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Subclinical hypothyroidism in obese Turkish adolescents: the relationship with anthropometry and fatty liver

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Aim: To evaluate whether subclinical hypothyroidism (SH) is associated with anthropometry and fatty infiltration of liver in obese adolescents.

Materials and methods: The adolescents attended with the complaint of obesity aged 11 to 15 years included in the study. Patients were diagnosed as obese adolescents with fatty liver. Age-, gender-, and body weight-matched obese adolescents without fatty liver seen during the same period served as controls. Clinical characteristics, laboratory parameters, and frequency of subclinical hypothyroidism (SH) of both groups were compared.

Results: The study population included 218 adolescents with obesity. Of 218, 30 (13.7%) had fatty liver at ultrasonography (group 1) and the remaining 188 obese adolescents did not have fatty liver and served as control (group 2). The mean ages of groups 1 and 2 were 12.7 ± 1.25 and 13 ± 1.39 years; the rate of female participants were 43.3% and 55.8%; and, weight:height ratios were 157.2 ± 24 and 151.3 ± 19.8 (P = 0.37, 0.24, and 0.54, respectively). The prevalence of SH in patients with fatty liver was 10% and was not significantly higher compared to the controls (6.4%, P = 0.55).

Conclusions: SH seems to be a secondary condition rather than a triggering factor for development of fatty liver in adolescent obese patients. There was no statistically significant relation between subclinical hypothyroidism and fatty liver.

Key words: Adolescent, anthropometry, fatty infiltration of liver, obesity, subclinical hypothyroidism

Obez Türk adolesan çocuklarda subklinik hipotiroidi: antropometri ve nonalkolik yağlı karaciğer hastalığı ile ilişkisi

Amaç: Bu çalışmanın amacı obez adolesanlarda subklinik hipotiroidi ile antropometri ve yağlı karaciğerin ilişkisinin belirlenmesi.

Yöntem ve gereç: Obezite nedeniyle başvuran 11-15 yaşlarındaki adölesanlar çalışmaya alındı. Vakalar ultrasonografide yağlı karaciğer saptanan adölesanlar olarak tanımlandı. Yaş cinsiyet ve vücut ağırlığı açısından farklılık göstermeyen obez adölesanlar kontrol grubu olarak belirlerlendi. Klinik bulgular, laboratuar bulguları ve subklinik hipotiroidi(SH) sıklığı karşılaştırıldı.

Bulgular: Çalışmaya toplam 218 obez adölesan alındı. Ultrasonografide yağlı karaciğer saptanan 30 adölesan; çalışma grubu (Grup 1) diğer adölesanlar (n = 188) kontrol grubu (Grup 2) olarak gruplandı. Grup 1 ve 2 nin yaş, cinsiyet, ve boya göre ağırlık ortalamaları farklı değildi (sırasıyla 12,7 ± 1,25 ve 13 ± 1,39 yıl, kızların oranı % 43,3 ve % 55,8; 157,2 ± 24 ve 151,3 ± 19,8, P = 0,37, 0,24 ve 0,54) idi. Grup 1 deki adölesanlarda SH sıklığı % 10, kontrol grubunda ise % 6,4 (P = 0,55) olarak saptandı.

Sonuç: Yağlı karaciğeri olan obez adölesanlarda SH sıklığı kontrol grubuna oranla yüksek saptanmamıştır. Bu çalışmanın sonuçları SH'nin yağlı karaciğer hastalığını tetikleyici olmaktan ziyade yağlı karaciğere sekonder bir durum olduğunu düşündürmüştür.

Anahtar sözcükler: Obezite, insulin rezistansı, nonalkolik yağlı karaciğer hastalığı, hepatik arter rezistif indeksi, adölesan

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Introduction

Obesity and its complication nonalcoholic fatty liver disease (NAFLD) continue to increase dramatically among adolescents (1). NAFLD is a spectrum of pathology ranging from fatty liver to the most severe form, called nonalcoholic steatohepatitis (NASH). NASH was found to be related with overt hypothyroidism in adults (2). SH is a preliminary stage of overt hypothyroidism, defined as a mild elevation of thyroid-stimulating hormone (TSH) level in patient with normal serum thyroxine level. In adults, SH has been found to be associated with hyperlipidemia (3,4), insulin resistance (5), and obesity (6). To the best of our knowledge, no study so far has compared the thyroid function of healthy obese children with fatty liver to appropriate controls. Therefore, our study was performed to investigate the frequency of elevated TSH levels in obese children with fatty liver and to search whether SH is associated with fatty liver as well as body composition and biochemical findings in obese adolescent patients.

Materials and methods

Case notes of 550 adolescents who were admitted to the Pediatric Gastroenterology Hepatology Clinics of Dokuz Eylül University Hospital from 1 January 1999 to 1 January 2006 with the complaint of obesity (defined as a weight:height ratio above 120) were examined. Of 550 patients, 1 patient with Cushing Syndrome, 26 patients using steroid, 15 patients with familial hyperlipidemia, 6 patients with growth hormone deficiency, 4 patients with diabetes, and 1 patient with complete gonadal dysgenesis were excluded. Patients with liver disease and who use lithium, amiodarone, metoclopramide, or domperidone were not included in the study. Of remaining 497 patients, 218 were (11-15 years old) enrolled in the study (Figure 1). Cases were defined as obese adolescents with fatty liver. Age-, gender-, and body mass index-matched obese adolescents without fatty liver at ultrasonography (US) seen during the same period were examined as controls. Physical examination findings and anthropometric measurements of all the patients were recorded. Weight:height ratios (W:H%) of the patients were calculated according to CDC charts (7). Clinical characteristics, biochemical findings, and frequency of SH of both groups were compared.

Biochemical tests of the patients were performed after a 12-h fasting period. Fasting serum glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transpeptidase (GGT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), total triiodothyronine (TT3), total thyroxine (TT4), and thyroid stimulating hormone (TSH) levels were measured. The thyroid stimulating hormone test was used for comparison purposes since it is the most commonly used test in diagnosis of hypothyroidism in children at early ages (8). Normal ranges of TT3, TT4, and TSH for 11-15 years age group were accepted as 1.09-2.95 nmol/L, 5.36-11.5 μg/dL, and 0.5-4.4 mU/L, respectively (9). Subclinical hypothyroidism is defined as the elevation of TSH level over 4.4 mU/L along with normal TT3 and TT4 levels. ALT and AST normal limits were 5-45 U/L (10). Total protein, albumin, total bilirubin, and prothrombin time were tested if the patients' ALT and AST levels were above the accepted values. Serologies of hepatotropic viruses and TORCH infection, serum copper and ceruloplasmin levels, serum alpha 1-

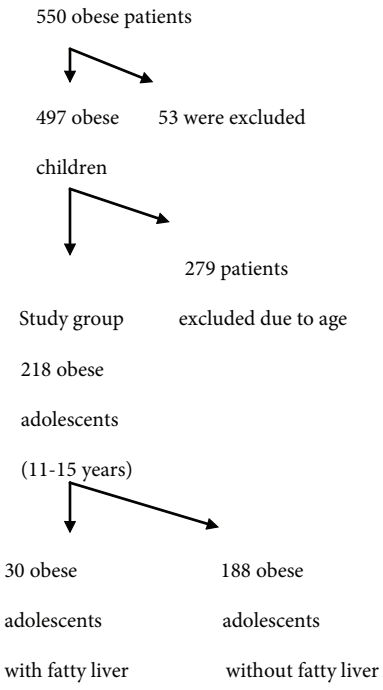

Figure 1. Characteristics of the study group.

antitrypsin level, and autoantibodies against nuclear, smooth muscle, liver, and kidney microsomal type-1 antigens were screened to eliminate infectious, metabolic, and immunologic liver pathologies.

Fatty liver was diagnosed by US. Three ultrasonographic criterias were used to confirm the fatty liver diagnosis (11,12). For each criterion, a score was assigned as an indicator of the level of fatty infiltration. A score of 2 (++) indicated a definitive positive finding of fatty infiltration. A score of one (+) indicated a probable fatty infiltration. When the fatty infiltration was negative (-), a score of zero was assigned. The sum of the scores for the 3 criteria was considered to be an indicator of the severity of fatty infiltration. Thus, the fatty liver indicator ranged from 0 to 6, where a total score of 3 or more was considered as an indication of fatty liver. The criteria and scoring assignments are described below.

1. The echo levels for the liver and kidney parenchyma were compared. An evaluation was made of the relative increase in the liver versus kidney surface echo level accompanied by a high contrast between liver and kidney parenchyma (liver-kidney echo discrepancy). A large discrepancy between hepatic and renal echoes resulted in a (++) finding. A slight increase in the liver echogenecity, which is a slight increase of liver and kidney echo discrepancy, was assigned a (+) evaluation. A negative (-) evaluation of fatty liver was made when the echo level was homogeneous and the contrast between the liver and the kidney parenchyma was unclear.

2. An assessment was made of echo penetration into the deep portion of the liver. Penetration of ultrasonography at the deepest portion of the liver is low due to the interference of the enhanced liver surface echogenecity, which results in the opacity of the lower part of the liver and the loss of visibility of the diaphragm. A (++) evaluation was given when both indicators were definitely present. The probable presence of both indicators resulted in a (+) score, while a (-) evaluation meant that the liver structure was clearly defined from the surface of the liver to the diaphragm.

3. The clarity of the hepatic vessels in the sonograph, especially the veins, was evaluated. When hepatic vessel structures were not clear and the identification of the vessel walls could not be made, a (++) evaluation was assigned. If loss of echoes from the vessel wall was observed, a (+) score was given. A (-) score resulted when the vessel structures and vessel walls could be clearly defined.

Data were analyzed by SPSS 11.0. The chi-square and Fisher's exact tests were used for comparing group ratios and Student's t test was used for comparing group averages. A P value less than 0.05 was considered significant. Power of the study for comparison of subclinical hypothyroidism frequency was calculated as 21.3.

Results

Table 1 shows the anthropometric, physical, and biochemical parameters of both groups. The study population consists of 218 adolescents with obesity. Thirty (13.7%) of them had fatty liver at ultrasonography (study group, group 1) and remaining 188 (86.3%) obese adolescents without fatty liver served as control (group 2). Data regarding age, gender, and weight:height ratios were similar in both groups. The mean ages of groups 1 and 2 were 12.7 ± 1.25 and 13.0 ± 1.39 years; the rate of female participants were 43.3% and 55.8%, and weight:height ratios were 157.2 ± 24 and 151.3 ± 19.8, respectively (Table 1). The mean fasting serum glucose levels of groups 1 and 2 were similar at admission. Mean ALT level of group 1 was higher than that of group 2 ($P < 0.0001$). Mean AST levels of groups 1 and 2 were similar. Mean GGT level of group 1 was higher than that of group 2 ($P = 0.028$). Mean LDL-C and TG levels of group 1 were all higher compared to group 2 ($P = 0.03$, $P = 0.007$, respectively). Mean total T3, total T4, and TSH levels of both groups were similar ($P = 0.18$, $P = 0.55$, $P = 0.36$, respectively). The prevalence of SH in patients with fatty liver was 10% and was not significantly higher compared to the control group (6.4%, $P = 0.55$).

Discussion

The purpose of this study was to find out whether SH is a triggering factor for fatty liver and our findings support the idea that thyroid hormone abnormalities associated with fatty liver are secondary. There was no

Table 1. Demographic, physical, and biochemical parameters of the patients with fatty liver (group 1) and the patients with normal liver echogenecity based on US (group 2).

	Mean ± SD (range)		P value*
	Group 1 n = 30	Group 2 n = 188	
Age (year)	12.7 ± 1.25 (11-15)	13 ± 1.39 (11-15)	NS
Gender (F / M) (n)	13 / 17	105 / 83	NS
Weight for height (%)	157.2 ± 24 (126-234)	151.3 ± 19.8 (118-229)	NS
Serum glucose (mg/dL)	93.8 ± 12.6 (74-136)	92.9 ± 9 (68-120)	NS
ALT (U/L)	33.7 ± 36 (10-190)	20.8 ± 6.5 (10-40)	**<0.0001**
AST (U/L)	25.1 ± 13.9 (11-77)	22.7 ± 11.6 (10-147)	NS
GGT (U/L)	21.8 ± 12.8 (9-74)	15.6 ± 8.3 (7-80)	**0.028**
TC (mg/dL)	174.8 ± 27.3 (134-247)	167.3 ± 26.2 (117-234)	NS
HDL-C (mg/dL)	43.6 ± 8 (30-67)	48 ± 9.7 (26-78)	**0.019**
LDL-C (mg/dL)	111.9 ± 45.3 (68-304)	100.7 ± 21.5 (60-157)	**0.030**
TG (mg/dL)	121.4 ± 42.3 (52-328)	99.3 ± 40.7 (40-337)	**0.007**
TT3 (nmol/L)	1.6 ± 0.45 (1-3.5)	1.56 ± 0.29 (1-2.8)	NS
TT4 (µg/dL)	8.2 ± 2.3 (1.35-11.7)	8.4 ± 1.7 (4-16.4)	NS
TSH (mU/L)	2.66 ± 1 (1.2-4.9)	2.48 ± 1.14 (0.7-5.95)	NS
SH (n,%)	3 (10%)	13 (6.4%)	NS

***NS:** Not significant

difference between groups 1 and 2 in terms of the frequency of SH, which gives the idea that SH is secondary to fatty liver and supports the idea that treatment with thyroxine would not help in protecting adolescents from fatty liver development. The prevalence of SH was 7.3% in all participants, which confirmed the finding of Stichell et al., 7.5% SH prevalence in obese adolescents (6). In this study, increased liver echogenecity resembling fatty liver at US images was observed in 13.7% of the patients. Prevalence of fatty liver was reported as 12% in a previous study (11).

The gold standard tool for the diagnosis of fatty liver is liver biopsy. However, liver biopsy is invasive and costly. Although imaging techniques have been helpful in assessing non-alcoholic fatty liver and steatosis, they lack the ability to identify fibrosis (12). Therefore, liver biopsy is preferred for the follow up of drug treatment patency and the detection of cirrhosis. On the other hand, US is recommended for the diagnosis of steatosis (1,13). Magnetic resonance imaging and US were used in some previous pediatric studies for diagnosis of fatty liver (12,14). In the present retrospective study, the assessment of the fatty liver was performed using US as recommended in the literature (12-14).

Fatty liver results from the accumulation of fatty acids in various forms, predominantly triglycerides (15,16). Our group 1 patients' lipid profiles were in favor of lipogenesis since triglycerides were significantly higher in this group compared to the control group. This can occur when the amount of fatty acid supplied to the liver from the gut or adipose tissue exceeds the amount needed for mitochondrial oxidation, phospholipid, and cholesterol ester synthesis (17). Also in hyperinsulinemia, fatty acids are esterified to triglycerides. Thus, the conjunction of high free fatty acid and insulin resistance, both directly related to increased visceral fat mass, play important complementary roles for the development of liver steatosis (18). Furthermore, the development of fatty liver may increase insulin clearance, which can initiate a vicious circle (19).

It has been suggested that increased hepatic oxidative stress, perhaps on hepatic mitochondria, causing their dysfunction (20,21). As a result mitochondria consume more oxygen but produce less ATP than usual. The increase in oxidative stress may arise from increased insulin resistance, increased free fatty acid metabolism, increased endotoxin levels in the liver, increased activity of cytochrome p-450 2E1, increased iron stores, and/or decreased antioxidant activities (22). Oxidative stress increases hepatic steatosis via lipid peroxidation increase and released cytokines lead to more mitochondrial damage. Mitochondrial injury can lead to mutation and loss of mitochondrial DNA. Mitochondrial DNA damage or loss was shown in nucleoside hepatotoxicity, alcohol consumption, aging, and Wilson disease (23). Since adenosine triphosphate (ATP) is critical for maintaining cellular integrity, its depletion may predispose to hepatocellular injury. Depletion of hepatic ATP levels was observed and the magnitude of this depletion was correlated with body mass index in a previous study (24). Mitochondrial ATP is a source of cyclic AMP, which is a second messenger for lots of hormones including TSH and TRH. With the depletion of ATP, the production of the second messenger c-AMP by adenylate cyclase decreases. Liver cells are one of the main targets of thyroid hormones and in case of the depletion of cyclic AMP, their action in hepatocytes would be affected. The clinical result is hepatocyte unresponsiveness to thyroid hormones and TSH level increases in order to overcome this decrease.

Support for the hypothesis that increased lipid levels together with lipid peroxidation, and decreased antioxidant defense in hypothyroidism has been reported before and also hypothyroidism has been found significantly related with insulin resistance (22,25). In a study by Rapa et al., it was shown that there is a wide range of clinical, biochemical, and genetic factors involved in pediatric subclinical hypothyroidism pathogenesis (26).

In the adult literature, it has been reported that higher levels of AST, ALT, and GGT likely reflect NAFLD (27-29). Results of the present study confirm that serum ALT and GGT levels of children with fatty liver are higher (30). There is a need for detailed studies regarding the relation of ALT and GGT with fatty liver in children.

Several limitations of this study should be considered. Since it is a retrospective study, ultrasonographic examinations were not performed using the same machine by the same radiologist. We were not able to compare insulin levels and investigate its relation with SH, since we did not have insulin measurement records of most children in the study. Another limitation is the power of the study (21.3). Since this is the first study on this topic and it is a retrospective study, we were not able to make power analysis before the study.

In conclusion, SH frequency in obese children with fatty liver is not higher than that in patients without fatty liver, which suggests that SH seems to be a result of fatty liver development. Further studies with a higher power to determine the cause and effect relationship between fatty liver, subclinical hypothyroidism, ALT, and GGT levels in obese adolescents are warranted.

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