Editorial

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Getting closer to a point-of-care diagnostic assessment in patients with chronic liver disease: Controlled attenuation parameter for steatosis

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In a worldwide scenario of pandemic obesity and metabolic syndrome, non-alcoholic fatty liver disease (NAFLD) is exponentially increasing. NAFLD *per se* has become the most frequent cause for referral for chronic liver disease evaluation (CLD) and an increasing cause of hepatocellular carcinoma and end-stage liver disease requiring liver transplantation in developed countries [1,2]. Fatty liver (steatosis) can be also found in patients with CLD of other aetiologies, since some CLD are themselves steatogenic (chronic hepatitis C virus – HCV infection; alcoholic liver disease), and since the metabolic syndrome can be superimposed to other liver diseases.

Detection of hepatic steatosis in CLD patients is relevant for several reasons. Just to cite some, NAFLD is a well recognized co-factor accelerating the progression of CLD [3] and reduces the likelihood of sustained virological response in patients with HCV [4]. Furthermore, in patients undergoing liver resection NAFLD independently increases the risk of postoperative complications and death [5]. Finally, in the setting of liver transplantation the presence of macrovesicular steatosis in the graft increases the 1-year risk of graft failure [6]. Therefore, an accurate method to detect and quantify liver steatosis would be extremely useful and as such it has been subject of research in the last 10 years.

The presence of fat within the liver tissue modifies its physical properties, making it visible by appropriate imaging techniques. The most sensitive and most accurate imaging method to assess fatty liver so far is magnetic resonance spectroscopy, that is able to diagnose steatosis when involving $\geqslant$5% of hepatocytes [7]. Regrettably, this technique cannot be used routinely given its high cost, and certainly it cannot be used as a point-of-care method to guide a rapid decision making in clinical practice.

Liver ultrasound (US) is accepted as the first line imaging technique to screen for liver steatosis given its low cost, safety and wide availability. US is accurate in detecting steatosis if this involves at least 20% of hepatocytes [8], gives results in real time and can be used as a point-of-care method, and allows mirroring changes in hepatic fat content over time. However, US assessment has substantial well-known limitations [7]: it relies upon a qualitative or at most upon a semi-quantitative assessment, it is operator-dependent (meaning that it requires a specific expertise), and it has a limited applicability in case of morbid obesity. Furthermore, the accuracy of US in diagnosing steatosis in patients with pre-existent CLD might be reduced by the presence of fibrosis, and has not been adequately assessed.

Controlled attenuation parameter (CAP) is a recently developed non-invasive technique that might overcome some of these limitations. CAP measures the degree of ultrasound attenuation due to hepatic fat at the standardized frequency of 3.5 MHz taking advantage of a technology named vibration-controlled elastography (VCTE™) implemented on FibroScan® (Echosens, Paris, France) [9]. The software provides a numerical value that is operator-independent and can be obtained by operators without experience in medical imaging simultaneously to LS measurement. CAP values range from 100 to 400 dB/m, and the final result is the median value of 10 valid measurements (note that CAP is calculated simultaneously with valid LS measurements) [9]. CAP values correlated well with the amount of steatosis assessed by liver biopsy in previous studies from different countries [9–15]; values >215 dB allowed the detection of fatty infiltration $\geqslant$10% of hepatocytes with a sensitivity over 90% in a recent study [10], while the CAP cut-off associated with significant steatosis (>33% of hepatocytes) varied among studies but was invariably >250 dB [9–15]. Furthermore, CAP values were not influenced by the presence of fibrosis or cirrhosis. These results were certainly promising, but were obtained in relatively small, selected populations (<150 cases), preventing to conclude what is the real applicability of the technique in detecting steatosis, and which factors may cause uncertainty on CAP results.

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; CLD, chronic liver disease; US, ultrasonography; CAP, Controlled attenuation parameter; AUROC, area under receiving operator characteristics curve; LS, liver stiffness.

In this number of Journal of Hepatology, de Ledinghen and colleagues [16] provide interesting data expanding the knowledge of this new method in CLD.

CAP performance was evaluated in a large prospective study including 5323 consecutive patients with CLD of various etiologies in whom the metabolic profile and LS by FibroScan® were also estimated. A subgroup of 440 patients (of whom 52% had steatosis, being this severe in 15%) simultaneously underwent liver biopsy. In this subset CAP confirmed an excellent diagnostic accuracy for steatosis detection, with an adjusted AUROC of 0.914 (95% CI 0.90–0.93). Taken together, the results of this [16] and previous studies [9–15], demonstrate that CAP allows a precise and reliable non-invasive diagnosis of liver steatosis in patients with CLD, and indicates that a "one-shot study" using the same equipment that gives results in real time can be used to diagnose both steatosis and fibrosis in this population.

CAP has the additional advantage of being quantitative. In the whole study population, factors independently associated with CAP values indicating significant steatosis (>33% of hepatocytes) were male gender, age >55 years, BMI, presence of metabolic syndrome, and alcohol abuse. Notably, while male gender and age >55 years increased by about 30% the risk of showing a CAP value of either 250–300 dB or >300 dB, obesity, metabolic syndrome and alcohol abuse (variables epidemiologically associated with a more severe fatty liver [17]) were more strongly associated with values of CAP >300 dB.

LS >6 kPa was also associated with high CAP values independent of the features of metabolic syndrome and alcohol abuse. This finding was not further analyzed, but is somehow disturbing since it implies either that a common factor can explain increases in both CAP and LS (such as can occur in patients with HCV-related CLD inducing both steatosis and fibrosis) or that false positive results of CAP might be observed in patients with increased LS. Additional data are required to clarify this issue.

Technical failure of the method (observed in 7.7% of cases) was also significantly associated with age >55 years, BMI, presence of metabolic syndrome, and with female gender. These results are not surprising considering that technical failures of LS with the standard M FibroScan® probe, that is used for CAP measurement, occur more often in such patients [18]. Clearly, a CAP algorithm for the FibroScan® XL probe, specifically designed for obese population, would be welcome.

Several other questions remain to be answered. The first regards the generalizability of the findings of de Ledinghen and colleagues [16] to primary care population, in which it is important to detect NAFLD since it is an independent predictor of cancer, cardiovascular disease, and mortality from any cause [17]. Studies targeting the general population are still scarce, but recent data confirm that CAP correlates with the features of metabolic syndrome in this setting [19,20].

The second question, to be addressed both in patients with CLD and in the general population, regards which CAP cut-off should be used to correctly identify the presence of liver steatosis and to estimate its amount. Given the well known limitations of liver biopsy (limited sampling of the liver, implying a risk of over- or underestimating steatosis even with morphometric analysis), studies comparing CAP with magnetic resonance spectroscopy, that gives a quantitative measure of fat content in the whole liver and is probably more accurate than biopsy [7], would be of great value. Future studies should also focus on assessing whether CAP is able to accurately mirror changes in steatosis over time. This would be important to consider CAP a reliable biomarker for assessing the effectiveness of new treatments for NAFLD in clinical trials.

A final issue regards how CAP compares with other non-invasive methods available in this field. Up to date conflicting results have been obtained in studies comparing CAP to serum indices of steatosis (Steatotest™ [BioPredictive, Paris, France], FLI and Hepatic Steatosis Index) [10,13,16,19]. Data comparing CAP with US in the general population are also inconclusive: although in one study CAP was able to detect steatosis in patients with normal US, suggesting that it might be more accurate [20], in another study both methods had a similar, good accuracy for the diagnosis of steatosis [19]. Analogous comparisons between these two point-of-care methods are lacking in patients with CLD, and should be performed in order to design diagnostic algorithms useful to correctly and non-invasively diagnose steatosis and its severity.

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Conflict of interest

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