Comparison of Controlled Attenuation Parameter and Liver Biopsy to Assess Hepatic Steatosis in Pediatric Patients

Nirav K. Desai, MD[1], Sarah Harney, BA[1], Roshan Raza, MD[1], Alyaa Al-Ibraheemi, MD[2], Nick Shillingford, MD[2], Paul D. Mitchell, MS[3], and Maureen M. Jonas, MD[1]

Objective To assess whether the degree of steatosis as determined by controlled attenuation parameter (CAP) measurements correlates with that observed on liver biopsies in a single-center pediatric and young adult cohort.

Study design This cross-sectional study included patients undergoing liver biopsy as part of standard clinical care between January 25, 2012, and April 1, 2015, at Boston Children's Hospital. Eligible patients, with a variety of liver diseases, had CAP measurements within 1 year of biopsy. CAP values were compared across histologic steatosis grades using ANOVA.

Results Sixty-nine patients (mean age, 16.0 ± 2.9 years; 62% male) were studied. CAP measurements were obtained at a median of 1.3 months (IQR, 0.5-3.2) after biopsy. Of the 69 subjects, 23 had steatosis on biopsy. Mean CAP value (dB/m) for subjects with no steatosis was 198 ± 37 vs 290 ± 47 for subjects with steatosis ($P < .0001$). There were statistically significant differences between CAP values in individuals with no steatosis vs mild/moderate steatosis ($P < .0001$), no steatosis vs marked steatosis ($P < .0001$), and mild/moderate vs marked steatosis ($P = .004$).

Conclusion This study demonstrated a difference in CAP between no steatosis and steatosis, and between grades of steatosis. CAP may be a useful noninvasive tool to detect hepatic steatosis in children. *(J Pediatr 2016;173:160-4)*.

Hepatic steatosis results from the accumulation of excess lipids in hepatocytes and is considered abnormal when the hepatic fat content exceeds 5% of liver weight. Nonalcoholic fatty liver disease (NAFLD) is currently the most common form of chronic liver disease in both children and adults.[1] Based on an autopsy study, 1 in 10 children or adolescents in the US has NAFLD.[2] A recent systematic review and meta-analysis of children ages 1-19 years reported a pooled mean prevalence of NAFLD of 7.6% among children treated at general clinics, and 34% among children treated at obesity clinics.[3] Aside from obesity and the metabolic syndrome, other diseases and medications can result in hepatic fat accumulation.[4]

The most commonly used noninvasive tests to diagnose NAFLD include liver enzymes and ultrasound imaging. However, these modalities lack sensitivity and the ability to consistently detect and quantify hepatic fibrosis. In the SAFETY study, the sensitivity of alanine aminotransferase for the detection of NAFLD, hepatitis B, and hepatitis C ranged from 32%-48% when using hospital-based cutoffs.[5] Ultrasound is machine and operator dependent, and is affected by extrahepatic adipose tissue; it has low positive predictive value, and has low sensitivity when steatosis is <30%.[6,7] Liver biopsy remains the standard for assessment of the degree of steatosis but is limited by invasiveness, cost, and the potential for sampling error, and rarely can result in complications.[8] Other methods include quantification of fat by computed tomography and magnetic resonance imaging (MRI), but these examinations are expensive and either involve radiation or require special technology, so are not used routinely at this time in clinical practice.[9]

A novel noninvasive method utilizing ultrasound, called the controlled attenuation parameter (CAP), has been developed to assess hepatic steatosis. Because fat affects ultrasound propagation, CAP is based on the radiofrequency ultrasound signal acquired by the transient elastography device (Fibroscan, Echosens, Paris, France). CAP is an estimate of the ultrasonic attenuation coefficient at 3.5 MHz. It is evaluated in the same region of interest as that used for liver stiffness measurement and uses the same radiofrequency data. CAP can only be acquired if the transient elastography liver stiffness measurement is valid (because it depends on an ultrasonic attenuation value).[10] These measures are reproducible, as well as operator and machine independent.[11]

Given the ability of CAP to detect and grade hepatic steatosis in adults, the aim of this study was to assess whether the degree of steatosis as determined by liver

BMI	Body mass index
CAP	Controlled attenuation parameter
MRI	Magnetic resonance imaging
NAFLD	Nonalcoholic fatty liver disease

From the [1]Division of Gastroenterology, Hepatology and Nutrition, [2]Department of Pathology, and [3]Clinical Research Center, Boston Children's Hospital, Boston, MA

Echosens (Paris, France) provided the FibroScan machine, technical support, and training of investigators for the purpose of this and other studies, but did not have a role in study design, collection/analysis/interpretation of data, writing of the manuscript, or the decision to submit the manuscript for publication.

http://dx.doi.org/10.1016/j.jpeds.2016.03.021

biopsy correlates with CAP measurements in a pediatric and young adult cohort with liver disease.

Methods

This cross-sectional study included children and young adults who underwent liver biopsy and CAP measurement at Boston Children's Hospital between January 2012 and April 2015. Patients with incomplete critical biochemical data or unavailable/uninterpretable biopsy specimens were not included. Patients were also excluded if they were not candidates for CAP because of ascites, pregnancy, or an implantable cardiac device (as suggested by the manufacturer). Clinical and biochemical data were the closest values within 6 months before or after the date of CAP measurement. Data collected included aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, and albumin. Anthropometric data includes height and weight. This study was approved by the Boston Children's Hospital Institutional Review Board. Written informed consent was obtained from parents, guardians, and subjects ≥18 years of age.

All subjects underwent liver biopsy for clinical indications. Histologic specimens were reviewed retrospectively by 1 of 2 pathologists who were blinded to clinical diagnosis, initial pathology assessment, and CAP measurement. A biopsy specimen was considered adequate for evaluation if ≥1.5 cm long and it contained a minimum of 6 portal tracts. Steatosis was categorized as none (S0, <5%), mild (S1, 5%-30%), moderate (S2, 31%-60%), or marked (S3, >60%).

Hepatic steatosis was measured by CAP using signals acquired by FibroScan (Echosens). CAP measures ultrasonic attenuation in the liver at 3.5 MHz at depth between 25 and 65 mm. CAP was performed by trained study investigators who were certified by the manufacturer and blinded to the liver biopsy results. All female subjects aged >12 years were required to have a negative urine pregnancy test before undergoing CAP. All subjects had a thoracic perimeter >75 cm and CAP measurements were ascertained using the "M" or "XL" probe according to the manufacturer's specifications. CAP measurements are not available using the "S" probe, so children with thoracic perimeter of <75 cm were excluded. The reported CAP measurement (dB/m) was the median of 10 measurements.

Statistical Analyses

Categorical data are reported as frequency (%) and continuous data as mean values ± SD when normally distributed and median (IQR) otherwise. CAP measurements were approximately normally distributed, but owing to the small sample size were analyzed both nonparametrically and parametrically. Results were consistent, and only parametric results are shown. Subjects with mild (n = 7) and moderate (n = 4) steatosis were combined to increase power. Two-group comparisons were made with Student *t* test, and 3-group comparisons with ANOVA. Pairwise comparisons were made using Fisher protected least significant difference. Receiver operator characteristic analysis was used to determine an optimal cut point for predicting steatosis from CAP measurements. Owing to the small number of subjects with steatosis, no attempt was made to determine CAP cutpoints for distinguishing mild, moderate, and marked steatosis. All tests were 2-sided, and $P < .05$ was established a priori as statistically significant. Analysis was performed with SAS version 9.3 (SAS Institute Inc, Cary, North Carolina).

Results

A total of 145 subjects were enrolled, of whom 76 were excluded from analysis owing to invalid measurements (n = 5; 3 patients with a fatty abdominal wall, 1 with high IQR, and 1 unknown), scan with S probe (n = 67), or lack of liver steatosis assessment on biopsy (n = 4). A total of 69 patients were analyzed (64 M probe and 5 XL probe).

The mean age of subjects was 16.0 ± 2.9 years, 84% were <18 years, and 62% were male. The median body mass index (BMI) was 22.6 kg/m^2 (IQR, 19.6-29.2). Subjects had a variety of liver disease diagnoses. These and other subject characteristics are shown in **Table I**. Subjects with steatosis were similar in age and sex to those without steatosis, but had greater BMI and greater prevalence of NAFLD (**Table II**).

The median time between liver biopsy and CAP measurement was 1.3 months (IQR, 0.5-3.2). The mean CAP measurement for patients without steatosis was 198 ± 37 vs 290 ± 47 dB/m for patients with steatosis ($P < .0001$; **Figure 1**, A). CAP also distinguished severity of steatosis. Mean CAP measurement for patients with no steatosis was 198 ± 37 dB/m compared with 265 ± 53 dB/m for patients with mild or moderate steatosis ($P < .0001$) and 313 ± 25 dB/m for patients with marked steatosis ($P < .0001$). In addition, the mean CAP in patients with mild or moderate steatosis was statistically different from that in patients with marked steatosis ($P = .004$; **Figure 1**, B). The effect of being overweight or obese (BMI ≥85th percentile if age <20 years; BMI ≥25 kg/m^2 otherwise) on CAP measurement was investigated by including an interaction for the effect of being overweight or obese (yes/no) with steatosis (yes/no) in an ANOVA. The interaction effect was not significant ($P = .81$). CAP measurements were statistically higher in patients with steatosis than those without steatosis, regardless of whether patients were overweight or obese ($P = .0008$) or normal weight ($P = .003$; **Table III**; available at www.jpeds.com). The sample size was too small to investigate whether or not being overweight or obese modifies the effect of CAP across steatosis severity levels (mild, moderate, marked). An optimal cut point of 225 dB/m for predicting steatosis was identified, with