Noninvasive assessment of liver steatosis using ultrasound methods

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Abstract

Hepatic steatosis is a condition frequently encountered in clinical practice, with potential progression towards chirrhosis and hepatocellular carcinoma. Ultrasonography (US) is one of the noninvasive imaging techniques used in the diagnosis of steatosis. We will review the US diagnostic criteria, the US performance in the diagnosis and grading of hepatic steatosis, the US steatosis models, but also its limitations in the diagnosis of steatosis. In addition, we will discuss 2 modern methods of assessing hepatic steatosis using ultrasounds, namely the computerized processing of data forming the US image and the controlled attenuation parameter measured with unidimensional transient elastography.

Keywords: steatosis, noninvasive, ultrasonography, computerized processing, controlled attenuation parameter

Introduction

Hepatic steatosis (HS) summarizes a wide spectrum of conditions characterized by triglyceride accumulation within the cytoplasm of hepatocytes. It is more frequent in patients who drink alcohol on a regular basis, but also in those who are not consumers (nonalcoholic fatty liver disease – NAFLD) [1]. In fact, HS is the primary lesion of NAFLD, which, as a consequence of the worldwide burden of visceral obesity, is now the main cause of chronic liver disease (CLD) in western countries [2].

Although HS was traditionally regarded as a relatively inconsequential physical condition, its role in the pathogenesis of various clinically important diseases has

recently been increasingly recognized [3]. HS can progress to steatohepatitis, fibrosis, even cirrhosis and hepatocellular carcinoma in some patients [4-6]. On the other hand, steatosis is a well recognized co-factor accelerating the progression of CLD [7], it reduces the likelihood of sustained virological response in patients with HCV [8] and, in patients undergoing liver resection, HS independently increases the risk of postoperative complications and death [9]. The assessment of HS plays an important role in the preoperative evaluation of liver donors for transplantation [10,11]. Especially the macrovesicular subtype is critical for donor selection, since it has been associated with a greater risk of primary nonfunction after transplantation [12,13].

HS is commonly observed in daily clinical practice and its prevalence is increasing in parallel with the pandemics of obesity and type 2 diabetes mellitus [14]. In a retrospective study performed on a hospital population of 14,009 patients, HS was found in 16.05% of cases using ultrasonography (US); steatosis was identified in 41% of all patients with diffuse liver diseases [15].

In histological terms, steatosis usually appears in the macrovesicular form and a lot less frequently in mi-

crovesicular form. The microvesicular and macrovesicular forms can also coexist. When the former is present alone, particular causes should be sought: steatosis in pregnancy, Reye's syndrome and certain drug-induced steatosis [16].

The more precise method for the detection of steatosis is the liver biopsy (LB) [17]. Compared to it, the clinical examination and laboratory tests have a rather low positive predictive value [18]. However, LB is invasive and may result in severe complications [19]. Furthermore, it is also susceptible to potential sampling errors and cannot be readily repeated for adequate patient follow-up [20,21]. Therefore, there has been increased debate on wether LB is the only accurate diagnostic method, or if it can be, at least to some extent, substituted by imaging diagnostic methods. Of these, computed tomography exposes the patient to radiation, lacks sensitivity for small amounts of fat and is susceptible to intermachine variability [22]. Proton magnetic resonance spectroscopy and magnetic resonance imaging provide high accuracy in the quantification of liver fat, but are limited by low availability, high cost and lack of standardization [23].

Ultrasonography (US) remains an accessible imaging method, without side effects and thus is potentially very useful for long-term monitorization of disease progression. Indeed, conventional B-mode US is the most common technique used to assess the presence of fatty liver in clinical settings and population studies [24].

Ultrasound diagnostic criteria for hepatic steatosis

It is very important to avoid false positive results when searching for steatosis using US, because the US aspect of steatosis is not entirely specific [16].

Primarily, the US changes in HS only become apparent at a hepatocyte fat accumulation above 15-20%. These changes include: hepatomegaly in various degrees; hyperechogenicity of the parenchyma ("bright liver") due to the high number of highly reflective interfaces produced by increased intracellular fat deposition; ultrasound attenuation in subcapsular areas; difficult visualisation of portal venules, gallbladder walls and liver capsule (because the increased liver echogenicity leads to decreased acoustic impedance between the parenchyma and the portal venule walls); the apparent dilatation of vessels (especially hepatic veins) and biliary ducts; false transonic aspect of the right kidney as compared to liver parenchyma [25,26] (fig 1).

According to some authors, the increased parenchymal echogenicity has a 0.87 positive predictive value for the steatosis diagnosis (confirmed by biopsy). When also considering the other diagnostic criteria stated above, the positive predictive value increases to 0.94 [27].
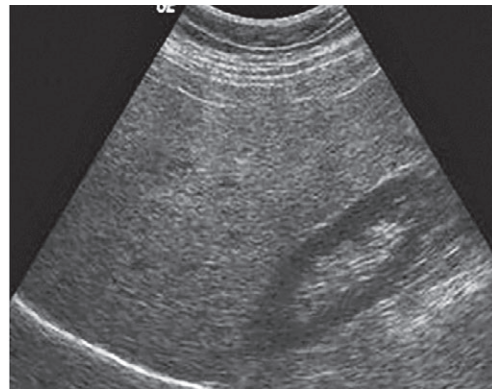

Fig 1. Liver steatosis. Hepatomegaly, hyperechogenicity of the parenchyma ("bright liver"), ultrasound attenuation in subcapsular areas, false transonic aspect of the right kidney as compared to liver parenchyma

Quantitative assessment of hepatic steatosis

The US evaluation of steatosis is mainly qualitative [28]. The qualitative grading is conveniently classified as mild, moderate or severe, or grade 0–3 with 0 being normal [29]. Grade 1 (mild) is represented by a mild diffuse increase in fine echoes in the hepatic parenchyma with normal visualisation of the diaphragm and intrahepatic vessel borders. Grade 2 (moderate) is represented by a moderate diffuse increase in fine echoes with slightly impaired visualisation of the intrahepatic vessels and diaphragm. Grade 3 (marked) is represented by a marked increase in fine echoes with poor or no visualisation of the intrahepatic vessel borders, diaphragm and posterior portion of the right lobe of the liver [30].

The US performance in detecting steatosis

Generally, it is considered that US has 60-94% sensitivity and 88-95% specificity in detecting hepatic steatosis [18]. US sensitivity decreases at lower degrees of fatty load, with 80% sensitivity at fat accumulation above 30%, as opposed to 55% when the fat content reaches only 10-19%. In addition, in morbidly obese patients US sensitivity and specificity decrease to 49% and 75% respectively [30].

In a metaanalysis including 34 studies and 2815 participants [24], the overall sensitivity of US to discriminate moderate to severe histologically defined fatty liver from the absence of steatosis was 84.8% (95% confidence interval [CI]: 79.5-88.9), the specificity was 93.6% (87.2-97.0), the positive likelihood ratio was 13.3% (6.4-27.6), the negative likelihood ratio was 0.16 (0.12-0.22),

and the summary area under the ROC curve was 0.93 (0.91-0.95).

Of the various criteria used to diagnose the presence of HS on US, the highest sensitivity and specificity for the presence of steatosis confirmed on histology is for macrovesicular steatosis ≥20% of the total liver area. With a greater area of fat deposition on histology, the sensitivity increased to 100% with only a small reduction in specificity [31].

In the study performed by Dasarathy et al [31], the hepatorenal echo contrast and liver brightness were able to identify the presence of hepatocyte fat accumulation ≥20% with a sensitivity of 96.4% and a specificity of 97.8%. The criteria for vascular attenuation had lower sensitivity and specificity (60.7% and 97.8% for portal vein blurring, respectively 92.9% and 95.6% for hepatic vein blurring). For the detection of the same amount of fat, the poor visualization of the diaphragm had 39.3% sensitivity and 93.3% specificity.

Even though the sensitivity and specificity of hepatic vein blurring was higher than that of portal vein blurring, the combination of increased hepatic echogenicity and portal vein blurring was a more accurate predictor of hepatic steatosis. This was related to the high concordance between increased echogenicity and hepatic vein blurring (97.3% agreement) so that adding hepatic vein blurring would not add any additional information. Hence, the combination of portal vein blurring and increased hepatic echogenicity was a better sonographic predictor [31].

In the metaanalysis by Hernaez et al, in studies where the accuracy of US parameters of fatty liver definition were evaluated individually, sensitivities of liver-to-kidney contrast, vessel wall brightness, and deep beam attenuation in detecting moderate to severe steatosis (histologically defined) were 98% (75%-100%), 81% (70%-89%), and 59% (45%-72%), respectively. The specificity was similar for all components (range 93%-95%) [24]. The conclusion of this metaanalysis was that US is an accurate, reliable tool to detect moderate to severe steatosis, with sensitivity and specificity of 84.8% and 93.6%, respectively [24]. On the other hand, the US performance in detecting lower steatosis grades is a lot weaker. In the study performed by Lee et al [3], US yielded low sensitivities for detecting all degrees of HS despite its relatively high sensitivities for moderate-to-severe degrees of HS. This reconfirms the results of previous studies which reported low US sensitivity in the range of 28–67% for the diagnosis of HS ≥ 3% or HS ≥5% [32,33]. In addition, US had a poor yield in the diagnosis of microvacuolar fat with an overall sensitivity of 43% and a specificity of 73% [31].

Factors influencing the US performance in detecting steatosis

In the study by Wang et al [34], the agreement rates between US and the histological findings were 74.3% in assessing the presence of steatosis and 61.4% in assessing steatosis severity. By using univariate analyses, body mass index (BMI) and necroinflamatory activity were associated with agreement between US and histology. The fibrosis score tends to influence the agreement between US and histology, almost reaching statistical significance (p=0.06). The age, sex, type of ultrasound machine and the status of viral hepatitis did not affect the agreement. By using multivariate analyses, the authors found that the fibrosis score, age and BMI were associated with agreement between US and histology. In fact, other studies had also found that several factors may affect the ability of US in diagnosing HS. For example, US in morbidly obese patients had the lowest accuracy and advanced fibrosis can reduce the sensitivity of US [30]. Regarding the relationship between age and the diagnostic accuracy of US, the possible explanation was that the aging process could change the echo texture of liver and/or kidney, and thus lead to a poor performance of US in older populations [34].

In the metaanalysis by Hernaez et al, when US was used to differentiate between the presence of histologically proven fatty liver alone and other pathological findings (such as hepatitis or fibrosis) or normal liver, the overall sensitivity was similar (87.2%; 95% CI: 77.8-93.0), but the specificity was substantially lower (79.2%; 95% CI: 72.8-84.4). Correspondingly, the positive likelihood ratio was lower (4.2; 95% CI: 3.3-5.4), but the negative likelihood ratio was unchanged (0.16; 95% CI: 0.09-0.28) [24].

Actually, liver fibrosis and inflammation may affect the diagnostic accuracy of US. A study with 118 biopsy-proven NAFLD patients found that the sensitivity of US was 100% for detecting moderate to severe histological steatosis in patients with mild histological fibrosis. However, it decreased to 77.8% in those with advanced histological fibrosis [35]. Thus, advanced fibrosis can decrease the sensitivity of US in detecting moderate to severe histological steatosis because the advanced fibrosis could cause echogenic abnormalities on US.

In the study by Dasarathy et al [31], as well as in other studies [36], US was unable to discriminate between NASH and HS. This may be related to the NASH diagnostic criteria that require histological evidence of ballooning changes [37] as well as the low diagnostic accuracy of US in diagnosing fibrosis or inflammation. These data are consistent with previous reports that US

is a sensitive method to diagnose HS, but not fibrosis or inflammation [27].

Intra- and interobserver variability in the diagnosis of HS

Intra- and interobserver variability is one of the major issues occuring in the US diagnosis of HS, since it is based on fairly subjective criteria. In the metaanalysis by Hernaez et al, the range of kappa values for intra-rater evaluation was 0.54-0.92 and for the inter-rater evaluation was 0.44-1.00 [24]. In the study by Lee et al, the performance of steatosis diagnosis through US differed quite significantly between 2 observers. For instance, for the diagnosis of hepatic steatosis ≥5%, the sensitivity, specificity, positive and negative predictive values for the 2 observers were 61.7% *vs* 53.3%, 81.2% *vs* 93.1%, 66.1% *vs* 82.1%, and 78.1% *vs* 77.1% respectively [3]. For the diagnosis of hepatic steatosis ≥30%, the differences occurred epsecially in steatose detection sensitivity. The sensitivity, specificity, positive and respectively negative predictive values for the 2 examiners were 81.8% vs 45.5%, 98% vs 98%, 75% vs 62.5%, and 98.7% vs 96.1% respectively [3]. In a retrospective US study, HS was evaluated by three independent, experienced radiologists in 168 patients and the examination was repeated one month later. The mean inter- and intra-observer agreement rates for the presence of increased liver fat were 72% and 76%. Intra-observer agreement for severity of fatty liver ranged from 55% to 68% [38]. These results reveal that the method is highly dependent on the subjective impression of the examiner.

The high observer variability in US appears to be due to its inherent subjective nature as well as to the limitation of the traditional four-point visual grading system [36]. Although the grading system is widely used for US evaluation of HS [36], it may be too simplistic as it collapses a wide range of different degrees of HS into the same grade. The grading system also exacerbates observer variability by forcing the examiner to bluntly categorize similar degrees of HS that lie around the border between two adjacent grades into either grade [3].

Doppler examination

The Doppler examination found, in 43% of steatosis patients, abnormal flow in the hepatic veins (biphasic or monophasic flow), usually found in only 2% of healthy individuals. This particularity may be explained by the compression exerted by the enlarged hepatocytes (due to fat deposition) on the hepatic veins. The difference in hepatic vein flow in steatosis patients as compared to healthy subjects is statistically significant. No correlation

was found between the degree of fatty infiltration and the flow pattern, nor between steatosis etiology and hepatic vein flow, but there is an increased tendency towards these changes in patients with hyperlipidemia [39]. A change in the hepatic vein flow may also occur in 50-73% of cirrhotic patients [40], due to the high fibrosis content leading to a decrease in parenchymal compliance.

The assessment of hepatic arteries reveals a significant decrease in the hepatic artery resistivity index in patients with severe steatosis, as compared to healthy individuals or patients with moderate steatosis [41].

Ultrasonographic models of steatosis

Steatosis may be found in various forms [42]: *diffusse, multinodular, hypersteatosis* (areas of relatively more steatotic areas of liver in patients with diffuse liver steatosis [43]), *focal geographic steatosis, focal nodular steatosis, intralesional steatosis* (in hepatic adenoma, hepatocellular carcinoma, regenerative nodules and rarely focal nodular hyperplasia [43-45]), *perilesional steatosis* (around metastases of insulinoma [42]), *subcapsular steatosis* (in patients with terminal renal illnesses and insulin-dependent diabetes mellitus under continuous peritoneal dialysis with insulin added to the peritoneal dialysate [43,46]) and *periportal and perivenular steatosis*.

Focal fatty infiltration usually appears geographic, but may be nodular and mass-like and, in this case, can result in a pseudotumor appearance (fig 2) [42,47].

Focal steatosis is characterized by more or less extensive hyperechoic areas alternating with areas of normal echogenicity. The latter (called "focal spared areas") appear falsely hypoechoic as compared with the rest of the hyperechoic parenchyma, leading to confusion with hepatic tumors.

At Doppler examination, these hypoechoic areas do not distort normal hepatic vessels and do not have the

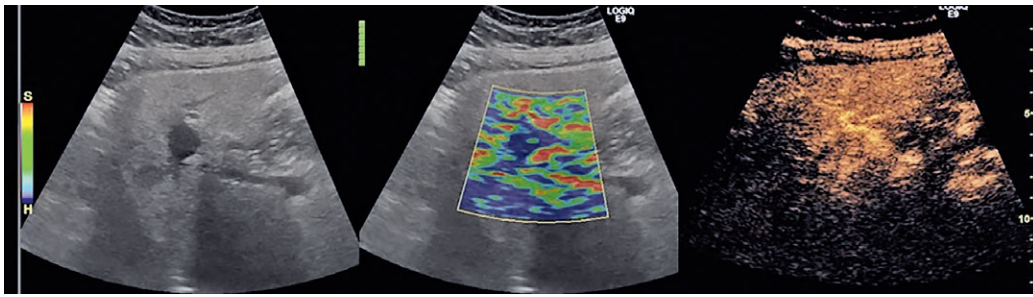**Fig 2.** Focal steatosis. Hyperechoic areas around the hepatic veins

Fig 3. Hypoechoic nodular image in a steatotic liver. The aspect suggests a sparing area in a steatotic liver or a tumoral lesion. The elastography identifies a stiff lesion. On CEUS, enhancement in the periphery of the nodule, beginning in the arterial phase, with centripetal progression of the contrast agent, tipical for a hemangioma. Final diagnosis: hemangioma in a steatotic liver.
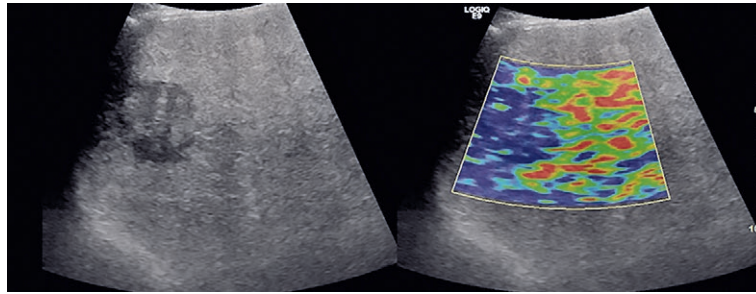

Fig 4. Round, hypoechoic, inhomogeneous image, with some echos within, located in a steatotic liver, investigated for the etiology. The structure appears on elastography to have significant stiffness.The final diagnosis was metastasis in a steatotic liver
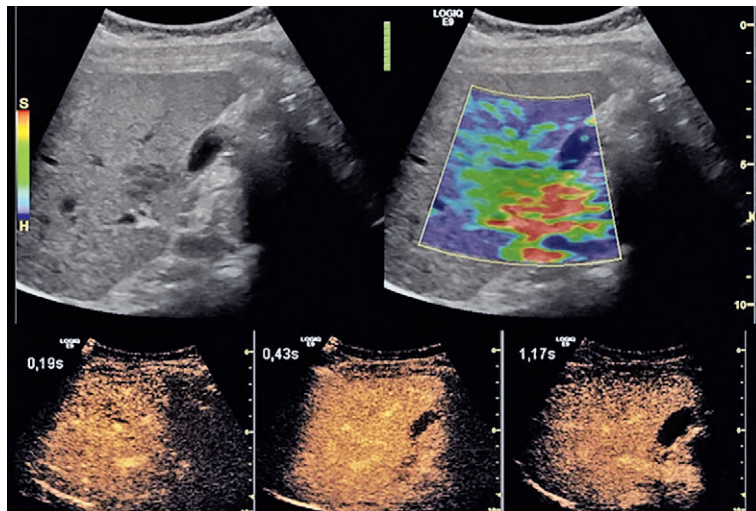

Fig 5. Focal sparing area in front of the portal vein. Hypoechoic image located anteriorly from the portal vein. The structure appears on elastography to have medium stiffness. On CEUS, the enhancement was homogeneous during the arterial, portal and parenchymal phases, without any apparent focal lesions.
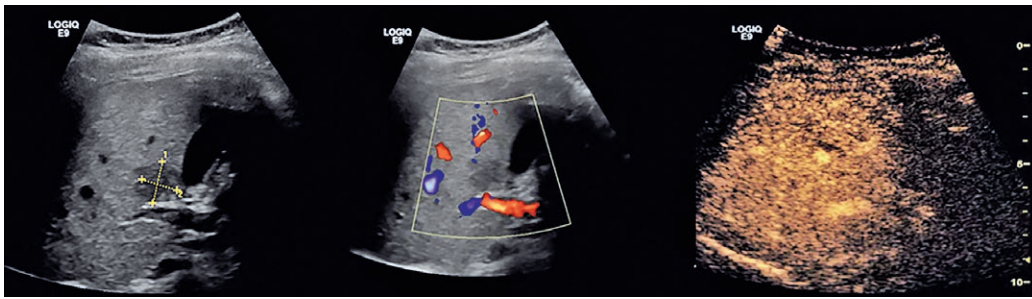
Fig 6. Focal sparing in the pericholecystic region. Hypoechoic image located around the galbladder in a steatotic liver. The Doppler examination cannot reveal any vessels within the lesion. On CEUS, the enhancement was homogeneous during the arterial, portal and parenchymal phases, without any apparent focal lesions.

hypervascular aspect of neoplastic tumors. Nevertheless, a clear differentiation from tumors is often difficult, requiring contrast enhanced US (CEUS), CT, MRI or even US-guided needdle biopsy [1] (fig 3, fig 4).

There are several types of hepatic fatty sparing: focal geographic sparing, focal nodular sparing, focal segmental or lobar sparing, perilesional sparing [42].

The fat-spared areas are most often found in the gallbladder bed and in the hepatic hilum, anteriorly from the portal vein bifurcation [48], but they can also be located around or distally from a tumor, due to the decrease in portal flow, arterio-portal shunts, hepatic venule compression around the tumor and/or the direct drainage of the arterial flow from the tumor in the neighbouring parenchyma [49] (fig 5).

In patients with a steatotic liver, Aubin et al [50] showed that usually fatty sparing occurs in segments IV and V, surrounding the gallbladder (fig 6); this situation was found more frequently in patients who still had their gallbladder (78%) than in cholecystectomised patients (33%). The authors suggested a venous explanation, as there are almost always small cystic veins that drain directly into the liver and which are severed during cholecystectomy [16]

The pathophysiological explanation for the particular locations of these types of steatosis or focal sparing was supported by a theory concerning insulin, which stimulates the conversion of glucose to fatty acids [16]. About 30% of the vascular supply to the liver comes from the hepatic artery and about 70% from the hepatic portal vein. The insulin content of the tributaries of the hepatic portal vein is very variable. Left, or more frequently right gastric veins drain directly into the liver (mainly into segment IV), lowering the insulin concentration in that particular area which becomes a focal area of hepatic parenchyma which is less fatty than the rest of the liver, although the rest of the parenchyma is steatotic. Similarly, the superior branch of the pancreaticoduodenal arcade may drain not into the portal vein itself,
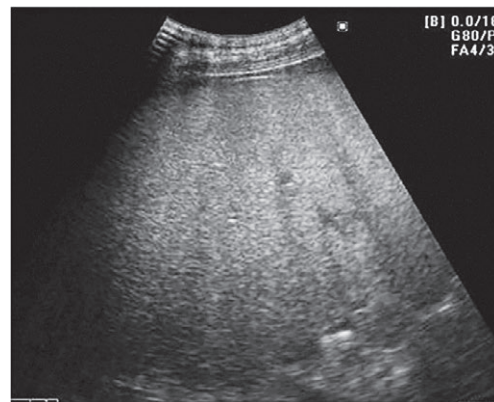

Fig 7. Liver with slightly higher echogenicity and moderate posterior attenuation, slightly inhomogeneous, without any focal lesions. On such an image the steatosis severity and the possible presence of fibrosis cannot be ascertained. The present image is usually described as „steatofibrosis".

but directly into the liver near the hilum, so that a localized area receives more insulin, increasing its fat content [16].

The increased echogenicity of the steatotic parenchyma may mask small hypo- or isoechoic tumors; this fact has the utmost importance especially during US check-ups in search of metastases in patients undergoing chemotherapy (certain chemotherapics may also induce steatosis) [51].

The limitations of ultrasonography in diagnosing hepatic steatosis

US has some limitations in diagnosing hepatic steatosis. The method cannot:
- differentiate between steatosis and steatohepatitis;
- establish with certainty the degree of fatty infiltration;
- differentiate between steatosis and other diffuse liver diseases characterized by increased echogenici-

ty [52, 53]. Of note, steatosis and fibrosis may have the same echographic appearance; for this reason, some authors use the term "steatofibrosis" in order to define the image obtained [18] (fig 7).

- always identify the spared or focal steatosis areas from hepatic focal lesions. In these cases, other imaging techniques (CEUS, CT, MRI) or even liver biopsy should be used.

Optimization of the usual ultrasonographic examination through computerized processing of the US image

One of the major problems of the usual US examination is the inability to differentiate between steatosis and fibrosis. Although they have a different pathologic basis, the main obstacle in discriminating between them is the lack of marked visual differences on the US image [54]. Attempts have been made to find ways of differentiating steatosis from fibrosis on the US image; some authors claim that only the fatty content increases the attenuation on the US image of cirrhosis patients [52], while others suggest that, in vitro, fibrosis also causes attenuation, but only half as much as fat [55]. Fibrosis may also be distinguished from fat by the "rougher" US texture it induces, as well as by the more definite outlining of the portal vein [18,33,56]. All these are, however, visual criteria, which depend upon the subjective interpretation of the examiner, limiting the reproducibility of the method and possibly leading to diagnostic errors. For these reasons, research is made to optimize the usual US image through the computerized analysis of the data making up the image.

The computerized processsing is based on the principle according to which the tissular changes occuring in some diseases (steatosis, chronic hepatitis, cirrhosis) induce physical and microarchitectural alterations (in density, viscosity, elasticity, homogeneity etc); these changes, although difficult to perceive visually, alter the propagation of ultrasounds and can therefore be identified through complex image analysis (ultrasonographic tissue characterization), as different from the normal texture pattern [57].

US tissue characterization may be performed through methods based on either the study of parenchymal echogenicity and ultrasound attenuation, or the quantification of textural parameters [57-60].

The majority of the studies used as a method for US image optimization the calculation of „the sonographic hepatorenal index" (SHRI). The SHRI is the mean liver brightness divided by the mean renal cortex brightness. An image including both liver and kidney is required, typically showing segment VI of the liver and the upper
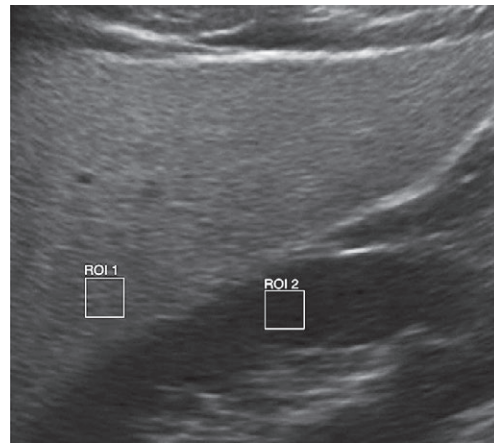

Fig 8. Quantification of echo intensity. Principle of the sonographic hepatorenal index. ROIs are placed over the liver parenchyma and renal cortex at the same depth. Mean echo intensities are determined on a standard US image. SHRI is calculated by dividing the mean liver brightness by the mean renal cortex brightness

pole of the right kidney [29]. Regions of interest (ROI) are selected in the liver parenchyma, excluding vessels, and in the renal cortex at the same field depth. The mean brightness of each ROI is determined using numerical values assigned to grey-scale pixels [29] (fig 8). Some ultrasound systems allow the placement of ROIs directly on the screen. Alternatively, a suitable image can be exported and ROIs placed using proprietary software or public domain programmes. Significant correlation between histological steatosis and the SHRI has been found in several studies. In addition, point estimates of SHRI for the prediction of steatosis grades less than moderate or severe appear to be superior to those of qualitative grading methods [29]. The sensitivity and specificity of SHRI varied in some studies between 93-100% and 54-93% respectively [61-63].

The major limitation of this approach is the use of a reference system (kidney), whose echogenicity may also be altered by intrinsic illnesses. On the other hand, the parameter to be quantified in these cases is liver echogenicity and, respectively, kidney echogenicity. Since the hepatic echogenicity is not only the result of steatosis, but also of superimposed fibrosis, an altered renal parenchymal echotexture with renal parenchymal disorders may affect in this case US evaluations of the liver [28]. Moreover, the presence of hepatic fibrosis in some patients makes the linear correlation between fatty infiltration and liver echogenicity unreliable [27].

Another approach would involve the ultrasound attenuation coefficient calculated in the US image [57,64]. In a group of biopsied patients with hepatitis C infection,

this coefficient was independently influenced only by steatosis, not by fibrosis or inflammation, and predicted mild steatosis and respectively moderate/severe steatosis with an AUROC of 0.734 and 0.842, respectively [64].

Noninvasive evaluation of liver steatosis using the Controlled Attenuation Parameter (CAP)

Knowing that fat interferes with ultrasound propagation, a novel attenuation parameter has been developed to detect and quantify liver steatosis. It is called the controlled attenuation parameter (CAP). This ultrasonic attenuation coefficient is an estimate of the total ultrasonic attenuation (go-and-return path) at the central frequency of the regular or M Fibroscan® probe, and is expressed in dB/m. CAP is evaluated using the same radio-frequency data and the same region of interest, as the region used to assess the liver stiffness for fibrosis prediction [65-67].

In a recent meta-analysis [68] assessing the CAP accuracy for steatosis detection, the summarized sensitivity and specificity values were 0.78 (95% confidence interval [CI], 0.69–0.84) and 0.79 (95% CI, 0.68–0.86) for steatosis involving <10% of hepatocytes, 0.85 (95% CI, 0.74–0.92) and 0.79 (95% CI, 0.71–0.85) for 11-33% fatty load, and 0.83 (95% CI, 0.76–0.89) and 0.79 (95% CI, 0.68–0.87) for 67-100% fatty load. The median optimal cut-off value of CAP was 232.5 dB/m, and the values ranged from 214–289 dB/m (for<10% fatty load), 255 dB/m, with a range of 233–311 dB/m (for 11-33% fatty load), respectively 290 dB/m, with a range of 266–318 dB/m (for 67-100% fatty load).

In comparison to other modalities, CAP is non-invasive, quantitative, and non-ionising. Furthermore, the procedure is easy to perform and provides immediate results; it is also machine-independent and does not require corrections to be made for gain, frequency, focusing or beam diffraction, and is also not subject to operator interpretation [65]. Compared to a liver biopsy, CAP is less prone to sampling error as it explores a liver volume ≈100 times larger [66]. CAP can be performed simultaneously to liver stiffness measurement and in the same liver volume, making possible the simultaneous evaluation of both fibrosis and steatosis [69].

However, other prospective studies are mandatory before recommending this technique and the proposed cut-offs for the prediction of steatosis grades.

In conclusion, ultrasonography is an established tool used as a screening modality with acceptable sensitivity and specificity in detecting fatty liver. Nevertheless, the drawbacks of this technique include its inaccuracy in differentiating fibrosis from steatosis, in reproducibility and in the exact quantification of fat accumulation. Using the computerized analysis of US images and especially the new elastographic techniques seem to increase the performance of steatosis detection using ultrasounds.

Conflict of interest: none

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