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Noninvasive Evaluation of Fibrosis and Steatosis in Nonalcoholic Fatty Liver Disease by Elastographic Methods

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Abstract

An increasingly common cause of chronic liver disease in adults and children is nonalcoholic fatty liver disease (NAFLD). The diagnosis of NAFLD was traditionally based on the histopathological changes of the liver, evaluated by needle liver biopsy, an invasive method, with potential adverse effects and great inter and intraobserver variability. The noninvasive methods for the assessment of both fibrosis and steatosis in patients with NAFLD have increasingly been studied lately. Of these noninvasive methods, in this chapter, we will focus on the methods assessing the stiffness of liver parenchyma, i.e. elastographic methods, of which, the most widely used are ultrasound elastography techniques. We will discuss the principal elastographic methods of some utility in NAFLD, i.e. shear wave elastography (SWE) (quantitative elastography), and especially transient elastography, point SWE (acoustic radiation force impulse elastography, ARFI) and two-dimensional real-time SWE (Supersonic). For each method usable in NAFLD cases, we will review the method principle, examination technique and performance in NAFLD evaluation.

Keywords: nonalcoholic fatty liver disease, fibrosis, steatosis, noninvasive, elastography

1. Introduction

An increasingly common cause of chronic liver disease in adults and children is nonalcoholic fatty liver disease (NAFLD) [1]. In adults, the prevalence of NAFLD ranges from 17% to 33% [2], whereas in children, from 2.6% to 9.6%; in obese children, the prevalence is significantly higher: 22.5%–44% [3]. NAFLD may present in various ways: as simple steatosis, nonalcoholic steatohepatitis, liver cirrhosis or even hepatocellular carcinoma (HCC) [2–5].

The diagnosis of NAFLD was traditionally based on the histopathological changes of the liver, evaluated by needle liver biopsy (LB). Unfortunately, this is an invasive method, with potential adverse effects and great inter and intraobserver variability [6–8]. In addition, the interpretation may be erroneous, because of the inhomogeneous distribution of fibrosis. In patients with HCV infection, for instance, differences of at least 1 stage between the right and left lobe in 33% of cases [7] or between 2 samples taken from the same area in even up to 45% of cases have been reported in literature [9]. In patients with nonalcoholic steatohepatitis (NASH), the inhomogeneous distribution of fibrosis appears to be even more pronounced than in HCV patients [10]. Some studies [8] showed that, when taking 2 samples from the right hepatic lobe in each NASH patient, agreement in fibrosis stage was found in only 47% of patients, while differences of at least 1 stage were found in 41% of cases, or 2 stages, in 12% of cases, respectively.

Lately, patients with NASH are increasingly evaluated using rapid, noninvasive methods of assessment of both fibrosis and steatosis. The diagnosis of liver steatosis has several implications in chronic liver diseases [11]. Indeed, in HCV patients, for instance, liver steatosis is associated with fibrosis progression and a decreased rate of sustained viral response [11–13]. Steatosis (which is the primary lesion in nonalcoholic fatty liver disease) may associate graft failure 1 year after liver transplantation, with increased risk of complications after liver resection and, last but not least, increased risk of death [11, 14–16].

The fibrosis may be assessed noninvasively using serum biomarkers (not liver-specific, but proven to correlate with fibrosis), as well as by measuring certain intrinsic physical properties of the liver parenchyma, such as liver stiffness (LS) or shear wave velocity (SWV) within the liver [17]. Of these noninvasive methods, in this chapter, we will focus on the methods assessing the stiffness of liver parenchyma, i.e. elastographic methods, of which, the most widely used are ultrasound (US) elastography techniques.

2. Classification of US-based elastography techniques

Elastography may be considered “a type of remote palpation that allows measurement and display of biomechanical properties associated with the elastic restoring forces in the tissue that act against shear deformation” [18].

In accordance to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) Guidelines [19, 20], the ultrasound elastographic techniques are either quantitative (shear wave elastography, SWE) or qualitative (strain elastography, real-time elastography). The quantitative techniques are as follows:

- Transient elastography (TE), the only method nonintegrated into a standard ultrasound system.
- Point SWE: Acoustic radiation force impulse elastography (ARFI) or ElastPQ technique.
- Real time SWE: Two-dimensional SWE (2D-SWE) or three-dimensional SWE (3D-SWE)

In the following sections, we will focus on the main quantitative ultrasound elastography techniques, which can help in the noninvasive assessment of nonalcoholic fatty liver disease.

3. Transient elastography (TE)

3.1. Principle

Transient elastography is performed using the Fibroscan® device (Echosens, Paris). The transducer of the device is placed in an intercostal space, above the right lobe, in a point of maximal hepatic dullness (typically the 9–11th intercostal space, on the midaxillary line). A mechanical vibrator is mounted on the axis of the transducer; the vibrator generates a painless vibration, inducing a train of elastic waves, which propagate through the skin and subcutaneous tissue to the liver. In parallel to the vibration, the transducer performs ultrasound acquisitions, at a frequency of 4 kHz. By comparing the ultrasonographic signals thus obtained, tissue deformation records, induced by the propagation of the elastic wave, can be drawn. The time necessary for the train of waves to propagate along the interest area, as well as the velocity of propagation, is recorded [21–25]. The liver stiffness may therefore be calculated using the formula: $E = 3\rho V_s^2$ (E —elasticity modulus; ρ —density, a constant of the material; V_s —the elastic wave propagation velocity within the liver parenchyma). Young's modulus (E) clinically corresponds to the LS and is typically referred to as E or LS. LS values range from 2.5 to 75 kPa. The stiffer the tissue, the higher the train wave propagation velocity [1, 24]. Lower values indicate a more elastic liver.

On the other hand, knowing that fat affects ultrasound propagation, a novel attenuation parameter has been developed to detect and quantify liver steatosis [25]. This parameter, called controlled attenuation parameter (CAP), is based on the ultrasonic properties of the radiofrequency back propagated signals acquired by the Fibroscan® [26]. 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 probe of the Fibroscan® probe, i.e. at 3.5 MHz, and is expressed in dB/m and ranges from 100 to 400 dB/m. CAP is evaluated using the same radiofrequency data, and the same region of interest, as the region used to assess the LS [26, 27]. It follows that the equipment can measure the liver stiffness (for the estimation of fibrosis) at the same time with CAP (for the estimation of steatosis) [25].

3.2. Examination technique

The patient is placed in a dorsal decubitus position, with the right arm in maximum abduction, in order to best expose the right quadrant, and the transducer is placed in direct contact with the skin, perpendicularly to the intercostal space, in an area of maximal dullness, free of any large vascular structure. The correct position is ensured either by visualizing the image of the A mode of the system or by using a different ultrasound equipment [22, 24].

When pressing the transducer button, the vibration is generated and transmitted to the liver. The software of the equipment analyses the tissue deformation records and measures the stiffness of the parenchyma. The results are expressed in kiloPascals (kPa) and represent the

median value of 10 valid measurements [22, 24]. At the same time, the software can measure the controlled attenuation parameter (CAP), expressed in dB/m.

The monitor of the device will display the instantaneous liver stiffness and CAP values, the median stiffness and CAP values resulting for each of the 10 valid measurements, the measurement success rate as well as the variation of the 10 measurements from the median (IQR).

A necessary condition for a correct assessment is the examination after an overnight fast or at least 2 hours after a meal, because a postprandial examination would increase the stiffness value due to increased hepatic blood flow [28, 29] and would lead to a false interpretation of liver stiffness. The influence of postprandial examination on CAP has not yet been proven.

The measurement can be performed even by a technician after a training period (approximately 100 cases) [30, 31], but the clinical interpretation of results must always be issued by an expert taking into account the demographic data, disease etiology and biochemical profile at the moment of the examination [32].

3.3. Parameters of the examination performance

In accordance to the manufacturer recommendations, the success rate is required to reach at least 60%, and the IQR to be less than 30% of the median (M) liver stiffness [24], although it appears that the best concordance with the biopsy is obtained when its value does not exceed 20% of the median [33].

According to the latest reports, however, the conventional definition of LS measurement accuracy is not relevant. The “success rate $\geq 60\%$ ” parameter is considered to be no longer necessary, and the examination accuracy depends on the IQR/M ratio, influenced by the median LS value. Three categories of measurement performance are therefore defined [34]:

- “very reliable”: $IQR/M \leq 0.10$
- “reliable”: $0.10 < IQR/M \leq 0.30$ or $IQR/M > 0.30$ and $LS < 7.1$ kPa
- “poorly reliable”: $IQR/M > 0.30$ and $LS \geq 7.1$ kPa

3.4. The liver volume examined by TE

The technique can measure the stiffness of a cylinder of parenchyma with a 1 cm diameter and a 4 cm height (the measurement is performed on a distance ranging from 25 and 45 mm from the skin); this represents around 1/500 of the entire liver volume, which is at least 100 times larger than the volume of a biopsy sample [22, 30, 32].

3.5. TE reproducibility

TE has a high degree of reproducibility, with a 0.93–0.98 intraobserver and interobserver correlation coefficient [35, 36]. Interobserver concordance is lower in patients with early stages of fibrosis, in those with $\geq 25\%$ steatosis and in patients with $BMI \geq 25$ kg/m².

3.6. Normal range of liver stiffness

The mean value of liver stiffness in healthy subjects without any known liver disease and with normal biochemistry and hematology tests is 5.5 ± 1.6 kPa according to some authors [37] and 4.8 ± 1.3 kPa according to others [38]. Age does not appear to influence this value, but stiffness is higher in men than in women. It is very difficult to establish the normal range of liver stiffness without biopsy, but the reverse is not feasible. In a group of HCV patients, without pathological changes on the biopsy sample, the liver stiffness was 4.84 ± 1.49 kPa [39]. In our unit, values of or above 5.3 kPa have a positive predictive value of 90% for the prediction of a fibrosis stage of at least F1.

3.7. Pathological changes influencing liver stiffness in NASH

Our studies performed on a group of biopsied NASH patients proved that LS correlated moderately with fibrosis ($r = 0.661$; $p < 0.0001$) and weakly, but significantly, with hepatocyte ballooning ($r = 0.385$; $p = 0.001$), lobular inflammation ($r = 0.364$; $p = 0.002$) and steatosis ($r = 0.435$; $p < 0.0001$). Of all of these elements, fibrosis was found in a multivariate analysis to be the only factor independently influencing LS in NASH patients [40]. Nevertheless, the correlation between liver stiffness and fibrosis is weaker in NASH ($r = 0.661$) than in hepatitis C ($r = 0.73$ – 0.79) [41, 42]; this correlation is supported also by the computerized analysis of the biopsy sample that quantifies the amount of fibrosis on the entire sample [43] and is explained by a different distribution pattern of fibrosis in the two conditions [40, 43].

3.8. Diagnostic performance of TE in quantifying fibrosis and steatosis in NASH

Unlike studies performed on diffuse liver diseases of viral etiology, those assessing the role of TE in evaluating NASH patients are rather scarce.

Although liver stiffness is strongly correlated with fibrosis in chronic hepatitis patients, this correlation is weaker in patients with steatohepatitis, because of a different pattern of fibrosis distribution, which, as mentioned earlier, leads to a lower performance of this technique in fibrosis prediction in NASH. Indeed, we observed that liver stiffness in NASH increases alongside the fibrosis stage, but there appears to be an apparent overlap of LS values, especially for the F1-F2 patients [40].

In a meta-analysis including 854 NASH patients [44], TE was found to have a very good performance in diagnosing stages $F \geq 3$ (Se 82%, Sp 82%) and F4 (Se 92%, Sp 92%), but only moderate in diagnosing significant fibrosis $F \geq 2$ (Se 79%, Sp 75%).

The cut-off values for the prediction of fibrosis resulting from various studies differ considerably in NAFLD patients, due to the different prevalence of fibrosis stages in the analyzed groups, as well as to the aim of the analysis (sensitivity $>90\%$ or specificity $>90\%$ or a maximal diagnostic accuracy). Therefore, the proposed cut-offs range between 5.3 and 7 kPa (for $F \geq 1$), with 61.7–93.48% sensitivity and 68–100% specificity (**Table 1**); 5.8–11 kPa (for $F \geq 2$), with 52.5–91.1% sensitivity and 50.3–91.7% specificity (**Table 2**); 7.8–12 kPa (for $F \geq 3$), with 75–100% sensitivity and 78–96.87% specificity (**Table 3**) and between 10.2 and 20 kPa

$\geq F1$	Cut-off (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Yoneda et al. [45]	5.9	0.93	86.1	88.9	97.1	59.3
Lupsor et al. [40]	5.3	0.879	93.48	78.26	89.6	85.7
Kumar et al. [46]	6.1	0.82	78	68	87	53
Imajo et al. [47]	7	0.78	61.7	100	100	86.6

Table 1. Performance of liver stiffness measurement compared with liver biopsy in the detection of fibrosis $\geq F1$ in nonalcoholic fatty liver disease patients.

(for the prediction of cirrhosis), with 70–100% sensitivity and 68–96.6% specificity (Table 4) [40, 45–50]. The studies have shown that TE performance is better for cirrhosis than for significant fibrosis [51, 52].

The available data indicate that, in patients with NAFLD, TE is a highly accurate, noninvasive method for the exclusion of advanced fibrosis and a moderately accurate method for the exclusion of significant fibrosis. According to the EFSUMB and EASL Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography, TE can be used in NAFLD patients to confidently exclude severe fibrosis and especially cirrhosis, with a high negative predictive value (around 90%) [17, 18].

The major challenge for the use of transient elastography in patients with NAFLD in clinical practice is the high rate of failure (no valid shot) or unreliable results (not meeting the manufacturer's first recommendations). In these patients, the failure rate varies between 3.8 and 50% [40, 45, 48, 51, 53–56] and appears to be correlated mainly with obesity [57]. In fact, different studies report increased failure rates owing to increased body mass index (BMI > 30 kg/m²) or waist circumference, which may interfere with the transmission of the push impulses and the tracking ultrasound, thus preventing a correct estimation of liver stiffness [17]. Apart from

$\geq F2$	Cut-off (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Yoneda et al. [45]	6.65	0.865	88.2	73.9	78.9	85
Lupsor et al. [40]	6.8	0.789	66.67	84.31	60	87.8
Wong et al. [48]	5.8 (Sn > 90%)	0.84	91.1	50.3	56.1	89.0
	7 (max DA)		79.2	75.9	69.6	84.0
	9 (Sp > 90%)		52.5	91.7	81.5	73.5
Kumar et al. [46]	7	0.85	77	78	75	81
Pathik et al. [49]	9.1	—	—	—	—	—
Imajo et al. [47]	11	0.82	65.2	88.7	88.2	66.2
Cassinotto et al. [50]	8.5	0.82	72	79	—	—

Table 2. Performance of liver stiffness measurement compared with liver biopsy in the detection of fibrosis $\geq F2$ in nonalcoholic fatty liver disease patients.

≥F3	Cut-off (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Yoneda et al. [45]	9.8	0.904	85.2	81.4	63.9	93
Lupsor et al. [40]	10.2	0.978	100	96.87	71.4	100
Wong et al. [48]	7.9 (Sn > 90%)	0.93	91.1	75.3	52.0	96.6
	8.7 (max DA)		83.9	83.2	59.5	94.6
	9.6 (Sp > 90%)		75.0	91.6	72.4	92.6
	9 (Se + Sp max)		85	88	68	95
Kumar et al. [46]	7.8 (Sn > 90%)	0.94	96	78	43	98
	11.2 (Sp > 90%)		71	93	57	91
	12		—	90	80	—
Pathik et al. [49]	12	—	90	80	—	—
Cassinotto et al. [50]	9.3	0.86	82	75	NR	NR
Imajo et al. [47]	11.4	0.88	85.7	83.8	75	91.9

Table 3. Performance of liver stiffness measurement compared with liver biopsy in the detection of fibrosis ≥F3 in nonalcoholic fatty liver disease patients.

obesity, measurement failure correlates also with more general features of the metabolic syndrome, as well as with limited operator experience [57].

A new transient elastography probe (XL) has been proposed to overcome these limitations for patients who are overweight or obese [54, 55, 58–60]. While the M probe, with a transducer central frequency of 3.5 MHz, can be used when the skin-to-liver capsule distance <2.5 cm (measurement depth 2.5–6.5 cm), the XL probe has a transducer central frequency of 2.5 MHz, so that the LS measurement can be made at a depth of 3.5–7.5 cm and, therefore, can be used

F4	Cut-off (kPa)	AUROC	Se (%)	Sp (%)	PPV (%)	NPV (%)
Yoneda et al. [45]	17.5	0.991	100	96.6	75	100
Wong et al. [48]	10.3 (Sn > 90%)	0.95	92.0	87.8	46.0	99.0
	10.3 (max DA)		92.0	87.8	46.0	99.0
	11.5 (Sp > 90%)		76.0	91.0	48.7	97.1
Kumar et al. [46]	11.8 (Se + Sp max)	0.96	90	88	41	98
	10.6 (Sn > 90%)		100	82	33	100
	19.4 (Sp > 90%)		70	98	78	97
Pathik et al. [49]	20	NR	90	80	NR	NR
Imajo et al. [47]	14	0.92	100	75.9	73	100
Cassinotto et al. [50]	10.2	0.87	89	68	NR	NR

Table 4. Performance of liver stiffness measurement compared with liver biopsy in the detection of cirrhosis in nonalcoholic fatty liver disease patients.

when the skin-to-liver capsule distance ranges between 2.5 and 3.5 cm. The measurement failure is significantly less frequent when using the XL probe than the standard M probe (1.1% versus 16%; $p < 0.00005$) [54]. Unreliable results were still observed with the XL probe, but only in 25%, as opposed to 50% of cases with the M probe ($p < 0.00005$) [57]. The main limiting factors for the XL probe are a skin-to-liver capsule distance >3.4 cm and extreme obesity (BMI > 40 kg/m²) [54].

It is worth mentioning that, when measured with the XL probe, the median LS is significantly lower than that measured with the M probe (6.9 kPa vs. 8.4 kPa, respectively) [55, 58]. In accordance to the existing literature, the LS cut-off values should be approximately 1.5–2 kPa lower for the same stage of fibrosis when the XL probe is used rather than the M probe [1]. As a result, the cut-off values defined for the M probe cannot be applied to the XL probe, as well.

3.9. Follow-up of patients

Monitoring the progression of fibrosis is also necessary in the follow-up of these patients. European Association for Study of Liver and Asociacion Latinoamericana para el Estudio del Hgado [17] and some authors [61] have shown that, indeed, LS measurement may be used to monitor hepatic fibrosis severity in patients with NAFLD, but additional prospective studies are necessary [1]. According to the existing guidelines, follow-up assessment by either serum biomarkers or TE for the progression of liver fibrosis should be performed among NAFLD patients at 3-year interval [17].

3.10. Errors of interpretation of LS values

The liver is an organ wrapped in a distensible but nonelastic envelope (Glisson's capsula). As a result, additional tissue abnormalities (edema, inflammation, cholestasis, congestion), may interfere with LS measurements, independently of fibrosis: increased cytolysis [62–64], extrahepatic cholestasis [65], congestive heart failure [66] and food intake [28, 29]. These error factors should be taken into consideration whenever interpreting LS values since they may overestimate the fibrosis stage [57]. The influence of steatosis on liver stiffness is still rather controversial; some studies indicate that steatosis may lead to higher liver stiffness, independently of fibrosis [53, 67], whereas others did not find the same effect [48]. It follows that more studies are needed to clarify this aspect, especially in NAFLD patients examined with both the M and the XL probe.

3.11. Prediction of steatosis in NAFLD patients using CAP measurements

The new parameter, which can be measured using the Fibroscan® equipment, the controlled attenuation parameter (CAP), has proven, in our and other authors' experience, to correlate significantly only with steatosis, not with other pathological anomalies encountered in patients with diffuse liver diseases (inflammation, ballooning or fibrosis) [26, 47, 54, 68–75].

An increase of the CAP value can be seen alongside the increase in steatosis grade, but there is some degree of overlap between adjacent grades, especially between moderate and severe steatosis [68].

The studies on the assessment of CAP performance in grading steatosis were predominantly aimed at groups of patients with various diffuse liver diseases, not only NAFLD. For the prediction of steatosis >10%, the CAP cut-off values vary in different studies between 214 dB/m and 289 dB/m, with a 64–91% sensitivity range and a 64–94% specificity range and the AUROC between 0.68 and 0.91. For the prediction of steatosis >33%, the cut-offs range between 259 dB/m and 311 dB/m, with a 57–89% sensitivity range and a 62–94% specificity range and the AUROC between 0.73 and 0.95. For the prediction of severe steatosis (>66%), the cut-offs range between 281 dB/m and 318 dB/m, with a 71–100% sensitivity range and a 47–82.5% specificity range and the AUROC between 0.70 and 0.93 [26, 47, 68–76]. According to these studies, CAP is useful in the detection of $S \geq 10\%$, $S \geq 33\%$ and $S \geq 66\%$, as a result of its good sensitivity and specificity; however, the exact cut-off values remain to be defined [1].

A recent meta-analysis including 2735 patients, 20% having NAFLD [77], has established the optimal CAP cut-offs for the prediction of mild, moderate and severe steatosis as, respectively, 248 dB/m, 268 dB/m, and 280 dB/m, with 66.8%, 77.3%, respectively 88.2% sensibility, and 82.2%, 81.2%, respectively 77.6% specificity (Table 5). According to this meta-analysis [77], covariates such as etiology, BMI and diabetes should be taken into account when interpreting CAP, but sex, age and fibrosis play a much smaller role. The authors recommend using the cut-offs established here, but deducting 10 dB/m from the CAP value for NAFLD/NASH patients, 10 dB/m for diabetes patients and deducting or adding 4.4 dB/m for each unit of BMI above or below 25 kg/m² over the range of 20–30 kg/m² [77].

In conclusion, CAP is a noninvasive method for the assessment of steatosis in chronic liver disease patients, including NASH, with a diagnosis accuracy of 76.11–82.06% [68], which is independently influenced only by the amount of steatosis. Due to its negative predictive value of 93.5–98.7%, CAP could become a useful clinical tool especially in excluding significant steatosis grades [68]. Large studies are required in order to develop new cut-off values for liver

	S0 vs. S1–S3	S0–S1 vs. S2–S3	S0–S2 vs. S3
Optimal cut off, dB/m	248 (237–261)	268 (257–284)	280 (268–294)
AUC	0.823 (0.809–0.837)	0.865 (0.850–0.880)	0.882 (0.858–0.906)
Sensitivity	0.688 (0.600–0.750)	0.773 (0.690–0.838)	0.882 (0.765–0.956)
False negative rate	0.312 (0.250–0.400)	0.227 (0.162–0.310)	0.118 (0.044–0.235)
Specificity	0.822 (0.761–0.897)	0.812 (0.749–0.879)	0.776 (0.720–0.821)
False positive rate	0.178 (0.103–0.239)	0.188 (0.121–0.251)	0.224 (0.179–0.280)

Table 5. Optimal CAP cut-off values, based on the maximal sum of sensitivity and specificity (Youden index) in predicting steatosis (modified after Karlas et al. [77]).

fibrosis staging using the XL probe and to investigate the differences between the CAP cut-off values used for the M and XL probes [1].

3.12. Advantages of transient elastography with controlled attenuation parameter

TE, the most widely used and validated noninvasive technique, offers several advantages [1, 26, 57, 68, 71]: it is user-friendly, machine-independent and painless, has a short duration of examination and does not require corrections to be made for gain, frequency, focusing or beam diffraction. This technique is highly reproducible, has well-defined quality criteria and allows the simultaneous assessment of liver stiffness (for fibrosis) and CAP (for steatosis) in the same region of the liver. Compared to liver biopsy, the technique is less prone to sampling errors as it explores a liver volume about 100 times larger. Furthermore, the method also has several clinical applications for patients with NAFLD.

3.13. Limitations of transient elastography with controlled attenuation parameter

TE does have some limitations [1], which may lead to measurement failure: ascites (the vibrations do not propagate through liquids), obesity (especially at BMI > 30 kg/m²) and narrow intercostal spaces. On the other hand, however, some of these limitations may be overcome by using the XL probe (for obese patients) and the S probe (for children). Another limitation of the technique is the overestimation of fibrosis because of increased liver stiffness due to high cytotoxicity, extrahepatic cholestasis and congestive heart failure.

3.14. Conclusion about the use of TE in NAFLD

In conclusion, TE may prove useful to NAFLD patients especially for the exclusion of significant fibrosis and cirrhosis. However, we must consider the rather high rate of measurement failure in these patients. The XL probe may overcome this problem in obese patients, but new cut-offs should be defined for the prediction of fibrosis, since the ones of the M probe are not applicable for the XL one [1, 57]. Follow-up assessment by TE for the progression of liver fibrosis should be performed among NAFLD patients at 3-year interval [17].

On the other hand, CAP provides a standardized noninvasive measure of hepatic steatosis. According to the latest and most comprehensive meta-analysis [77], the optimal cut-offs for the prediction of mild, moderate and severe steatosis are 248, 268, and 280 dB/m, respectively. Some authors recommend using the cut-offs established here, but deducting 10 dB/m from the CAP value for NAFLD/NASH patients, 10 dB/m for diabetes patients and deducting or adding 4.4 dB/m for each unit of BMI above or below 25 kg/m² over the range of 20–30 kg/m² [77]. Longitudinal data are needed to demonstrate how CAP relates to clinical outcomes.

4. Acoustic radiation force impulse elastography (ARFI)

Of the “Point SWE” techniques, we will review some features of the ARFI technique (acoustic radiation force impulse elastography), the only technique in this category whose role in the assessment of NAFLD patients has, albeit insufficiently, been analyzed.

4.1. Principle

The ARFI imaging technology involves the mechanical excitation of tissue using short-duration acoustic pulses (push pulses) in a region of interest chosen by the examiner, producing shear waves that spread away from the region of interest, perpendicularly to the acoustic push pulse, generating localized, micron-scale displacements in the tissue [78–80]. Simultaneously, detection waves of lower intensity than that of the push pulse are generated. The shear wave velocity—SWV (m/s) can be calculated taking into account the place and moment of interaction between the shear waves and the detection waves [80–83]. The stiffer the tissue, the higher the shear wave velocity [80–83]. The shear wave velocity is measured in a smaller volume than in transient elastography (10 mm long and 6 mm wide), but, unlike TE, it can be chosen by the operator under B-mode visualization [57], since ARFI is implemented on some ultrasound equipments, alongside the B-mode, color Doppler and contrast modes [17, 80, 84].

4.2. Examination technique

The patient is placed in a dorsal decubitus position, with the right arm in maximum abduction. The transducer is placed in an intercostal space, and the region of interest (10/5 mm) is chosen in an area of the right liver parenchyma (segments 5 or 8), 1–2 cm below the liver capsule; the measurement is performed after asking the patient to hold his/her breath after an expiration to prevent breathing movements [85]. In general, the median value of 10 valid measurements of the shear wave is taken into consideration; sometimes, no valid measurement can be obtained. When taking into account the manufacturer recommendations, we can identify some possible causes, which, alone or in combination, may lead to this situation:

- excessive movements of the liver tissue—for instance, cardiac pulsations transmitted to the liver parenchyma (impaired estimation of shear wave velocity);
- marked signal attenuation in obese patients (impaired identification of the shear wave by the system);
- marked tissue stiffness (impaired estimation of shear wave velocity—shear wave outside of the confidence interval).

On the whole, however, the failure rate of ARFI is significantly lower than that of TE (2.9% vs. 6.4%, $p < 0.001$), especially in patients with ascites or obesity [86].

Ten valid measurements are performed in the right liver lobe, a median value is calculated and the result is expressed in meters/second.

pSWE measurements using Virtual Touch Quantification (VTQ®) in healthy populations range between 1.01 and 1.59 m/s, but in most studies the range is 1.07–1.16 m/s [87–89].

4.3. Errors of interpretation of LS values using the ARFI technique

Like TE, ARFI results are influenced by food intake [90] as well as necroinflammatory activity and aminotransferase levels [91], all of which lead to an overestimation of liver fibrosis and have to be taken into account when interpreting the results [17].

LS values obtained with ARFI, in contrast to TE values, have a narrow range (0.5–4.4 m/s). Defining cut-off values for discriminating certain fibrosis stages is therefore restricted, as well as making management decisions.

4.4. Diagnostic performance of ARFI in NASH

There are few studies assessing the performance of ARFI in NAFLD. The majority of studies included patients with diffuse liver diseases, with only a fraction of NAFLD patients. In most studies, the cut-offs for the prediction of F1 vary between 1.105–1.34 m/s, with 76.7% sensitivity and 71.4% specificity; for $F \geq 2$, between 1.137–1.179 m/s, with Se 71–97% and Sp 67–92%; for $F \geq 3$, between 1.45–2.20 m/s, with Se 75–100% and Sp 68–95.2%, and for the prediction of cirrhosis, between 1.61–2.90 m/s, with Se 74–100% and Sp 67–96% [92–98].

ARFI performs better in severe fibrosis and cirrhosis than in significant fibrosis, with AUROCs ranging from 0.91 to 0.98 and from 0.66 to 0.86, respectively [97].

A systematic review of seven studies with a total of 723 patients who underwent shear wave velocity measurements with VTQ® technique to evaluate the diagnostic efficacy of pSWE in patients with NAFLD showed that the summary Se and Sp of ARFI in detecting significant fibrosis were 80.2 and 85.2% [99], which is not an appropriate endpoint [17].

In conclusion, ARFI elastography appears to be modestly accurate in detecting significant fibrosis, but performs well in predicting severe fibrosis and cirrhosis in NAFLD patients. As for its use in the follow-up of patients, no data are available for this technique for the moment.

5. Two-dimensional SWE (2D-SWE)

5.1. Principle

2D-SWE is based on the combination of a radiation force induced in tissues by focused ultrasonic beams and a very high frame rate ultrasound imaging sequence capable of catching in real time the transient propagation of resulting shear waves [17, 19, 100]. The shear wave speed is estimated by a Doppler-like acquisition over a region of interest (ROI) and it is used to calculate the tissue stiffness. The relationship between Young's modulus (E) and the shear wave (c) is $E = 3\rho c^2$ (ρ = tissue density) [19, 20, 100, 101].

The elasticity is displayed using a color-coded image superimposed on a B-mode image: stiffer tissues in red and softer tissues in blue [19, 20, 100, 101]. In addition, a quantitative measurement of the liver stiffness in the chosen region of interest is performed. The equipment allows the visualization of results both in kPa and in m/s, with a maximum value reaching 300 kPa (10 m/s) [102, 103].

Almost all 2D-SWE studies for liver applications have been carried out using Supersonic Imagine equipments (Aixplorer, Supersonic Imagine, Aix en Provence, France), because other companies have only recently introduced 2D-SWE products [17].

5.2. The examination technique

The examination is performed after an overnight fast, with the patient placed in a dorsal decubitus position, with the right arm in maximum abduction, in order to enlarge the intercostal spaces and ensure the best access to the right liver lobe parenchyma [103]. The region of interest (ROI) for the elastography examination is placed in the center of the screen, choosing an homogeneous area of parenchyma, free of any large vascular structure and at least 2 cm below the liver capsule, to prevent any risk of overestimation of fibrosis due to the higher capsular and subcapsular fibrosis content. The ROI with color-coded elastographic information is displayed overlapped on the 2D image; its size can be adjusted up to 3×3 cm, and the depth, although adjustable, should be kept within 8 cm [102].

There is no consensus on the *number of measurements* required for a good quality assessment [20]: some studies recommend 3 [104–106], 4 [107] or 5 [108–110].

Similar to pSWE/ARFI, *quality criteria* for 2D-SWE remain to be defined. Until now, such criteria have only been proposed in a study on patients with portal hypertension, but they still require validation on prospective studies on large groups of biopsied patients [106]: “highly reliable” (when the ratio between standard deviation/median LS ≤ 0.10 and measurement depth < 5.6 cm); “reliable” (when standard deviation/median LS > 0.10 or measurement depth ≥ 5.6 cm); respectively “unreliable” (when standard deviation/median LS > 0.10 and measurement depth ≥ 5.6 cm). The “highly reliable” and “reliable” measurements are considered acceptable; only the “unreliable” ones are considered unacceptable for evaluation and should be rejected [106].

5.3. Technique failure

The liver stiffness cannot be assessed by 2D-SWE in around 10.4% of cases, more frequently in obese patients or in patients with a thoracic wall thicker than 25 mm in the intercostal spaces [111]. Generally speaking, the following factors may be associated with a higher rate of invalid measurements: narrow intercostal spaces [107], high BMI and thoracic wall thicker than 25 mm in the intercostal spaces [111].

5.4. Normal range of liver stiffness as evaluated by 2D-SWE

Studies performed on subjects with healthy livers, pathologically confirmed potential donors, yielded a mean normal value of liver stiffness in 2D-SWE of 4.4–4.9 kPa (range 2.2–6.2 kPa), not correlated significantly with age, BMI or steatosis [100, 105, 107, 109].

5.5. Performance of 2D-SWE in assessing nonalcoholic steatohepatitis

Some studies on the performance of this method in diffuse liver diseases of various etiologies included a certain proportion of NASH patients. The resulting cut-offs varied between 6.2–7.8 kPa for $\geq F1$, 7.1–10.49 kPa for $\geq F2$, 8.7–11.5 kPa for $\geq F3$ and 9.59–18.1 kPa for F4 [112]. 2D-SWE performance for the prediction of each fibrosis stage seems to be similar when

including all patients, regardless of etiology, as well as when including only viral hepatic diseases, with AUROCs between 0.80 and 0.82 [103]. In two meta-analyses, with a total of 2303 and 934 patients, respectively, the summary area under the curve (AUC) was 0.85 for $\geq F1$, 0.87–0.88 for $\geq F2$, 0.93–0.94 for $\geq F3$ and 0.92–0.94 for F4 [112, 113].

In a study performed on 291 NAFLD patients, the chosen cut-offs for the prediction of $\geq F2$ were 6.3 kPa (Se 90%, Sp 50%) and 8.7 kPa (Se 71%, Sp 90%), with AUROC 0.86; for the prediction of fibrosis $\geq F3$, 8.3 kPa (Se 91%, Sp 71%) and 10.7 kPa (Se 71%, Sp 90%), with AUROC 0.89 and for the prediction of cirrhosis, 10.5 kPa (Se 90%, Sp 72%) and 14.4 kPa (Se 58%, Sp 90%), with AUROC 0.88 [50].

6. Conclusions: SSI, Fibroscan® or ARFI?

After comparing the performance in the assessment of NAFLD of the three elastographic methods discussed above, we can conclude, on the preliminary results, that the diagnostic performance according to the AUROC values for the diagnosis of significant fibrosis, severe fibrosis and cirrhosis is good for SSI (0.86–0.89); good for Fibroscan® (0.82–0.87) and fair or good for ARFI (0.77–0.84) [50]. The AUROC values for diagnosing severe fibrosis or cirrhosis are particularly good for SSI or Fibroscan® (0.86 and 0.89) [50].

The prediction of steatosis, however, can at this moment only be made using the controlled attenuation parameter measured with Fibroscan®.

As for the causes of measurement failure or unreliable results, we mention clinical factors related to obesity (BMI > 30 kg/m², waist circumference \geq 102 cm or increased wall thickness), which are associated with liver stiffness measurement failures when using SSI or Fibroscan® and with unreliable results when using ARFI [50].

In conclusion, SSI, Fibroscan® and ARFI are valuable diagnostic tools for the staging of liver fibrosis in NAFLD patients. However, the diagnostic accuracy of SSI appears to be superior to that of ARFI for the diagnosis of F2 or above [50]. Most of the cut-off values for SSI for the diagnosis of different stages of liver disease are quite similar to those of Fibroscan®; this is an issue of great importance for the applicability of this technique and its wide dissemination among radiologists and hepatologists in their daily practice. However, as for the M probe of Fibroscan®, the SSI technique remains limited by a high failure rate in cases of obesity, whereas ARFI has a high rate of unreliable results [50].

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