Annals of Pediatric Research

Research Article
Published: 28 Sep, 2020

A Comparison between Body Mass Index, Alanine Amino Transferase and Quantitative Liver Magnetic Resonance Imaging for NAFLD in a Pediatric Population

James A Lee[1], Candace S Percival[1], Shaprina R Williams[1], Justin G Peacock[2], Christian L Carlson[2] and Blaine A Tuft[1]*

[1]Department of Pediatrics, Brooke Army Medical Center, USA

[2]Department of Radiology; Brooke Army Medical Center, USA

Abstract

We aim to highlight early findings from our epidemiologic trial investigating the association of Body Mass Index (BMI) and Alanine Amino Transferase (ALT) with liver steatosis and fibrosis using a post-processing MRI technique in a pediatric population. From the baseline data our findings were as expected, elevated BMI was associated with higher ALT values. Interestingly BMI percentage as a percent of the 95th percentile did not correlate as well as absolute BMI. This may suggest there are other mechanisms involved in the initiation of hepatocellular injury leading to higher ALT levels aside from the severity of obesity or suggest there is a threshold BMI that is permissive in the development of NAFLD. MRI was able to detect a significantly larger number of patients with potential liver disease than BMI or ALT alone. Moving forward, we hope to expand our data to include other biomarkers and investigate their associations with imaging end points. Further studies should be dedicated to investigating the correlation between histopathology and MRI scores to determine values for diagnostic purposes and the associations between those scores and liver-associated morbidity in pediatric patients.

Keywords: Body mass index; Liver magnetic resonance imaging; Pediatric patients; Liver biopsy

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Correspondence:
James A Lee, Department of Pediatrics, Brooke Army Medical Center, 3112 N 58th St, Omaha, NE 68104, USA, E-mail: james.a.lee310.mil@mail.mil

Received Date: *14 Aug 2020*
Accepted Date: *23 Sep 2020*
Published Date: *28 Sep 2020*

Citation:
Lee JA, Percival CS, Williams SR, Peacock JG, Carlson CL, Tuft BA. A Comparison between Body Mass Index, Alanine Amino Transferase and Quantitative Liver Magnetic Resonance Imaging for NAFLD in a Pediatric Population. Ann Pediatr Res. 2020; 4(4): 1045.

Abbreviations

NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steato Hepatitis; ALT: Alanine Amino Transferase; LMS: LiverMultiScan™; LIF: Liver Inflammation and Fibrosis; MRE: Magnetic Resonance Elastography

Introduction

The current epidemic of obesity has led to an increasing number of co-morbid conditions; such as, diabetes, cardiovascular disease and non-alcoholic fatty liver disease [1,2]. Non-Alcoholic Fatty Liver Disease (NAFLD) has become the most common cause of chronic liver disease among children and its prevalence will likely continue to grow as the percentage of the population with obesity continues to increase [1,3,4]. Fatty infiltration can range in severity from simple, reversible steatosis to Non-Alcoholic Steato Hepatitis (NASH) associated with cirrhosis, end-stage liver disease, and hepatocellular carcinoma [5]. Although the exact prevalence of NAFLD is unknown, estimated prevalence is roughly one-third to two-thirds in pediatric patients with obesity [3]. The gold standard for diagnosis is liver biopsy which is often subject to sampling error and interpretation inter-observer variance in addition to the associated cost, pain, potential complications [6-9]. Currently, NASPGHAN Guideline for the Diagnosis and Treatment of NAFLD recommends selective screening of higher risk patients (obese or overweight with central adiposity, insulin resistance, pre-diabetes or diabetes, dyslipidemia, sleep apnea or family history of NAFLD/NASH) with Alanine Amino Transferase (ALT) measurement, regardless of its limitations [10]. Newer post-processing software Magnetic Resonance Imaging (MRI) techniques have been validated to accurately quantify hepatic steatosis in both adult and pediatric patients but further research is needed to determine its cost effectiveness for potential use in screening and expansion into the diagnostic domain [11,12]. LiverMultiScan™ (LMS), perspectum diagnostics multi parametric MRI technique, has shown promising results in adults for the detection of fatty liver disease in lieu of liver biopsies. LMS uses T1 and T2 mapping, and proton density fat fraction to evaluate liver

fibrosis, hemosiderosis, and steatosis, respectfully. In pediatric and adult patients, MR sequences similar to LMS has proven to correlate with steatosis grade by liver biopsy and has the ability to differentiate nonalcoholic Steato hepatitis from NALFD [11,13-15]. Liver Inflammation and Fibrosis (LIF) scores ≥ 2 have been associated with increased liver associated morbidity in adult patients with biopsy-confirmed chronic liver disease, including patients with NAFLD [16]. Utilizing this software in children may be a viable and safe method to determine the prevalence and natural history of liver steatosis, fibrosis, and hemosiderosis, as well as offer a non-invasive method to more safely conduct clinical trials on the effectiveness of interventions (i.e. diet, drugs, and exercise) in the treatment of NAFLD. This paper aims to highlight early findings from our prospective clinical trial investigating the association of BMI and ALT and liver fibrosis, steatosis and hemosiderosis based on a novel MRI technique, LMS, in United States military dependents with obesity.

Methods

Study design

This was a prospective trial in children ages 10 to 17 years old who were identified as being overweight or obese (BMI greater than 85th percentile for age and gender) in at least 1 of the pediatric clinics at Joint Base San Antonio. A universal protocol was implemented to obtain demographic data, vital signs, fasting blood draws and MRI studies for each enrolled patient. The parents and/or legal guardians of all subjects provided written informed consent and assent was obtained from all children above 13 years old. The protocol was approved by the institutional review board of Brooke Army Medical Center. The second phase of the study, not discussed in detail as it is currently underway, includes nine months of behavioral interventions followed by repeat fasting laboratory and MRI studies.

Patient selection

The target patient population for this study included both male and female dependents of active duty and retired personnel who were overweight or obese based on BMI greater than 85th or 95th percentile for age and gender. Subjects were recruited from the following clinics: Health Habits, Pediatric Endocrinology, Pediatric Gastroenterology, Adolescent medicine, and general pediatric clinics at Brooke Army Medical Center and the general pediatric clinic at Wilford Hall Ambulatory Surgical Center.

Inclusion criteria

- Eligible patients from the San Antonio Military Medical Center Healthy Habits clinic and pediatric endocrine, pediatric gastroenterology, adolescent, and general pediatric clinics, as well as from Wilford Hall's pediatric clinic.
- Overweight (BMI>85% and <95% for age and gender) or obese (BMI >/= 95% for age and gender).
- 10 to 17 years old.
- Cognitively able to understand and provide written informed assent.
- Written informed consent from parent or legal guardian.

Exclusion criteria

- Prior history of liver disease to include chronic hepatitis B or C, hemochromatosis, Wilson's disease, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, HIV, biliary atresia, or Caroli/choledochal disease.
- Pregnancy
- Current use of medications associated with liver disease/ failure (i.e. antifungals, methotrexate, valproic acid, etc).
- Carrying an implantable active medical device such as a pacemaker, vagal nerve stimulator, defibrillator, or non-MRI compatible cochlear implant.
- Previous claustrophobia/anxiety with MRI scanner or developmental delays that may result in failed MRI scan (e.g. Autism spectrum disorder, anxiety disorder).
- Alcohol use

Data collection

Fasting lab studies were conducted at the initial visit. An array of studies were collected for the protocol, but here we will highlight the results of ALT. Liver biopsies were not routinely obtained. Subjects also had non-invasive MRI and Magnetic Resonance Elastography (MRE) of the liver. The MRI scan was analyzed with liver multi scan post-processing software. Siemen's MRE was processed on Agfa PACS.

MR specifics

LMS used T1 mapping, T2*, and proton density fat fraction to evaluate liver inflammation and fibrosis, hemosiderosis, and steatosis, respectfully. LMS is software developed by Perspectum Diagnostics. This post-processing software is FDA approved for the Siemens MR systems in adults; however, the 1.5T Avanto and Siemens 3T WIP with E11 software utilized at BAMC in this study were still investigational at the time of the study. MRE was performed using a Siemens system with a low-frequency (60 Hz), mechanical shear wave. An automated inversion algorithm then processes the data to give tissue stiffness in kilopascals which correlates to liver fibrosis. Diagnostic considerations for MRE were as follows: <2.5 kPa - normal, 2.5 to 2.9 kPa- normal or inflammatory, 3 to 3.5 kPa- Stage 1 or 2 fibrosis, 3.6 to 4 kPa- Stage 2 or 3 fibrosis, 4.1 to 5 kPa- Stage 3 or 4 fibrosis, >5 kPa- Stage 4 fibrosis or cirrhosis.

Data analysis

BMI was based of CDC BMI gender-specific growth charts. To calculate BMI percentage >95th percentile, the patients BMI was divided by the BMI representing the 95th percentile for the patients age and gender and multiple by 100 to give a percentage. Correlation was determined using Pearson correlation coefficients. ANOVA testing was used to detect differences in means among stratified groups. An a priori significance level was set with α value of 0.05.

Results

Preliminary data was analyzed on the first 36 patients to complete the fasting laboratory exams and MRI. Table 1 summarizes the patient's baseline data. Patients ranged from 10 to 17 years old. Average age was 13.7 years and male to female ratio was 1:1.12.28/36 patients were obese and 16 of those were severely obese. Mean BMI and BMI as percentage of the 95th percentile was 31.04 kg/m^2 (22.06 to 42.6 kg/m^2) and 118.8% (87.2 to 159.7%) respectively. Mean ALT was 30.4 U/L (8 to 137 U/L).Of note, only 5 patients (patients 16, 20, 26, 32 and 34) had an ALT greater than or equal to twice the Upper Limit of Normal (ULN) for gender. Within this initial data we had several findings. Male patients had a significantly higher ALT, mean of 41.18 *vs.* 20.84 U/L (p=0.01) and while BMI was also higher, 32.32 *vs.* 29.89 kg/m^2 this was not significant (p=0.09). BMI, both absolute

Table 1: Patient demographics.

Age	Gender (M:F)	BMI	BMI% of 95th%ile	ALT
13.7	01:01.1	31	125.9	30.8

Table 2: BMI, ALT and imaging end points.

	Mean	95% CI	Range	
BMI	31.03	1.74	22.06	42.6
BMI% of 95th % ile	118.81	6.21	87.16	159.7
ALT	30.83	8.72	8	137
Fat Content	5.66	2.09	0.6	27.1
Iron Content	1.06	0.05	0.9	1.5
LIF	2.15	0.21	1.2	3.2
MRE	2.14	0.09	1.7	2.9

and percentage of the 95th percentile, did not have a statistically significant correlation to ALT; however, absolute BMI did have a stronger correlation (r=0.3, r^2=0.1, p=0.07 and r=0.16, r^2=0.02, p=0.4, respectively). In the 5 patients meeting diagnostic criteria for NAFLD, they were older, mean of 15.6 *vs.* 13.4 years old (p=0.04), BMI mean was higher compared to the remainder of the cohort, 34.2 *vs*. 30.53 kg/m^2 (p=0.053) and 80% were male, compared to 42% males (p=0.067). Table 1 represents patient's baseline information. BMI is expressed in kg/m^2; BMI percentage of the 95th percentile is expressed as a percent, patients <95th percentile are consider overweight, patients with BMI percentage >20% above the 95th percentile are considered severely obese (i.e. >120%); ALT is expressed in U/L; Table 2 is a summary of the mean values for BMI, ALT and imaging data. Mean values for liver fat percentage were 5.66% (0.6% to 27.1%), iron content was 1.06 mg/g (0.9 to 1.5 mg/g), LIF score was 2.15 (1.2 to 3.2), MRE was 2.14 kPa (1.7 to 2.9 kPa). Absolute BMI significantly correlated to LIF (r^2=0.4 and p=0.0001) and MRE (r^2=0.2 and p=0.009) but did not correlate to liver fat or iron content. BMI as percentage of the 95th percentile correlated with LIF and MRE as well (r^2=0.27, p=0.002 and r^2=0.2, p=0.008, respectively). ALT correlated well with liver fat content (r^2=0.34 and p=0.0005) and LIF score (r^2=0.36 and p=0.0003). The strongest correlation observed between the baseline patient data and the imaging endpoints was between absolute BMI and LIF score. With respect to the 5 patients with an ALT greater than or equal to twice the ULN, liver fat content was higher, mean of 14.14% *vs.* 4.37% (p=0.004), iron content was higher, mean of 1.16 *vs.* 1.05 mg/g (p=0.13), LIF scores were higher, mean of 2.93 *vs*. 2.03 (p=0.04), and MRE scores were higher, mean of 2.38 *vs.* 2.1 kPa (p=0.09). The 25 patients (69%) had a LIF score ≥ 2. These patients had higher age, mean of 14.2 *vs.* 12.5 years old (p=0.04), higher BMI, mean of 32.81 *vs.* 27.02 kg/m^2 (p=0.002), higher ALT, mean of 37.76 *vs*. 13.82 U/L (p=0.006), and higher MRE, mean of 2.21 *vs.* 1.97 kPa (p=0.006), than the patients with LIF<2. Table 2 represents mean data for BMI, ALT and imaging endpoints. BMI is expressed in kg/m^2; BMI percentage greater than the 95th percentile is expressed as a percent, patients <95th percentile are consider overweight, patients with BMI percentage >20% above the 95th percentile are considered severely obese (i.e. >120%); ALT is expressed in U/L; Fat content is expressed as a percent; Iron content is expressed a mg iron per gram of dry liver weight; LIF is the Liver Inflammation and Fibrosis score (no units), a score >2 confers an increased risk of liver associated morbidity in adult patients with chronic liver disease; MRE is Magnetic Resonance Elastography and is presented in kilo Pascals; Table 3 highlights the correlations for BMI (kg/m^2), BMI percentage in relation to the 95th percentile (%), and ALT (U/L) to the imaging endpoints. Fat content (%); Iron content (mg iron per gram of dry liver weight); LIF (Liver Inflammation and Fibrosis score); MRE (kPa); *statistically significant data. Table 4 summarizes patient data after grouping patients by weight classification. Overweight is the 85th to 95th percentile, obese is >95th percentile but not classified as severe obesity, severe obesity is a BMI greater than 120% of the 95th percentile. BMI (kg/m^2); BMI as a percentage of the 95th percentile (%); ALT (U/L); Fat content (%); Iron content (mg iron per gram of dry liver weight); LIF (Liver Inflammation and Fibrosis score); MRE (kPa); *statistically significant data. Table 5 summarizes patient data

Table 3: Correlation between BMI, ALT and imaging results.

	Absolute BMI			BMI% of 95th % ile			ALT		
	r	r^2	p	r	r^2	p	r	r^2	p
Fat Content	0.21	0.04	0.2	0.2	0.04	0.2	0.58	0.34	0.0005*
Iron Content	0.06	-	0.7	0.03	0.0009	0.86	0.32	0.1	0.06
LIF	0.63	0.4	0.0001*	0.52	0.27	0.002*	0.6	0.36	0.0003*
MRE	0.44	0.19	0.008*	0.45	0.2	0.008*	0.23	0.05	0.18

Table 4: BMI Stratification.

Weight Classification	Age	BMI	BMI % of 95th % ile	ALT	Fat Content	Iron Content	LIF	MRE
Over weight	14.25	25.14	93.96	24.38	2.46	1.04	1.61	1.98
Obese	12.5	28.34	112.48	29.58	6.41	1.08	2.12	2.05
Severely obese	14.38	36.01	135.97	34.13	6.84	1.08	2.44	2.29
p value	0.1	-	-	0.71	0.26	0.82	0.004*	0.02*

Table 5: ALT Stratification.

ALT	Age	BMI	BMI % of 95th % ile	ALT	Fat Content	Iron Content	LIF	MRE
Normal	12.5	29.03	118	15.55	2.8	1.04	1.84	2.03
Elevated	15.09	33.26	121.77	32.36	7.23	1.09	2.37	2.23
≥ 2x ULN	15.6	34.2	125.91	85.8	14.14	1.16	2.93	2.38
p value	0.001*	0.03	0.67	-	0.0003*	0.25	8x10-5*	0.02*

Table 6: Average LIF Scores.

	Overweight	Obese	Severely Obese
Normal ALT	1.38	1.94	2.05
Elevated ALT	1.95	2.4	2.48
≥ 2x ULN ALT	2.1	3.15	3.13

after grouping patients by ALT scores. Normal is less than 22U/L for females and 26U/L for males, elevated is 22 ≤ ALT<44 for females and 26 ≤ ALT<52 for males, ≥ 2x ULN is ≥ 44 for females and ≥ 52 for males. BMI (kg/m^2); BMI as a percentage of the 95th percentile (%); ALT (U/L); Fat content (%); Iron content (mg iron per gram of dry liver weight); LIF (Liver Inflammation and Fibrosis score); MRE (kPa); *statistically significant data. Six patients (16.7%) had an MRE that could be considered abnormal, ≥ 2.5 kPa can represent normal or inflammatory changes, but no patients had a MRE above 3, the threshold value for consideration of hepatic fibrosis. When compared to the patients with MRE <2.5 kPa, patients with an abnormal MRE had higher age, mean of 15.3 *vs.* 13.4 years old (p=0.03), higher BMI, mean of 35.19 *vs.* 30.21 (p=0.02), higher ALT, mean of 37.83 *vs.* 28.97 U/L (p=0.19), higher fat content, mean of 9.37 *vs.* 5% (p=0.09), higher iron content, mean of 1.1 *vs.* 1.06 mg/g (p=0.19) and higher LIF scores, mean of 2.62 *vs.* 2.06 (p=0.008). With regards to imaging endpoints, males had a higher liver fat content, mean of 8.31 *vs.* 3.41% (p=0.02), higher iron content, mean of 1.11 *vs.* 1.03 mg/g (p=0.06), higher LIF scores, mean of 2.47 *vs.* 1.86 (p=0.0008), and higher MRE, mean of 2.25 *vs.* 2.04 (p=0.02). Table 6 illustrates the relationship between weight classification and ALT to LIF scores. In the group of overweight patients with a normal ALT, LIF scores averaged 1.38. Compare that to the severely obese patients with an ALT two times greater than the ULN whose LIF score average was 3.13. The combined relationship between weight classification and ALT to LIF scores is statistically significant (p=0.01).

Discussion

The overall scope of this study is to investigate the epidemiology and associations between biomarkers and non-invasive imaging modalities as it relates to NAFLD. Here we presented early findings from our study. The largest weakness of our study is the lack of tissue samples. The associations and conclusions we draw are dependent upon the assumption LMS and MRE data and cut offs from adult patients can be accurately applied to children and adolescents. Table 6 illustrates the relationship between weight classification and ALT to LIF scores. Overweight is the 85th to 95th percentile, obese is >95th percentile but not classified as severe obesity, severe obesity is a BMI greater than 120% of the 95th percentile. Normal ALT (U/L) is less than 22 for females and 26 for males, elevated is 22 ≤ ALT<44 for females and 26 ≤ ALT<52 for males, ≥ 2x ULN is ≥ 44 for females and ≥ 52 for males. Green correlates to normal/borderline liver disease, yellow correlates to borderline/mild liver disease, orange correlates to moderate liver disease, and red correlates to severe liver disease. We found BMI to be positively correlated with ALT as expected; however, absolute BMI (r^2 of 0.1) had a stronger correlation to ALT as compared to BMI percentage of the 95th percentile (r^2=0.02). Either the categorical classification of weight is not as useful as the BMI itself with regards to NAFLD or there may be other mechanisms involved in the initiation of hepatocellular injury leading to high ALT levels aside from the severity of obesity. Previous studies have demonstrated NASH is more common in patients with an ALT twice the upper limit of normal [5]. Patients in this cohort had an ALT meeting those criteria. Statistically significant differences were found between this group and the remainder of the cohort in the context liver fat content and LIF. Reaffirming that a higher ALT is associated with evidence of increased liver fat content and inflammation. On the other hand, 69% patients had LIF scores ≥ 2. A LIF ≥ 2 is considered to represent moderate liver disease and has been associated with increased liver associated morbidity in adult patients with biopsy-confirmed chronic liver disease. If we were to assume this score of ≥ 2 corresponded to clinically relevant diagnosis of NAFLD, the prevalence of NAFLD in this cohort would match the previous population estimates of estimates of 30% to 60%. This also suggests the use of ALT thresholds of greater than or equal to two times the upper limit of normal to screen for NAFLD could under recognize early or mild disease. With regards to MRE, a MRE ≥ 2.5 kPa was found in 6/36 patients. Based off adult literature, a score of 2.5 to 2.9 kPa can represent normal liver or a mild inflammatory state and any stage fibrosis would result in a score >2.9 kPa. None of our patients had MRE score greater than 2.9 kPa which suggests the prevalence of fibrosis in pediatric patients is low, or as other authors have mentioned, the type and location of steatosis and fibrosis may preclude the use of MRE in pediatric patients. For example, children are more prone to higher grades of steatosis and portal-based fibrosis compared to adults who have lower grade steatosis and centrilobular fibrosis, which would result in a different liver micro architecture and ultimately varying observed stiffness [17,18]. Although the use of adult cut offs used for interpreting MRE data has been cautioned against in the pediatric population, we found patients with an "abnormal" MRE, ≥ 2.5 kPa, were more likely to have a higher BMI (p=0.02) and higher LIF score (p=0.008). The higher BMI in this subgroup may be related to the difficulties in performing Elastography with a large body habitues, but in combination with the associated elevation in LIF scores which should not be altered by body habitues, an elevated MRE is suggestive of early or mild liver inflammation. That said, the use of MRE with LMS could provide useful information to providers giving a more complete description of liver histology without the need for invasive biopsy. However, the use of MRE alone in the screening of NALFD likely will not prove useful as the overall prevalence of fibrosis in children with NAFLD is low.

Conclusion

The overall scope of this study is to investigate the associations between biomarkers and non-invasive imaging modalities as it relates to NAFLD. From the baseline data our findings were as expected, elevated BMI was associated with higher ALT values. Higher BMI and ALT values were significantly associated with higher LIF scores, illustrated best in Table 6. Given this data, it appears that LIF could be used in pediatric patients as a safe, non-invasive imaging strategy for screening and diagnosing NAFLD, and monitoring its evolution while at the same time detecting earlier stages of hepatic steatosis and inflammation. Use of MRE in combination with the LIF may give clinicians a more complete picture of liver pathology, but MRE alone will not likely prove useful. MRI was able to detect a significantly larger number of patients with potential liver disease than ALT alone. Moving forward, we hope to expand our data to include other biomarkers and investigate their associations with imaging end points. Further studies should be dedicated to investigating the correlation between histopathology and LIF scores to determine values for diagnostic purposes and the associations between LIF scores and liver-associated morbidity in pediatric patients.

Funding

Received funding from the Department of the Air Force, Wilford Hall Ambulatory Surgical Center, 59th Clinical Research Division, Lackland Air Force Base, Joint Base San Antonio, Texas.

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