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Non-invasive diagnosis of liver steatosis: ready for primetime?

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Hepatic steatosis is defined as the presence of fat in at least 5% of hepatocytes or intrahepatic fat that make up at least 5% of the liver weight. Hepatic steatosis is associated with a number of liver diseases including non-alcoholic fatty liver disease (NAFLD), which is becoming the most prevalent cause of liver disease worldwide, especially in Western countries such as Switzerland [1]. NAFLD is made up of a spectrum of liver disorders, ranging from "simple" steatosis to non-alcoholic steatohepatitis, liver fibrosis and cirrhosis. Although patients with NAFLD have increased cardiovascular morbidity and mortality, liver-driven morbidity and mortality are strongly associated with advanced liver disease and advanced liver fibrosis [2]. Other liver diseases are also associated with hepatic steatosis. For instance, hepatitis C virus infection (in particular genotype 3), alcohol liver disease (ALD) or certain drugs may lead to steatosis.

The prevalence of steatosis is closely linked to the prevalence of NAFLD and, to a lesser extent, ALD in the general population. NAFLD is strongly associated with features of metabolic syndromes such as obesity and type 2 diabetes. This close association explains the increasing prevalence of NAFLD in Western countries, with prevalence estimations approaching 25% in Europe [3]. Alternatively, recent modelling data has shown that the median prevalence of chronic liver disease and cirrhosis in Europe was 833 per 100,000 and around 600 per 100,000 in Switzerland [4].

The formal diagnosis of steatosis relies on liver histology based on a liver biopsy, which is an invasive procedure that is not required in the majority of cases. Due to the high prevalence of liver steatosis, in particular in the context of an increase in NAFLD incidence, there has been renewed interest to identify non-invasive tools to assess the presence of liver disease. A number of non-invasive tools, including biomarkers or imaging techniques, have been developed for the non-invasive diagnosis of liver steatosis. Controlled attenuation parameter (CAP) uses the attenuation of ultrasonic waves in the liver to assess the presence and grade of liver steatosis [5]. The measurement of CAP is integrated in the FibroScan device (Echosens, Paris, France), a physical probe used to measure vibration-controlled transient elastography (VCTE), which is a measure of liver stiffness and itself a rapid and non-invasive technique for the diagnosis and staging of liver fibrosis.

The study by Dr Baumeler and colleagues now published in *Swiss Medical Weekly* assessed the diagnostic performance of CAP for the diagnosis of liver steatosis in a wide variety of liver diseases including NAFLD [6]. Using liver histology as the gold standard, they assessed 224 patients with a paired liver biopsy and CAP measurement at a tertiary referral centre in Switzerland (Cantonal Hospital St Gallen). As expected, they found significantly increasing CAP values with increased levels of histological steatosis and an area under the receiver operating curve (AUROC) of 0.78 for differentiating the absence from the presence of steatosis, although the AUROC was slightly increased when comparing higher levels of steatosis (no or early steatosis versus advanced steatosis). The authors also identified independent factors associated with increased CAP, namely male sex, body mass index, liver stiffness, histological steatosis and the presence of NAFLD. The cohort of patients included a wide variety of liver disease aetiologies (mostly hepatitis B or C virus infection and NAFLD); however, an analysis of the 52 patients with NAFLD (23% of the total) revealed higher CAP values in patients with NAFLD but no difference in CAP values between patients with simple steatosis and those with non-alcoholic steatohepatitis, which is a more advanced form of the disease.

This study builds on previous studies investigating the place of CAP as a non-invasive tool for assessing liver steatosis in a variety of liver diseases. For instance, a recent systematic review including 9 studies involving 1297 patients with NAFLD found a pooled sensitivity of 87% and a specificity of 91% for detecting mild steatosis, although precise cut-offs have yet to be defined [7]. Similarly, a study including 269 patients abusing alcohol who underwent simultaneous CAP, ultrasound and liver biopsy showed that CAP can be used to diagnose any steatosis and moderate steatosis with fair accuracy (AUROCs of 0.77 and 0.78, respectively). Furthermore, they showed that CAP was superior to the diagnosis of liver steatosis based on a "bright liver" echo pattern on a regular ultrasound [8]. Interestingly, in this study the authors found that CAP was decreased in patients with short-term alcohol abstinence, thereby underlining its potential role as a dynamic assessment of liver steatosis.

Although the study by Baumeler and colleagues was limited by the heterogeneity of the patient population and a relatively limited number of patients with NAFLD or ALD

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(the most common causes of liver steatosis in clinical practice), it is timely and helpful to highlight key challenges in the non-invasive detection of liver steatosis. Firstly, the authors must be praised for highlighting their "real-life" approach; although studies generally assess the performance of CAP in specific aetiologies, Baumeler and colleagues combined different aetiologies of liver disease and identified the diagnostic performance of CAP in a population of patients that would receive a typical general hepatological consultation. However, this approach raises further questions, especially as CAP thresholds vary across aetiologies of liver disease. Furthermore, the usefulness of CAP in autoimmune hepatitis, drug-induced liver injury, primary biliary cholangitis and sarcoidosis (total of 20% of the study population) is unclear and its relevance unknown. Secondly, as underlined in this paper, specific cut-offs to detect steatosis remain controversial and can change according to confounding factors. Thirdly, the vast majority of liver steatosis seen by the general practitioner and specialist will be linked to NAFLD, ALD or possibly hepatitis C virus infection. The authors acknowledge that their limited sample size, in particular for patients with NAFLD, limit their analysis for these specific important aetiologies. Fourthly, this study also highlights the limitations intrinsic to CAP measurements, namely the use of the M or XL probe and unreliable measurement in some patients. Specifically, it remains unclear whether CAP measurements with the XL probe, a probe developed for obese patients that was used in 20% of patients in this study, are comparable with the standard M probe. In addition, CAP measurements were considered unreliable according to the standard criteria in 13% of patients, therefore slightly limiting the potential generalisability of this technique.

Overall, this study is part of a growing base of evidence underlining the non-invasive diagnosis of liver steatosis in general and CAP in particular. One of the major unresolved questions is the place of CAP in the diagnosis of patients with steatosis and liver disease as well as its place in the context of multiple other non-invasive tools for steatosis diagnosis. Further studies will need to compare CAP to other strategies for the diagnosis of liver steatosis and to establish whether CAP is cost-effective and efficient in this situation, in particular when compared to a simple liver ultrasound. Although the role of CAP is unclear for the diagnosis of liver steatosis, one potential application of this technique would be in NAFLD screening in the general or a specific at-risk population. Given the increase in NAFLD prevalence and its strong associations with type 2 diabetes and obesity, there have been increasing efforts to screen for liver disease in these populations [9, 10]. Coupled with VCTE measurement within the FibroScan probe as well as non-invasive assessment of liver steatosis informing liver disease aetiology and liver fibrosis, the ability to determine the stage of liver disease could become a powerful tool for large scale liver disease screening. For instance, Kwok and colleagues showed that in 1799 patients with type 2 diabetes, 72.8% had increased CAP values and 17.7% had increased VCTE, thereby suggesting significant liver steatosis and fibrosis, respectively [9]. Nevertheless, the prognostic relevance of liver steatosis remains uncertain, and screening for liver steatosis without an assessment of liver fibrosis is probably not cost-effective and will not help to efficiently stratify patients at the highest risk of liver disease progression [10].

In conclusion, the study by Baumeler and colleagues highlights the diagnostic performance of CAP for detecting liver steatosis in a wide variety of liver disease aetiologies, including NAFLD. However, future research should compare CAP to alternate diagnostic strategies for liver steatosis and better characterise its exact place in the growing diagnostic arsenal for liver steatosis. In the context of the overwhelming NAFLD epidemic already affecting one in four patients in Europe, we should urgently define diagnostic and screening strategies for advanced liver disease and assess whether liver steatosis assessment, including CAP, adds diagnostic and/or prognostic information to allow for improved risk stratification management of this growing population.

Disclosure statement

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References

1 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402. doi: http://dx.doi.org/10.1016/j.jhep.2015.11.004. PubMed.

2 Hagström H, Nasr P, Ekstedt M, Hammar U, Stål P, Hultcrantz R, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol. 2017;67(6):1265–73. doi: http://dx.doi.org/10.1016/j.jhep.2017.07.027. PubMed.

3 Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84. doi: http://dx.doi.org/10.1002/hep.28431. PubMed.

4 Pimpin L, Cortez-Pinto H, Negro F, Corbould E, Lazarus JV, Webber L, et al.; EASL HEPAHEALTH Steering Committee. Burden of liver disease in Europe: Epidemiology and analysis of risk factors to identify prevention policies. J Hepatol. 2018;69(3):718–35. doi: http://dx.doi.org/10.1016/j.jhep.2018.05.011. PubMed.

5 Sasso M, Beaugrand M, de Ledinghen V, Douvin C, Marcellin P, Poupon R, et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. Ultrasound Med Biol. 2010;36(11):1825–35. doi: http://dx.doi.org/10.1016/j.ultrasmedbio.2010.07.005. PubMed.

6 Baumeler S, Jochum W, Neuweiler J, Bergamin I, Semela D. Controlled attenuation parameter for the assessment of liver steatosis in comparison with liver histology: a single-centre real life experience. Swiss Med Wkly. 2019;149:. doi: http://dx.doi.org/10.4414/smw.2019.20077. PubMed.

7 Pu K, Wang Y, Bai S, Wei H, Zhou Y, Fan J, et al. Diagnostic accuracy of controlled attenuation parameter (CAP) as a non-invasive test for steatosis in suspected non-alcoholic fatty liver disease: a systematic review and meta-analysis. BMC Gastroenterol. 2019;19(1):51. doi: http://dx.doi.org/10.1186/s12876-019-0961-9. PubMed.

8 Thiele M, Rausch V, Fluhr G, Kjærgaard M, Piecha F, Mueller J, et al. Controlled attenuation parameter and alcoholic hepatic steatosis: Diagnostic accuracy and role of alcohol detoxification. J Hepatol. 2018;68(5):1025–32. doi: http://dx.doi.org/10.1016/j.jhep.2017.12.029. PubMed.

9 Kwok R, Choi KC, Wong GL-H, Zhang Y, Chan HL-Y, Luk AO-Y, et al. Screening diabetic patients for non-alcoholic fatty liver disease with controlled attenuation parameter and liver stiffness measurements: a prospective cohort study. Gut. 2016;65(8):1359–68. doi: http://dx.doi.org/10.1136/gutjnl-2015-309265. PubMed.

10 Ginès P, Graupera I, Lammert F, Angeli P, Caballeria L, Krag A, et al. Screening for liver fibrosis in the general population: a call for action. Lancet Gastroenterol Hepatol. 2016;1(3):256–60. doi: http://dx.doi.org/10.1016/S2468-1253(16)30081-4. PubMed.

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