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Can portal vein pulsatility index be used as predictive parameter with hepatic artery resistive index for liver fibrosis in nonalcoholic hepatosteatosis?

Nonalkolik hepatosteatozda portal ven pulsatilite indeksi hepatik arter rezistif indeksi ile karaciğer fibrozisi öngörüsü için prediktif parametre olarak kullanılabilir mi?

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ABSTRACT

Aim: Nonalcoholic fatty liver disease (NAFLD) is a clinical entity with a broad spectrum of isolated liver steatosis, steatohepatitis and even cirrhosis. In the development of hepatitis or cirrhosis, flow changes in the hepatic artery and portal vein may be detected. The aim of this study was to investigate the significance of the changes in hemodynamic findings according to the steatosis grade in patients with nonalcoholic hepatosteatosis.
Materials and Methods: the study was performed with B-mode and Doppler ultrasonographic (US) measurements of patients who applied to the radiology department for abdominal ultrasonography examination between February and September 2018. Hepatic artery resistive index (HARI) and portal vein pulsatility index (PVPI) were evaluated. Thirty patients without steatosis and 30 patients from each 3 hepatosteatosis grade were included into the study. As the criteria for inclusion of patients in the study, there was no history of additional disease. p<0.05 values were considered statistically significant.
Results: HARI was significantly lower in grade 3 steatosis than the control group, grade 1 and 2 steatosis (p<0.05). In grade 3 steatosis, portale vein diameter was significantly wider than the control group, grade 1 and 2 steatosis (p<0.05). PVPI was significantly lower in grade 2 steatosis than the control group and grade 1 steatosis (p<0.05). Significant hemodynamic changes were detected in the hepatic artery and portal vein when compared with control and patients groups.
Conclusion: The evaluation of PVPI is considered as a noninvasive valuable method as if HARI in the evaluation of liver parenchymal damage in NAFLD.

Keywords: nonalcoholic, hepatosteatosis, hepatic artery resistive index, portal vein pulsatility index

ÖZ

Amaç: Nonalkolik yağlı karaciğer hastalığı (NAYKH); izole karaciğer yağlanması, steatohepatit hatta siroza kadar uzanan geniş bir spektrumu barındıran klinik antitedir. Hepatit ya da siroz gelişiminde hepatik arter ve portal vendeki akım değişiklikleri saptanabilir. Çalışmanın amacı nonalkolik hepatosteatozlu hastalarda steatoz evresine göre hemodinamik bulgulardaki değişikliğin anlamlı olup olmadığının araştırılmasıdır.
Gereç ve Yöntem: Çalışma Şubat-Eylül 2018 tarihleri arasında Radyoloji Bölümüne batın ultrasonografi tetkiki için başvuran hastalardan bakılan B-mod ve Doppler ultrasonografik ölçümlerle yapılmıştır. Hepatik arter rezistif indeksi (HARİ) ve portal venin pulsatilite indeksi (PVPİ) değerlendirildi. Steatozu olmayan 30 hasta ve her 3 hepatosteatoz evresinden 30'ar hasta çalışmaya dahil edildi. Hastaların çalışmaya dahil edilme kriteri olarak ek hastalık öyküsünün olmamasına bakıldı. <0.05 değerler istatistiksel olarak anlamlı kabul edildi.
Bulgular: Evre 3 steatozda HARİ kontrol grubu, evre 1 ve 2 steatozdan anlamlı olarak daha düşüktü (p< 0.05). . Evre 3 steatozda, portal ven çapı evre 0, evre 1, evre 2 den anlamlı (p<0.05) olarak daha yüksekti. Evre 2 steatozda, PVPİ kontrol grubu ve evre 1 steatozdan anlamlı olarak daha düşüktü (p<0.05). Kontrol ve hasta grupları ile karşılaştırıldığında hepatik arter ve portal vende anlamlı hemodinamik değişiklikler saptanmıştır.
Sonuç: PVPİ, NAYKH'de parankim hasarının değerlendirilmesinde, HARİ gibi noninvaziv değerli bir yöntem olarak görülmektedir.

Anahtar Kelimeler: nonalkolik, hepatosteatoz, hepatik arter rezistif indeks, portal ven pulsatilite indeksi

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a common health problem, developed generally as a complication of obesity [1, 2]. NAFLD can progress and become the cause of hepatitis, whereas Nonalcoholic steatohepatitis (NASH) is an inflammatory form and can progress to fibrosis, cirrhosis or hepatocellular carcinoma (HCC) [3]. Clinical examinations and biochemical laboratory tests, including transaminases, are not sufficient in differentiating hepatitis, cirrhosis and HCC. Biopsies are the gold standard for differential diagnosis but they incur some risks and complications [4, 5], therefore, noninvasive methods may be useful in the evaluation of parenchyma involvement. Doppler ultrasonography (US) parameters such as hepatic artery resistive index (HARI), have been used for evaluating fatty liver and follow up microcirculatory resistance of liver, and can give information about formation of NASH [6] . On the other hand, portal vein pulsatility index (PVPI) can also give similar information about NASH formation [7] though HARI is useful in evaluating the development of fibrosis, since hemodynamic evaluations don't provide a definitive diagnosis. We think that an additional hemodynamic parameter will strengthen the diagnostic approach and therefore, the purpose of this study was to investigate the significance of the changes in hemodynamic findings according to the steatosis grade in patients with nonalcoholic hepatosteatosis.

MATERIALS AND METHODS

This retrospective and randomized study was conducted with the patients who applied to radiology departments for abdominal ultrasonography (US) evaluations between February-September 2018. Patients were informed for consent and the required approval was received from the Institutional Review Board (IRB) application (dated 06.11.2019 and numbered 596). The patients were questioned about the history of alcohol use were examined for HbA1c and fasting blood glucose and those with diabetes were excluded from the study. Patients with a history of malignancy or cardiac diseases and drug use that can cause liver steatosis, such as steroids, were also excluded from the study. Free of additional diseases, 30 patients without steatosis and 30 patients from each 3 hepatosteatosis grade were included into the study and were evaluated by the Doppler US in terms of HARI, PVPI and other hepatic artery and portal vein velocities. The B-mode US was used for spleen and liver dimensions. Ultrasound examination was done by two radiology specialists with Toshiba Aplio 500 (Toshiba, Tokyo, Japan) ultrasound device and 6.0-1.9 MHz convex transducer. As a standard position for evaluation, the patients were in the supine position with breath held during inspiration. Resistive index and pulsatility index were calculated with the formulas [(Peak systolic velocity - End diastolic velocity) / Peak systolic velocity] and [(Peak systolic velocity - End diastolic velocity) / Average velocity], respectively.

Statistical analysis

Mean, standard deviation, median lowest, highest, frequency and ratio values were used in descriptive statistics of the data. The distribution of variables was measured by the Kolmogorov–Smirnov test. The Kruskal-Wallis, Mann-Whitney U test was used for the analysis of quantitative independent data. The Chi-squared test was used to analyze qualitative independent data. For statistical significance, $p<0.05$ values were accepted. $p<0.05$ values were considered statistically significant.

RESULTS

The patients' ages were between 36 and 57 years and the mean age was 44.2±4.5 (sd). The age of the patients in the control group was significantly lower than the patients in all three groups with steatosis. There was no significant difference for age between grade 1-2-3 steatosis patients. The number of female and male patients were equal and no significant difference was found between the control group and the patients groups, in terms of gender distribution.

Portal vein diameter (PVD) was significantly higher in grade 3 hepatosteatosis patients than in the control group and in grade 1-2 hepatosteatosis patients. PVD was significantly higher in grade 2 hepatosteatosis patients than in the control group and the grade steatosis 1 patients. There was no significant difference for PVD between grade 1 steatosis patients and the control group.

Liver and spleen size, hepatic artery and portal vein end-diastolic and peak-systolic velocities, PVD, portal vein mean velocity, minimum-maximum-median-mean values for HARI and PVPI are shown in Table 1.

Table 1: Maximum, median and mean values for liver and spleen size, hepatic artery and portal vein end-diastolic and peak-systolic velocities, PVD, portal vein mean velocity, HARI and PVPI

	Min-Max	Median	Mean±sd
Hepatic Artery End Diastolic Velocity	5.6-52.6	14.6	15.2±4.5
Hepatic Artery Peak Systolic Velocity	28.8-88.0	47.0	48.0±9.2
Hepatic Artery Resistive Index	0.47-0.84	0.68	0.68±0.1
Diameter of Portal Vein	7.5-12.2	10.0	9.9±1.1
Portal Vein End Diastolic Velocity	8.3-16.2	12.4	12.2±1.8
Portal Vein Peak Systolic Velocity	10.3-19.5	15.4	15.4±1.9
Portal Vein Average Speed	9.5-17.8	13.8	13.8±1.7
Portal Vein Pulsatility Index	0.08-0.49	0.21	0.23±0.09
Spleen size (mm)	69.0-115.0	93.5	92.9±10.4
Liver size (mm)	130.0-175.0	148.0	150.4±10.6

HARI was significantly lower in grade 3 steatosis patients than the grade 1-2 steatosis patients and the control group, and significantly lower in patients with grade 2 steatosis than the control group and the grade 1. There was no statistically significant difference between the grade 1 steatosis patients and the control group in terms of HARI.

PVPI was significantly lower in grade 3 steatosis than in the control group and grade 1 steatosis patients, and significantly lower in grade 2 steatosis patients than in the control group and grade 1 steatosis patients. There was no statistically significant difference in PVPI values between grade 1 steatosis patients and the control group, and between grade 2 and 3 steatosis groups.

Table 2 shows the statistical comparison between hepatic artery end-diastolic and peak-systolic velocity values, PVD and mean velocity, portal vein end-diastolic and peak-systolic velocity values, liver and spleen dimensions.

DISCUSSION

NAFLD is the involvement of steatosis in liver without the other common causes of steatosis, such as alcohol, drugs, other metabolic conditions or hereditary disorders [5,6]. Although the diagnosis is confirmed radiologically, the definitive diagnosis is made histopathologically [8]. NAFLD includes non-alcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH), the latter of which may progress to fibrosis, cirrhosis or hepatocellular carcinoma [9].

NAFLD is the most common cause of chronic liver disease. It is thought that one fourth of chronic liver disease in the world is caused by steatosis [10]. There were few studies about the prevalence of hepatic steatosis in Turkey, however, important data has emerged in recent studies about the prevalence of hepatosteatosis in this country. According to a review study, published in 2019, the prevalence of NAFLD in Turkey is considered to be about or above 30% [6].

Biopsy is a valuable method to show the presence of NASH and the degree of fibrosis, as well as to evaluate the prognosis of the disease [8]. On the other hand, US and Doppler US are generally used in the evaluation of fatty liver as a cheap, simple and rapid assessment method. In addition, hepatic artery flow studies were performed with Doppler US to evaluate the development of fibrosis in hepatosteatosis patients [10].

In a study by Tana C et al., HARI was significantly lower in NAFLD patients than controls and, likewise, significant differences were found between subgroups [10]. In another study, Mihmanli I et al. found HARI value significantly lower in fatty liver patients [11]. In our study, HARI was also significantly lower in grade 2 and 3 steatosis patients than the lower grade and control groups. On the other hand, no statistically significant difference was found between grade 1 steatosis patients and the control group. These radiological findings suggest that there is no significant development of fibrosis in the early stage, though histopathological and radiological comparisons are needed to confirm this hypothesis.

There are also studies examining the effectiveness of Doppler US in the evaluation of hepatosteatosis

Table 2: Statistical evaluation results of HARI, HVPI, hepatic artery end-diastolic and peak-systolic velocity values, PVD and mean velocity, portal vein end-diastolic and peak-systolic velocity values, liver and spleen size

		Control group	Grade 1	Grade 2	Grade 3	p value	Control group-Grade 1	Grade 0-2	Grade 0-3	Grade 1-2	Grade 1-3	Grade 2-3
Hepatic Artery End Diastolic Velocity	Mean±sd	12.0±1.8[23]	12.8±4.6[23]	16.8±2.8[3]	19.1±3.8	0.000[K]	1.000	0.000	0.000	0.000	0.000	0.016
	Median	11.8	11.6	16.2	18.5							
Hepatic Artery Peak Systolic Velocity	Mean±sd	49.9±8.8	46.3±10.4	49.0±10.0	46.8±5.9	0.266[K]	0.062	0.372	0.165	0.337	0.383	0.848
	Median	48.4	42.8	47.3	46.9							
Hepatic Artery Resistive Index	Mean±sd	0.75±0.06[23]	0.72±0.08[23]	0.64±0.06[3]	0.59±0.07	0.000[K]	0.221	0.000	0.000	0.000	0.000	0.005
	Median	0.75	0.75	0.64	0.59							
Diameter of Portal Vein	Mean±sd	9.0±0.5[23]	9.3±0.9[23]	10.6±0.8	10.7±0.8	0.000[K]	0.290	0.000	0.000	0.000	0.000	0.776
	Median	9.0	9.0	11.0	10.9							
Portal Vein End Diastolic Velocity	Mean±sd	12.7±1.6[1]	11.2±1.9	12.8±1.3[1]	12.4±1.6[1]	0.002[K]	0.001	0.663	0.455	0.001	0.014	0.325
	Median	12.6	10.7	12.9	12.3							
Portal Vein Peak Systolic Velocity	Mean±sd	16.6±1.4[123]	14.6±2.1	15.6±1.4	15.0±1.8	0.000[K]	0.000	0.005	0.001	0.052	0.451	0.186
	Median	16.7	14.2	15.2	14.6							
Portal Vein Average Speed	Mean±sd	14.7±1.4[1]	12.9±1.9	14.2±1.3[1]	13.7±1.7	0.001[K]	0.000	0.149	0.052	0.003	0.107	0.228
	Median	14.8	12.5	14.2	13.4							
Portal Vein Pulsatility Index	Mean±sd	0.27±0.09[23]	0.27±0.11[23]	0.20±0.05	0.19±0.06	0.001[K]	0.626	0.002	0.001	0.026	0.012	0.647
	Median	0.28	0.24	0.20	0.18							
Spleen Size (mm)	Mean±sd	90.8±11.2	96.2±9.3	93.2±11.0	91.2±9.4	0.186[K]	0.081	0.510	0.841	0.257	0.045	0.390
	Median	92.5	95.5	95.0	91.5							
Liver Size (mm)	Mean±sd	138.8±3.2[123]	147.9±9.1[23]	152.8±7.0[23]	161.9±5.5	0.000[K]	0.000	0.000	0.000	0.009	0.000	0.000
	Median	139.0	147.0	154.0	162.0							

K Kruskal-Wallis (Mann-Whitney u test) / X^2 (Chi-squared) test

[1] Difference with grade 1 p<0.05 / [2] Difference with grade 2 p<0.05 / [3] Difference with grade 3 p<0.05

in children. In the study of Hizli S et al., decreasing in HARI values in children was correlated with the fatty liver and development of fibrosis [12]. It should be noted that pediatric patients were excluded from our study.

Although HARI has been evaluated in similar studies, PVPI has rarely been evaluated to predict the development of fibrosis. In a study evaluating NAFLD patients, a statistically significant difference was found in terms of PVPI value when compared with the control group, although there was no significant difference between steatosis grades [7]. In our study, PVPI was significantly lower in patients with grade 2 and 3 steatosis than the lower grades and the control group. There was no statistically significant difference in PVPI between grade 1, the control group and between grade 2-3 groups. Therefore, it may not be meaningful to evaluate fibrosis between closer groups and at low stages.

In another study, with the examining portal vein flow changes in NAFDL patients, no significant correlation was found between portal vein velocity and hepatosteatosis grades [13]. In our study, although a significant decrease was observed in grade 1 hepatosteatosis patients compared to the control group, no statistically significant difference was found in higher grades.

In one study, HARI and portal vein velocity were significantly decreased with increasing steatosis stage and the mean portal vein velocity was significantly lower with increasing of stage [14].

The presence of additional diseases are likely to affect the portal flow measurements. In many studies, it is stated that heart diseases change portal vein flow [15,16] and portal vein flow measurements in one particular study with type 1 and 2 diabetics, differed from non-diabetic patients [17]. Therefore, patients with additional diseases, such as diabetes and heart diseases, were excluded from our study.

According to another result of our study, PVD increases with steatosis stage and this finding is consistent with the literature. It should be noted that the limitation of our study is that the definitive diagnosis of fibrosis development was not made by biopsy.

In conclusion; HARI is a Doppler US parameter that has been proposed by many researchers for a long time, to predict the development of fibrosis in NAFLD patients. Similarly, in our study, HARI showed significant changes with increased steatosis. For PVPI, a limited number of studies are found in the literature and some studies have not yielded significant results. However, in our study, statistically significant changes were observed for PVPI with increasing steatosis stage, and we think that it can be used as a Doppler US parameter as well as HARI for predicting fibrosis development.

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