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Editorial

Usefulness of ultrasonography for the diagnosis of difuse liver disease

Liver cirrhosis represents the end stage of chronic liver disease and a serious public health concern with some 800,000 deaths worldwide each year (1). It is histologically defined by the presence of diffuse changes in liver architecture by fibrosis and regeneration nodules, which together with intrahepatic vascular distortion and reduced functioning mass lead to portal hypertension and hepatocellular insufficiency. The term "silent or compensated cirrhosis" is used when the disease has not developed any major complications: ascites, digestive bleeding, jaundice or hepatic encephalopathy. Therefore, the diagnosis of chronic liver disease in cirrhotic stage implies a change in its management and prognosis, as these patients must be monitored more closely, including screening for esophageal varices and hepatocarcinoma, and receive specific therapeutic measures to prevent disease progression (2).

Liver biopsy is the diagnostic procedure of choice to define chronic liver disease stage (3). However, it is a technique that is scarcely accepted by patients, requires hospitalization, may result in complications (morbidity, 3%; mortality, 0.03%), and plays no role during follow-up. In addition, biopsy interpretation is limited by intrapersonal and interpersonal variability according to training, dedication, and particularly biopsy size, as well as sampling errors, which subestimate cirrhosis in one third of patients (4-6).

All these data sparked interest in the development of non-invasive methods to detect liver cirrhosis by using biochemical tests and/or imaging techniques such as ultrasonography. These procedures would be crucial for the screening of cirrhotic-stage chronic liver disease, and could obviate the need for liver biopsy in its diagnosis. Currently, around 25% of patients undergoing liver biopsy for sustained hypertransaminasemia already have thus far unsuspected cirrhosis.

Conventional ultrasonography is considered a first-line imaging technique for the initial assessment of patients with suspected or established liver disease, and/or the monitoring of diffuse liver disease and its complications given its harmlessness, low cost, accessibility, and diagnostic performance. Few studies have examined the usefulness of ultrasounds for the prediction of liver cirrhosis in patients with no signs of advanced disease using a proper strategy (7-10). In contrast, the sonographic diagnosis of decompensated cirrhosis is relatively straightforward because of a wide, well-defined echographic semiologyv (11). Edge nodularity, parenchymal echogenicity changes, and altered liver morphology —particularly caudate lobe size (12,13)— represent direct evidence for the diagnosis of liver cirrhosis using gray-scale ultrasounds; however, none of these signs in isolation may be considered enough for a definite diagnosis. Moreover, subjectivity in the assessment of border and parenchymal changes turn sonography into a technique highly dependent on operator skills and equipment quality. Therefore, verifying the procedure's repro-

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ducibility using clinical validation trials, if possible by different work teams and echographers, is essential. Several reports in the literature have tried to find combinations of sonographic parameters to improve the efficacy of ultrasounds in the diagnosis of liver cirrhosis, including portal hypertension signs, but no consensus exists as of today. The 2001 Interactive Table for Consensus of Asociación Española de Ecografía suggested that two of the three direct signs should be required for a sonographic diagnosis "suggestive of cirrhosis", and that the term 'liver cirrhosis pattern' should be reserved for cases with all three direct signs and/or unequivocal evidence for portal hypertension (14).

The study by Macías et al. (15) reported in this issue of *Revista Española de Enfermedades Digestivas* validates, compares, and demonstrates the usefulness and applicability of two sonographic diagnostic models for unsuspected liver cirrhosis in patients with chronic liver disease of varying etiology using liver biopsy as gold standard: the Bologna and Cadiz scales. The Cadiz scale, defined by this same team in 2003 following the analysis of all 18 sonographic variables known to be associated with liver cirrhosis (including Bologna variables), may diagnose cirrhosis with an accuracy of 89% by using a model made up with liver echostructure, portal caliber, and splenic area (10). In turn, the Bologna scale obtained a diagnostic accuracy of 80% by combining reduce portal flow velocity and liver surface irregularity (9).

On analyzing the validity of all five sonographic variables included in the diagnostic models for silent liver cirrhosis they find that: a) the most robust echographic sign is liver border assessment; b) liver border assessment, parenchymal changes, and portal vein caliber are highly specific parameters -98%, 98%, and 88%, respectively; c) spleen size is a sonographic sign with poor sensitivity and specificity; and d) portal velocity is a useless parameter.

As in other studies, liver edge nodularity has moderate sensitivity (72%) and high specificity (98%) for the diagnosis of compensated liver cirrhosis. Liver border assessment is a simple technique that provides a high positive predictive value (PPV) and should therefore be accurate in identifying patients with a high probability of advanced fibrosis or cirrhosis while avoiding the risks of liver biopsy. In general, false negative results derive from micronodular cirrhosis, use of low-frequency transducers, and explorer subjectivity, whereas false positive results are due to liver tumors or diffuse nodular hyperplasia (16-20). Berzigotti et al. have recently demonstrated that the use of high-frequency transducers together with the objective measurement of 2-cm linear segment on the surface of the liver's left lobe may reduce the number of uncertain cases (irregular borders) and increase accuracy and reproducibility (21).

A cirrhotic liver has parenchymal changes because of fibrosis that result in an heterogeneous sonographic pattern with predominant large-grain hyperechogenicity. These changes have a low diagnostic sensitivity and accuracy because of their subjectivity, but a specificity of 98% and a very low number of false positive findings, likely due to liver steatosis.

Increased portal caliber is a most important sign for the diagnosis of portal hypertension. In this study it was a highly specific though scarcely sensitive parameter in detecting silent liver cirrhosis.

Splenomegaly is considered a highly applicable, indirect sign of portal hypertension that occurs in 30% to 90% of cirrhotic patients; such disparity is primarily due to the measurement strategy used to assess spleen size. This group has a sensitivity of 63% and a specificity of 84% for the diagnosis of compensated cirrhosis using 12 cm and 50 cm^2 as diameter and longitudinal area upper limits, respectively (11).

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Reduced portal flow velocity is a common finding in advanced cirrhosis, though inconsistent in early stages. In this study portal velocity (a variable used by the Bologna scale) does not allow a differentiation of cirrhotic patients, which reveals that reproducibility limits the value of Doppler studies as non-invasive strategy for the diagnosis of chronic liver disease severity.

When assessing the usefulness of sonographic models for the diagnosis of unsuspected liver cirrhosis, the Cadiz scale has greater accuracy and specificity, and the same sensitivity when compared to the Bologna scale, but these differences are non-significant (AUC: 0.92; sp: 89.8%; s: 84% *vs.* AUC: 0.86; sp: 79.5%; s: 84%, respectively). Interestingly, the combined use of both scales does not improve accuracy but does increase specificity to 97% with a PPV of 96%, very useful for the diagnosis in a population at risk (sustained hypertransaminasemia). Importantly, liver edge assessment alone offers a higher accuracy versus the Bologna scale in predicting cirrhosis, and its specificity and PPV are better than those provided by both scales whether alone or combined (we do not know whether these differences are significant).

This study also questions the role of liver biopsy as the gold standard for the diagnosis of liver cirrhosis since one third of false positive patients with ultrasounds exhibit portal hypertension during short-term follow-up, meaning a substaging of disease using liver biopsy.

In recent years new technologies have been developed that once applied to sonography have rekindled the interest of researchers in this technique, with multiple studies performed that had an impact on the clinical management of chronic diffuse liver disease. Most relevant sonography advancements no doubt included the possibility of measuring liver rigidity to estimate fibrosis extent, and the study of liver perfusion using contrast-enhanced ultrasounds.

Transient elastography (TE) (FibroScan®, Echosens, Paris, France) is based on the use of ultrasounds (5 MHz) and low-frequency, low-amplitude elastic waves (50 Hz) whose propagation velocity is directly related to tissue elasticity (22): the faster the propagation speed, the lower the tissue elasticity. FibroScan® measures a liver cylinder 1 cm. in diameter and 2 cm in length (which represents a sample 100 times greater than that obtained with biopsy collection), and is user-friendly, reproducible, and comfortable for patients. However, it has some limitations: a) in obese patients the adipose tissue severely attenuates both the friction wave and ultrasounds; b) the exam is operator-dependent; and c) velocity is not consistent throughout the parenchyma, and this may reveal heterogeneity in fibrosis distribution o a faulty procedure. TE has proven useful in the diagnosis of liver cirrhosis of any etiology and its complications, since liver rigidity correlates with fibrosis stage and portal pressure level, respectively (23,24). While the combined assessment of liver border nodularity using high-resolution ultrasonography and liver elasticity using FibroScan® has been seen to be better than either technique alone in detecting liver cirrhosis, further studies are needed to compare gray-scale accuracy with FibroScan® in the diagnosis of compensated liver cirrhosis (21).

Acoustic radiation force impulse (ARFI) imaging is a new technique for the measurement of liver elasticity with the advantage of being integrated in a conventional echograph (Acuson 2000®, Virtual Touch Quantification mode, Siemens Medical Solutions, Mountain View, Ca, USA); it may avoid structure interferences (e.g. intrahepatic vessels) by allowing the user to select the region to be studied. In preliminary studies it offers results similar to those obtained with FibroScan® (25).

Contrast-enhanced sonography, in turn, has proven not only capable of bedside diagnosing hepatocarcinoma within a cirrhotic liver, but late-stage parenchymal en-

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hancement (using Levovist®) and/or the time taken by the contrast to reach the suprahepatic veins are also associated with liver fibrosis severity (26).

In conclusion, advances in ultrasound imaging techniques are likely to allow cirrhosis identification as interpreted from liver biopsy in the near future. Today, assessing the combined usefulness of non-invasive methods in the diagnosis of liver cirrhosis seems a reasonable option: biochemical markers, conventional sonography, and elastography. However, further research is needed as they all require greater predictive accuracy.

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