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Sonographic hepatic-renal ratio as indicator of hepatic steatosis: comparison with ^{1}H magnetic resonance spectroscopy

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Abstract

The aim of this study was to determine the diagnostic performance of ultrasound (US) in the quantitative assessment of steatosis by comparison with proton magnetic resonance spectroscopy (^{1}H-MRS) as a reference standard. Three liver echo-intensity indices were derived: US hepatic mean gray level, hepatic-renal echo-intensity ratio (H/R), and hepatic-portal blood echo-intensity ratio. The ^{1}H-MRS degree of steatosis was determined as percentage fat by wet weight. Regression equations were used to estimate quantitatively hepatic fat content. The hepatic fat content by ^{1}H-MRS analysis ranged from 0.10% to 28.9% (median value, 4.8%). Ultrasound H/R was correlated with the degree of steatosis on ^{1}H-MRS (R^2= 0.92; $P < .0001$), whereas no correlation with ^{1}H-MRS was found for hepatic mean gray level and hepatic-portal blood echo-intensity ratio. A receiver operating characteristic curve identified the H/R of 2.2 as the best cutoff point for the prediction of ^{1}H-MRS of at least 5%, yielding measures of sensitivity and specificity of 100% and 95%, respectively. In this pilot study, US H/R exhibits high sensitivity and specificity for detecting liver fatty changes. Our results indicate that quantitative evaluation of hepatic fat content can be performed using US H/R and could therefore be a valuable analytic tool in clinical investigation.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has reached epidemic proportions in different populations around the world and may affect any age and ethnic group [1,2]. Nonalcoholic fatty liver disease is frequently associated with obesity, type 2 diabetes mellitus, hypertension, and hyperlipidemia [3-5], all of which have been associated with insulin resistance and an increase in the risk of cardiovascular disease [6-8]. Recently, carotid atherosclerosis has been detected in patents with NAFLD even with no or mild alterations in liver tests [9,10]. The prevalence of steatosis increases to 57% to 74% in severely obese subjects [11]. It affects 9.6% of children and adolescents aged 2 to 19 years and 22% to 55% of obese children [12,13]. Most patients with liver steatosis are asymptomatic [14]; and less than 50% of patients will have elevated alanine transaminases [15], which are usually less than 2 times the upper limit of normal.

Therefore, an accurate, low-cost, and noninvasive imaging modality of screening that can quantitatively evaluate hepatic fat content in a large population including children and that could be easily repeated during follow-up is ideally needed in clinical practice.

Ultrasonography (US) is usually the first imaging modality for the evaluation of hepatic steatosis, although unenhanced computed tomography and magnetic resonance imaging are sensitive and objective tools for the demonstration and quantification of hepatic steatosis [16-18]. Proton magnetic resonance spectroscopy (^{1}H-MRS) provides a

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sensitive, quantitative, and noninvasive method to accurately assess hepatic triglyceride content in vitro and in vivo [19-21]. In a recent population-based study of ^{1}H-MRS in 2349 individuals without known liver disease or identifiable risk factors for hepatic steatosis (obesity, diabetes mellitus; with minimal alcohol consumption) and with normal liver function test results, the 95th percentile of hepatic triglyceride content was 55.6 mg/g [22]. A liver fat content greater than 50 mg/g (5% by wet weight) is considered diagnostic of hepatic steatosis [22,23]. Proton magnetic resonance spectroscopy fat measurement has been demonstrated to correlate with liver biopsy results [21,23-26] and has great potential for serial monitoring of fatty liver disease [27]. However, it is expensive and is far less available than US; and a number of obese patients may not fit in the magnets.

Ultrasonography is a simple noninvasive technique that is widely used in clinical practice to detect hepatic steatosis [28-32]; however, it has been unable to provide a precise determination of hepatic fat content.

The purpose of the present study was to compare US with hepatic ^{1}H-MRS findings to identify an accurate quantitative ultrasonic method to assess hepatic fat content.

2. Methods

2.1. Subjects

Ultrasonography and ^{1}H-MRS examinations were performed in 40 individuals (age range, 28-65 years; body mass index [BMI] range, 18.7-38.3 kg/m^2) who were participating in a metabolic study on postprandial lipid metabolism performed at the Department of Internal Medicine. This study included 23 obese patients (BMI ≥30 kg/m^2; range, 30.6-38.3), 17 normal-weight individuals, and 17 patients with type 2 diabetes mellitus. The obese and diabetic patients were recruited at the outpatient clinic. The normal-weight controls were volunteers recruited from hospital employees.

The participants did not have a history, clinical symptoms, or signs of liver disease or any other disease apart from diabetes; nor were they vegetarians or engaged in intensive physical activity. They were not taking any hypolipidemic drug or drugs that could cause steatosis. All participants had alcohol consumption less than 30 g/d, normal fasting plasma concentration of both triglyceride (<1.7 mmol/L) and cholesterol (<5.5 mmol/L), normal renal function, and absence of proteinuria in spot urine collection. Diabetic patients were in stable glycemic control on diet alone (hemoglobin A_{1c} = 6.5 ± 1.5%).

The protocol for the study was approved by the Ethics Committee of the University Hospital, and informed consent was obtained from all participants.

During the first admission, anthropometric measurements were performed; and fasting venous blood samples were drawn for determination of plasma electrolytes, creatinine, glucose, total cholesterol, triglycerides, high-density lipoprotein cholesterol, and hemoglobin A_{1c}; all subjects underwent both US and ^{1}H-MRS on the same day.

2.2. US study

All examinations were performed with an Eco-color Doppler HDI 5000 Sono-CT (Philips Medical Systems, Bothell, WA) by using a broad-bandwidth (C5-2 MHz) curved-array transducer; US studies were performed by 2 experienced radiologists (CM and MC) who were unaware of the patient's clinical details and laboratory findings. The time-gain compensation was set to adjust the tissue echogenicity as constant as possible regardless of the depth, and the power control was set at a constant level. Five parameters including parenchyma echogenicity, far gain attenuation, portal vein wall blurring, and diaphragm and renal blurring were assessed in right coronal subcostal view, right intercostal view at anterior, mid and posterior axilla line, and sagittal subcostal view, in the supine and lateral positions. A US B-mode evaluation of renal parenchyma echogenicity was also performed. The radiologist graded each US examination according to the presence and severity of liver steatosis by using the following criteria [31-35]:

1. Normal liver echo texture was considered to represent *absence of steatosis*.
2. The presence of hyperechogenic liver tissue (compared with the adjacent kidney cortex) with fine and tightly packed echo targets and of normal beam penetration with normal visualization of diaphragm and portal vein borders was considered as *mild steatosis*.
3. The moderate and diffuse increase of echo intensity with decreased beam penetration (with slightly decreased visualization of diaphragm) associated with a decrease in visualization of silhouetting of the portal vein borders was considered as *moderate steatosis*.
4. The marked increase in echoes intensity with no visualization of portal vein border, obscured diaphragm and posterior portion of the right lobe, and reduced visibility of kidney was considered as *severe steatosis*.

All images were transferred to a personal computer and reviewed by 1 of the 2 radiologists involved in scanning (CM). Echo intensity analysis of digitized B-mode images was performed by using Osiris software (OSIRIS 4.19 University Hospital of Geneva).

A region of interest (ROI) in the liver parenchyma was selected so that no blood vessels or other focal hypo/hyperechogenicity was crossed to obtain a sample of liver parenchyma alone, avoiding liver lesions. To obtain a parameter independent of the gain settings, another 2 ROIs were identified: (1) portal vein to obtain a sample of blood and (2) renal cortex with no large vessels, renal sinus, or medulla. A straight line starting from the ROI selected in the hepatic parenchyma and continuing toward the kidney was manually drawn, and another ROI in the adjacent right kidney cortex was selected along the focusing area of the

image at the same distance from the probe and near the center line of the image to avoid distorting effects in ultrasonic wave patterns (Fig. 1A, B). Using the scaling line on the image for calibration, the height of the ROI in the hepatic and renal parenchyma was set to obtain an area of 1 × 1 cm (1600 pixels) for hepatic parenchyma and 0.5 × 0.5 cm (441 pixels) for renal parenchyma. The ROI in the portal vein was calibrated on the internal diameter of the vein. The gray scale mean value of the frequency distribution of the gray values of the pixels within the 3 ROIs was used as measurement of echo intensity. Two echo-intensity ratios (hepatic-kidney and liver-portal) were then calculated from the results of hepatic intensity divided by renal intensity and portal intensity. To assess the intraobserver agreement of the US ratio measurements, the first 10 patients were reexamined with the same protocol by one of the authors. The absolute mean difference for all ratios was less than 3%.

2.3. Measurement of hepatic triglyceride content using ^{1}H-MRS

The ^{1}H-MRS measurements were performed on a 1.5-T MR scanner (Intera; Philips Medical Systems, Eindhoven, the Netherlands) equipped for proton spectroscopy acquisitions. Sagittal, coronal, and axial slices covering the whole liver were preliminarily acquired for positioning of the spectroscopy acquisition voxel (Fig. 1C). A single voxel of 8 cm^3 (2 × 2 × 2 cm) was placed within the right lobe avoiding major vascular structures and subcutaneous fat tissue because no significant differences were found between right and left lobe MRS measurements [22]. The proton spectrum was acquired using the body coil after shimming over the volume of interest by means of a point-resolved spectroscopy (PRESS) sequence with the following parameters: repetition time = 3000 milliseconds, echo time = 40 milliseconds, 1024 data points over 1000 KHz spectral width, 16 acquisitions. Signal intensities of the water peak at 4.8 ppm (S_w) and the methylene groups that represent intracellular triglyceride in the liver at 1.4 ppm (S_f) were calculated as the integral of the 2 peaks after correcting signal for phase shifting and baseline drift by time domain fitting routine (AMARES-MRUI, http://www.mrui.uab.es/mrui/). Signal decay was corrected for the different T_2 decay of water and fat using mean T_2 relaxation times of 50 and 60 milliseconds for water and fat, respectively. Hepatic fat percentage was calculated using the formula $100 * S_f / (S_f + S_w)$ [24]. These values represent a relative quantity of water and fat in the volume of interest. To convert these values to absolute concentrations (weight/volume) expressed as percentage fat, equations validated by Longo et al [24,36] were applied.

2.4. Statistical analysis

Continuous data were expressed as mean ± SD. χ^2, McNemar test, and regression analysis were applied when appropriate. A receiver operating characteristic (ROC) curve was calculated to determine the optimal threshold for detection of steatosis by US hepatic-renal (H/R) ratio. The optimal threshold value was used as the cut point to determine the sensitivity and specificity of H/R for detecting the presence of liver fat content at ^{1}H-MRS of at least 5%. Statistical analysis was performed using Statistical Package for Social Sciences version 10.0 software (SPSS, Chicago, IL).

Levels of statistical significance were set at a 2-tailed P value < .05.

3. Results

In 2 patients, obesity and bowel gas limited the visualization of the structures of interest, making it impossible to obtain a good image of the portal vein and to calculate the hepatic-portal ratio, although all other measurements could be performed. No individuals had increased renal echogenicity. Most patients had normal or only slightly increased levels of plasma transaminases (aspartate aminotransferase: median, 23 IU; range, 15-63 IU; alanine aminotransferase: median, 25 IU; range, 14-106 IU).

Hepatic fat content determined by ^{1}H-MRS analysis ranged from 0.10% to 28.9% (median value, 4.8%). By application of the current criteria for diagnosis of steatosis, 50% of the subjects (20/40) had a hepatic fat content exceeding 5.0%.

Four patients with increased echogenicity according to subjective US grading were normal by ^{1}H-MRS. In contrast, one normal liver by visual grading had steatosis by ^{1}H-MRS (5.12%) (Table 1).

The echo intensity of liver parenchyma in the selected ROI and the US hepatic-portal ratio were not significantly correlated to the hepatic ^{1}H-MRS (echo intensity: median, 49.0; range, 19.3-117.9; R^2 = 0.057; US hepatic-portal ratio: median, 2.5; range, 1.1-10.8; R^2 = 0.14). There was a significant correlation between US H/R ratio and the degree of steatosis on ^{1}H-MRS expressed as percentage fat by wet weight (median, 2.3; range, 1.0-9.2; R^2 of the model, 0.92; P < .001) (Fig. 2A). This correlation was also maintained in patients who were obese according to the World Health Organization criteria [1,37]. In the 23 patients with BMI of at least 30 kg/m^2, the H/R ratio was strictly correlated to the degree of fat content on ^{1}H-MRS expressed as percentage fat by wet weight (R^2= 0.912; P < .0001) (Fig. 2B).

The ROC curve of H/R ratio in the prediction of liver fat content at ^{1}H-MRS of at least 5% is shown in Fig. 3. The area

Fig. 1. A and B, Ultrasound evaluation of hepatic echo intensity. Comparison of hepatic echo intensity (mean gray levels, ROI 2) to renal echo intensity (mean gray levels, ROI 1) in (A) a normal individual (n.3) (H/R ratio = 1.35) and in (B) an individual (n.18) with steatosis (H/R ratio = 5.85). C, Measurements of hepatic triglycerides contents using ^{1}H-MRS. The water peak has a chemical shift of 0 ppm, whereas the methylene group of fat has a chemical shift of 3.4 ppm relative to the water peak. The height of the signal is in arbitrary units. The fat index of this spectrum was 8.46%.

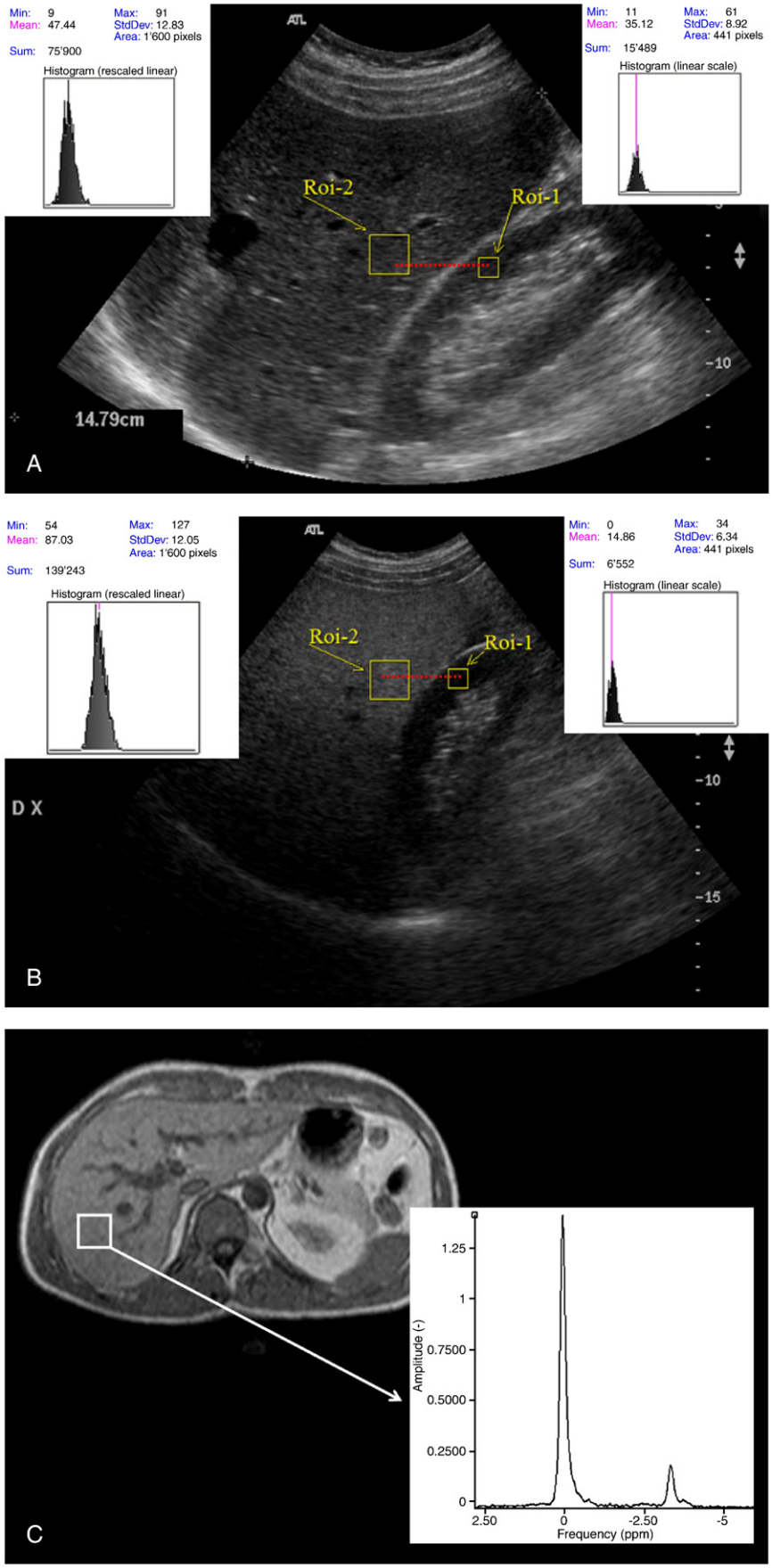
Min: 9
Mean: 47.44
Max: 91
StdDev: 12.83
Area: 1'600 pixels
Sum: 75'900
Histogram (rescaled linear)
Min: 11
Mean: 35.12
Max: 61
StdDev: 8.92
Area: 441 pixels
Sum: 15'489
Histogram (linear scale)
Roi-2
Roi-1
14.79cm
A
Min: 54
Mean: 87.03
Max: 127
StdDev: 12.05
Area: 1'600 pixels
Sum: 139'243
Histogram (rescaled linear)
Min: 0
Mean: 14.86
Max: 34
StdDev: 6.34
Area: 441 pixels
Sum: 6'552
Histogram (linear scale)
Roi-2
Roi-1
D X
B
Amplitude (-)
1.25
1
0.7500
0.5000
0.2500
0
2.50
0
-2.50
-5
Frequency (ppm)
C

Table 1
Sensitivity and specificity of US visual grading and H/R ratio for the diagnosis of steatosis, in comparison with ^{1}H-MRS evaluation of hepatic fat content

		^{1}H-MRS	
		Steatosis (>5%wet weight)	Normal (<5%wet weight)
US visual grading	Steatosis	19	4
	Normal	1	16
	Total	20	20
	Sensitivity	0.95	
	Specificity		0.80
US H/R ratio	Steatosis	20	1
	Normal	0	19
	Total	20	20
	Sensitivity	1.00	
	Specificity		0.95

under the ROC curve for H/R ratio was 0.996 (0.986-1.007). The best cutoff point for H/R ratio was the value 2.2. The diagnostic performance of this H/R cutoff in the prediction of steatosis was 100% sensitivity and 95% specificity. In our group of patients, the only false-positive H/R ratio was in an obese patient with BMI of 38.3 and a suboptimal US examination with limited visualization of the portal vein. The results of linear regression analysis show that a 1-unit increase of H/R ratio corresponds to an increase of ^{1}H-MRS fat index of 3.08% and to an increase in liver fat content of about 30.82 mg/g. The accuracy of the predicted value of ^{1}H-MRS by means of the linear regression results was ±5%.

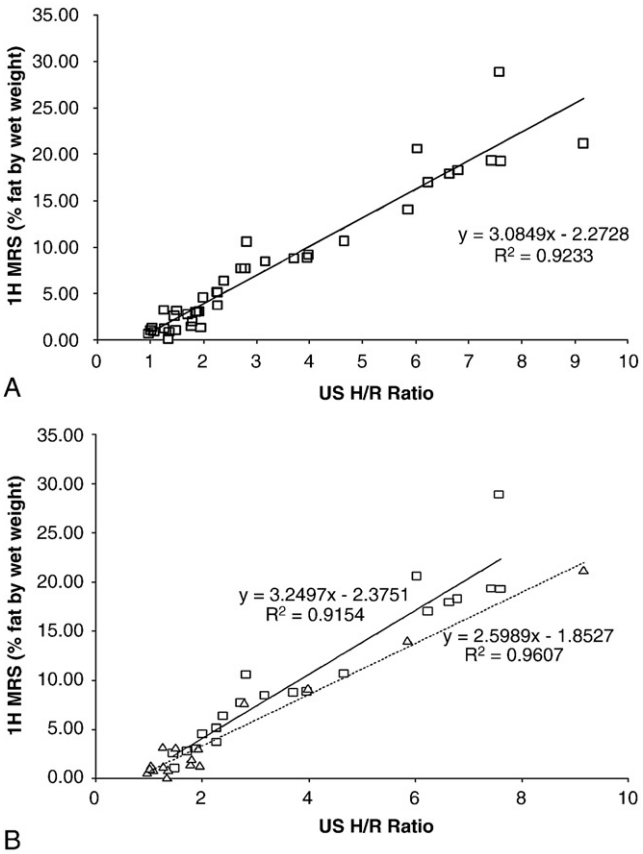

Fig. 2. A, Linear regression analysis between hepatic triglycerides contents by ^{1}H-MRS and US H/R ratio. B, Linear regression analysis between hepatic triglycerides contents by ^{1}H-MRS and US H/R ratio in individuals with BMI less than 30 kg/m^2 (triangles, dotted line) and at least 30 kg/m^2 (squares, straight line).

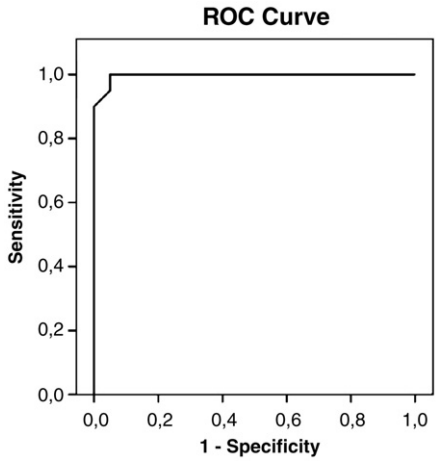

Fig. 3. Receiver operating characteristic curve of US H/R ratio for diagnosing steatosis (^{1}H-MRS hepatic fat content >5%).

4. Discussion

This study has examined the capacity of different US approaches to predict the degree of hepatic fat content measured by ^{1}H-MRS. Our data revealed a very good correlation between US H/R ratio and hepatic triglyceride content measured by ^{1}H-MRS.

The echogenicity of the liver subjectively compared with that of the kidney is known to be a clinically useful marker of steatosis. Previous studies found a linear relationship between the hepatic total lipid concentration and US backscatter coefficient [38]. We did not find any correlation between echo intensity of liver parenchyma and fat content by ^{1}H-MRS. Our results are, instead, in agreement with previous studies that proposed the use of ratios and differences of liver and renal cortical echo amplitude as a means of overcoming variability due to subjective evaluation [39,40].

In our population, using the ROC curve, we have shown that hepatic echo intensity slightly more than double that of renal parenchyma (H/R ratio >2.2) can be used as cutoff point to define hepatic steatosis with US, with a sensitivity of 100% and specificity of 95%.

All 5 cases incorrectly assigned at US visual examination were normal or had mild steatosis with ^{1}H-MRS. This demonstrates that US visual examination is accurate for detecting moderate to severe hepatic steatosis but that the diagnosis of mild steatosis can be difficult without a computer-aided method.

One limitation of our study is that spectroscopy, rather than histologic examination, was used as the reference. Pathologic examination of biopsied specimens from the liver remains the criterion standard in current clinical practice to establish the diagnosis of steatosis. However, liver biopsy is an invasive procedure with a morbidity rate of 3% and a mortality rate of 0.03% [41]. Histology correlates well with ^{1}H-MRS hepatic triglyceride content [21,24,26,36]. Moreover, histomorphologic assessment of intracellular fat vacuoles does not directly measure hepatic triglyceride concentration and may not be an appropriate reference standard for liver fat quantification. Spectroscopically determined fat fraction is equivalent to tissue triglyceride concentration, and several clinical trials [42-44] on NAFLD have used spectroscopic magnetic resonance as an outcome measure. Therefore, spectroscopy may be a more appropriate reference standard than histology in accurately assessing fat quantification.

Inhomogeneous distribution of the hepatic fatty infiltration may result in sampling errors whatever methodology is used, US, ^{1}H-MRS, or, even more so, liver biopsy. In the presence of areas of focal or spared steatosis as in the "geographical type," in which usually entire segments or even entire lobes are affected [45], the measurements of echo intensity in only 1 ROI could not be representative of the entire liver and, therefore, not allow an accurate quantification of steatosis. In this case, averaging results from several areas at standardized locations would provide a more representative quantification.

One possible limitation to the use of H/R ratio is the presence of renal diseases. In fact, several diseases have been reported to cause an increase in cortical echogenicity of the kidney. The increase in cortical echogenicity is a result of changes within the glomeruli, tubules, and interstitium and is correlated with serum creatinine level. Therefore, the comparison of liver echogenicity to renal cortex is only valid if the level of serum creatinine is normal and a kidney disease is excluded by clinical and laboratory signs [46-48,49].

It has been previously reported that the sensitivity and specificity of US for detecting fatty infiltration decrease as BMI increases [34]. The sensitivity and the specificity of US in diagnosing steatosis in morbidly obese patients were 49.1% and 75%, respectively. This could be a limitation in studying populations with a high prevalence of obesity. In our study, the correlation between US H/R ratio and the degree of steatosis at MRS was also maintained in patients with class I to II obesity (BMI = 30-39.9 kg/m^2, World Health Organization classification) [37], as shown in Fig. 2B. We did not evaluate extremely obese patients because of the technical problems in performing US and magnetic resonance imaging studies in such patients. However, these difficulties concern only extremely obese patients.

Liver fibrosis causes heterogeneity in parenchyma echotexture and could make the evaluation of fatty liver more difficult. The interference of liver fibrosis on bright liver echo pattern was evaluated by Palmentieri et al [50] who showed that only steatosis significantly correlated with bright liver echo pattern. None of the patients with severe or moderate fibrosis without steatosis demonstrated a discrepancy higher than expected in the echo amplitude between the liver and kidney parenchyma. Thus, the presence of bright liver pattern may be considered a clinical sign specific of steatosis. However, further studies are required to investigate the effect of pure steatosis (without fibrosis) and steatosis with fibrosis on liver parenchyma.

In conclusion, the US H/R ratio demonstrated a very high correlation with ^{1}H-MRS for a wide range of hepatic lipid content (1%-30%). Therefore, this quantitative US ratio may be considered a simple, noninvasive, and low-cost analytic tool in the clinical evaluation of liver steatosis.

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