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OBSERVATIONAL STUDY

Controlled attenuation parameter for evaluating liver steatosis in chronic viral hepatitis

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Abstract

AIM: To assess the performance of controlled attenuation parameter (CAP) in patients with chronic viral hepatitis.

METHODS: CAP is a new technique that measures the attenuation in the liver of an ultrasound beam, which is directly related to lipid accumulation. Consecutive patients undergoing liver biopsy for chronic viral hepatitis were studied using the M probe of FibroScan device (Echosens, Paris, France). The device estimates liver steatosis in decibel per meter (dB/m). An expert operator performed all measurements. Steatosis was graded according to Kleiner's classification. Pearson or Spearman rank coefficient was used to test correlation between two study variables. Linear regression was used for multivariate model to assess the association between CAP and other variables. Receiver operating characteristic curve analysis was performed to calculate area under the curve (AUROC) for S0 *vs* S1-S3 and S0-S1 *vs* S2-S3.

RESULTS: 115 subjects (85 males and 30 females) were prospectively studied. The mean values of CAP were 227.1 ± 43.1 for S0; 254.6 ± 38.9 for S1; 297.8 ± 49.4 dB/m for S2-S3. In univariate analysis CAP showed a significant correlation with age, body mass index (BMI), degree of steatosis, and cholesterol. Multivariate regression analysis confirmed the correlation with the degree of steatosis [coefficient, 1.2 (0.60-1.83); $P < 10^{-5}$] and BMI [coefficient, 4.1 (0.5-7.8); $P = 0.03$] but not with all other variables. Optimal cutoff values for S $\geqslant$ 1 and S $\geqslant$ 2 were 219 dB/m [AUROC, 0.76 (0.67-0.84); sensitivity, 91.1% (78.8-97.5); specificity, 51.6% (38.7-64.2); positive predictive value, 56.9% (44.7-68.6); negative predictive value, 89.2% (74.3-97.0); positive likelihood ratio, 1.88 (1.4-2.5); negative likelihood ratio, 0.17 (0.07-0.5)] and 296 dB/m [AUROC, 0.82 (0.74-0.89); sensitivity, 60.0% (32.3-83.7); specificity, 91.5% (83.9-96.3); positive predictive value, 52.9% (27.8-77.0); negative predictive value, 93.5% (86.3-97.6); positive likelihood ratio, 7.05 (3.2-15.4); negative likelihood ratio, 0.44 (0.2-0.8)], respectively.

CONCLUSION: Controlled attenuation parameter could be a useful tool in the clinical management of patients with chronic viral hepatitis for detecting liver steatosis.

Key words: Liver steatosis; Noninvasive techniques; Controlled attenuation parameter; Transient elastography; Chronic liver disease

Core tip: A number of factors may affect response to treatment of patients with chronic viral hepatitis and it is well known that patients with liver steatosis are less responsive to antiviral drugs. On the other hand, early stages of liver steatosis are usually reversible with appropriate intervention. Controlled attenuation parameter (CAP) is a new method for non-invasive quantification of liver steatosis. The results of our study show that CAP is highly and significantly correlated with the extent of liver fat accumulation and it could be a useful tool in the clinical setting to diagnose the presence/absence of liver steatosis.

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INTRODUCTION

In developed countries liver steatosis is a major health problem since 20%-30% of the population is affected with nonalcoholic fatty liver disease[1,2]. Moreover, steatosis, oxidative stress, and insulin resistance have been proposed as important factors in hepatitis C virus (HCV) infection and are reported to be closely interconnected and responsible of accelerating the progression of fibrosis[3,4]. In patients with chronic hepatitis C the presence of liver steatosis affects the response to treatment and can predict the occurrence of hepatocellular carcinoma independently of fibrosis stage[5-7]. Steatosis is a relatively common finding in hepatitis B virus (HBV)-infected patients and metabolic host factors rather than viral factors are responsible for this finding in these patients[8].

Liver histology is the reference standard for grading steatosis even though sampling variability due to the uneven distribution of lipid accumulation throughout the liver parenchyma does exist[9]. On the other hand, liver biopsy (LB) is an invasive procedure which has some risk of morbidity and mortality, and it is not the ideal procedure to follow up patients[10]. Recently, a novel controlled attenuation parameter (CAP) for the assessment of liver steatosis has been developed[11]. CAP is based on the properties of ultrasound signal acquired by transient elastography (Fibroscan®, Echosens, Paris) using the postulate that fat affects ultrasound propagation[12]. Transient elastography is a technique that noninvasively estimates the elasticity of liver parenchyma, which is directly related to the amount of fibrosis. Several studies have shown significant positive correlation between liver stiffness measurements (LSM) and the stage of liver fibrosis[13-22]. CAP is evaluated using the same radio-frequency data, and the same region of interest used to assess LSM[23].

The aim of this study was to assess the performance of CAP in detecting liver steatosis in patients with chronic viral hepatitis undergoing liver biopsy in the same day.

MATERIALS AND METHODS

Subjects

This was a single center cross-sectional study. The performance of CAP was prospectively estimated in a cohort of consecutive patients undergoing LB for chronic viral hepatitis. Inclusion criteria were the presence of serum markers of infection with HBV/HCV, or HCV/HIV coinfection and serum alanine aminotransferase (ALT) levels > 1.5 the upper normal limit, either persistently or intermittently. Exclusion criteria was decompensated liver cirrhosis. As a rule, patients with clinically overt cirrhosis were not scheduled for LB.

Subject characteristics, epidemiological data, and biochemical tests were recorded. LB was performed on the same day as CAP and LSM, as day case procedure.

The study protocol was approved by the institutional Ethics Committee and it was in accordance with the Helsinki Declaration of 1975. Participants gave their informed written consent.

Controlled attenuation parameter

CAP and LSM were obtained by using the FibroScan® 502 touch (Echosens, Paris, France). The device estimates liver stiffness in kilopascal (kPa) and liver steatosis in decibel per meter (dB/m). The principles of CAP have been described elsewhere[11]. As of today, CAP measurement is available only on the M probe of the Fibroscan device, and it is computed only when the associated liver stiffness measurement is valid. Thus, all patients were studied by using the M probe of the Fibroscan device after fasting for at least six hours. All examinations were carried out by the same physician with three years of experience in LSM (M.Z.). As reported in the literature, only LSM with 10 validated measurements and an interquartile range/mean (IQR/M) < 30% for values higher than 7.1 kPa were considered reliable[24]. CAP examinations with no successful measurements after at least 10 attempts were deemed as failures.

Liver biopsy and histology

Ultrasound-assisted percutaneous LB was performed by three experienced physicians (C.F., G.M., and E.B.) by using an intercostal approach. A disposable 1.4-mm-diameter modified Menghini needle (Hepafix; Braun, Melsungen, Germany) was used. All biopsy specimens were fixed in formalin and embedded in paraffin. The length of each LB specimen (in centimetres) was recorded.

The specimens were interpreted on site by a single expert liver pathologist (B.D.B.), blind to CAP and LSM results, but not to the patient's clinical and biochemical data. Fibrosis and necro-inflammation were evaluated semiquantitatively according to the METAVIR system[25]. Steatosis was expressed as a percentage of fat in the hepatocytes and graded according to the method of

Table 1 Main clinical and demographic characteristics of the subjects *n* (%)

Characteristics	Total, *n* = 115	S0, *n* = 66	S1, *n* = 33	S2-S3, *n* = 16
Sex, females	30 (24.1)	16 (24.2)	10 (30.3)	4 (25.0)
Age, yr (mean ± SD)	43.1 ± 10.5	41.3 ± 11.0	46.8 ± 8.6	43.0 ± 11.1
BMI, kg/m^2 (mean ± SD)	24.8 ± 4.2	24.0 ± 3.5	25.6 ± 5.2	26.7 ± 3.6
BMI ⩾ 25 kg/m^2	57 (50.0)	28 (42.4)	18 (56.2)	11 (68.7)
AST, IU/L (IQR)	43 (28-73)	39 (25-59)	52 (31-88)	45 (35-73)
ALT, IU/L (IQR)	63 (38-110)	54 (33-73)	70 (38-142)	98 (63-125)
Alkaline phosphatase, IU/L (mean ± SD)	72.2 ± 25.5	77.1 ± 27.8	65.4 ± 16.9	62.6 ± 24.6
GGT, IU/L (IQR)	48 (26-88)	39 (20-57)	58 (32-133)	73 (40-106)
Total bilirubin, μmol/L (IQR)	0.69 (0.49-0.92)	0.70 (0.46-1.06)	0.64 (0.55-0.92)	0.70 (0.54-0.86)
Platelets count, 10^3/mm^3 (mean ± SD)	221 ± 78	229 ± 81	204 ± 66	223 ± 90
Prothrombin time, % (mean ± SD)	93.9 ± 12.6	93.4 ± 11.5	94.2 ± 15.0	95.4 ± 12.2
HCV infection	82 (71.3)	44 (66.7)	26 (78.8)	12 (75.0)
HBV infection	28 (24.3)	18 (27.3)	7 (21.2)	3 (18.7)
HCV/HIV infection	5 (4.3)	4 (6.1)	0 (0)	1 (6.2)
Fibrosis score (Metavir)				
F0	14 (12.2)	9 (13.6)	5 (15.1)	0 (0)
F1	42 (36.5)	29 (43.9)	7 (21.2)	6 (37.5)
F2	31 (27.0)	17 (25.8)	10 (30.3)	4 (25.0)
F3	18 (15.6)	9 (13.6)	7 (21.2)	2 (12.5)
F4	10 (8.7)	2 (3.0)	4 (12.1)	4 (25.0)
Activity grade (Metavir)				
A0	12 (10.4)	8 (12.1)	3 (9.1)	1 (6.2)
A1	66 (57.4)	43 (65.1)	14 (42.4)	9 (52.2)
A2	19 (16.5)	7 (10.6)	9 (27.3)	3 (18.7)
A3	18 (15.6)	8 (12.1)	7 (21.2)	3 (18.7)
LSM, kPa (IQR)	6.7 (5.1-9.1)	6.4 (4.9-8.4)	6.7 (4.8-9.5)	8.0 (5.6-11.1)
CAP, dB/m (mean ± SD)	244.4 ± 49.1	227.1 ± 43.1[a]	254.6 ± 38.9[b]	297.8 ± 49.4[d]

SD values represent mean, and interquartile range (IQR) values represent median. [a]$P < 0.05$ (S0 *vs* S1); [b]$P < 0.01$ (S1 *vs* S2-S3); [d]$P < 0.01$ (S0 *vs* S2-S3). BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: Gamma-glutamyl transferase; CAP: Controlled attenuation parameter; LSM: Liver stiffness measurement.

Kleiner *et al*[26] as S0, steatosis in less than 5% of hepatocytes; S1, 5%-33%; S2, 34%-66%; and S3, more than 66%. For the purpose of this study, S2 and S3 grades were grouped in the subsequent statistical analysis.

Statistical analysis

Sample size considerations for performance of CAP: A total sample size of 115-which includes 50 subjects with the disease, *i.e.* a prevalence approximately 45%-achieves 83% power to detect a change in sensitivity and in specificity from 0.80 to 0.90 using a one-sided binomial test. The target significance level is 0.05.

Descriptive statistics were produced for demographic, clinical and laboratory characteristics for this study sample of patients. The Shapiro-Wilk test was used to test the normal distribution of quantitative variables. When quantitative variables were normally distributed, the results were expressed as mean values and SD, otherwise median and interquartile range (IQR; 25th-75th percentile) were reported; qualitative variables were summarized as counts and percentages. One-way ANOVA or Kruskal-Wallis analysis of variance by ranks, with Bonferroni correction, was used to analyze differences among patients undergoing liver biopsy. Pearson or Spearman rank coefficient was used to test correlation between two study variables. Linear regression was used for multivariate model to assess the association between CAP and other variables. The diagnostic performance of CAP was assessed by using receiver operating characteristic (ROC) curves and the area under the ROC (AUROC) curve analysis.

Data analysis was performed with STATA statistical package (release 11,1, 2010, Stata Corporation, College Station, Texas, United States) and Medcalc (Version 11.2, 2011 MedCalc Software bvba, Be).

RESULTS

From February 2012 to November 2013, 115 subjects were enrolled into the study. For all patients the consumption of alcohol was less than 20 g/d. The characteristics of the study population is shown in Table 1.

In six patients (5.2%) the examination failed with the M probe of the Fibroscan device. No unreliable measurements were obtained. In all patients LB was performed on the same day as CAP and LSM measurements, no complication was observed. The mean length of the LB specimen was 2.2 (0.73) cm. At histology, all specimens contained ⩾ 10 portal tracts. None of the specimens showed steatohepatitis or siderosis. Sixty-six (57.4%) subjects were S0, 33 (28.7%) S1, 11 (9.6%) S2, and 5 (4.3%) S3.

In univariate analysis CAP showed a significant correlation with age, body mass index (BMI), degree of steatosis, and cholesterol. Corresponding *r* values were 0.29 ($P = 0.002$); 0.55 ($P < 10^{-3}$); 0.55 ($P < 10^{-3}$); 0.35 ($P = 0.04$), respectively. LSM showed a significant correlation with METAVIR stage, METAVIR grade, AST, and platelets. Corresponding *r* values were 0.41 ($P < 10^{-3}$); 0.28 ($P = 0.003$); 0.26 ($P = 0.02$); 0.23 ($P = 0.04$) respectively.

Table 2 Sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, negative likelihood ratio of controlled attenuation parameter best cut-off values

	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV% (95%CI)	NPV% (95%CI)	+LR (95%CI)	-LR (95%CI)
S ⩾ 1	91.1 (78.8-97.5)	51.6 (38.7-64.2)	56.9 (44.7-68.6)	89.2 (74.3-97.0)	1.88 (1.4-2.5)	0.17 (0.07-0.5)
S ⩾ 2	60.0 (32.3-83.7)	91.5 (83.9-96.3)	52.9 (27.8-77.0)	93.5 (86.3-97.6)	7.05 (3.2-15.4)	0.44 (0.2-0.8)

PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio.

Multivariate regression analysis confirmed the correlation with the degree of steatosis [coefficient, 1.2 (95%CI: 0.60-1.83); $P < 10^{-5}$] and BMI [coefficient, 4.1 (95%CI: 0.5-7.8); $P = 0.03$] for CAP, and with METAVIR stage for LSM [3.1 (coefficient, 95%CI: 0.25-5.9); $P = 0.03$)] but not with all other variables.

The mean values of CAP were 227.1 ± 43.1 dB/m for S0; 254.6.4 ± 38.9 dB/m for S1; 297.8 ± 49.4 dB/m for S2-S3. ROC curve analysis showed that optimal cut-off values for the diagnosis of steatosis - S0 *vs* S1-S3 (S ⩾ 1) - and for the assessment of significant steatosis-S0-S1 *vs* S2-S3 (S ⩾ 2)-were 219 dB/m [AUROC, 0.76 (95%CI: 0.67-0.84)] and 296 dB/m [AUROC, 0.82 (95%CI: 0.74-0-89)]. The corresponding sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio are reported in Table 2. CAP demonstrated excellent negative predictive value for assessing and grading steatosis. For the diagnosis of liver steatosis 35 of 109 (32.1%) subjects were misclassified, of these 31 were false positive cases and 4 false negative. The 31 false positive cases had a significantly higher BMI compared to the 33 true negative cases [25.6 (3.4) *vs* 22.1 (2.3); $P < 0.0001$].

DISCUSSION

The availability of new and more effective treatment options for patients with chronic hepatitis has questioned the utility of liver biopsy, that is an invasive procedure not free of risks. As a consequence, non-invasive methods for assessing liver fibrosis are becoming widely used[13-22,24]. They have no complications and can be performed also to monitor progression or improvement of liver fibrosis over time. On the other hand, a number of factors may affect response to treatment of patients with chronic viral hepatitis and it is well known that patients with liver steatosis are less responsive to antiviral drugs[6]. In patients with chronic hepatitis C liver steatosis is associated with the progression of liver fibrosis[5]. Thus, there is a need to noninvasively and reliably assess not only fibrosis but also fatty infiltration of the liver. Moreover, early stages of liver steatosis are usually reversible with appropriate intervention. Magnetic resonance imaging shows high accuracy for quantification of liver steatosis, but it has high cost and is too complex to be used to monitor the disease[27]. Ultrasound is a low cost imaging modality but it lacks sensitivity for detection of mild steatosis. CAP is a new method for quantification of liver steatosis, and it has the advantage of being measured at the same time as liver stiffness and it is not influenced by fibrosis[11,12].

The results of our study show that CAP is highly and significantly correlated with the percentage of liver fat accumulation and it could be a useful tool in the clinical setting to diagnose the presence/absence of liver steatosis. In our series, in the detection of liver steatosis CAP misclassified one third of cases. Nonetheless, the technique showed a high sensitivity, thus it was able to confidently identify patients with liver steatosis.

The optimal cut-off value obtained in our series for the diagnosis of steatosis (S ⩾ 1) is similar to that obtained by Sasso *et al*[12] in a series of patients with chronic hepatitis C and by de Lédinghen *et al*[28] in a series of patients with chronic hepatitis of mixed etiologies.

We observed that the performance of CAP in detecting and quantifying liver steatosis was moderate compared to what was found in other series which included patients with alcoholic liver disease and metabolic syndrome[11]. These differences may be due to the low prevalence of steatosis in our series of patients with chronic viral hepatitis.

In our study CAP values were not influenced by fibrosis stage or necro-inflammation but, in addition to the degree of liver steatosis, a correlation between CAP and BMI that persisted in multivariate analysis after correction for confounding variables was found. We would like to underline that in our series the false positive cases for S=0 had significantly higher BMI. This finding could be due to the comparison with a histological classification that is fairly subjective for low grades of liver steatosis. Moreover, it should be underlined that we compared a method that gives continuous measurements - such as CAP-to liver histology, which gives a semiquantitative grading of steatosis in a categorical scale. On the other hand, the histological grading of fatty infiltration of the liver is not a perfect gold standard because it examines only a small sample and this could lead to sampling bias especially when fat is heterogeneously distributed throughout the liver as it may happens in mild steatosis[29]. This difference could reduce the information given by the CAP method. CAP is evaluated in the same region of interest of LSM, which is a volume at least 100 times bigger than a biopsy sample thus more representative of liver parenchyma[14]. Further studies aimed at comparing CAP also with techniques that give a quantification of the fat in the liver may help understanding whether there is any limitation when using as reference a histological classification of liver steatosis based only in a four-point scale.

The optimal cutoff value to assess significant steatosis

(S ⩾ 2) was similar to that obtained in another series and it had only a fair positive predictive value, probably due to the low prevalence of subjects with grade S2 or more in our study population[30].

This study has limitations. First, even though consecutive subjects were studied, a low prevalence of severe obesity was observed in our cohort. Second, we did not assess the correlation with biochemical markers of liver steatosis because they were available only for some subjects. Nonetheless, BMI could be regarded as a surrogate marker of the metabolic syndrome, thus we believe that this is not a flaw of the study. Third, the accuracy of the method was evaluated in a small number of subjects. Fourth, the patients undergoing liver biopsy had chronic viral hepatitis, thus the applicability of the cutoffs in the general population and in patients with nonalcoholic fatty liver disease could be limited and needs to be further validated to determine the possible influence of etiology.

In conclusion, CAP could be a useful tool in the clinical management of patients with chronic viral hepatitis for detecting liver steatosis. Further studies in larger series are needed to assess the value of CAP in grading liver steatosis.

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COMMENTS

Background

In developed countries liver steatosis is a major health problem since 20%-30% of the population is affected with nonalcoholic fatty liver disease. Moreover, steatosis, oxidative stress, and insulin resistance have been proposed as important factors in hepatitis C virus infection and are reported to be closely interconnected and responsible of accelerating the progression of fibrosis.

Research frontiers

Liver histology is the reference standard for grading steatosis even though sampling variability due to the uneven distribution of lipid accumulation throughout the liver parenchyma does exist. On the other hand, liver biopsy is an invasive procedure which has some risk of morbidity and mortality, and it is not the ideal procedure to follow up patients. Recently, a novel controlled attenuation parameter (CAP) for the noninvasive assessment of liver steatosis has been developed.

Innovations and breakthroughs

A number of factors may affect response to treatment of patients with chronic viral hepatitis and it is well known that patients with liver steatosis are less responsive to antiviral drugs. Moreover, early stages of liver steatosis are usually reversible with appropriate intervention. Magnetic resonance imaging shows high accuracy for quantification of liver steatosis, but it has high cost and is too complex to be used to monitor the disease. Ultrasound is a low cost imaging modality but it lacks sensitivity for detection of mild steatosis. CAP is a new method for quantification of liver steatosis, and it has the advantage of being measured at the same time as liver stiffness and it is not influenced by fibrosis.

Applications

CAP could be a useful tool in the clinical management of patients with chronic viral hepatitis for detecting liver steatosis. Further studies in larger series are needed to assess the value of CAP in grading liver steatosis.

Terminology

CAP is a measure of the ultrasound attenuation which corresponds to the decrease in amplitude of ultrasound waves as they propagate through the liver. The unit of measure is decibel per meter.

Peer review

The manuscript is well documented and interesting. The performance of methodology and the statistical analysis are very well established. The study is in agreement with previous ones that have shown the correlation of CAP with liver steatosis. He also believes that the development and standardization of CAP will be a useful tool in the future in detecting and measuring steatosis. Concerning the limitations of the study He agrees with the authors that CAP needs to be further validated in a larger number of patients with respect to the etiology of steatosis (viral hepatitis, non-alcoholic fatty liver disease), but the efforts the authors have done still remains reliable.

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