The value of transabdominal ultrasound for assessment of the severity of liver steatosis as compared to liver biopsy

Abstract: The purpose of our paper was to evaluate the performance of ultrasound (US) for assessment of the severity of liver steatosis as compared to a pathological examination, which is presently considered to be the gold standard, in patients that have undergone liver biopsy for various reasons. We performed echo-assisted liver biopsy in 161 patients with chronic hepatitis with the US aspect of “bright liver” with “posterior attenuation”, using modified Menghini needles. Following the US examination, the severity of liver steatosis was estimated as minimal, mild, moderate, or severe according to the Hepburn classification: absent (affecting 0% to 2% of the hepatocytes), minimal (2% to 10%), mild (10% to 30%), moderate (30% to 60%), and severe (more than 60% of the hepatocytes). The results of this study showed that the sensitivity of US for the prediction of histological steatosis of at least moderate severity was 0.64, with 0.77 specificity, 0.55 positive predictive value, and 0.94 negative predictive value. The overall accuracy was 0.75. This study showed that the transabdominal ultrasound evaluation of the fatty liver is a quite good predictor, perhaps sufficient for most purposes, for the estimation of the severity of liver steatosis in the moderate to severe range.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most frequently occurring diseases in the modern world. The main factors incriminated in its pathogeny are obesity caused by increased food intake, diabetes mellitus, dyslipidemia, and lack of exercise [1]. Several studies have revealed a dramatic increase of obesity in developed countries; for example, in the United States, the incidence of obesity has doubled in the last 10 years [2]. Also, it is known that a large number of obese patients have liver steatosis in various degrees of severity. The estimated prevalence of NAFLD in Western populations ranges from 20% to 30% [3], and it is considered to be part of the metabolic syndrome [4]. From the hepatological point of view, non-alcoholic steato-hepatitis (NASH) is known to be a cause of liver cirrhosis [5-7].

The procedure for assessment of a patient with fatty liver disease is not standardized; it includes biological tests (usually, AST, ALT, or Steato-Test and NASH-Test) [8,9], imaging techniques (mainly ultrasound, but also CT scans or MRI) [1,10-12] and liver biopsy (LB) [9,13,14].

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The aim of the present paper is to evaluate the performance of ultrasound (US) examination for assessment of the severity of liver steatosis, as compared to a pathological examination, which is considered to be the “gold standard”, in patients that have undergone liver biopsy for various causes. Liver biopsy is not usually performed for staging NASH (usually it is performed only in clinical trials), so we used the liver biopsies performed in patients with chronic hepatitis in which steatosis was found by an ultrasound examination.

2. Material and Methods

2.1. Patients
Our study is retrospective and descriptive, and aims to evaluate the capacity of US examination to predict the severity of liver steatosis, as compared to liver biopsy (LB), which is considered to be the “gold standard”. We included 161 cases seen over a period of 24 months in 2005 and 2006.

2.2. Ultrasound examination
We analyzed all patients in which the US examination described liver steatosis (“bright” liver with “posterior attenuation”, as compared to the normal echogenicity of the right kidney) and in which LB was performed for various reasons, most frequently for chronic hepatitis C. The US examination was performed with multifrequency probes on the Siemens VersaPro and Siemens Adara ultrasound machines.

Following the US examination, the severity of liver steatosis was evaluated as minimal, mild, moderate, or severe (according to the subjective assessment of the “brightness” of the liver and the intensity of “posterior attenuation”). A semi-quantitative scale was used, ranging from 0 to 3 (0, no steatosis; 0.5, minimal steatosis; 1, mild steatosis; 2, moderate steatosis; 3, severe steatosis). The US examination was performed by 4 experienced ultrasonographers who had performed US examination on a daily basis for at least 5 years, and who had previously agreed upon the US criteria for the evaluation of steatosis.

2.3. Liver biopsy
The LB was performed with US assistance, using modified Menghini needles 1.4 or 1.6 mm in diameter (Hepafix; B.Braun AG, Melsungen, Germany). The biopsy was performed immediately after the US examination.

2.4. Morphopathological assessment
The fragments obtained by LB were interpreted by a single experienced pathologist, according to Hepburn’s classification of steatosis [15], using haematoxylin-eosin and Sudan black stains, as follows: no steatosis, 0% to 2% of the hepatocytes with steatosis; minimal steatosis, 2% to 10% of the hepatocytes with steatosis; mild steatosis, 10% to 30% of the hepatocytes with steatosis; moderate steatosis, 30% to 60% of the hepatocytes with steatosis; severe steatosis, more than 60% of the hepatocytes with steatosis.

2.5. Statistical analysis
The Epi Info program was used for the descriptive statistical analysis of the group and for univariant analysis.

For the risk analysis we transformed ordinal variables into dichotomous variables by establishing thresholds. The statistical significance of the risk factors was assessed using chi square and Fisher tests (for groups smaller than 5).

The pathological exam was considered to be the correct one and the US diagnosis was considered to be a risk factor.

3. Results

3.1. Patient population
Our study included 161 patients in whom we evaluated the severity of steatosis by US examination and in whom LB had been performed. The patients were divided into 2 groups: group I included 66 patients in whom the US examination was performed by an expert ultrasonographer (level III in the multilevel system of EFSUMB); and group II included 95 patients in whom the US examination was performed by 4 senior ultrasonographers with more than 5 years experience in liver ultrasound (level II in the multilevel system of EFSUMB).

According to the etiology of steatosis, among the 161 patients there were 102 cases (63.4%) of HCV chronic hepatitis; 39 cases (24.2%) of HBV chronic hepatitis; 9 cases (5.6%) of NASH; 5 cases (3.1%) of ASH; 4 cases (2.5%) of HBV+HCV chronic hepatitis; and 2 cases (1.2%) of HBV+HDV chronic hepatitis (Figure 1).

3.2. Ultrasound evaluation of steatosis
Regarding the US assessment of steatosis, we found a predominance of mild cases (49.7%, 80 patients); among the other patients, 15.5% (25) had minimal steatosis, 28.6% (46) had moderate steatosis, and 6.2%...
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3.3. Morphopathological assessment of steatosis

On the pathological exam we also observed a predominance of the mild cases (50 patients, 31.1%), but we also found a significant number of patients without steatosis: 36 patients, or 22.4%, had a false positive US test. The distribution of patients according to the severity of steatosis was similar for both methods of evaluation (US and pathological exam) (Figure 2).

3.4. Concordance between the US and the pathological assessment of steatosis

In order to assess the concordance between the two methods of diagnosis, we compared the proportions using the chi square test. We established thresholds for the US severity of liver steatosis (minimal, mild and moderate). The risk analysis for each threshold of US steatosis confirmed the prognostic value of US examination (odds ratio above 6); the p value was well below 0.05, confirming the statistical significance of the calculated indices (Table 1).

We also evaluated the concordance between the two methods of assessment of liver steatosis according to the experience of the physician performing the US exam. We divided the 161 patients into two groups: in group I, 66 patients in whom the US examination was performed by an expert ultrasonographer (level III in the multilevel system of EFSUMB); and in group II, 95 patients in whom the US examination was performed by 4 senior ultrasonographers with more than 5 years experience in liver ultrasound (level II in the multilevel system of EFSUMB). We maintained the same thresholds of US evaluation of steatosis. The results of our analysis confirmed the predictive value of US examination for each degree of steatosis, with better chances of prediction in group I. Considering this, we interpreted the analyzed risk factor as a predictive factor (Table 2).

The chi square test, used to test the significance of differences between the risk indicators for the two strata (group I, expert ultrasonographer vs. group II, senior ultrasonographers), showed a lack of statistical significance (p > 0.05). Thus, even if the experience of the examiner improved the concordance between the two diagnostic methods, this conclusion can not be generalized, and further studies are needed.

We analyzed the power of US examination for the diagnosis of at least moderate steatosis. The receiver operating characteristic (ROC) curve obtained demonstrates a good discrimination power for this test (Figure 3). Thus, for the diagnosis of steatosis of at least moderate severity, the US examination had 64% sensitivity, 77% specificity, 55% positive predictive value, and 94% negative predictive value. Also, the analysis of the area under the receiver operating characteristic (AUROC) demonstrates good accuracy for the diagnosis of liver steatosis of at least moderate severity (c = 0.75).
4. Discussion

Considering the constant increase of NAFLD incidence in the general population in the last years, non-invasive imaging methods are needed for the mass evaluation of steatosis. If, in a patient, the imaging methods reveal the presence of steatosis, and if the aminotransferases persistently increase, it is highly probable that that patient has NASH (differentiated from ASH by the absence of alcohol abuse).

"Bright liver echo pattern" with "posterior attenuation" on ultrasound is usually considered a sign of hepatic steatosis, but interference with liver fibrosis makes this sign more difficult to use [15].

A study performed by Palmentieri et al. [16] compared the "bright liver" echo pattern to the liver biopsy. The study showed, in 235 patients, that the inter-observer concordance in US evaluation was high, and that the "bright liver" echo pattern was found in 67% of patients with steatosis of any degree on biopsy and in 89% of patients with moderate or severe steatosis (≥ 30% of hepatocytes with steatosis on biopsy).

In the Palmentieri study, the sensitivity, specificity, positive predictive value, and negative predictive value of the "bright liver" echo pattern and the "posterior attenuation" for the assessment of steatosis were 64%, 97%, 96% and 65%, respectively. In the subgroup of patients who had moderate or severe steatosis (≥ 30% of hepatocytes with steatosis on biopsy), the sensitivity, specificity, positive predictive value and negative predictive value were 91%, 93%, 89% and 94%, respectively.

We obtained similar results in the present study: we found that the sensitivity of US for the diagnosis of at least moderate steatosis is 64%, but with a lower specificity (77%). We also found a good negative predictive value (94%), meaning that in the absence of the "bright liver" aspect on US, the probability of finding steatosis on the liver biopsy is close to zero.

Mathiesen et al. [17] compared US to hepatic histology for the diagnosis of steatosis in a series of 165 patients who had been referred because of a slight-to-moderate increase of aminotransferases over a period of more than 6 months. Steatosis was graded as none, mild, moderate, or severe. In that study, US had a sensitivity of 90%, a specificity of 82%, a positive predictive value of 87%, and a negative predictive value of 87% for detection of steatosis. Also, the value of US for the diagnosis of moderate-to-pronounced fatty infiltration was 86.6% (correct classification). But it must be noted that this study was performed in patients referred because of slightly to moderately raised aminotransferases lasting more than 6 months before the study began, whereas in our study, the only inclusion criterion was "bright liver" found at the US examination.

Fishbein et al. [18] compared liver biopsy, US, and MRI for the assessment of steatosis in 38 patients. The steatosis pattern on histology was macrovesicular, microvesicular, or mixed. According to this study, for microvesicular fatty liver, MRI was better correlated to steatosis than ultrasound (r = 0.77, p < 0.01 vs. r = 0.41, p < 0.05). In macrovesicular steatosis, MRI and US both correlated well with the histological fat content (r = 0.92, p < 0.01 vs. r=0.90, p < 0.01). The authors’ conclusion was that both hepatic MRI and US are useful in identifying severe fat accumulation, but that MRI is superior to US in detecting and quantifying the fatty metamorphosis in the liver. As a comment upon this study, considering the high cost of MRI as well as the similar results of US and MRI for the assessment of macrovesicular steatosis, we conclude that the US examination should be the usual method for the assessment of steatosis in daily practice.

There are some studies that tried to improve the performance of US for the evaluation of liver steatosis. Kim et al. [19] compared the performance of artificial neural networks (ANNs) as applied to ultrasonographic images to the performance of radiologists for predicting macrosteatosis. Regarding sensitivity for predicting macrosteatosis, no statistically significant differences were found between ANNs (88.9%) and radiologists (p > 0.05). However, the specificity of ANNs (96.1%) was significantly higher than that of the radiologists (p < 0.003). Also, Gaitini et al. [20] demonstrated that using computer-aided diagnosis in severe steatosis, a highly
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accurate “ultrasonic biopsy” is obtained (sensitivity >90%).

However, the problem arising from the US evaluation of the fatty liver is that NAFLD and NASH (steatosis and steatohepatitis) can not be differentiated. Ataseven et al. [21] demonstrated that ultrasonography findings do not reflect the histopathological severity in patients with NASH, and that the results appear to be the same for CT. Also, Saadeh et al showed that differences between NASH and nonprogressive NAFLD were not apparent with any radiological modality (US, CT, MRI), and that for the diagnosis of NASH, only the severity of steatosis was reflected by the radiological methods [22].

Reviewing the published data regarding the value of US for the diagnosis of steatosis, we have concluded 1) by using multiple criteria to diagnose steatosis, the positive predictive value can be as high as 94% in high prevalence populations [17]; 2) the performance tends to improve with the severity of steatosis [23]; 3) ≥30% steatosis on biopsy seems to be the optimal threshold for radiological (or ultrasound) detection of steatosis [22]; 4) NASH and NAFLD can not be differentiated by means of radiological methods [22].

Considering the published data, we conclude that US can be used for the assessment of steatosis, especially moderate and severe steatosis, which are the stages with clinical consequences. As well as other imaging methods, the US examination can estimate only the severity of steatosis, but not the inflammatory lesions (NASH). Data obtained from imaging methods, correlated with persistently increased aminotransferases, and in the absence of other etiological factors (hepatitis viruses, alcohol abuse, and so forth), can suggest that such a patient has NASH. But proof of steatohepatitis can be obtained only by LB and a pathological exam.

Our study showed that transabdominal ultrasound evaluation of the fatty liver seems to be quite a good predictor, for the estimation at moderate and severe of liver steatosis: our results had a sensitivity of 64%, specificity of 77%, a positive predictive value of 55%, a negative predictive value of 94%, and an accuracy of 0.75). The experience of the examiner can somewhat improve the quality of prediction (but the differences were not statistically significant), so that the US assessment of steatosis can be made with confidence by any experienced ultrasonographer.

References


