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Controlled Attenuation Parameter as a Noninvasive Method to Detect and Quantify Hepatic Steatosis in Chronic Liver Disease: What Is the Clinical Relevance?

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Keywords
Steatosis · Controlled attenuation parameter · Chronic hepatic disease

Controlled Attenuation Parameter, um Método Não-Invasivo para Detectar e Quantificar a Esteatose Hepática na Doença Hepática Crónica: Qual É a Relevância Clínica?

Palavras Chave
Esteatose · Controlled attenuation parameter · Doença hepática crónica

Ectopic accumulation of lipids in the liver, also known as hepatic steatosis, is a common finding [1]. It occurs in 90% of the heavy drinkers [2] and 20–30% of the nondrinkers [3], dubbed alcoholic and nonalcoholic fatty liver disease, respectively. Because of its growing prevalence in the general population, there is also a growing association of hepatic steatosis and other forms of chronic liver disease such as viral, autoimmune, and metabolic liver diseases [4].

The gold standard for the diagnosis and quantification of hepatic steatosis has been liver biopsy. However, liver biopsy has accuracy issues due to the nonhomogeneous distribution of liver steatosis throughout the liver that imposes important sample errors. In addition, it is an invasive procedure, with an unneglectable risk of complications [5]. As such, the search for noninvasive methods to diagnose and quantify liver steatosis has been a matter of intense research in the last decade. Magnetic resonance-derived techniques such as spectroscopy and measurement of proton density fat fraction are highly reliable methods, probably superior to liver histology, particularly proton density fat fraction, which allows quantification of hepatic steatosis throughout the liver [6]. However, those methods are expensive, time-consuming, and not widely available. Ultrasonography and tomography scan has similar accuracy, although the latter is more expensive and imposes exposure to radiation [7]. They have excellent accuracy for moderate-to-severe steatosis (85% sensitivity and 94% specificity). However, sensitivity decreases dramatically for steatosis <30% [8]. Ultrasonography allows subjective semiquantification of steatosis. Since recently, the elastography Fibroscan© probe can incorporate the measurement of the degree of ultrasound attenuation by hepatic fat, controlled attenuation parameter (CAP) allowing indirect quantification of liver ste-

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atosis [6]. CAP results are expressed in decibels per meter (dB/m) and range from 100–400 dB/m. CAP has been consistently shown, in more than 20 small studies, to be able to separate different grades of steatosis, albeit with some degree of overlap between different grades [6]. Furthermore, cutoffs vary between studies, though values higher than 250 dB/m consistently associate with at least moderate steatosis. Studies comparing the accuracy of CAP and ultrasonography for the diagnosis of liver steatosis are discordant, with some suggesting CAP to be superior, whereas others finding similar accuracy [9, 10]. CAP is, however, less accurate than magnetic resonance-derived techniques [11].

CAP has some limitations. It is only available in the Fibroscan M probe, though a CAP algorithm for the Fibroscan XL probe is being developed [12]. Failure to obtain a CAP measurement occurs in 6–8% and associates with older age, a higher body mass index, presence of the metabolic syndrome, and female gender [13].

In this issue of *Portuguese Journal of Gastroenterology*, Andrade et al. [14] presented a prospective study in 159 patients with chronic liver disease from different etiologies and compared liver steatosis determined by CAP and liver histology. The authors included patients with nonalcoholic fatty liver disease (NAFLD) and chronic viral hepatitis. They described a high accuracy for detecting mild steatosis (S1, 5–33%), moderate (S2, 34–66%), and severe steatosis (S3, >66%) with AUROC 0.822, 0.956, and 0.976, respectively, which is better than previously described in the literature [15]. As expected, in this study, significant steatosis (which was considered when at least S2), associated with metabolic factors such as arterial hypertension, dyslipidemia, type 2 diabetes mellitus, and body mass index. It did not associate with the degree of fibrosis or necroinflammatory activity. However, more important than this analysis would be to determine which factors could have an impact on the accuracy of CAP to detect/quantify hepatic steatosis. For example, it has been described in the literature that, unlike hepatic elastography, CAP is not affected by the cause of chronic liver disease [16]. However, CAP accuracy is affected by obesity and larger skin-to-capsule distance, which may cause overestimation of steatosis. In fact, a skin-to-capsule distance higher than 25 mm is associated with a 60–70 dB/m increase in CAP measurements [17]. Similarly, for lower grades of hepatic steatosis, the presence of significant fibrosis (defined as liver elastography higher than 10.1 kPa) may overestimate steatosis, with a higher CAP determination [18]. The reverse is also true, that is, liver elastography increases according to CAP. Some authors even advocate that, in patients with NAFLD, CAP should always be considered in order to avoid overestimation of liver fibrosis [18].

The next question that needs to be answered is to what extend the diagnosis of liver steatosis influences the management of patients with chronic liver disease. Regarding chronic hepatitis B (CHB), evidence does not support a role of hepatic steatosis on the progression of chronic liver disease, prognosis, or response to antiviral treatment [19–21]. In CHB, hepatic steatosis did not associate with increased levels of aminotransferases and negatively associated with HB viral load [22]. It also associated with an increased rate of HB antigen loss in 1 study [23]. On the contrary, the presence of nonalcoholic steatohepatitis can be a cause of increased aminotransferases in an inactive HB antigen carrier, which may lead to unnecessary antiviral treatment [24]. Probably, patients with CHB, liver steatosis, and persistent increase in aminotransferases should perform a liver biopsy to distinguish between viral-induced versus nonalcoholic steatohepatitis-induced aminotransferase elevation and better select for antiviral treatment.

Regarding chronic hepatitis C (CHC), the impact of liver steatosis on the prognosis and response to interferon treatment is complex and depends on the nature of hepatic steatosis, whether it is genotype 3 viral related or metabolism related [25]. With the advent of direct antiviral therapies, which are highly effective and have virtually universal indication in patients with CHC, liver steatosis is now a matter of lesser importance in CHC.

Lastly, it is important to determine the real relevance of the degree of liver steatosis in the prognosis/management of patients with NAFLD. Is there any interest in quantifying liver steatosis? The amount of liver steatosis does not seem to correlate with liver prognosis [26, 27], and there is no evidence of long-term benefits for the progression of liver disease in strategies that achieve improvement of liver steatosis [28]. However, there is accumulated circumstantial evidence that not only the presence of liver steatosis, but also the severity of steatosis correlates with adverse cardiovascular outcomes. Several epidemiological studies and meta-analyses showed that NAFLD associated with different markers of subclinical atherosclerosis (increase in carotid intima media thickness, impaired flow-mediated vasodilation, increased arterial stiffness or coronary artery calcification) [29], as well as with more than 50% increased risk for fatal and nonfatal cardiovascular events [30]. The increase in cardiovascular events was 250% in patients with severe steatosis [30, 31]. Furthermore, subclinical markers of atherosclerosis present a dose-response increase in preva-

lence according to steatosis grading by ultrasonography [32–37]. Finally, a small study reported a dose-dependent decrease in carotid intima media thickness, according to the decrease in the amount of steatosis, after a therapeutic intervention in patients with NAFLD [38]. That decrease was independent of weight loss.

In conclusion, CAP seems to be a reliable, easy method to detect and quantify liver steatosis. It should always be taken into consideration when performing hepatic elastography, since high CAP values may influence the measurement of elastography. It is not yet understood what the clinical relevance of detecting hepatic steatosis in non-NAFLD chronic liver diseases is. Regarding steatosis quantification, it does not seem to have an impact on liver prognosis, but it may influence cardiovascular prognosis, and long-term, noninvasive monitoring of hepatic steatosis quantification may have a clinical impact in the near future.

Statement of Ethics

This study did not require informed consent or review/approval by the appropriate ethics committee.

Disclosure Statement

The authors have no conflicts of interest to declare.

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