A common characteristic of all chronic liver diseases is the occurrence and progression of fibrosis toward cirrhosis. Consequently, liver fibrosis assessment plays an important role in hepatology. Besides its importance for prognosis, determining the level of fibrosis reveals the natural history of the disease and the risk factors associated with its progression, to guide the antifibrotic action of different treatments. Currently, in clinical practice, there are three available methods for the evaluation of liver fibrosis: liver biopsy, which is still considered to be the ‘gold standard’; serological markers of fibrosis and their mathematical combination – suggested in recent years to be an alternative to liver biopsy – and, more recently, transient elastography (TE). TE is a new, simple and noninvasive method used to measure liver stiffness. This technique is based on the propagating speed of an elastic shear wave within the liver. Currently, there are only a few studies that have evaluated TE effectiveness in chronic liver diseases, mostly in patients infected with the hepatitis C virus. Further studies are needed in patients with chronic liver disease, to assess the effectiveness of the fibrosis treatment.

Key Words: HCV; Hepatic fibrosis; Liver biopsy; Transient elastography

In 1958, Menghini (1) published the first description of liver biopsy (LB) as it pertained to the study of fibrosis. Since then, LB has become the gold standard in the evaluation of liver fibrosis. However, the use of LB has several limitations, including physical and mental discomfort of patients, which may lead to a high percentage of refusals, nonnegligible morbidity and occasional mortality (2). Fibrosis is evaluated by histological semiquantitative scores, among which the META VIR fibrosis scoring system is the most used (3); it is able to detect different degrees of fibrosis, from absence of fibrosis (F0) to cirrhosis (F4), and shows a better intra- and interobserver reproducibility than other scales (ie, the Knodell, Ishak and Scheuer scales). Histological fibrosis scores do not provide a dynamic picture of the disease, but only information about the diagnosis and prognosis, such as the necroinflammatory activity and the presence of steatosis. Moreover, these scores do not have the power to assess small changes in the degree of liver fibrosis (eg, in the course of an antiviral treatment). This technique is the power to assess small changes in the degree of liver fibrosis and prognosis, such as the necroinflammatory activity and the presence of steatosis. However, in clinical practice, there are three available methods for the evaluation of liver fibrosis: liver biopsy, which is still considered to be the ‘gold standard’; serological markers of fibrosis and their mathematical combination – suggested in recent years to be an alternative to liver biopsy – and, more recently, transient elastography (TE). TE is a new, simple and noninvasive method used to measure liver stiffness. This technique is based on the propagating speed of an elastic shear wave within the liver. Currently, there are only a few studies that have evaluated TE effectiveness in chronic liver diseases, mostly in patients infected with the hepatitis C virus. Further studies are needed in patients with chronic liver disease, to assess the effectiveness of the fibrosis treatment.

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Finally, its accuracy in assessing fibrosis is questionable because the reproducibility is poor due to sampling errors, and even in cases of adequately sized specimens, intra- and interobserver discrepancies are found (3-5). In recent years, many research groups have been working to develop noninvasive methods that are capable of detecting and quantifying liver fibrosis. As a result, different biochemical markers of fibrosis, along with their mathematical combinations, have been described in the literature, in particular for chronic hepatitis C virus (HCV) infections (6). More recently, the assessment of liver fibrosis by a noninvasive method based on physical measurements, called transient elastography (TE) (FibroScan, Echosens, France), has been proposed (7).

ELASTICITY MEASUREMENT

Elasticity is defined as the ability of a material to deform under the action of a mechanical force. The elasticity of a tissue can be estimated based on the speed of propagation of a transverse shear elastic wave. The higher the speed of propagation of that wave, the higher the stiffness of the tissue. TE measures the speed of propagation in relatively homogenous organs such as...
correlated with the degree of hepatic fibrosis. Ziol et al (9) patients with HCV infection shows that elasticity is directly

The statistical analysis of data obtained in large studies on centres, but it is now becoming more common.

When first developed, TE was used in only a small number of (META VIR score F0 and F1) and cirrhosis (F4) (Table 1) (9).

performances for the detection of low-degree liver fibrosis patients with chronic HCV infection, with good diagnostic

Elasticity depends mostly on the degree of liver fibrosis, while

intercostal spaces considered to be limiting factors (7,8).

The measurement failure rate is between (7). Ten acquisitions are considered necessary, with the rate of unsuccessful percentage required to accept such a measurement (7). A panel discussion is in progress to define the number of acquisitions to determine a measurement and the successful percentage required to accept such a measurement (7). Ten acquisitions are considered necessary, with the rate of valid measurements always higher than 50%. The intra- and interobserver coefficients of variation are 3.2% and 3.3%, respectively, indicating very good reproducibility and operator independence (7). The measurement failure rate is between 5% and 10%, with obesity, ascites or the presence of narrow intercostal spaces considered to be limiting factors (7,8).

Elasticity depends mostly on the degree of liver fibrosis, while steatosis and inflammatory activity take on a marginal role in the absence of fibrosis and cirrhosis. Not influenced by extrahepatic diseases Correlated with fibrosis area

the liver by using ultrasound pulses to localize the shear elastic wave at different times (7). The measuring device is equipped with a probe consisting of an ultrasonic transducer mounted on the axis of a vibrator. A low-frequency and mild amplitude vibration is transmitted from the vibrator to the tissue by the transducer itself. This vibration induces an elastic shear wave that propagates through the tissue. In the meantime, ultrasound acquisitions are performed to follow the propagation of the shear wave (7). The propagation speed is defined by the Young modulus and expressed in kilopascals. The probe is applied perpendicularly to the skin (with a small amount of gel film) through one of the right-side intercostal spaces along the midaxillary line. The measurement of the speed is taken along a cylinder of tissue ranging from 25 mm to 65 mm of depth under the skin. This corresponds to a volume of liver tissue approximately 100 times larger than that of a LB specimen and represents approximately 1% of the total organ volume. The examination is noninvasive and can be performed on ambulatory patients in an outpatient setting or at the bedside of a hospitalized patient. TE can be performed by hepatologists or medical staff (physician, resident, medical student or nurse) after a single training session provided by a certified trainer.

Results of the measurements range from 1.3 kPa to 75.4 kPa (7). A panel discussion is in progress to define the number of necessary acquisitions to determine a measurement and the successful percentage required to accept such a measurement (7). Ten acquisitions are considered necessary, with the rate of valid measurements always higher than 50%. The intra- and interobserver coefficients of variation are 3.2% and 3.3%, respectively, indicating very good reproducibility and operator independence (7). The measurement failure rate is between 5% and 10%, with obesity, ascites or the presence of narrow intercostal spaces considered to be limiting factors (7,8).

ELASTOGRAPHY FOR CHRONIC HCV INFECTION ASSESSMENT

The statistical analysis of data obtained in large studies on patients with HCV infection shows that elasticity is directly correlated with the degree of hepatic fibrosis. Ziol et al (9) compared TE with LB in 327 patients with HCV. Based on their chosen trade-offs between sensitivity and specificity, they proposed 8.8 kPa as a cut-off point for a fibrosis score equal to or greater than F2 and 14.6 kPa for cirrhosis (Table 2). The areas under the receiver operating characteristic (ROC) curve were 0.79 (95% CI 0.73 to 0.84) for F2, 0.91 (95% CI 0.87 to 0.96) for F3, and 0.97 (95% CI 0.93 to 1) for F4. A study by Castera et al (10) evaluated the performance of TE in patients with chronic HCV infection, in comparison to and combined with currently available biochemical markers (FibroTest [BioPredictive, France] and the aspartate transaminase in the platelets ratio index [APRI]). LBs were performed on the same day as a reference. The TE and FibroTest diagnostic values were very similar and only slightly better than the APRI score. The detected cut-offs were similar to those described by Ziol et al (9) with 7.2 kPa for F2 and 12.5 kPa for cirrhosis (F4). The best performance was obtained by combining TE and FibroTest, with areas under the ROC curve of 0.88 (95% CI 0.82 to 0.92) for F2, 0.95 for F3 (95% CI 0.91 to 0.97) and 0.95 for F=4 (95% CI 0.91 to 0.97) (Table 2). An Italian study (11) compared LB, biochemical markers of fibrosis and TE in 40 HCV-infected patients with normal transaminases. The conclusion of that study was that among HCV carriers with normal transaminases, TE was better than FibroTest for the noninvasive detection of fibrosis. Moreover, TE can monitor fibrosis progression in HCV-infected patients subjected to antiviral treatments. Preliminary data from a group of 211 patients treated with pegylated interferon and ribavirin (12) show an important reduction in the elastography values, affirming the antifibrotic action of the therapy, and correlating with the sustained virological
response. Recently, Carrion et al (13) evaluated the prospective diagnostic accuracy of TE to assess the severity of HCV recurrence after liver transplantation in 124 patients. In that cohort, 169 liver biopsies and 129 hepatic hemodynamic studies were performed to determine the hepatic venous pressure gradient (HVPG). At the same time, patients underwent TE. Liver fibrosis turned out to be mild (F2 to F3) in 96 cases and significant (F2 to F4) in 73 cases. HVPG turned out to be normal (less than 6 mmHg) in 69 cases and elevated (greater than or equal to 6 mmHg) in 60 (46%). Using a liver stiffness cut-off value of 8.5 kPa for the diagnosis of fibrosis, F2 sensitivity, specificity, negative predictive value and positive predictive value were 90%, 81%, 79% and 92%, respectively. Areas under the ROC curve for diagnosis of fibrosis greater than or equal to F2, greater than or equal to F3 and equal to F4 were 0.90, 0.93 and 0.98, respectively. There was a close direct correlation between liver stiffness and HVPG, and the area under the ROC curve for diagnosis of portal hypertension was 0.93. Finally, none of the cases with liver stiffness below the cut-off value showed either bridging fibrosis (F3), cirrhosis (F4) or significant portal hypertension (HVPG greater than or equal to 10 mmHg). The authors concluded that TE is an extremely valuable tool to assess the severity of HCV recurrence after liver transplantation and reduces the need for follow-up LBs.

OTHER LIVER DISEASES

Foucher et al (14) evaluated the accuracy of TE in detecting cirrhosis in 711 patients with chronic liver diseases of various etiologies. The results of that study redefined the elastometric cut-off for the diagnosis of hepatic fibrosis stage and, in particular, for the diagnosis of cirrhosis (Table 2). In the same study, the authors identified that the cut-off directly correlated with the presence of complications in cirrhosis; in particular, esophageal varices stage 2 and 3 (27.5 kPa), Child-Pugh B and C cirrhosis (37.5 kPa), past history of ascites (49.1 kPa), hepatocellular carcinoma (53.7 kPa) and variceal bleeding (62.7 kPa). Those data and, in particular, the ability to detect esophageal varices in cirrhotic patients was subsequently confirmed by Kazemi et al (15). In that study, the authors focused on the TE cut-off value for the presence of esophageal varices. One hundred forty patients with cirrhosis underwent both an esophageal endoscopy and a FibroScan trial. They determined that hepatic elasticity values under 20 kPa predicted the absence of second- and third-degree esophageal varices and gastric fundal varices, with a negative predictive value of 99%, which would thus avoid the use of esophagogastroduodenoscopy in 50% of cases.

The difference in elastometric cut-off for cirrhosis diagnosis reported in the studies by Ziol et al (9), Castera et al (10) and Foucher et al (14) depends on the variability of the study population. Based on an analysis of the data present in the literature, we determined that variations in elastographic cut-off depended on the different liver diseases considered and, consequently, on the different pathological mechanisms that produce the fibrosis. A French multicentre study (16) performed in patients suffering from chronic hepatitis B virus infection reported that the TE accuracy in measuring the fibrosis stage and detecting the presence of cirrhosis was not significantly different from that obtained in patients with chronic HCV. In particular, the area under the ROC curve was 0.81 (95% CI 0.74 to 0.86) for F2, 0.92 (95% CI 0.86 to 0.95) and 0.90 (95% CI 0.81 to 0.91) for F=4. A study of 245 patients referred to an outpatient alcohol clinic, described a cirrhosis diagnosis value of 13 kPa (17). That study confirmed the TE effectiveness for the diagnosis of cirrhosis; however, it did not confirm the effectiveness of the technique in screening for hepatic fibrosis in very heavy drinkers. In a prospective study, De Ledinghen et al (18) evaluated liver stiffness measurement using TE in 72 HIV-HCV coinfected patients and compared it with other noninvasive methods. In that study, the area under the ROC curve was 0.72 (95% CI 0.60 to 0.84) for F2 and 0.97 (95% CI 0.94 to 1.0) for cirrhosis. For the diagnosis of cirrhosis, the optimal cut-off value of liver stiffness was 11.8 kPa. Moreover, the study reported the superiority of TE relative to the ratio of aspartate aminotransferase to alanine aminotransferase and relative to the APRI score for a noninvasive diagnosis of virus-related hepatic fibrosis. The authors concluded that liver stiffness measurement is a promising noninvasive method to assess fibrosis in HIV-infected patients with chronic HCV infection. Recently, our research group evaluated TE in cholestatic liver diseases (19), particularly in primary biliary cirrhosis (51 patients) and primitive sclerosing cholangitis (21 patients), detecting the cut-off value to be 7.3 kPa for F2, 9.8 kPa for F=3 and 17.3 kPa for F=4 (Table 2). The area under the ROC curve was 0.92 (95% CI 0.87 to 0.98) for F2, 0.95 (95% CI 0.91 to 0.99) for F=3 and 0.96 (95% CI 0.93 to 1) for F=4. These cut-offs were similar to the values described in studies that focused on viral diseases (9,10) and with different etiologies (14) for fibrosis stages F2 and F=3. However, regarding cirrhosis (F=4), the cut-off reported in our study is more relevant to the other papers, like in the Foucher et al paper (14). Recently, Ganne-Carrie et al (20) evaluated TE accuracy in detecting cirrhosis in 1257 patients with chronic liver diseases of various etiologies, who were enrolled in a prospective multicentre study. Two hundred fifty patients were excluded because of unsuitable biopsy specimens (132 patients) and unreliable TE measurement (118 patients). Because the study overlapped with a previous one (9), the analysis was performed on 775 new patients, including 120 who were suffering from cirrhosis. The ROC curve analysis was used to assess the diagnostic accuracy. The area under the ROC curve was 0.95 (95% CI 0.93 to 0.96) in the whole population. The optimal cut-off for the diagnosis of cirrhosis was 14.6 kPa (positive and negative predictive values were 74% and 96%, respectively), with discrepancies among the etiological groups. This result, compared with other studies, suggests that the cut-off values for the diagnosis of cirrhosis is specific for each etiological group. It can be assumed that this difference is a consequence of discrepancies in fibrosis lesions in different diseases.

TE was performed in 104 children with chronic liver disease, including infants younger than six months of age with a good performance compared with LB (21). The area under the ROC curve was 0.91 (95% CI 0.79 to 1.0) for F2 and 0.88 (95% CI 0.75 to 1.0) for F=4. These data are important in the follow-up of children with chronic liver disease to avoid repeated LBs.

Finally, Laharie et al (22) evaluated liver fibrosis with TE and other noninvasive biochemical methods (FibroTest, APRI and hyaluronate) in 54 Crohn’s disease patients treated with methotrexate. Two subgroups of patients were compared: a cumulative dose of methotrexate of more than 1500 mg and methotrexate-naïve. Average TE values were similar in the two groups (5.5 kPa and 4.5 kPa, respectively). No significant
correlation was observed between TE, FibroTest, APRI and hyaluronic values and the cumulative dose of methotrexate. The authors concluded that TE is a reliable, noninvasive method to detect liver fibrosis and could be recommended for such patients.

CONCLUSIONS
TE is a new, rapid and noninvasive method of fibrosis assessment that offers specialists a new way of supervising patients who are suffering from chronic liver diseases (6,18). TE provides a quantitative operator-independent measurement of liver stiffness. The best known contributor to liver stiffness is the amount of fibrosis; however, recent findings suggest that inflammation, interstitial fluid and even vascular conditions can have an impact on the stiffness measurement obtained by TE. Thus, TE has the potential to provide much more information than just an assessment of fibrosis, and specialists must put the elastographic results in perspective with the rest of their clinical findings. In clinical practice, high TE values may be accurate when assessing the severity of liver disease, detecting the presence of complications and, consequently, providing a follow-up program. In particular, TE allows us to predict the presence of large esophageal varices in patients with cirrhosis and may help to select patients for endoscopic screening (14,15). On the contrary, the role of TE in assessing the hepatocellular carcinoma risk needs further investigation.

Although validated for chronic HCV infection, TE effectiveness will have to be confirmed in other chronic liver diseases, in which specific consensus cut-off has yet to be developed. As a follow-up of liver fibrosis in a treated or non-treated patient, LB is questionable. If the preliminary data that are present in the literature are confirmed, TE would be useful to assess the efficacy of fibrosis treatment. Finally, all other chronic liver diseases, such as chronic cholestatic diseases, alcoholic liver disease, hereditary hemochromatosis, drug-related iatrogenic chronic conditions or the follow-up after liver transplantation, could benefit from a TE assessment for the diagnosis of fibrosis.

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