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THE EFFECT OF FATTY LIVER DISEASE ON PORTAL VEIN FLOW IN OBESE ADOLESCENTS

OBEZ ADOLESANLARDA YAĞLI KARACİĞER HASTALIĞININ PORTAL VEN AKIMINA ETKİSİ

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Öz

Amaç
Çocuklarda obezitenin artması, nonalkolik yağlı karaciğer hastalığının pediatrik yaş grubunda en önemli kronik karaciğer hastalığı haline gelmesine neden olmuştur. Bu çalışmada alkolik olmayan karaciğer yağlanması (NAFLD) olan obez çocuklarda portal ven çapı ve kan akım hızını değerlendirmesi ve normal sağlıklı çocuklarla karşılaştırması amaçlanmıştır.

Gereç ve Yöntem
10-18 yaş arası 71 obez adolesan hasta, transaminaz yüksekliği ve ultrasonda hepatosteatoz (NAFLD grubu ve NAFLD olmayan grup) varlığına göre iki gruba ayrıldı. Kontrol grubu olarak 30 sağlıklı ergen çalışmaya dahil edildi. Her hastadan açlık glukozu, insülin, transaminaz düzeyleri ve tiroid fonksiyonları için kan örnekleri alındı. İnsülin direnci HOMA indeksi kullanılarak hesaplandı. Portal ven ölçümleri, bifurkasyon öncesi ana portal venden yapıldı.

Bulgular
NAFLD grubunda portal ven çapı (8.5 ± 0.9 mm) hem kontrol grubuna (7.8 ± 2.0 mm) hem de NAFLD olmayan obez gruba (7.6 ± 1.1 mm) göre istatistiksel olarak anlamlı derecede geniş olarak saptandı (p= 0.004) ve (p=0.002). NAFLD olmayan obez grup ile kontrol grubu arasında anlamlı fark yoktu (p=0.460, p=0.214). Portal ven Vmax, Vmin, RI, S/D açısından gruplar arasında anlamlı fark yoktu. İnsülin direncine göre sınıflandırılan obez gruplarda portal ven çaplarında farklılık olmamasına rağmen, Vmax (33.9 ± 10.3 ve 28.6 ± 10.6 cm/sn, p= 0.03) ve Vmin (24.8 ± 6.2 ve 20.5 ± 5.5 cm/sn) insülin direnci grubunda önemli ölçüde farklıydı.

Sonuç
Bu çalışmada NAFLD olan obez adolesanlarda portal ven çapı ve akım hızlarının (Vmax ve Vmin) arttığı belirlendi. Bu nedenle özellikle ergenlik döneminde insülin direnci olan obez hastalarda hepatik portal ven steatozuna bağlı hepatik venöz akımda direnç geliştiği düşünüldü. Bu bulgu, karaciğer yağlanmasının devam etmesi durumunda erişkin dönemde portal çapının artacağını ve bunun da portal hipertansiyona yol açacağını düşündürmektedir.

Anahtar Kelimeler: Doppler ultrasonografi, Hepatosteatoz, Obezite

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Abstract

Objective
The increase in obesity in children has caused nonalcoholic fatty liver disease to become the most important chronic liver disease in the pediatric age group. In this study, we aimed to evaluate the portal diameter and blood flow velocity in obese children with fatty liver (NAFLD) and to compare them with normal healthy children.

Material and Method
71 obese adolescent patients aged 10-18 years were divided into two groups (NAFLD group and non-NAFLD group) according to the presence of elevated transaminases and the presence of hepatosteatosis on ultrasound. 30 healthy adolescents were included in the study as the control group. Blood samples were taken from each patient for fasting glucose, insulin, transaminases, and thyroid functions. Insulin resistance was calculated using the HOMA index. Portal vein measurements were performed from the main portal vein before bifurcation.

Results
The portal vein diameter (8.5 ± 0.9 mm) of the NAFLD group was statistically significantly wide compared to both the control group (7.8 ± 2.0 mm) and the non-NAFLD obese group (7.6 ± 1.1 mm) (p= 0.004) and (p= 0.002). There was no significant difference between the non-NAFLD obese group and the control group (p=0.460, p=0.214). There was no significant difference between the groups in terms of portal vein Vmax, Vmin, RI, S/D. Although there was no difference in portal vein diameter in the obese groups classified according to insulin resistance, Vmax (33.9 ± 10.3 and 28.6 ± 10.6 cm/sec, p= 0.03) and Vmin (24.8 ± 6.2 and 20.5 ± 5.5 cm/sec) were significantly different in the insulin resistance group.

Conclusion
In this study, it was determined that portal vein diameter and flow velocities (Vmax and Vmin) increased in obese adolescents with NAFLD. Thus, we suggest that resistance develops in hepatic venous flow due to hepatic portal vein steatosis, especially in obese patients with insulin resistance in adolescence. This finding suggests that when fatty liver continues, portal diameter will increase in adulthood, leading to portal hypertension.

Keywords: Doppler ultrasonography, Hepatosteatosis, Obesity

Introduction

Childhood obesity has an increasing prevalence all over the world, especially in developed countries. The prevalence of obesity in the childhood age group in European countries varies between 2% and 13% (1, 2). Studies have shown that obesity significantly increases the risk of hypertension, type 2 diabetes, hyperlipidemia, cardiovascular system diseases and even some types of cancer (colon, breast, gallbladder, endometrium) (3).

Non-alcoholic fatty liver disease (NAFLD) divided into two subgroups as nonalcoholic steatosis and nonalcoholic steatohepatitis. In patients with nonalcoholic fatty liver disease, fatty liver is observed, but there is no inflammatory infiltration. While Non-alcoholic steatohepatitis is a disease in which findings such as hepatocytes ballooning, inflammatory infiltration, Mallory bodies, megamitochondria and fibrosis are seen, as in alcoholic liver disease, together with fatty liver (4).

NAFLD is a clinicopathological diagnosis that requires excluding other causes of liver disease (including chronic alcohol use) and delineated by macrovesicular fat deposition in hepatocytes. NAFLD is probably the most common cause of chronic liver disease in children (4, 5). The most important risk factors are obesity and insulin resistance and the prevalence of NAFLD has increased rapidly with the increase in the frequency of these risk factors in children (6, 7).

NAFLD covers a wide range of conditions from steatosis to steatohepatitis and fibrosis. NAFLD can progress to end-stage liver diseases such as liver cirrhosis, liver failure and hepatocellular carcinoma (8, 9). Fat in the liver can cause asymptomatic elevation of liver enzyme levels. Alanine aminotransferase (ALT) is considered the most specific marker of liver damage (10). Although both liver enzymes are not consistent with fibrosis, liver fat infiltration has been reported to be associated with the degree of inflammation in adults and children (11, 12).

The liver is the organ with the most blood supply in the human body. Doppler ultrasonography is a noninvasive, important and reliable method in the

diagnosis and progression of liver diseases, especially in chronic diseases (13). Although this examination method is increasingly used in liver diseases, there are not enough clinical studies on changes in Doppler ultrasound parameters that may occur due to obesity (14, 15). About 80% of the blood coming to the normal liver is from the portal vein and 20% from the hepatic artery. When there is a deterioration in portal blood flow for any reason, there is an increase in hepatic arterial blood flow in order to maintain hepatic blood supply (14). Easy to apply and color Doppler ultrasonography, which is a cheaper method (RDUS), about the presence, direction, velocity, flow rate, presence of collaterals and flow methods in the portal system provides important information (16).

Materıal and Method

A study group was formed of 16 obese adolescents with high ALT levels (≥40 IU/ml) and 55 obese adolescents with normal ALT levels (<40 IU/ml). A total of 71 obese and 30 normal-weight adolescents were randomly recruited from children admitted to the General Pediatrics outpatient clinic of Suleyman Demirel University between October 2018 and May 2019. A single radiologist performed an upper abdomen ultrasound and portal vein Doppler ultrasound in the radiology department for all participants.

The patients with hepatitis B, Hepatitis C, autoimmune hepatitis, drug-related liver damage, Wilson's disease, alpha 1 antitrypsin deficiency, lysosomal storage diseases, cystic fibrosis, etc., may lead to hepatosteatosis, were excluded.

Metabolic Parameters

Serum glucose, ALT, calcium were studied by spectrophotometric method in a Beckman Coulter AU 5800 (USA) biochemistry autoanalyzer. Serum insulin levels were measured in a Roche Cobas 6000 e600 (Germany) hormone autoanalyzer using electrochemiluminescence immunoassay (ECLIA) method. Serum cortisol levels and serum vitamin D levels were measured in a Roche Cobas e601 (Germany) hormone autoanalyzer using electrochemiluminescence immunoassay (ECLIA) method. Platelet and MPV measurements in whole blood were studied on the Beckman Coulter Unicel DXH 800 (USA) device by coulter method by detecting and measuring electrical resistance changes as a particle (eg a cell) in a conductive liquid passes through a small opening. Insulin sensitivity index was derived from fasting blood samples. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting insulin concentration (μU/mL) x fasting glucose concentration (mg/dL) /405 (17). Insulin resistance was defined in adolescents as HOMA-IR levels greater than 3.16 (18).

Imaging Techniques

Upper abdomen and Doppler ultrasound measurements were performed after 4 hours of fasting, in the lateral decubitus position, in deep inspiration. Portal vein measurements were performed from the main portal vein before the bifurcation. Liver dimensions were measured as right lobe long axis and left lobe AP diameter.

Statistical Analysis

Descriptive results are shown as mean and standard deviations (SD) as the variables normally distributed. A Kolmogorov-Smirnov test was applied to test the normality of variables. The Pearson's correlation test (r) analyzed the correlations among numerical data. Comparison between groups was performed using ANOVA (post hoc: Kruskal Wallis with Bonferroni correction). A probability value of <0.05 was considered significant. The SPSS version 18 (SPSS, Chicago, IL, USA) was used for statistical analyses.

Results

The mean age of the healthy control group was 14.9 ± 1.4 years, the mean age of the non-NAFLD obese adolescent group was 14.0 ± 1.9 years, and the mean age of the NAFLD obese adolescent group was 14.5 ± 2.4 years. There was no difference in terms of the mean age of the groups (p=0.409). BMI was 21.5 ± 3.1 kg/m2 in healthy control patients, 31.6 ± 4.1 kg/m2 in non-NAFLD patients, and 30.2 ± 3.5 kg/m2 in NAFLD patients (p<0.05).

In terms of portal vein diameter, the portal vein diameter (8.5 ± 0.9 mm) of the NAFLD group was statistically significantly increased compared to both the control group (7.8 ± 2.0 mm) and the non-NAFLD obese group (7.6 ± 1.1 mm) (p=0.004 and p=0.002, respectively). There was no significant difference between the non-NAFLD obese group and the control group (p=0.460, p=0.214). There was no significant difference between the groups in terms of portal vein Vmax, Vmin, RI, S/D. Demographic characteristics, metabolic parameters and portal vein Doppler ultrasonography results were summarized in Table1.
Patient's mean values according to insulin resistance in obese adolescents and comparisons between groups were evaluated. Although there was no difference in portal vein diameter in the obese groups classified according to insulin resistance, Vmax (33.9 ± 10.3 and 28.6 ± 10.6 cm/sec, p= 0.03) and Vmin

Table 1 Demographic characteristics of patients and mean values of metabolic parameters and comparison between groups

		Obese adolescents	
	Control	**Non-NAFLD**	**NAFLD**
Female/Male	15/15	34/21	4/12
Age (years)	14.9 ± 1.4	14.0 ± 1.9	14.5 ± 2.4
BMI (kg/m²)	21.5 ± 3.1	31.6 ± 4.1#	30.2 ± 3.5
Glucose (mg/dL)	94.4 ± 10.8	94.8 ± 12.2	93.0 ± 11.7
Insulin (µU/mL)	18.2 ± 10.5	34.8 ± 63.9	27.7 ± 11.5
HOMA-IR (mg/dL)	4.3 ± 2.6*	9.2 ± 21.3	6.3 ± 2.6
Cortisol (µg/dL)	10.5 ± 4.7	12.0 ± 11.1	12.2 ± 4.9
ALT (U/L)	14.0 ± 4.7*	18.2 ± 7.1#	58.5 ± 14.4β
Portal vein diameter (mm)	7.8 ± 2.0	7.6 ± 1.1	8.5 ± 0.9β
Vmax (cm/sn)	35.8 ± 21.1	32.0 ± 9.9	35.5 ± 12.2
Vmin (cm/sn)	24.3 ± 8.5	23.6 ± 6.1	24.9 ± 7.0
S/D (Vmax/ Vmin)	1.4 ± 0.3	1.3 ± 0.2	1.4 ± 0.4
Resistive index (RI)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1

NAFLD: Non-alcoholic fatty liver disease BMI: Body mass index, HOMA-IR: Insulin resistance test, ALT: Alanine aminotransferase, Vmax: Highest systolic rate , Vmin: Minimum velocity at the end of diastole, RI: Resistive index , S/D: Vmax/ Vmin, *: Group 0-1 results with p<0.05, β: Results between groups 0-2 with p<0.05, #: Results between group 1-2 with p<0.05

Table 2 Mean values according to insulin resistance in obese adolescents and comparison between groups

	Obese adolescents		
	IR	**Non-IR**	**p value**
Glucose (mg/dL)	95.7 ± 12.9	89.4 ± 5.8	**0.04**
Insulin (µU/mL)	38.7 ± 62.5	12.7 ± 3.8	**0.03**
HOMA–IR (mg/dL)	10.1 ± 20.9	2.8 ± 0.8	**0.01**
Cortisol (µg/dL)	12.4 ± 10.9	10.9 ± 5.4	0.61
ALT (U/L)	28.7 ± 21.0	21.8 ± 9.3	**0.02**
Portal vein diameter (mm)	7.8 ± 1.2	7.5 ± 0.8	0.19
Vmax (cm/sn)	33.9 ± 10.3	28.6 ± 10.6	**0.03**
Vmin (cm/sn)	24.8 ± 6.2	20.5 ± 5.5	**0.01**
Resistive index (RI)	0.2 ± 0.1	0.2 ± 0.0	0.26

IR: Insulin resistance, HOMA-IR: Insulin resistance test , ALT: Alanine aminotransferase, Vmax: Highest systolic rate, Vmin: Minimum velocity at the end of diastole, RI: Resistive index

Table 3 Correlations of portal vein diameter (mm) with other metabolic parameters

	NAFLD		Non-NAFLD	
	r	p	r	p
Age	0.254	0.343	0.235	0.08
BMI (kg/m²)	0.405	0.120	0.171	0.211
Glucose (mg/dL)	0.201	0.455	0.083	0.547
Insulin (µU/mL)	-0.219	0.415	0.004	0.977
HOMA-IR (mg/dL)	-0.178	0.509	0.003	0.983
Cortisol (µg/dL)	-0.025	0.926	0.510	0.000
ALT (U/L)	0.146	0.590	-0.015	0.914
Vmax (cm/sn)	0.335	0.204	0.058	0.671
Vmin (cm/sn)	-0.063	0.815	0.011	0.937
S/D	0.462	0.071	0.022	0.874
Resistive index (RI)	0.558	0.025	0.147	0.290

NAFLD: Non-alcoholic fatty liver disease, BMI: Body mass index, IR: Insulin resistance, HOMA-IR: Insulin resistance test, ALT: Alanine aminotransferase, Vmax: Highest systolic rate, Vmin: Minimum velocity at the end of diastole, RI: Resistive index, S/D: Vmax/ Vmin, r: Pearson correlation coefficient

(24.8 ± 6.2 and 20.5 ± 5.5 cm/sec) were significantly different in the insulin resistance group (Table 2).

The relationship between portal vein diameter and age, BMI, glucose, insulin, HOMA-IR, cortisol, ALT, Vmax, Vmin, Vmax/Vmin, RI was evaluated in NAFLD and non-NAFLD patients. It was found that portal vein diameter and Vmax/Vmin ratio, resistive index correlation were found in NAFLD patients. As the portal vein diameter increases, the Vmax/Vmin ratio decreases inversely (Table3).

Discussion

Doppler ultrasound is a clinically accepted and widely used method in abdominal examinations, especially in evaluating liver vascularity (19). However, the effects of intrahepatic fat deposition and inflammatory changes in the flow model of the hepatic and portal veins are unknown (20). Balci et al. Evaluated patients with hepatosteatosis (n=105) and healthy individuals (n=35) (20). There is homogeneous diffuse fat infiltration in patient groups. They concluded that as fat infiltration severity increases, portal vein blood flow velocity decreases (21). Similarly, they found that statistically significant difference in portal venous velocity between the control group and patients with NAFLD (21). In our study, the portal vein diameter of the NAFLD group (8.5 ± 0.9 mm) was statistically significantly increased compared to both the control group (7.8±2.0 mm) and the non-NAFLD obese group (7.6 ± 1.1 mm) in terms of portal vein diameter (p= 0.004 and p= 0.002).

Erdoğmuş et al. (22) found that portal vein Vmax (peak maximum velocity=maximum velocity) and Vmin (peak minimum velocity=minimum velocity) values were significantly lower in patients with fatty liver in a study they conducted with 60 obese and 20 healthy volunteers in the adult age group. And showed a decrease in vascular compliance in the liver as a result of fatty infiltration. Dietrich et al. (20) found that Vmax and Vmin decreased with increasing fat infiltration. In our study, no significant difference was found between Vmax and Vmin. There was no significant difference between the groups regarding portal vein Vmax, Vmin, RI, and S/D. Although there was no difference in portal vein diameter in the obese groups classified according to insulin resistance, Vmax (33.9 ± 10.3 and 28.6 ± 10.6 cm/sec, p= 0.03) and Vmin (24.8 ± 6.2 and 20.5 ± 5.5 cm/sec) were significantly different in the insulin resistance group (p= 0.01) increased.

The mean values of portal vein diameter in patients with portal hypertension were found to be different in many studies. For example, Webb et al. (23) 10 mm, and Bolondi et al. (24) published it as 13 mm. Goyal et al. (25) reported the portal vein diameter as 19.4±2.5 mm in patients and 10.4±1.6 mm in the control group in their study. Er et al. (26) portal vein diameter was measured as 14.1±2.4 mm in the patient group and 9.5±0.9 mm in the control group. There was a statistically significant difference between the two groups regarding portal vein diameter. Balci et al. concluded that the pulsatility index and the mean velocity of portal vein blood flow declined as the severity of fat infiltration rose. However, they found no relationship between the degree of hepatic fat fraction and portal venous velocity.

Similarly, they found that the portal venous velocity difference between NAFLD patients and the control group was statistically significant. They thought that by examining portal venous velocities using Doppler ultrasound in patients with NAFLD, portal Doppler values could be useful in the diagnosis of the disease and in monitoring the response to treatment (21). It was found that portal vein diameter and Vmax/Vmin ratio, resistive index correlation was found in our NAFLD patients. As the portal vein diameter increased, the ratio of Vmax/Vmin decreased proportionally.

Mihmanlı et al., in their article published in 2005 (27), reported that the resistive index decreased with the increase in the degree of steatosis. They stated that the reason for this is that there is compression on the portal triad structures by fat infiltration and that the portal vein is affected earlier and the diastolic flow of the hepatic artery increases, leading to a decrease in the resistive index in order to compensate for the decrease in its flow. Demir et al. The differences in fasting insulin and HOMA-IR levels between the control group and group 1 showed that fatty liver was associated with more insulin resistance even in the early stages that ultrasound could detect. When the control group and NAFLD obese adolescents were compared, they showed a statistically significant difference between fasting insulin and HOMA-IR (28). Mean values for insulin resistance in obese adolescents and comparisons between groups were made. A statistically significant difference was detected in glucose, insulin, HOMA-IR, cortisol, ALT, portal vein diameter, Vmax, Vmin, and resistive index parameters between those with and without insulin resistance.

The relationship between portal vein diameter and age, BMI, glucose, insulin, HOMA-IR, cortisol, ALT, Vmax, Vmin, Vmax/Vmin, RI was evaluated in NAFLD and non-NAFLD patients. Portal vein diameter increased in patients with high ALT levels. No significant increase was observed in obese but normal ALT patients and the control group. As portal vein diameter increased in patients with high ALT, Vmax and Vmin levels decreased inversely. In conclusion, portal vein diameter increases in patients with hepatosteatosis. As the portal vein diameter increases, Vmax and Vmin also decrease. Metabolically poor prognosis is evident in patients with insulin resistance and decreased Vmax.

Conflict of Interest Statement
The authors have no conflicts of interest to declare.

Ethical Approval
This study was approved by Suleyman Demirel University Faculty of Medicine Clinical Research Ethics Committee Decision No. 225 on 23/12/2018. Study was conducted in line with the principles of the "Helsinki Declaration".

Consent to Participate and Publish
Written informed consent to participate and publish was obtained from all individual participants included in the study.

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Availability of Data and Materials
Data are available on request due to privacy or other restrictions.

Authors Contributions
MA: Data curation; Formal analysis; Validation; Visualization; Writing-original draft.

AA: Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing-review & editing.

HA: Formal analysis; Investigation; Visualization; Writing-review & editing.

ÖP: Conceptualization; Resources; Supervision; Writing-review & editing.

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