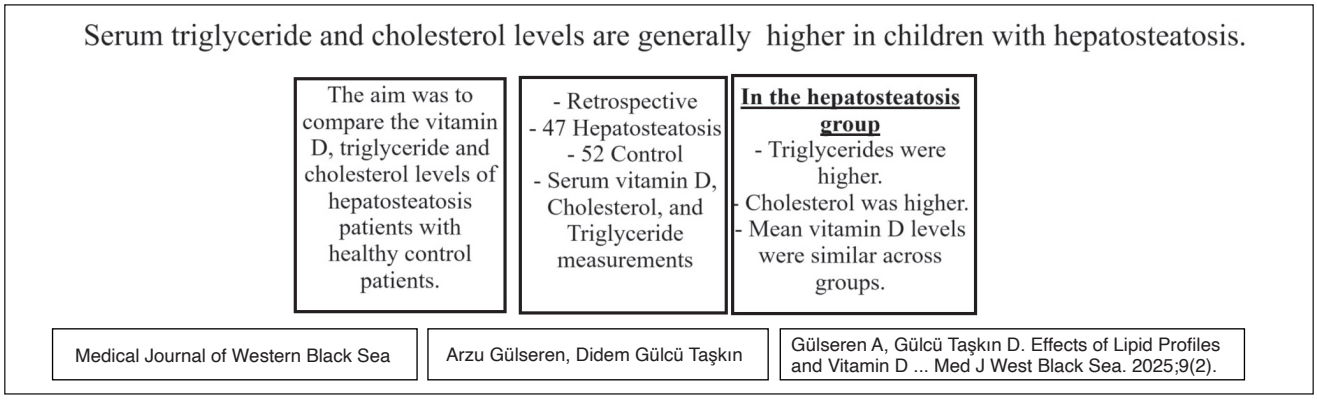
GRAPHICAL ABSTRACT



ABSTRACT

Aim: The aim of the study was to compare vitamin D, triglyceride and cholesterol levels of hepatosteatosis patients with healthy control patients.

Material and Methods: Ninety-nine patients with hepatosteatosis and healthy control patients were included in our study retrospectively. The patients included in the study were patients who applied to the pediatric gastroenterology outpatient clinic between 2020 and 2023.

Results: A total of 99 patients, 47 (47.5%) with hepatosteatosis and 52 (52.5%) in the control group, were included in our study. Mean ALT values were 35.2 ± 19.5 and 28.3 ± 13.0 in the hepatosteatosis and control groups, respectively (P= 0.039). Mean triglyceride (136 ± 28 vs 125 ± 24; P= 0.042) and cholesterol (165 ± 20 vs 154 ± 20; P= 0.010) levels were higher in the hepatosteatosis group than in the control group and the result was found to be significantly different. Mean vitamin D levels did not differ between the groups. Vitamin D deficiency was found to be high in both groups, but no difference was analyzed between the groups (72.3% vs 61.5%; P= 0.491).

Conclusion: Triglyceride and cholesterol levels were found to be higher in patients with hepatosteatosis. Fasting blood glucose is higher in the hepatosteatosis group. Based on these results and the literature, patients with hepatosteatosis pose a risk for important diseases such as metabolic syndrome and cardiovascular diseases such as atherosclerosis in the following years.

Keywords: Cholesterol, hepatosteatosis, triglyceride, vitamin D

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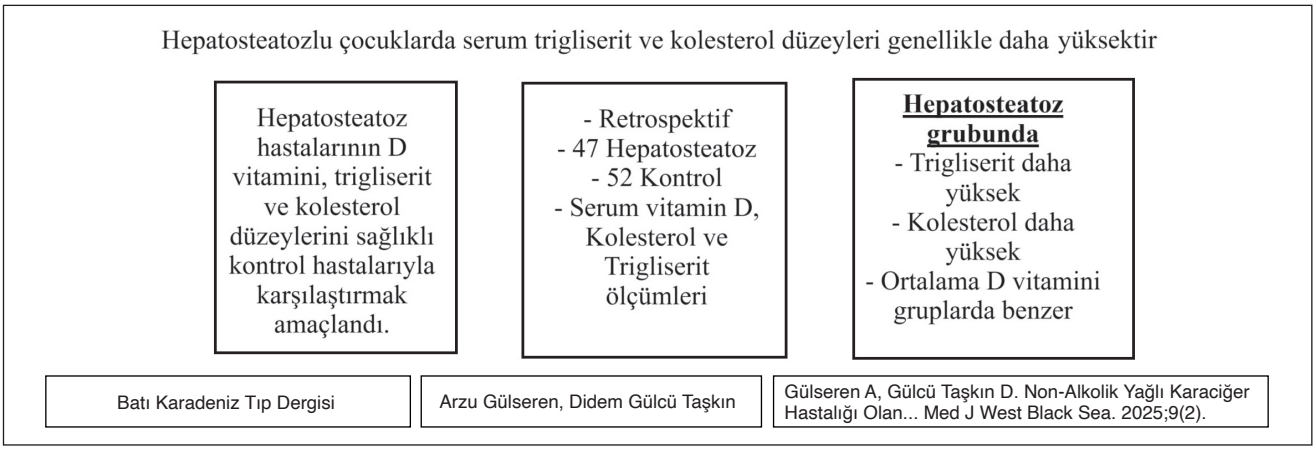
GRAFİKSEL ÖZET



ÖZ

Amaç: Çalışmanın amacı hepatosteatoz hastalarının D vitamini, trigliserit ve kolesterol düzeylerini sağlıklı kontrol hastalarıyla karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmamıza retrospektif olarak hepatosteatozlu 99 hasta ve sağlıklı kontrol hastaları dahil edildi. Çalışmaya dahil edilen hastalar 2020-2023 yılları arasında çocuk gastroenteroloji polikliniğine başvuran hastalardı.

Bulgular: Çalışmamıza hepatosteatozlu 47 (%47,5) ve kontrol grubunda 52 (%52,5) olmak üzere toplam 99 hasta dahil edildi. Ortalama ALT değerleri hepatosteatoz ve kontrol gruplarında sırasıyla 35,2 ± 19,5 ve 28,3 ± 13,0 idi (P= 0,039). Ortalama trigliserit (136 ± 28 vs 125 ± 24; P= 0.042) ve kolesterol (165 ± 20 vs 154 ± 20; P= 0.010) düzeyleri hepatosteatoz grubunda kontrol grubuna göre daha yüksekti ve sonuç anlamlı olarak farklı bulundu. Ortalama D vitamini düzeyleri gruplar arasında farklılık göstermedi. Her iki grupta da D vitamini eksikliği yüksek bulundu, ancak gruplar arasında fark analiz edilmedi (%72.3 vs %61.5; P= 0.491).

Sonuç: Hepatosteatozlu hastalarda trigliserit ve kolesterol düzeyleri daha yüksek bulundu. Açlık kan şekeri hepatosteatoz grubunda daha yüksektir. Bu sonuçlara ve literatüre dayanarak, hepatosteatozlu hastalar ilerleyen yıllarda metabolik sendrom ve ateroskleroz gibi kardiyovasküler hastalıklar gibi önemli hastalıklar için risk oluşturmaktadır.

Anahtar Sözcükler: Kolesterol, hepatosteatoz, trigliserid, D vitamini

INTRODUCTION

Simple hepatosteatosis is an excessive accumulation of lipids in the liver characterized by fat deposition, hepatocyte damage, inflammation and varying degrees of fibrosis (1). Although the definitive diagnosis is made by liver biopsy, this interventional procedure is not performed frequently due to complications such as inflammation and bleeding (2). The diagnosis is generally made by ultrasonography. Grade determination is performed sonographically. Hepatosteatosis is often associated with metabolic syndrome, obesity, insulin resistance, dyslipidemia and type 2 diabetes (3).

Although the pathogenesis of hepatosteatosis is not fully known, according to the "2 strikes" theory, insulin resistance, which is the main cause of triglyceride accumulation in hepatocytes, increases the sensitivity of liver cells to the "second strike". These include oxidative stress damage, cytokines, endotoxins, as well as damage from environmental toxins that can lead to steatohepatitis or fibrosis (4). While the role of Vitamin D in the regulation of calcium and bone homeostasis is well established, there is evidence that Vitamin D also has immunomodulatory, anti-fibrotic and anti-inflammatory properties (5). Necroinflammation and fibrosis and hepatosteatosis are more common in vitamin D deficiency (5). Low serum 25(OH)D concentrations may indicate malnutrition or a more sedentary lifestyle with less time spent outdoors, resulting in less sunlight exposure. It is also possible that low serum 25(OH)D levels in obese individuals reflect vitamin D retention in adipose tissue (6). The aim of the study was to compare vitamin D, triglyceride and cholesterol levels of hepatosteatosis patients with healthy control patients.

MATERIALS and METHODS

Ninety-nine patients with hepatosteatosis and healthy control patients were included in our study retrospectively. The patients included in the study were patients who applied to the pediatric gastroenterology outpatient clinic between 2020 and 2023. Patients under 18 years of age and diagnosed sonographically with hepatosteatosis were included in the study. Patients with congenital metabolic diseases, fat metabolism diseases, and cases with any medical condition

known to impair vitamin D absorption or metabolism or to be a major cause of fecal incontinence, including stage ≥3 chronic kidney disease, chronic liver disease, were excluded from the study. Patients were consulted by a metabolic physician to exclude metabolic diseases. The patients in the control group generally consisted of patients who applied for reasons such as abdominal pain and frequent vomiting and no underlying disease could be detected. The ages of the patients in the control group were matched to be similar to the case group (95% confidence interval value: 8-12). In this way, it was aimed to make the comparison of laboratory values, which may change depending on age, more reliable. All stages of conducting the research, including data collection, processing, statistics and literature search, were carried out in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The age of the patients in years and their gender were noted from the retrospective system review. Body mass index was calculated by dividing the weight in kilograms by the square of the height in meters (7). Height was measured with bare feet on a wall-mounted meter. Weight was measured on a digital scale while wearing light clothing. Aspartate aminotransferase (AST) (IU/L), alanine aminotransferase (ALT) (U/L), alkaline phosphatase (ALP) (IU/L), parathormone (pg/mL), calcium (mg/dL), phosphorus (mg /dL), serum glucose (mg/dL), high density lipoprotein (HDL) (mg/dL), low density lipoprotein (LDL) (mg/dL), triglyceride (mg/dL) and cholesterol (mg/dL) values were examined retrospectively from the system. The values before sonography and closest to the date of sonography were noted.

At admission, a venous sample was collected in a clotted tube for serum vitamin D analysis, and 25-hydroxy vitamin D levels were measured by electrochemiluminescence immunoassay. Vitamin D deficiency was defined as a total serum vitamin D level ≤20 ng/mL (8,9). Patients with total serum vitamin D levels ≥30 ng/mL were classified as vitamin D adequate (9). Patients with serum levels between 21 and 29 ng/mL were classified as having vitamin D deficiency (9).

Abdominal ultrasonography data were evaluated retrospectively. The system presented by Lee and Park (10) was used for grading hepatosteatosis. In this classification, mild echogenicity in the liver parenchyma was defined as grade 1, further increase in echo or slight impairment in imaging of the diaphragm and intrahepatic vessels was defined as grade 2, and severe increase in parenchymal echogenicity and inability to distinguish the echo of the diaphragm and intrahepatic vessels was defined as grade 3 hepatosteatosis (10). There was no patient with grade 3 hepatosteatosis in our study.

Statistical analysis

Chi-square test was used to examine the relationship between categorical variables and numbers and percentages were used to express the data. Normal distribution analysis was performed with the Shapiro-Wilk test. Student's T test was used to compare numerical data. Numerical data showing normal distribution were expressed as mean and standard deviation. Receiver operating characteristic (ROC) analysis evaluated vitamin D, triglyceride and cholesterol levels, which can be used to predict hepatosteatosis. Area under curve was measured in ROC. Ideal cut-off values and sensitivity and specificity values were calculated accordingly. Data recording and statistical analyzes were performed using SPSS (statistical package for the social sciences) software (version 17, SPSS, Inc, Chicago, IL). A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

A total of 99 patients, 47 (47.5%) with hepatosteatosis and 52 (52.5%) in the control group, were included in our study. Of the patients with hepatosteatosis, 34 (72.3%) were found to be grade 1 and 13 (27.7%) were grade 2. Clinical and laboratory data of the groups are given in Table 1. The ages of the hepatosteatosis and control groups were similar (10.0 ± 3.6 years vs 10.6 ± 3.8 years; P= 0.404). Girls were more common in both groups (53.2% vs 55.8%; P= 0.478). Body mass index (BMI) was similar between the groups (22.7 ± 4.3 kg/m^2 vs 22.8 ± 4.7 kg/m^2; P= 0.911). Although AST was higher in the hepatosteatosis group, the result was not significant (33.1 ± 20.9 IU/L vs 26.8 ± 10.8 IU/L; P= 0.060). Mean ALT values were 35.2 ± 19.5 U/L and 28.3 ± 13.0 U/L in the hepatosteatosis and control groups, respectively (P= 0.039). ALP, parathormone, calcium, phosphorus and fasting serum glucose values did not differ in hepatosteatosis and control groups. Although HDL levels were higher in the control group, the result was not significant (46 ± 5 mg/dL vs 48 ± 4 mg/dL; P= 0.071). LDL level did not differ significantly between the groups. Mean triglyceride (136 ± 28 mg/dL vs 125 ± 24 mg/dL; P= 0.042) and cholesterol (165 ± 20 mg/dL vs 154 ± 20 mg/dL; P= 0.010) levels were higher in the hepatosteatosis group than in the control group and the result was found to be significantly different. Mean vitamin D levels did not differ between the groups. Vitamin D deficiency was found to be high in both groups, but no difference was found between the groups (72.3% vs 61.5%; P= 0.491).

ROC analysis of vitamin D, triglyceride and cholesterol levels, which can be used to determine hepatosteatosis, was analyzed in Figure 1. The area under curve (AUC) value of vitamin D in predicting hepatosteatosis was 0.419 and was not statistically significant (95% CI: 0.305-0.532, P= 0.164). Triglyceride (95% CI: 0.507-0.731, AUC= 0.619; P= 0.041) and cholesterol (95% CI: 0.550-0.764, AUC= 0.657; P=

Table 1. Clinical and laboratory characteristics of hepatosteatosis patients

	Hepatosteatosis (47)	Control (52)	P
Age, (years) [b]	10.0 ± 3.6	10.6 ± 3.8	0.404
Gender, [a]			0.478
- Female	25 (53.2)	29 (55.8)	
- Male	22 (46.8)	23 (44.2)	
Height, (cm) [b]	136 ± 18	140 ± 20	0.291
Weight, (kg) [b]	44 ± 21	47 ± 22	0.489
Body mass index, (kg/m^2) [b]	22.7 ± 4.3	22.8 ± 4.7	0.911
Aspartate Aminotransferase, (IU/L)[b]	33.1 ± 20.9	26.8 ± 10.8	0.060
Alanine Aminotransferase, (U/L) [b]	35.2 ± 19.5	28.3 ± 13.0	0.039
Alkaline phosphatase, (IU/L) [b]	224 ± 45	221 ± 44	0.738
Parathormone, (pg/mL) [b]	54 ± 15	55 ± 15	0.935
Calcium, (mg/dL) [b]	9.5 ± 0.7	9.5 ± 0.7	0.718
Phosphorus, (mg/dL) [b]	4.7 ± 0.3	4.7 ± 0.3	0.989
Fasting blood glucose, (mg/dL) [b]	87 ± 5	85 ± 5	0.312
High density lipoprotein, (mg/dL) [b]	46 ± 5	48 ± 4	0.071
Low density lipoprotein, (mg/dL) [b]	94 ± 10	92 ± 8	0.297
Triglyceride, (mg/dL) [b]	136 ± 28	125 ± 24	0.042
Cholesterol, (mg/dL) [b]	165 ± 20	154 ± 20	0.010
Vitamin D, (ng/dL) [b]	19.4 ± 11.6	20.4 ± 9.8	0.626
			0.491
- Vitamin D deficiency [a]	34 (72.3)	32 (61.5)	
- Vitamin D insufficient [a]	9 (19.1)	15 (28.8)	
- Vitamin D sufficient [a]	4 (8.5)	5 (9.6)	

a: Noun (%), **b:** mean ± standard deviation

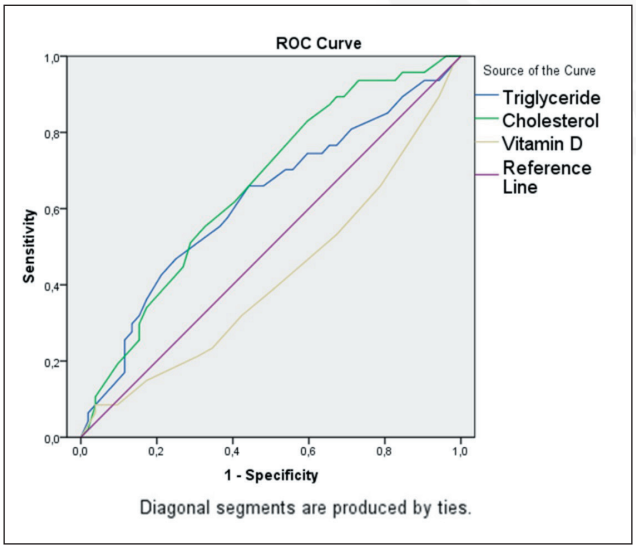


Figure 1: Receiver operating characteristic (ROC) curve of Vitamin D, Triglyceride and Cholesterol to identify patients likely to hepatosteatosis.

0.007) levels were significant in predicting hepatosteatosis. The cut-off for the triglyceride value was >125. According to this value, 66.0% sensitivity and 55.8% specificity were analyzed. The ideal cut-off for cholesterol was >157, with a sensitivity of 51.1% and specificity of 71.2%.

DISCUSSION

Although the diagnosis of hepatosteatosis can be easily made sonographically, vitamin D, HDL, LDL, cholesterol and triglyceride values were compared in patients with hepatosteatosis and healthy patients in order to reduce the workload and support it with laboratory data. Triglyceride and cholesterol values were analyzed to be higher in hepatosteatosis patients. Cholesterol level above 157 mg/dL can predict hepatosteatosis with 51.1% sensitivity and 71.2% specificity.

Mean serum 25(OH)D concentrations were significantly lower in those with hepatosteatosis compared to those without hepatosteatosis (3,11,12). In multivariate logistic regression analysis, serum 25(OH)D concentration was shown to be an independent predictor of hepatosteatosis. In the literatüre, there was an inverse relationship between

the severity of hepatosteatosis and serum 25(OH)D concentrations (11,13,14). Vitamin D treatment in children and adolescents with obesity and hypovitaminosis D was reported to not improve the severity of hepatic steatosis on ultrasonography at 6 months (11). In our study, although vitamin D was lower in patients with hepatosteatosis, it was found to be not statistically significant (19.4 ± 11.6 ng/dL vs 20.4 ± 9.8 ng/dL; P = 0.626). Besides, vitamin D deficiency was found to be high in both groups, but no difference was analyzed between the groups (72.3% vs 61.5%; P= 0.491). Although our study result is different from the literature, it can be repeated with a larger number of patients.

Body mass index value is higher in patients with hepatosteatosis (15). In our study, body mass indexes were found to be similar in the hepatosteatosis and control groups. Triglyceride values were found to be higher in the hepatosteasosis group (15-17). Cholesterol level does not differ between groups. The risk of metabolic syndrome is 10 times higher in patients with hepatosteatosis than in normal patients (18). Hypertriglyceridemia is the most common metabolic syndrome risk factor in children with hepatosteatosis (16). In our study, similar to the literature, it was shown that triglyceride and cholesterol levels were found to be higher in the hepatosteatosis group than in the control group. The cut-off for the triglyceride value was >125 mg/dL. According to this value, 66.0% sensitivity and 55.8% specificity were analyzed. The ideal cut-off for cholesterol was >157 mg/dL, with a sensitivity of 51.1% and specificity of 71.2%. It is an important risk factor for metabolic syndrome in the future.

Patients with hepatosteatosis have more insulin resistance than healthy patients (13,17). This may contribute to atherosclerosis in the future. AST and ALT values were found to be higher in hepatosteatosis cases than in the healthy control group (13,15). In our study, fasting serum glucose value was found to be higher in the hepatosteatosis group, but the result did not appear to be significant. The mean ALT value was found to be significantly higher in the hepatosteatosis group. Hepatosteatosis poses a risk for metabolic syndrome in older ages.

Study Limitation

The shortcomings of our study are that it is retrospective in nature and includes a small number of patients. There is a lack of standardization in the timing of serum samples and ultrasound examinations due to the retrospective nature of the study. The lack of long-term follow-up is also an important limitation. The unequal distribution of grade 1-2 patients in hepatosteatosis presents limitations in terms of subgroup analysis. There may be differences between observers due to the variety of sonographers who performed grade assessments in terms of hepatosteatosis. There may have been differences in vitamin D measurements due to seasonal changes.

Conclusion

In conclusion, triglyceride and cholesterol levels were found to be higher in patients with hepatosteatosis. Fasting blood glucose is higher in the hepatosteatosis group. Vitamin D deficiency does not show any significant difference between groups. Based on these results and the literature, patients with hepatosteatosis pose a risk for important diseases such as metabolic syndrome and cardiovascular diseases such as atherosclerosis in the following years.

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Author Contributions

Concept, Design, Writing, Statistics, Data collection, Literature Search, Approval: **Arzu Gülseren,** Design, Editing, Editing, Data collection, Literature Search, Approval: **Didem Gülcü Taşkın.**

Conflicts of Interest

The authors does not have a Conflict of interest statement.

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Ethical Approval

Local ethics committee approval was obtained from our center (Decision no: 151, Decision no: 30/07/2024).

Review Process

Extremely and externally peer-reviewed.

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