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Effects of Nonalcoholic Fatty Liver Disease on the Hepatic Vein and Artery

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Abstract

Objective: To evaluate the effect of the different stages of non-alcoholic fatty liver disease on hepatic vein waveform pattern and hepatic artery resistance index.

Methods: 32 patients diagnosed with non-alcoholic fatty liver disease and 14 healthy volunteers as a control group were included in the study. In both groups, liver size was measured and the degree of fatty infiltration was graded by gray-scale ultrasonographic examination. Hepatic vein waveform pattern was assessed and hepatic artery resistance index was measured by duplex Doppler ultrasonography examination. The degree of fatty infiltration was compared with hepatic vein waveform pattern and hepatic artery resistance index values in the patient group.

Results: Liver echogenicity was grade 1 in 15 patients, grade 2 in 12 patients, and grade 3 in 5 patients. In the control group, liver echogenicity was not increased. Liver size was increased with the degree of fatty infiltration ($p<0.001$). The presence of biphasic or monophasic hepatic vein waveform pattern in non-alcoholic fatty liver disease patients was statistically significant ($p=0.04$). However, mean hepatic artery resistance index was not significantly different ($p=0.38$). Both hepatic vein waveform pattern and hepatic artery resistance index were not related to the degree of fatty infiltration ($p=0.99$ and $p=0.81$, respectively).

Conclusion: Vascular compliance of the liver can vary with the fatty infiltration of hepatocytes. This effect can be displayed as abnormal hepatic vein waveform pattern rather than alterations in hepatic artery resistance index values by duplex Doppler ultrasonography.

Keywords: Ultrasonography, Doppler ultrasonography, non-alcoholic fatty liver disease, hepatic artery resistive index, hepatic vein waveform pattern.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a frequent disorder that affects the general population at a rate of 15-25% [1]. The main features of the disease, with the exception of alcohol consumption, are fatty infiltration or lipid deposition in the hepatocytes in addition to elevated liver function tests [2-4]. Although NAFLD is accepted as a benign disease, it can progress to non-alcholic steatohepatitis, which is the advanced state of the disease, and can be complicated with liver fibrosis, cirrhosis, and even liver failure [4-6].

Early diagnosis and treatment of liver damage is important to prevent liver failure. Gray-scale ultrasonography (US) is an initial, easy to use and widely available imaging modality for NAFLD, but gives limited information about the severity of the disease [7,8]. Duplex Doppler US (DDUS) studies on hepatic vein, portal vein and hepatic artery can give more information about parenchymal damage and the severity of the disease due to changes affecting vascular compliance in the liver [3,9-12]. But the effect of NAFLD on the hepatic vein waveform pattern (HVWP) and the hepatic artery resistance index (HARI) is not certain. In this study we aimed to evaluate the effects of different stages of NAFLD on HVWP and HARI.

Materials and Methods

Patients

This prospective study was approved by the Institutional Ethics Committee and informed written consent was obtained from all of the reviewed subjects.

Thirty-two patients diagnosed as having NAFLD and referred from the medical gastroenterology department were included in the study. Inclusion criteria were elevated liver function tests and hyperechogenic liver by gray-scale US examination. Exclusion criteria were taking vasoactive medications, steroids or alcohol, presence of cirrhosis, splenomegaly, autoimmune, viral or drug induced hepatitis, and cardiac disease. To compare the gray-scale US and DDUS findings, 14 healthy volunteers, who had normal liver function tests, normal gray-scale US liver and spleen, Body Mass Index (BMI) between 20 – 25, no autoimmune, viral or drug induced hepatitis, no diabetes mellitus, no history of alcohol consumption, and no cardiac disease were enrolled in the study as a control group. In both patient and control groups, subjects having liver masses or vascular malformations detected at gray-scale US screening were also excluded from the study.

Scanning and Equipment

Gray-scale US and DDUS examinations were performed with a CH6-2 MHz convex array transabdominal probe (Siemens Acuson Antares™ ultrasound system, Premium Edition, Erlangen, Germany)

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after at least 8 hours of fasting by one of three radiologists who had 2-4 years of experience with sonography. Radiologists were blinded to the diagnosis and initial imaging findings of the subjects. Patients and control groups were in supine position for the gray-scale US and DDUS examinations. Both gray- scale US and DDUS studies were performed at deep inspiration and breathholding without using tissue-harmonic imaging. At gray-scale US examination, the entire liver was examined and the maximum antero-posterior diameter of the liver was measured. The degree of fatty infiltration was graded by gray-scale US as:

- Grade 0 (none): Normal liver echogenicity.
- Grade 1 (mild): Minimally increased diffuse liver echogenicity; intrahepatic vessels and the diaphragm could be visualized.
- Grade 2 (moderate): Moderately increased diffuse liver echogenicity; intrahepatic vessels and the diaphragm could be visualized slightly.
- Grade 3 (severe): Markedly increased diffuse liver echogenicity; weak penetration through the liver by the gray-scale US evaluation [7].

After gray-scale US examination, DDUS was performed by the same radiologist. For each subject, proper color gain, pulse repetition frequency, wall filter setting, Doppler angle and sample volume were used. HVWP was evaluated at the left lateral decubitus position to use a right lateral intercostal approach. Sample volume was positioned at the right hepatic vein and 3-5 cm away from the inferior vena cava to eliminate pulsations coming from the inferior vena cava and right atrium. HVWP was classified as monophasic, biphasic without a reverse flow and regular triphasic pattern with reverse flow. Monophasic and biphasic waveform patterns were accepted as abnormal. The hepatic artery was evaluated at the portal hilum at the right lateral supine position. Measurements were taken manually and the US equipment calculated the RI automatically from the spectral Doppler waveforms using the built-in software. Mean RI values were obtained from at least 3 spectral Doppler waveforms.

Statistical Analysis

Subjects were placed in two groups as NAFLD and control group to compare the degree of fatty infiltration and HVWP and HARI values. Statistical analyses were made using Chi-square test and Chi-square Fisher's exact test. The mean HARI values between groups were compared using Student t-test and Mann-Whitney U tests. Statistical significance was set as $p<0.05$ and bidirectional.

Results

The study included 46 subjects, 33 males and 13 females. Of the subjects in this study, 32 were in the NAFLD group and 14 were in the control group. The NAFLD group mean age was 47.69 ± 14.34 years (range 19-74 years) and the control group mean age was 37.21 ± 20.98 years (range 18-75 years). The mean age of NAFLD and control groups was not statistically different ($p>0.05$).

At gray-scale US examination there was no increased echogenicity in the control group and the degree of fatty infiltration was graded as grade 0. In the NAFLD group, 15 were grade 1, 12 were grade 2, and 5 were grade 3. Mean liver antero-posterior diameter was 142.43 ± 10.99 mm in the control group and 159.09 ± 15.72 mm in the NAFLD group ($p=0.36$). We evaluated the relationship between liver size and the degree of fatty infiltration and found that liver size was increased significantly with the degree of fatty infiltration ($p<0.001$) (Table1) (Figures 1 and 2).

Groups	Mean ± Std. Deviation (mm)	95% Confidence Interval		p
		Lower Bound	Upper Bound	
Control (n=14)	142.43 ± 10.995	136.08	148.78	< 0.001
Grade 1 FI (n=15)	155.13 ± 14.706	146.99	163.28	
Grade 2 FI (n=12)	156.75 ± 14.201	147.73	165.77	
Grade 3 FI (n=5)	176.60 ± 12.095	161.58	191.62	
Total (n=46)	154.02 ± 16.290			

Abbreviations: FI; fatty infiltration, n; number.

Table 1: Relation of liver size with the degree of fatty infiltration.

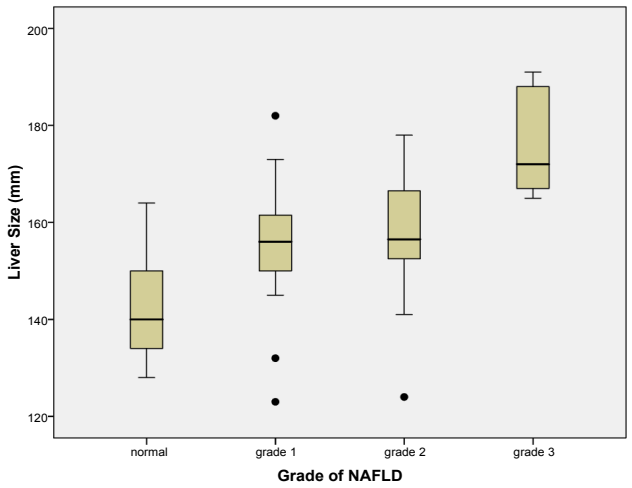

Figure 1: Relation of liver size and the degree of NAFLD. Liver size increases with the degree of NAFLD.

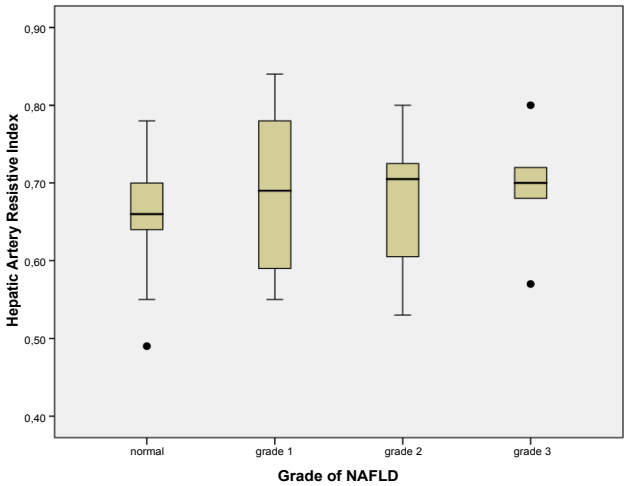

Figure 2: Hepatic arterial resistive index. Mean HARI was similar in NAFLD and control groups.

In all subjects, the hepatic vein and artery were visualized. HVWP was triphasic for all subjects in the control group. In the NAFLD group, HVWP was triphasic in 21 patients, biphasic in 6 patients and monophasic in 5 patients. The presence of biphasic or monophasic HVWP in NAFLD patients was statistically significant ($p=0.04$). But

there was no significant relation between the degree of fatty infiltration and HVWP (p=0.99).

Mean HARI was 0.68 ± 0.09 in the NAFLD group and 0.65 ± 0.07 in the control group (p=0.38). When we compared the patients according to the degree of fatty infiltration, the difference in HARI was not significant (p=0.81) (Figure 2). Also, the mean HARI values of patients with monophasic or biphasic HVWP and triphasic HVWP in the NAFLD group were 0.69 ± 0.086 and 0.68 ± 0.096, respectively, and this difference was not significant (p=0.85).

Discussions

Liver biopsy remains the best diagnostic tool for evaluating, grading and fibrosis in NAFLD, but gray-scale US, which is easy to use, widely available and the least invasive imaging method, can show the hepatic steatosis and accepted as a diagnostic test for NAFLD [7,13,14]. In recent years, Doppler US and DDUS based indices have gained importance in evaluating the severity of NAFLD. In our study, we found that HVWP was abnormal in NAFLD, but could not demonstrate a good relationship with HARI.

Hepatomegaly is a prevalent finding in patients with NAFLD and liver size increases as the degree of NAFLD increases [3,10,15]. In our study, similar to the medical literature, we found that liver size was increased with an increase of fatty infiltration with a statistically significant difference.

The hepatic vein has a characteristic triphasic waveform pattern, consisting of three peaks, which are antegrade systolic and diastolic flow, and a short retrograde flow by right atrial systole [16]. An alteration in pressure of the right atrium, hepatic parenchymal compliance or pressure differences during respiration in the thoracic or abdominal cavity affects the triphasic waveform pattern [17]. Parenchymal liver diseases like NAFLD, cirrhosis, or cardiac disease can cause biphasic or monophasic HVWP [3,4,9,16,18]. Pedersen et al. found that abnormal HVWP can be seen in healthy populations, but with no further evaluation for liver disease [19]. Mohammadinia et al. and Oguzkurt et al. found that abnormal HVWP was significantly different between healthy and NAFLD groups [3,16]. But Oguzkurt et al. who used computed tomography for grading NAFLD, did not find a relation with the degree of fatty infiltration, while Mohammadinia et al. who used liver biopsy for grading NAFLD, found a significant relation [3,16]. In the current study we found that abnormal HVWP was significantly different in the NAFLD group, and hypertrophic hepatocytes as a result of fatty infiltration altered the hepatic vascular compliance, but we could not show a relation between abnormal HVWP and the severity of the disease.

HARI can be related to hepatic vascular compliance and might have a potential use for evaluating vascular resistance in NAFLD. Fibrosis of the liver parenchyma or fat deposition in NAFLD can affect and decrease vascular compliance and decrease the portal vein inflow [12]. To compensate the blood flow to the liver, hepatic artery diastolic flow increases and makes HARI lower than normal [10]. But Colli et al. found higher HARI values in alcoholic or viral-related cirrhosis than in a control group, indicating fibrosis in the liver [20]. Hızlı et al. found higher HARI values in NAFLD in a pediatric group than a control group with a statistically significant difference, while Mihmanli et al., Mohammadinia et al. and Mohammadi et al. found lower HARI values than in a control group in adults [3,10-12]. Also Mihmanli et al. and Mohammadinia et al. found lower HARI values were significantly related to the severity of the fatty infiltration [3,10]. In our study, similar to Hızlı et al., we found higher HARI values in the NAFLD group than in the control group but with no significant difference [11]. Also, the severity of the fatty infiltration or the presence of abnormal HVWP did not affect the HARI values in our study. We found similar HARI values in moderate and severe NAFLD, as did Mohammadinia et al. who found higher HARI values in control and mild hepatosteatosis groups [3]. The differences between the studies might be due to the techniques or site of hepatic artery used for Doppler US examination. There is no uniform or standardized measurement of HARI among studies. Some authors used proper intrahepatic hepatic artery segments, while others used the hepatic artery segment at the porta hepatitits or where the hepatic artery crosses the main portal vein [3,10-12,20]. Piscaglia et al. studied HARI and measured HARI at porta hepatitis and from the intrahepatic branches. The intrahepatic HARI was significantly different in liver cirrhosis, chronic hepatitis and control groups, while HARI at the porta hepatitis was not [21]. Also age, gender or ethnicity may vary measurements of HARI [21,22].

We had some limitations in this study. First, we did not use BMI to compare with the alterations in HVWP and HARI. Second, our NAFLD group was heterogeneous and the control group was relatively small. Third, we did not evaluate the interobserver and intraobserver reliability of our findings. Finally; we didn't evaluate the HVWP and HARI after various treatments of NAFLD which could demonstrate and solidify the relation between the alterations in hepatic Doppler parameters and fatty infiltration of hepatocytes.

In conclusion, the fatty infiltration of hepatocytes can increase liver size and can have an effect on the vascular compliance of the liver. This effect can be shown by an abnormal HVWP rather than HARI. HARI has limitations in evaluating NAFLD because of the absence of a certain measurement site. Further studies comparing HARI from the porta hepatitis and intrahepatic segments in NAFLD are essential to solidify our findings.

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