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Hepatic steatosis is highly prevalent but is not correlated with stiffness in autoimmune hepatitis

Sai Chalasani, Karan Mathur, MD, Nicole Shammas, Eric Orman, MD, Raj Vuppalanchi, MD, Craig Lammert, MD*

Abstract

The prevalence and impact of hepatic steatosis among patients with autoimmune hepatitis (AIH) is not well described.

We conducted a cross-sectional study to determine the prevalence of hepatic steatosis in AIH patients and examined its relationship with hepatic fibrosis using vibration controlled transient elastography. Liver stiffness measurement (LSM), controlled attenuation parameter (CAP), gender, current age, and body mass index (BMI) were collected from 277 AIH patients. Hepatic steatosis was defined as CAP >263 db/m.

The study participants were mostly female (82%) with an average age of 49 years and BMI 29.7 kg/m^2. Mean LSM was 12.5 (standard deviation 13.5) kPa and CAP was 244 (standard deviation 63) db/m. The prevalence of coexisting steatosis was 33.2%, and steatosis did not correlate with LSM ($r = 0.05$, $P = .46$). In this study, only gender (females with 31% lower LSM on average compared to males, $P = .001$) and BMI (each unit increase of BMI resulted in a 1.48% increase on average LSM, $P = .01$) correlated with LSM. Male gender had significant association with increased LSM, after controlling for age, BMI, and CAP ($P = .001$).

This exploratory study using noninvasive vibration controlled transient elastography revealed hepatic steatosis is highly prevalent in patients with AIH but not associated with liver fibrosis.

Abbreviations: AIH = autoimmune hepatitis, BMI = body mass index, cACLD = compensated advanced chronic liver disease, CAP = controlled attenuation parameter, GRACE = genetic repository of autoimmune liver diseases and contributing exposures, LSM = liver stiffness measurement, NAFLD = non-alcoholic fatty liver disease, NASH = non-alcoholic steatohepatitis, s.d. = standard deviation, VCTE = vibration controlled transient elastography.

Keywords: autoimmune hepatitis, body mass index, controlled attenuation parameter, fibroscan, inflammation, liver stiffness measurement, male, stiffness, vibration controlled transient elastography

1. Introduction

Autoimmune hepatitis (AIH) is a rare chronic progressive inflammatory disorder affecting genetically susceptible individuals in whom external environmental factors trigger a cascade of T cell mediated response.[1] Obesity in autoimmune conditions has garnered increased interest due to its recent exponential rise.[2] There is limited data on how non-alcoholic fatty liver disease (NAFLD), an obesity-related liver disease may affect AIH in terms of prevalence, treatment, and outcomes.[3–5] Thus, the American Association for the Study of Liver Diseases have recently updated AIH guidelines to suggest screening AIH patients for metabolic syndrome, as its presence may require modification of the commonly used glucocorticoid regimen in AIH.[6]

NAFLD has a huge epidemiologic burden on a global level, with its prevalence estimated to be about 24% worldwide.[2,7] The prevelance of NAFLD among patients with AIH is currently unknown. Accurate diagnosis and treatment of concurrent NAFLD and AIH are important as these clinical entities can be hard to differentiate clinically since IAIHG diagnostic score[8] for AIH can be falsely elevated due to non-specific rise in autoantibodies in NAFLD[9] and overlapping histological findings.[3] Importantly, treatment of AIH with corticosteroids can also contribute to NAFLD development and progression.[10]

Very limited studies have reported clinical or histologic assessments of coincident AIH and NAFLD. One retrospective study by De Luca-Johnson et al determined patients with coincident AIH and NASH on histology had worse clinical outcomes when compared to patients with AIH and simple steatosis and AIH alone.[5] A larger retrospective Japanese study revealed patients with histologic evidence of both AIH and NAFLD were more likely male, older, and had more histologi-

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This retrospective study collected information from previously collected database. Local IRB approved the methodology utilized in this study.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Indiana University School of Medicine, Indianapolis, IN.

* Correspondence: Craig Lammert, Indiana University School of Medicine, 702 Rotary Circle, Suite 205, Indianapolis, IN 46202 (e-mail: clammert@iu.edu).

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cally progressive fibrosis compared to those with AIH alone.[3] Both studies utilized liver histology to determine outcomes and non-invasive diagnostic methods were not evaluated.

Vibration controlled transient elastography (VCTE) is a promising noninvasive tool in assessing advanced fibrosis with NAFLD[11,12] and a recent systematic review showed that VCTE had good performance in fibrosis staging of AIH.[13] Furthermore, VCTE by FibroScan (Echosens, Paris, France) also allows measurement of controlled attenuation parameter (CAP), a parameter that correlates to the degree of hepatic steatosis.[12] VCTE is therefore an attractive tool to noninvasively evaluate the degree of hepatic fibrosis and steatosis among patients with AIH. We aimed to determine the prevalence of NAFLD in patients with AIH and examine its relationship with hepatic fibrosis using VCTE.

2. Methods

2.1. Participants

AIH patient data were collected from 2 separate cohorts: Genetic Repository of Autoimmune Liver Diseases and Contributing Exposures (GRACE) Study at Indiana University and 2 national Autoimmune Hepatitis Association (AIHA) patient conferences held in Indianapolis in 2017 and 2019. The present study and included cohorts conform to the ethical guidelines of the 1975 Declaration of Helsinki, and have been approved by the Institutional Review Board of Indiana University.

The GRACE study[14] has been described previously. Briefly, this ongoing AIH patient repository was initiated in 2014 to collect retrospective and prospective AIH cases in order investigate genetic and environmental underpinnings of disease development. VCTE (performed via FibroScan, 502 Touch) was collected among GRACE participants at time of clinical appointments between 2014 and 2018 (Fig. 1). If multiple examinations were present, the most recent VCTE data was used in this study. All AIH patients within the GRACE study had confirmed AIH per recent clinical guidelines.[8]

The AIHA (www.aihep.org) is a national non-for-profit patient organization with the objective of providing high quality disease education and research opportunities to over 1700 current members. During the 2017 and 2019 AIHA patient conferences, complimentary VCTE (FibroScan, 502 Touch) was offered to AIH patients in attendance (Fig. 1). VCTE was advertised to conference registrants 2 months before each conference and interested individuals signed up in person for a dedicated 10-minute appointment after confirmation of AIH diagnosis. Because of the unique nature of this study, the clinical variables collected were limited to gender, current age, body mass index (BMI), and VCTE measurements.

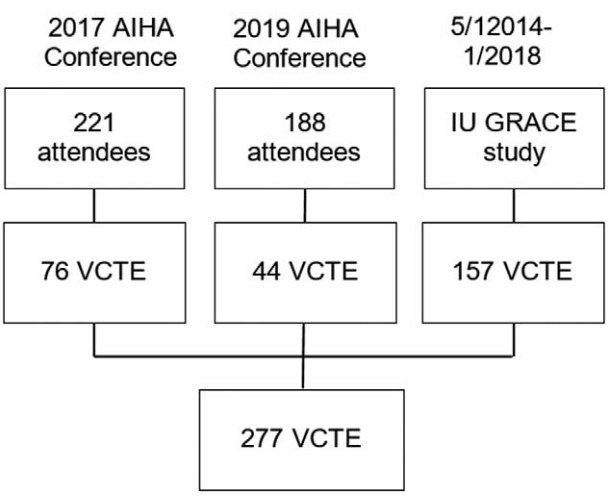

Figure 1. Flowchart of AIH patient Groups and VCTE examinations. AIH = autoimmune hepatitis, VCTE = vibration controlled transient elastography.

2.2. VCTE and measurements

VCTE collects liver stiffness measurements (LSM) and CAP simultaneously. Automatic probe selection tool within the machine recommended the probe size, either M+ or XL+, for use at the time of exam. VCTE was conducted in standard fashion[15] with patients laying supine with right arm fully abducted, while LSM and CAP measurements were collected via the right hepatic lobe through an intercostal space. Median LSM was recorded in kPa, whereas CAP was in db/m. Only participants fasting for 3 hours before examination were eligible for exam in both the GRACE and AIHA groups. Nurses or research technicians certified by the manufacturer performed VCTE included in this study.

We used a CAP cutoff of 263 db/m in order to examine prevalence of steatosis within our study cohort. Recently, Siddiqui et al[12] used as 90% fixed sensitivity among a large NAFLD cohort with paired VCTE and liver biopsy data to identify a CAP value of 263 db/m providing 0.35 specificity and 0.96 positive predictive value for detecting the presence of >= 5% of steatosis. We further evaluated our cohort according to the definition of compensated advanced chronic liver disease (cACLD) as defined by the recent Baveno VI Consensus.[16] Accordingly, LSM measurements of 10 to 15 kPa was identified as suggestive of cACLD and >15 kPa was highly suggestive of cACLD.

2.3. Data analysis

Continuous variables were summarized using means and standard deviations (s.d.). *P*-values were obtained using the Students *t* test. The relationships between LSM and other characteristics were examined using linear regression. Due to its skewness, LSM was log transformed in the models and the resulting beta coefficients transformed for interpretation. Multiple linear regression examined the independent associations of the factors with LSM adjusted for the other factors in the model. Analyses were performed using Stata SE (v 15.1).

3. Results

In total, there were 277 AIH patients included in the final analysis (157 VCTE from the GRACE Study and 120 from AIHA conferences) (Fig. 1). The study cohort was mostly female (82%) and were 49 years-old (s.d. 15.4) on average with a BMI of 29.7 kg/m^2 (s.d. 7.2). The mean LSM for the cohort was 12.5 kPa (s.d. 13.5) and CAP was 244 db/m (s.d. 63). According to the Baveno VI Consensus, 57.4% of the study cohort had at least suggestive and 20.6% had highly suggestive cACLD.

Using a cutoff of 263 db/m,[12] the prevalence of steatosis in our cohort was 33.2%. Steatosis did not correlate with LSM ($r = 0.05$, $P = .46$). Patients with steatosis had higher BMI (33 kg/m^2 vs 27.8 kg/m^2, $P < .001$) and tended to be more often male

Table 1

Comparison of gender according to patient characteristics.

	Females n = 227	Males n = 50	*P*-value
Age, years	50 (15)	48 (17.5)	NS
BMI, kg/m^2	30 (8)	29 (5.6)	NS
CAP, db/m	240 (64)	262 (54)	**.009**
LSM, kPa	11.3 (11.9)	18 (18.4)	**.009**

BMI = body mass index, CAP = controlled attenuation parameter, LSM = liver stiffness measurement.

(44.9% vs 31.4%, $P < .07$) compared to patients without steatosis. There was no difference among steatosis groups according to the Baveno VI Consensus of cACLD of highly suggestive, suggestive, or unlikely.

Given a higher proportion of males among the patients with steatosis, we compared clinical characteristics according to gender (Table 1). BMI and current age were no different according to gender, yet differences existed according to parameters of VCTE. The mean LSM in males (18 kPa [s.d. 18.4]) was higher compared to females (11.3 kPa [s.d. 11.9], $P = .009$). Further, males were more likely to have at least suggestive or highly suggestive cACLD (57.1%) than females (32.3%, $P = .002$). The mean CAP was also different according to gender (males: 262 db/m [s.d. 54] vs females: 240 db/m [s.d. 64], $P = .009$).

Gender and BMI both correlated with LSM in this study, but not CAP or current age (Table 2). Female participants had LSM values 31% lower than males on average ($P = .001$) and each increase in unit of BMI resulted in a 1.48% increase on average in LSM values. A linear regression model was used to assess both gender and BMI association with increased stiffness while controlling for age and CAP. Gender remained significantly associated with increased LSM (females had 30.1% lower LSM values than males on average, $P = .001$). In this model, BMI was no longer strictly statistically significant (1.4% increase in average LSM per increased unit of BMI, $P = .052$).

4. Discussion

Many believe that NAFLD will continue to burden global healthcare, yet its concurrent impact on preexisting chronic liver disease progression, treatment, and outcomes are not well established. Despite the rarity of AIH, establishment of coincident AIH-NAFLD remains key, as histologic data has suggested that these patients have increased risk of progressive fibrosis and higher enzyme and immunoglobulin G levels after treatment than those with AIH alone.[3] Notwithstanding, other non-invasive testing measures have also identified NASH patients with increased risk of cardiovascular outcomes as well.[17]

In this large cross-sectional study of AIH patients using VCTE along with recent criteria for detecting steatosis[12] we observed prevelance of steatosis at 33.2%. Interestingly, CAP did not correlate with LSM, yet gender was significantly associated with LSM in a regression model. Males had on average a 30.1% higher LSM value compared to females when controlling for current age, BMI, and CAP.

Based on known underlying prevalence of NAFLD in the general population, we would expect that nearly 30% of any specific liver disease group should have at least concurrent NAFLD and less so non-alcoholic steatohepatitis (NASH).[2] Using noninvasive testing, our study revealed a NAFLD prevelance of 33.2%, which was higher than Japanese (17%) and similar to recent North American (30%) histologic studies. In comparison to the De Luca-Johnson study,[5] we had over 200 more patients in our cohort but were only able to identify NAFLD based on CAP and unable to discern patients with NASH. This may be important, as the De Luca-Johnson study determined AIH patients with concurrent NASH were more likely to present with cirrhosis and have decreased survival due to liver-related death.[5] CAP did not correlate with LSM in our study (Table 2), but given our study size and number of male patients (n = 50) we were able to identify a robust association between gender ($P = .001$) and stiffness.

Incomplete biochemical response (normalization of liver tests and immunoglobulin G) to immunosuppressant therapy in AIH occurs in approximately 15%[18] of patients with nearly 10% having treatment failure.[19] The heterogeneity of biochemical response is unclear among AIH patients, yet some have hypothesized unknown genetic determinants or environmental factors/triggers could be attributable.[20] Hard to treat patients may also be enriched with those having concurrent NASH, yet natural history studies in AIH have lacked the clinical resolution to identify this as a contributing factor. Data from the Takahasi study[3] show that AIH patients with NAFLD have higher levels of liver enzymes and immunoglobulin G after treatment and are more likely to have advanced fibrosis at presentation compared to AIH alone. In fact, metabolic liver injury has been shown to potentiate the severity of AIH (increased inflammatory cell infiltrate, fibrosis, and number of liver autoantigen-specific T-cells) in a CYP2D6 mouse model of AIH.[21]

In our study, CAP and current age had no association with measured LSM. CAP was not surprising given simple steatosis with AIH has not shown impact on clinical outcome previously[5] and we anticipated only a small fraction of the AIH-NAFLD cohort (92 patients) would have AIH-NASH. Young onset of AIH as well as cirrhosis at diagnosis has been a predictor of worse overall outcomes, yet young onset has not correlated with more advanced fibrosis.[22] In our study, gender was correlated with LSM, and males had on average 30.1% higher stiffness than females ($P = .001$). Males and females were similar in age and

Table 2

Linear regression with and without adjustment for patient characteristics.

Risk factor	Unadjusted % change stiffness/unit	*P*-value	Adjusted % change stiffness/unit	*P*-value
Gender	−31 (−44.5, −14.3)	**.001**	−30.1 (−45.3, −13.7)	**.001**
Age	−0.2 (−0.75, 0.35)	.47	−0.12 (−0.69, 0.46)	.69
BMI	1.48 (0.28, 2.69)	**.01**	1.4 (−0.01, 2.8)	.052
CAP	0.08 (−0.05, 0.22)	.23	0.01 (−0.15, 0.17)	.94

BMI = body mass index, CAP = controlled attenuation parameter.

BMI, but did have higher CAP levels than females (262 db/m vs 240 db/m, $P = .009$) (Table 1). Gender differences in AIH studies remains limited and only few studies have shown to male patients have higher frequencies of DRB1*03:01, worse overall survival, and increased development of hepatocellular cancer.[22,23] Despite not being strictly statistically significant, increasing BMI also tended to associate with higher LSM. We speculate that other unmeasured metabolic factors beyond elevated CAP may have a role in the development and evolution of concurrent NASH and AIH. Therefore, future studies of coincident AIH and NAFLD should further examine other metabolic risk factors, PNPLA3 genetic variants, and consider treatment course (corticosteroids) to date.

Despite our sample size, our study does have limitations worth noting. We utilized a novel approach to collect patients for study but this inherently limited our ability to collect clinical information and codify AIH diagnostic criteria (AIHA conference patients). Patients attending the AIHA patient conference have a high likelihood of accurate disease reporting, as we have shown AIH patients recruited for the GRACE study from social media have excellent diagnosis congruency with their treating physicians.[14] Furthermore, the cross-sectional nature of this study limits the application for the current management of AIH. However, this data demonstrates the coexistence of NAFLD and AIH in many and solidifies the clinical importance of taking an aggressive individualized approach in subgroups of AIH such as males, elevated BMI, and those with poor biochemical response (possibly related to NASH). These factors should be carefully examined as we design the larger prospective AIH studies we need to fully elucidate clinical heterogeneity.

In summary, our cross-sectional study of AIH patients with non-invasive VCTE data suggest that AIH with concurrent NAFLD is prevalent and male gender may be a risk factor for more advanced fibrosis. More studies are needed to further investigate these observations.

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Author contributions

Conceptualization: Raj Vuppalanchi, Craig Lammert.
Formal analysis: Nicole Shammas, Eric Orman.
Writing – original draft: Sai Chalasani, Karan Mathur, Nicole Shammas, Craig Lammert.
Writing – review and editing: Sai Chalasani, Karan Mathur, Eric Orman, Raj Vuppalanchi, Craig Lammert.

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