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Evaluation of Portal Venous Velocity with Doppler Ultrasound in Patients with Nonalcoholic Fatty Liver Disease

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Purpose: We examined the relationship between portal venous velocity and hepatic-abdominal fat in patients with nonalcoholic fatty liver disease (NAFLD), using spectral Doppler ultrasonography (US) and magnetic resonance imaging (MRI).
Materials and Methods: In this prospective study, 35 patients with NAFLD and 29 normal healthy adults (control group) underwent portal Doppler US. The severity of hepatic steatosis in patients with NAFLD was assessed by MRI through chemical shift imaging, using a modification of the Dixon method. Abdominal (intra-abdominal and subcutaneous) fat was measured by MRI.
Results: The difference in portal venous velocity between the patients with NAFLD and the control group was significant ($p < 0.0001$). There was no correlation between the degree of abdominal or hepatic fat and portal venous velocity ($p > 0.05$). There were strong correlations between the hepatic fat fraction and subcutaneous adiposity ($p < 0.0001$), intraperitoneal fat accumulation ($p = 0.017$), and retroperitoneal fat accumulation ($p < 0.0001$).
Conclusion: Our findings suggest that patients with NAFLD have lower portal venous velocities than normal healthy subjects.
Index terms: *Nonalcoholic fatty liver disease; Ultrasound (US); Magnetic resonance (MR)*

INTRODUCTION

The prevalence of adult obesity is increasing dramatically worldwide (1). Many disorders accompany obesity, including sleep apnea, gall bladder disease, cardiovascular disease, dyslipidemia, hyperinsulinemia, type 2 diabetes mellitus, and nonalcoholic fatty liver disease (NAFLD). NAFLD is increasingly recognized as a potential complication of obesity (2-9). NAFLD ranges from simple steatosis, through fibrosis, to cryptogenic cirrhosis. NAFLD is the most common cause of elevated liver enzyme concentrations and is currently the third leading cause of liver cirrhosis (2-9). A liver biopsy is the gold standard for the determination of hepatic fat morphology and severity. Since biopsy is an invasive procedure, its use is limited. Non-invasive techniques, such as magnetic resonance imaging (MRI), have also been used to examine total or regional body fat (intra-abdominal or subcutaneous fat) and hepatic fat content (2-10).

Intra-abdominal adipose tissues can be sub-divided into intraperitoneal and retroperitoneal adipose tissues. Such regional adiposity is believed to be important because venous drainage of the intraperitoneal adipose tissue goes directly to the liver, through the portal vein, whereas the retroperitoneal adipose tissue drains into the systemic

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circulation. Thus, free fatty acids, glycerol, and other adipocytokines that are released from the intraperitoneal adipose tissue may influence the hepatic metabolism of glucose, triglycerides, insulin, and other substrates and hormones. The portal fat hypothesis is based on this unique pattern of venous drainage (2-10).

In the present study, we examined the relationship between portal venous velocity and hepatic-abdominal steatosis. The confirmation of a relationship between these entities would suggest that alternative non-invasive modalities, such as duplex US and MRI examinations, could be used for the management of patients with NAFLD. A second aim was to determine the relationship between the hepatic fat fraction and abdominal-subcutaneous lipid accumulation in patients with NAFLD.

MATERIALS AND METHODS

Subjects

Between August 2006 and May 2007, 35 patients with NAFLD attending our gastroenterology outpatient clinic were enrolled (M:F = 23:12; mean age, 46 ± 10 years; range, 26-70 years). The diagnosis of NAFLD was based on abnormal levels of serum aminotransferases. Body mass index (BMI) was calculated in each subject. Patients with a BMI between 25 and < 30 were regarded overweight and a BMI > 30 were regarded as obese. Fifteen patients had type 2 diabetes mellitus. Malignant and infectious diseases (viral hepatitis) were excluded by appropriate clinical, laboratory, and imaging investigations. Heart disease was excluded based on medical history, physical findings, chest radiograph, electrocardiography, and echocardiography. In all 35 patients, appropriate visualization of the liver vessels was achieved by transabdominal B-mode sonography, and adequate Doppler sonography was obtained by duplex scanning.

The control group was made of 29 normal healthy adults (M:F = 14:15; mean age, 42 ± 8 years; range, 23-65 years) and examined by B-mode and duplex Doppler sonography. All healthy subjects had liver function test results within normal ranges. Chronic liver (infectious, metabolic, toxic auto-immune) diseases and heart diseases were ruled out by appropriate testing.

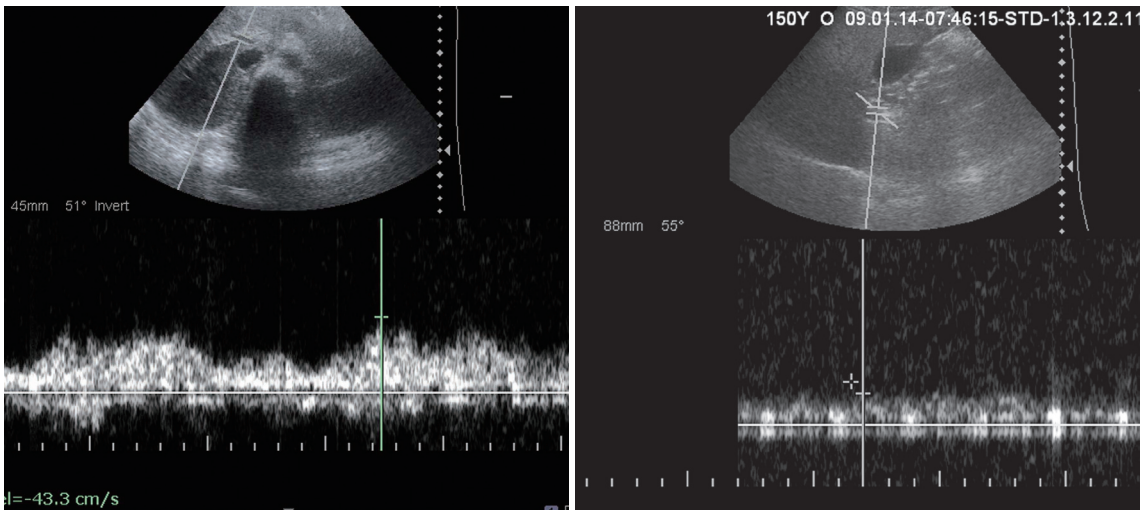
The present study (project number: KA06/236) was approved by our Institutional Ethics Committee. Each patient provided written informed consent to participate in this study.

Radiologic Examination

All patient and control subject sonographic examinations were performed using the Antares Ultrasound System (Siemens Inc., Mountain View, CA), equipped with a multifrequency (2-5 MHz) convex transducer. All patients with nonalcoholic steatohepatitis underwent a "hyperechogenic liver with B-mode" US examination, whereas the control subjects underwent a normal liver parenchyma US examination. Both the patients and control subjects fasted overnight before US. All eight segments of the liver were carefully scanned, and subjects with vascular malformations or hepatic masses (e.g., cyst or hemangioma) were excluded. Doppler US of the portal vein showed a wide spectrum of different flow patterns and velocity in healthy patients. An important limitation of Doppler US is reproducibility or accurate measurements. To compensate for this limitation, we standardized each measurement. For each duplex scanning, the sample gate was adjusted between 6-10 mm (depending on the diameter of the vessel). Moreover, the portal vein spectral analyses were always recorded for at least 2-3 cycles. The transducer was oriented along the longitudinal axis of the main portal vein using a paramedian or slightly oblique plan. The point of measurement was midway between the confluence of the splenic and superior mesenteric veins and the bifurcation of the portal vein during quiet inspiration by the same sonographer. The Doppler angle was always < 60°. The maximum (V_{max}) and minimum (V_{min}) velocities (cm/s) were recorded in each patient and healthy subject and were photodocumented (Fig. 1). The difference between V_{max} and V_{min} was calculated as a parameter of biphasic (slightly pulsatile) or monophasic oscillation.

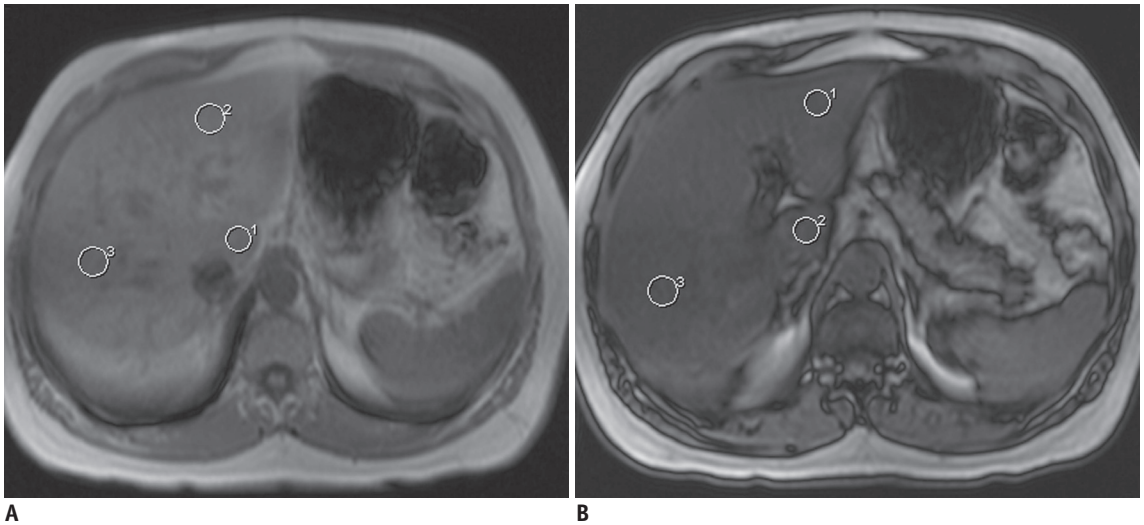
All MRI studies were performed with the 1.5 Tesla clinical MR imaging system (Magnetom; Siemens Medical Systems, Erlangen, Germany) and a phased array body coil. All MRI examinations were performed with the following protocol: transverse dual fast in and out and phase T1-weighted gradient echo sequences of the upper abdomen, from the diaphragm to the umbilical level (repetition time [ms]/ echo time [ms], 100/2.38-4.97; flip angle, 70°; 30 sections acquired in a 44/3 second multi-breath hold). Section thicknesses were 7 mm and the matrix size was 145 × 256 (phase frequency encoding).

Image post-processing was performed using a workstation (Volume Wizard; Siemens Medical Systems). For each image pair (one in-phase and one out-of-phase image at corresponding levels), a region of interest (ROI) was drawn



A B

Fig. 1. Spectral Doppler US of maximum velocities in portal veins of control subjects and patients with nonalcoholic steatohepatitis (NAFLD).
A. Maximum velocity (V_{max}) in portal vein of normal subject (43.30 cm/s). **B.** V_{max} in portal vein of patient with NAFLD (18.10 cm/s).



A B

Fig. 2. In-phase (A) and out-of-phase (B) images, with corresponding signal intensities, are shown for individual with steatosis (32%). Circle in each image represents region of interest. Region of interest signal intensities are from same slice. In-phase and out-of-phase images were used to derive hepatic fat fraction, according to equation: fat fraction = $SI_{in\text{-}phase}$ - ($SI_{out\text{-}of\ phase}$ / 2 $SI_{in\text{-}phase}$).

in the liver in five different segments (segments 8, 7, 4, 6, and 1), using an adjustable, round cursor. The ROI selected in each image was at least 2.0-2.5 cm^2 and was located in the liver parenchyma to exclude contamination from blood vessels, motion artifacts, or partial volume effects. The mean pixel signal intensity (SI) values for each ROI and for each of five liver segments were recorded. Hepatic fat fractions were calculated using a modified Dixon method (MR chemical shift imaging) from the mean pixel signal intensity data, using the formula: fat fraction = $SI_{in\text{-}phase}$ - ($SI_{out\text{-}of\ phase}$/2 $SI_{in\text{-}phase}$) (11-14).

For each patient, five separate fat fractions were obtained, one in each of the five image slice pairs (Fig. 2). The calculated fat fractions were then averaged to determine the mean fat fraction. The hepatic fat fraction was considered to be normal when a value was below 9% (11-14).

Measurements of adipose tissue (subcutaneous, intra-retroperitoneal) were performed manually using a workstation (Volume Wizard). In all patients with NAFLD, adipose tissue was measured in a single image at the level of the umbilicus, as these values have been found to be

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excellent surrogate measures of whole-abdomen values (15, 16).

On T1-weighted MR images, adipose tissues are clearly demarcated as bright areas, with signal intensities that are higher than those of other tissues. Intra-abdominal adipose tissues were separated into intra- and retro-peritoneal adipose tissue compartments using anatomical points such as the ascending-descending colon, aorta, and inferior vena cava. This was achieved by visual mapping of the anatomic area of a single slice at the level of the umbilicus on the computer screen using a mouse pointer (Fig. 3). The pixels in each anatomic area were counted and converted into a volume by multiplying the number of pixels by the voxel size (voxel size, 2.4 × 1.6 × 7.0 mm = 26.88 mm^3). The adipose tissue mass in each compartment was calculated.

Statistical Analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences version 11.0 (SPSS Inc., Chicago, IL). A Pearson's correlation was used to test whether there was an association between hepatic fat fraction with intra-abdominal and subcutaneous adipose tissue. The Student's *t* test was used to compare differences in portal vein velocity between healthy control subjects and patients with NAFLD. Differences exhibiting a *p* value less than 0.05 were deemed to be statistically significant.

RESULTS

All patients with NAFLD were obese, which was defined as a body mass index (BMI) > 30.

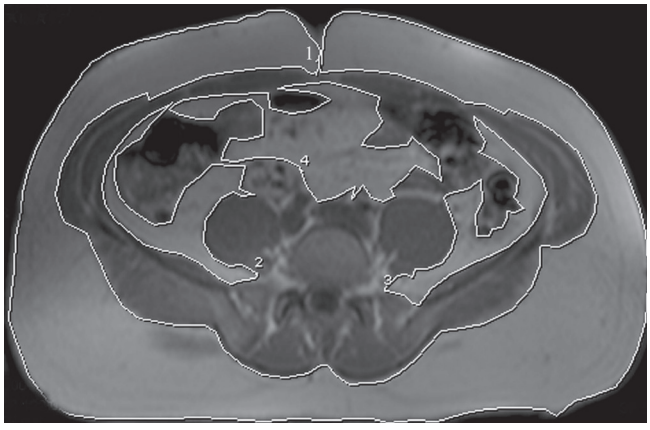

Fig. 3. Axial T1-weighted MR image at umbilical level, with outlined subcutaneous adipose tissue and intra-abdominal adipose tissue (intra- and retro-peritoneal) compartments. Subcutaneous adipose tissue; section 1, retroperitoneal adipose tissue; sections 2 and 3, intraperitoneal adipose tissue; section 4.

The hepatic fat fraction in all patients with NAFLD was > 9% (range, 9-46%). The portal vein waveform was biphasic (slightly pulsatile) in all healthy subjects and patients with NAFLD. The difference in portal venous velocity between patients with NAFLD and the controls was significant ($p < 0.0001$). A flat waveform was not seen in any patient with NAFLD. The mean portal vein velocity in the controls was 32.15 cm/s (range, 13.60-55.00 cm/s), compared to 27.60 cm/s (range, 18.10-46.60 cm/s) in patients with NAFLD.

There was no correlation between the degree of hepatic fat fraction and portal venous velocity ($p > 0.05$, R: 0.27). Similarly, there was no correlation between portal venous velocity and subcutaneous or abdominal adiposity ($p > 0.05$, R: 0.34). However, there was a strong correlation between the degree of subcutaneous adiposity and the hepatic fat fraction ($p < 0.0001$, R: 0.84). There was also a strong correlation between the hepatic fat fraction and intraperitoneal fat accumulation ($p = 0.017$, R: 0.63). Similarly, there was a strong correlation between the hepatic fat fraction and retroperitoneal fat accumulation ($p < 0.0001$, R: 0.73).

DISCUSSION

The normal flow pattern in the portal vein is biphasic with undulation (17). Dietrich and colleagues (17) observed a decrease in undulation for the portal vein flow pattern in 135 patients with chronic hepatitis C who had undergone liver biopsies. The pattern was associated with portal inflammation but not with other parameters of the histologic activity index or intrahepatic fat deposition. They reported that this flattening was due to both a reduction in the maximum velocity and an increase in the minimum velocity. Icer and Kara (18) studied 17 patients with cirrhosis and 20 healthy subjects; the portal vein Doppler spectral waveform was changed in patients with cirrhosis compared with the healthy subjects. Healthy subjects had a more pulsatile pattern and broader spectrum than cirrhosis patients. Barakat et al. (19) studied 148 patients with cirrhosis and 54 healthy subjects and showed that a flat, non-pulsatile pattern tended to increase in relation to the portal vein as the liver disease progressed. All these previous studies (17-19) demonstrated that portal vein Doppler spectral waveform alterations are dependent upon liver texture, with changes seen in association with, for example, cirrhosis, viral hepatitis, and portal inflammation. However, we excluded such patients, since

these diseases are more harmful than NAFLD and damage the liver texture. In contrast to the above-mentioned findings, we did not see a flat waveform in any patient with NAFLD.

Balci et al. (20) studied 105 patients with hepatosteatosis and 35 healthy subjects. Their patient group was homogenous with diffuse fatty infiltration. They concluded that the pulsatility index and mean velocity of the portal vein blood flow decreased as the severity of fatty infiltration increased. However, we found no correlation between the degree of hepatic fat fraction and portal venous velocity ($p > 0.05$). Similarly, we found that the difference in portal venous velocity between the patients with NAFLD and the control group was statistically significant ($p < 0.0001$). However, the fatty infiltration score was determined solely on the basis of gray-scale images of the liver parenchyma, where other (more reliable) radiologic methods existed.

The examination of portal venous velocities using US in patients with NAFLD indicate that the portal vein pulse Doppler values may be useful for disease diagnosis and the monitoring of responses to treatment. As a methodology, it involves no radiation exposure, is readily available, and is inexpensive. Determination of the Doppler spectral waveform in patients with NAFLD, who are diagnosed based on abnormal levels of serum aminotransferases, prolongs the duration of a typical US examination by only 1-2 minutes.

Various epidemiologic studies have noted associations between increased waist-to-hip-circumference ratio and impaired glucose tolerance, type 2 diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, hyperuricemia, (13-16) and atherosclerotic vascular diseases (21-23). Bjorntorp (6) stated that fat in the intraperitoneal region may be more harmful and may influence insulin sensitivity. In another study, Jensen and Johnson (5) reported that intraperitoneal adipose tissue contributed to only about 15% of the total systemic free fatty acid (FFA) inflow; the majority of FFAs (75%) came from non-splanchnic adipose tissues in the upper body such as the head, neck, trunk, and upper extremities. Likewise, we found that there was a strong correlation between the hepatic fat fraction and the levels of subcutaneous adiposity as well as the intraperitoneal and retroperitoneal fat accumulation. According to our findings, regional adiposity, for example, intraperitoneal adipose tissue, does not influence the hepatic fat fraction more than other regional fat accumulation.

In summary, the main portal vein velocities in patients with NAFLD were lower than those in healthy subjects. However, the portal vein flow pattern was not changed by the degree of hepatic fat accumulation in patients with NAFLD. In summary, abdominal obesity is an important disorder that can influence hepatic fat accumulation; hence, it is important to find less invasive techniques such as described in this study to detect NAFLD.

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