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The association of lipid metabolism and non-alcoholic fatty liver disease in children with obesity

Obez çocuklarda lipid metabolizması ile non-alkolik yağlı karaciğer hastalığı ilişkisi

İlhan Hazer[1], Hilmi Onur Kabukçu[2], Murat Yağcı[2], Zeynep Ertürk[2], Gonca Kılıç Yıldırım[3], Birgül Kirel[1]

[1]Division of Pediatric Endocrinology, Department of Pediatrics, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey
[2]Department of Pediatrics, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey
[3]Division of Pediatric Nutrition and Metabolism, Department of Pediatrics, Eskişehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey

The known about this topic

Obesity, insulin resistance and dyslipidemia are important risk factors for non-alcoholic fatty liver disease. Non-alcoholic fatty liver disease may occur in patients with abetalipoproteinemia and hypobetalipoproteinemia characterized by low lipid levels.

Contribution of the study

The frequency of non-alcoholic fatty liver disease was not found to be different between patients with hypolipidemia, normal lipids, and hyperlipidemia.

Abstract

Aim: Obesity, insulin resistance, and hyperlipidemia have been shown as risk factors for non-alcoholic fatty liver disease. In this study, the association between lipid and lipoprotein metabolism abnormalities and the presence of non-alcoholic fatty liver disease was investigated in patients with obesity.

Material and Methods: In this study, the clinical, laboratory and imaging findings of 357 children and adolescent patients (199 girls and 158 boys) aged 2–18 years who were diagnosed as having obesity between 2013 and 2018 were retrospectively analyzed. The clinical and laboratory features of the patients who were diagnosed as having non-alcoholic fatty liver disease using ultrasonography were compared with patients who did not have non-alcoholic fatty liver disease. All lipid and lipoprotein levels were defined as hypo-, normo- and hyperlipidemic in comparison with the reference values according to age and sex.

Results: The frequency of non-alcoholic fatty liver disease was 44.5% in the entire study group and was higher in males ($p<0.05$). The body weight, body mass index, alanine aminotransferase, glucose, insulin, non-high-density lipoprotein-cholesterol, and HOMA-IR scores were found to be higher in the patients with non-alcoholic fatty liver disease, whereas the high-density lipoprotein-cholesterol level was lower ($p<0.05$). There was no difference in the frequency of non-alcoholic

Öz

Amaç: Obezite, insülin direnci ve hiperlipidemi non-alkolik yağlı karaciğer hastalığı risk etmenleri olarak gösterilmektedir. Bu çalışmada obezite tanılı hastalarda lipid ve lipoprotein metabolizması anormallikleri ile non-alkolik yağlı karaciğer hastalığı varlığı arasındaki ilişkili araştırılmıştır.

Gereç ve Yöntemler: Bu çalışmada; 2013–2018 yılları arasında obezite tanısı alan, yaşları 2–18 yıl arasında değişen 357 çocuk ve ergen hastanın (199 kız, 158 erkek) klinik, laboratuvar ve görünteleme bulguları geriye dönük olarak incelendi. Ultrasonografi ile non-alkolik yağlı karaciğer hastalığı saptanan hastaların klinik ve laboratuvar özellikleri non-alkolik yağlı karaciğer hastalığı olmayan hastalar ile karşılaştırıldı. Tüm lipid ve lipoproteinler kendi içlerinde yaşa ve cinsiyete göre referans değerleri ile karşılaştırılarak; hipo-, normo- ve hiperlipidemik olarak kaydedildi.

Bulgular: Tüm çalışma grubunda non-alkolik yağlı karaciğer hastalığı görülme sıklığı %44,5 idi ve erkeklerde sıklık daha yüksekti ($p<0,05$). Non-alkolik yağlı karaciğer hastalığı olan hastalarda vücut ağırlığı, vücut kitle indeksi, alanin aminotransferaz, glukoz, insülin, non-yüksek dansiteli lipoprotein-kolesterol ve HOMA-IR skoru daha yüksek; yüksek dansiteli lipoprotein-kolesterol ise daha düşüktü ($p<0,05$). Total kolesterol, trigliserid ve düşük dansiteli lipoprotein-kolesterol düzeyleri için

Cont. ➡

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Corresponding Author/Sorumlu Yazar: Birgül Kirel E-mail/E-posta: birkirel9@gmail.com
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fatty liver disease among the patients with low, normal, and high total cholesterol, triglyceride and low-density lipoprotein-cholesterol levels (p>0.05). The frequency of lipid metabolism disorder (hypolipidemia and/or hyperlipidemia) was found as 77.5% in all patients.

Conclusion: Non-alcoholic liver disease and lipid metabolism disorders are common in children and adolescents with obesity. The frequency of non-alcoholic fatty liver disease in hypolipidemic, normolipidemic, and hyperlipidemic patients was not different. This finding indicated that the increase in the amount of body fatty tissue and insulin resistance were more important risk factors in the development of non-alcoholic fatty liver disease.

Keywords: Hyperlipidemia, hypolipidemia, NAFLD, obesity

oluşturulan hipo-, normo- ve hiperlipidemik gruplar arasında non-alkolik yağlı karaciğer hastalığı sıklığı farklı değildi (p>0,05). Tüm hasta grubunda lipid metabolizması bozukluğu (hipolipidemi ya/ya da hiperlipidemi) sıklığı %77,5 idi.

Çıkarımlar: Obez çocuk ve ergenlerde non-alkolik karaciğer hastalığı ve lipid metabolizması bozuklukları sıklıkla saptanmaktadır. Hipolipidemik, normalipidemik ve hiperlipidemik hastalarda non-alkolik yağlı karaciğer hastalığı sıklığı farklı değildir. Bu bulgu da non-alkolik yağlı karaciğer hastalığı gelişiminde vücut yağ dokusu miktarı artışının ve insülin direncinin daha önemli rolü olan risk etmenleri olduğuna işaret etmiştir.

Anahtar sözcükler: Hiperlipidemi, hipolipidemi, NAFLD, obezite

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in childhood and is characterized by more than 5% fat deposition in hepatocytes in the absence of causes such as alcohol consumption, viral infections, metabolic and autoimmune diseases, and drug use (1–3).

The incidence of non-alcoholic fatty liver disease was found as 7.8% in a meta-analysis published in 2015 involving a general population composed of children and young adults, and 34.2% in obese subjects (4). The frequency of NAFLD in childhood has gradually increased in parallel with the increasing frequency of obesity. In our country, the incidence of NAFLD was reported as 23–62% in children with obesity (5–7).

Obesity, insulin resistance (IR), and dyslipidemia are considered significant risk factors for NAFLD (8). In obese individuals, dyslipidemia characterized by increased levels of triglyceride (TG) and low-density lipoprotein-cholesterol (LDL-C) levels and decreased levels of high-density lipoprotein cholesterol (HDL-C) is observed. Obesity is the most common cause of secondary dyslipidemia (9). In patients with obesity, hyperlipidemia is considered an independent risk factor for the development of NAFLD and an increase in non-HDL-C and TG levels is considered responsible for NAFLD (10, 11). On the other hand, NAFLD may be a clinical finding of primary hypolipidemia characterized by decreased levels of plasma lipids and lipoproteins.

Abetalipoproteinemia is a rare autosomal recessive disease caused by a mutation in the microsomal triglyceride transfer protein (MTTP) gene and characterized by the absence of the lipoproteins that contain apobetalipoprotein B (Apo B) in plasma. Familial hypobetalipoproteinemia is another cause of primary hypolipidemia, which occurs as a result of apoB gene mutations with autosomal dominant inheritance, characterized by low levels of ApoB and LDL-C in plasma. Findings such as steatorrhea, diarrhea, peripheral neuropathy, retinitis pigmentosa, and NAFLD are observed in the clinical picture in both diseases (12, 13). In patients with abetalipoprotemia and homozygous familial hypolipoproteinemia, total cholesterol (TC), TG, and LDL-C are too low to be measured, and hypobetalipoproteinemia heterozygous carriers have a TC level below 150 mg/dL and an LDL-C level between 20 and 50 mg/dL. These carrier subjects have risk in terms of developing NAFLD, even though they are clinically asymptomatic (14, 15).

We could not find any study in the literature comparing the frequencies of NAFLD in hypo-, normo-, and hyperlipidemic obese pediatric and adolescent patients. In this study, it was aimed to investigate the relationship between lipid and lipoprotein metabolism abnormalities and the presence of NAFLD in patients who were followed up because of obesity.

Material and Methods

Three hundred fifty-seven pediatric and adolescent patients aged between 2 and 18 years who were examined in the outpatient clinics at the Departments of Pediatric Endocrinology and Pediatric Nutrition and Metabolism between 2013 and 2018, whose body weight-for-height (BWH) values were 120% and above, whose serum lipid and lipoprotein levels were measured, and in whom NAFLD was investigated using hepatobiliary ultrasonography (USG), were included in our study.

The patients were examined retrospectively and the age, sex, body weight (BW), height, BWH, body mass index (BMI) (kg/height^2) values measured on the date closest to the date of hepatobiliary USG, and the serum glucose, insulin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), free T4 (fT4), thyroid-stimulating hormone (TSH), total cholesterol (TC), TG, LDL-C, HDL-C, and non-HDL-C levels were recorded.

Non-HDL-C levels were calculated using (TC – HDL-C) formula (16). Total cholesterol, TG, LDL-C, HDL-C levels were compared with the reference values by age and sex

Table 1. Clinical properties and laboratory findings in the patients with and without non-alcoholic fatty liver disease[a]

	NAFLD (+) (n=159)	NAFLD (–) (n=198)	p
Age (months)	146.2±37.5	137.9±42.4	0.052
Female/Male (n, %)	79/80 (49.7/50.3)	120/78 (60.6/39.4)	**0.039**
BW (kg)	72±22.6	59.8±19.7	**<0.001**
Height (cm)	156 (143–164)	150 (138–159)	**0.03**
BMI (kg/m^2)	29.4 (25.9–33.4)	25.6 (23.5–28.5)	**<0.001**
BWH (%)	158 (140–174)	142.5 (128–154)	**<0.001**
Glucose (mg/dL)	85 (80–91)	85 (80.7–90)	0.49
Insulin (uU/mL)	20.1 (11.9–27.5)	14.6 (9.3–21)	**<0.001**
TC (mg/dL)	175 (139.5–199)	181 (148–203)	0.39
TG (mg/dL)	113 (79–167)	116 (81–178)	0.06
LDL-C (mg/dL)	115 (83–134)	130 (90–141)	0.07
HDL-C (mg/dL)	44 (38–51)	46 (40–54)	0.76
non-HDL-C (mg/dL)	62 (34–78)	88 (53–96)	**<0.001**
ALT (U/L)	24 (16–36)	18 (14–23)	**<0.001**
AST (U/L)	23 (19–34)	22 (19–25)	**0.01**
sT4 (ng/dL)	1.22 (1.12–1.33)	1.23 (1.14–1.34)	0.26
TSH (mIU/mL)	2.8 (2.1–3.6)	2.73 (1.93–3.65)	0.98

a: Data with normal distribution are expressed as mean±SD and the data that do not have a normal distribution are expressed as median (25–75th percentile) values. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BWH: Body weight-for-height; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; NAFLD: Non-alcoholic fatty liver disease; TG: Triglyceride; fT4: Free t4; TSH: Thyroid-stimulating hormone; BW: Body weight; BMI: Body mass index

and recorded as low (<5p), normal (5–95 p) or high (>95 p) (17). Three groups were established according to the patients' LDL-C levels. Group 1 was composed of patients with low LDL-C levels (n=57), group 2 comprised patients with normal LDL-C levels (n=143), and group 3 constituted patients with high LDL-C levels (n=157).

The HOMA-IR score was calculated using the (glucose) x (insulin) /405 formula. A HOMA-IR score of >3.42 was considered IR-positive (18).

The study was conducted in accordance with the principles of the Helsinki Declaration and approval was obtained from Eskişehir Osmangazi University Non-interventional Clinical Research Ethics Committee (decision number: 10, date: 11.12.2018).

Statistical Analysis

The IBM SPSS 21 package program was used for the analysis of the data. Values belonging to quantitative data are expressed as mean +/- standard deviation (SD) or median (25–75 percentile), and qualitative data are expressed as frequency and percentages. The compatibility of the quantitative data with normal distribution was evaluated using the Shapiro-Wilk test. The difference between groups for variables that were distributed normally was evaluated using the t-test and one-way analysis of variance (ANOVA). The difference between groups for variables that were not distributed normally was evaluated using the Mann-Whitney U test and the Kruskal-Wallis test. The relationship between qualitative variables was examined using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results

The incidence of NAFLD was found as 44.5% in the entire study group (n=158); it was higher in male patients (p<0.05). The clinical characteristics and laboratory results of the patients who did and did not have NAFLD are shown in Table 1. No difference was found between the patients who did and did not have NAFLD in terms of age, LDL-C, TC, TG, fT4, TSH, and glucose levels (p>0.05). In patients with NAFLD, BW, height, BMI, BWH, insulin and non-HDL-C values were found to be higher (p<0.001); ALT, AST, and HOMA-IR scores were found to be higher; and HDL-C levels were found to be lower (p<0.05).

In the entire study group, increased LDL-C levels were found with a rate of 43.9% (n=157), increased TG levels were found with a rate of 44.3% (n=156) (hypertriglyceridemia), increased TC (hypercholesterolemia) was found with a rate of 26.5% (n=94), and decreased HDL-C levels

Table 2. Clinical properties and laboratory findings in the study groups that were established by low density lipoprotein-cholesterol levels[a]

	Group 1 (n=57)	Group 2 (n=143)	Group 3 (n=157)	p
Age (months)	165.5 (132–190)	135.5 (105–157)	144 (116–178)	**<0.001**
Female/Male (n, %)	30/27 (53/47)	77/66 (54/46)	92/65 (59/41)	0.62
BW (kg)	70.6±25.5	62.9±20.7	65.4±20.7	0.08
Height (cm)	157.5 (139–166)	150.5 (137–161)	152 (141–161)	0.07
BMI (kg/m^2)	28.5 (24.2–32.4)	26.5 (24.3–29.6)	27.3 (24.6–30.3)	0.39
BWH (%)	148 (128–172)	150 (138–164)	152 (129–162)	0.07
Glucose (mg/dL)	85 (81–91)	85 (81–90)	84 (80–89)	0.45
Insulin (uU/mL)	19.7 (10.6–26.1)	16.1 (10.1–22.7)	15.3 (10.6–25.3)	0.67
TC (mg/dL)	111 (99–121)	157 (141–174)	202 (192–216)	**0,00**
TG (mg/dL)	79.5 (50–110)	93 (71–126)	129 (96–187)	**0,00**
LDL-C (mg/dL)	40 (35–53)	46(40–53)	45(39–52)	0.20
HDL-C (mg/dL)	41 (18–78)	62 (33–111)	85 (43–144)	**0,00**
AST (U/L)	24 (18.7–36)	22 (18–27.2)	22 (19–27)	0.12
ALT (U/L)	21 (15–42)	19 (15–25)	18 (15–31)	0.23
fT4 (ng/dL)	1.2 (1.12–1.32)	1.26 (1.14–1.35)	1.21 (1.12–1.33)	0.42
TSH (mIU/mL)	2.8 (1.9–3.5)	2.6 (1.9–3.6)	2.8 (2.1–3.6)	0.47

a: Data with normal distribution are expressed as mean±SD and the data that do not have a normal distribution are expressed as median (25–75th percentile) values. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BWH: Body weight-for-height; HDL-C: High-density lipoprotein-cholesterol; LDL-C: Low-density lipoprotein-cholesterol; NAFLD: Non-alcoholic fatty liver disease; TG: Triglyceride; fT4: Free t4; TSH: Thyroid-stimulating hormone; BW: Body weight; BMI: Body mass index

were found with a rate of 9.8% (n=35). TC, TG, LDL-C, and HDL-C levels were found as normal in 22.5% of the patients (n=70). At least one lipid abnormality (hypo- and/or hyperlipidemia) was found in 77.5% of the patients.

Table 2 shows the clinical characteristics and laboratory findings of the groups established according to the LDL-C levels. No difference was found between the three groups in terms of sex distribution, height, BWH, and BMI values, serum ALT, AST, sT4, TSH, glucose and insulin levels, and HOMA-IR scores (p>0.05). Age was found to be higher in group 1 compared with group 2 and 3, and in group 3 compared with group 2 (p<0.001). The TG, TC, non-HDL-C levels were found to be lower in group 1 compared with group 2 and 3, and in group 2 compared with group 3 (p<0.001).

The frequency of NAFLD was not different between group 1, 2, and 3 (52.6%, 44.7%, 41.3%, respectively) (p>0.05). However, a numerically higher frequency of NAFLD was found in group 1. There was no difference in terms of the frequency of NAFLD between the groups established by the levels of triglyceride and TC being low, normal, and high (p>0.05). The frequencies of NAFLD in hypo-, normo-, and hyperlipidemic patients by lipid and lipoprotein levels are shown in Table 3.

Table 3. The frequency of non-alcoholic fatty liver disease in hypo-, normo- and hyperlipidemic patients

	NAFLD (+)	NAFLD (-)	p
By TG levels (n, %)			
Low	1 (16.7)	5 (83.3)	
Normal	79 (42.8)	105 (57.2)	0.18
High	76 (48.4)	81 (51.6)	
By TC levels (n, %)			
Low	22 (46.8)	25 (53.2)	
Normal	99 (46.5)	114 (53.5)	0.48
High	37 (39.4)	57 (60.6)	
By LDL-C levels (n, %)			
Low	30 (52.6)	27 (47.4)	
Normal	64 (44.8)	79 (55.2)	0.34
High	65 (41.4)	92 (58.6)	

LDL-C: Low-density lipoprotein-cholesterol; NAFLD: Non-alcoholic fatty liver disease; TG: Triglyceride; TC: Total cholesterol

In group 1 (n=57), NAFLD was found in five (40%) subjects (n=12) who had an LDL-C level of <50 mg/dL, which was the borderline value for heterozygous hypobetalipoproteinemia carrier state, and in 55% (n=25) of the patients who had an LDL-C level of ≥ 50 mg/dL (n=45). The

frequency of NAFLD was not different between these two groups (p>0.05).

In patients who had hypertriglyceridemia, the levels of insulin, ALT, LDL-C, and TC were found to be higher, and the levels of HDL-C were found to be lower compared with patients who had low and normal TG levels (p<0.05); there was no difference in terms of age, sex, height, BWH, BMI, AST, and glucose levels (p>0.05). In patients who had high total cholesterol levels, BWH, insulin, and HOMA-IR scores, LDL-C levels were found to be higher compared with patients who had normal and low TC levels (p<0.05); there was no difference in terms of age, height, BW, BMI, TG, HDL-C, ALT, AST, and glucose levels (p>0.05). Increased TC levels were found to a greater extent in male patients (p<0.05).

In patients who were found to have insulin resistance (n=172), HDL-C levels were found to be lower, and triglyceride levels and the frequency of NAFLD were found to be higher compared with patients who did not have IR (p<0.05). The frequency of IR was not different between group 1, 2, and 3 (p>0.05).

Discussion

In Turkey, the incidence of NAFLD was found as 23–62% in children and adolescents with obesity in different studies (5–7). In our study, the incidence of NAFLD in children and adolescents with obesity was found as 44.2%, similar to the literature, and the incidence was found to be higher in male patients. In obese individuals, free fatty acids increase with the increase in lipolysis. Free fatty acids lead to hepatosteatosis by causing an increase in the production of VLDL and TG in the liver by inhibiting lipoprotein lipase (19). It is known that an increase in BMI increases hepatosteatosis and IR (8, 20–22). The findings that the BW, BMI, BWH, serum non-HDL-C and insulin levels and HOMA-IR scores were higher in patients who had NAFLD, and both TG and the frequency of NAFLD were higher in subjects who had IR in our study, suggest that obesity, hyperlipidemia, and IR are involved in the development of NAFLD.

The frequency of dyslipidemia, which is considered another independent risk factor for NAFLD, is increased in obese individuals (23). In pediatric and adolescent patients with obesity, the frequency of dyslipidemia ranges between 43% and 69%. In these patients, hypertriglyceridemia is found to be the most common dyslipidemia (24–26). In our study, dyslipidemia was present with a rate of 77.5% in children and adolescents with obesity; hypertriglyceridemia and increased LDL-C were the most common lipid metabolism abnormalities.

It has been reported that increased TG and non-HDL levels in obese children and adolescents increases the frequency of NAFLD (22, 27). In our study, it was found that levels of non-HDL-C were high in patients with NAFLD, and in contrast to the literature, the levels of TG were not different. When our patients were divided into three groups in terms of TG, TC, and LDL-C levels as hypolipidemic, normolipidemic, and hyperlipidemic, however, it was found that the frequency of NAFLD was not different between these groups. This finding and the fact that the hypolipidemic groups had a NAFLD frequency as high as the hyperlipidemic groups suggested that the increase in BMI and IR or other factors were more efficient in the development of NAFLD compared with changes in lipid metabolism.

In our study, the presence of hypolipidemia was found with a considerably high rate (52.6%) in obese patients according to LDL-C levels. Non-alcoholic fatty liver disease is a clinical finding of primary hypolipidemia. In patients with obesity, hepatosteatosis develops with an increase in the production of VLDL and TG. In cases of primary hypolipidemia, TG accumulates in hepatocytes and NAFLD develops with disruption of VLDL-TG secretion from the liver, independent from other metabolic abnormalities such as obesity and IR (28). It was thought that the reason for hypolipidemia could be primary hypolipidemia such as abetalipoproteinemia and familial hypobetalipoproteinemia in our patients with LDL-C levels below 50 mg/dL.

Recently, it was proposed that some polymorphisms in the MTTP gene, the mutations of which lead to abetalipoproteinemia, and polymorphisms in the TMSF6F2 gene could be associated with increased TG deposition in the liver, increased NAFLD, non-alcoholic steatohepatitis (NASH), and cirrhosis accompanied by decreased serum lipids and lipoproteins (29, 30).

Because our patients did not have systemic and other severe clinical findings of primary hypolipidemias other than NAFLD, it was thought that patients who had LDL-C levels below 50 mg/dL and were asymptomatic or had a mild clinical picture could be heterozygous carriers of primary hypolipidemia or could be carrying the relevant polymorphisms reported in the literature. Genetic analysis was not performed in patients who had hyperlipidemia in our study.

Patients with hypolipidemia are generally missed in outpatient clinics and not evaluated in detail when they do not present with severe signs such as steatorrhea, diarrhea, and peripheral neuropathy. The presence of NAFLD should be investigated in patients with hypolipidemia because severe and chronic NAFLD may lead to complications such as

NASH and cirrhosis, as mentioned above. Non-alcoholic fatty liver diseases were investigated in our patient group who had hypolipidemia because they were obese.

The limitations of our study included the retrospective design and the fact that the diagnosis of NAFLD was made using USG rather than a liver biopsy. In addition, genetic analysis was not performed to determine the etiology in patients who had hypolipidemia.

In conclusion, the frequency of NAFLD is increased in children and adolescents with obesity. The frequency of NAFLD is not different between hypolipidemic, normolipidemic and hyperlipidemic patients. These findings suggest that the amount of body adipose tissue and IR are risk factors that have a greater role in the development of NAFLD.

Ethics Committee Approval: Our study was conducted in accordance with the Declaration of Helsinki. Approval was obtained from Eskişehir Osmangazi University Non-Interventional Clinical Research Ethics Committee (date: 11.12.2018, decision number: 10).

Informed Consent: As it was a retrospective study, consent was not obtained from the patients.

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