Analysis of correlation between liver fat fraction and AST and ALT levels in overweight and obese children by using new magnetic resonance imaging technique

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ABSTRACT

Background/Aims: *Proton density fat fraction (PDFF) magnetic resonance (MR) imaging can be a useful technique for volumetric measurements of liver fat. The purpose of our study was to evaluate the correlation between liver fat fraction (LFF) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in children who are overweight and obese.*

Materials and Methods: *Overall, 25 children, aged 9-17 years, were included. Patients with a body mass index (BMI) z-score between 85-95th percentile (12 of 25 patients) were assigned to the overweight group, and those with BMI z-score above 95th percentile (13 of 25 patients) were assigned to the obese group. The control group comprised 12 healthy children with BMI z-score below 85th percentile. Liver fat fraction measurements were performed on 3D volume measurement workstation by using PDFF magnetic resonance (MR) images. Spearman's correlation coefficients between liver fat fraction and AST and ALT levels were evaluated individually for overweight, obese, and control groups. Receiver operator characteristics (ROC) analysis was also performed.*

Results: *In the overweight and obese groups, the liver proton density fat fraction and AST levels had a strong correlation (r=0.716, p<0.001). In addition, the LFF and ALT levels demonstrated a strong correlation (r=0.878, p<0.001). ROC analysis ascertained an optimal liver fat fraction threshold of 114 for predicting AST level (sensitivity=75%, specificity=89%). ROC analysis ascertained an optimal LFF threshold of 114 for predicting ALT level (sensitivity=80%, specificity=90%).*

Conclusion: *Our results indicate a strong correlation between LFF values and AST and ALT levels in children who are overweight and obese.*

Keywords: *Liver fat fraction, AST, ALT, children, MR, imaging*

INTRODUCTION

Lately, nonalcoholic fatty liver disease (NAFLD) has emerged as a common clinical issue in children and adolescents just as in adults, and the estimated prevalence is 9.6%-20% (1, 2). NAFLD is secondary to the accumulation of triglycerides in the hepatocytes. It is a potential risk factor for cardiovascular diseases, metabolic syndrome, diabetes, and hyperlipidemia (3). NAFLD is typically diagnosed based on increased serum alanine aminotransferase (ALT) or detection of enlarged hyperechogenic liver parenchyma on ultrasonography (US) images (4, 5). Liver biopsy is the gold standard technique to analyze NAFLD semi-quantitatively, but is an invasive procedure with a high risk of morbidity in children (6).

Distribution of fat tissue in the body, especially the accumulation of visceral fat tissue, is considered a crucial factor for metabolic syndrome, obesity, and cardiovascular disease. Subcutaneous, visceral, and hepatic fat can be evaluated using imaging methods, such as US, computed tomography (CT), and magnetic resonance (MR) imaging (7, 8). However, US has limited ability for quantifying the visceral, subcutaneous, and hepatic fat contents. CT is a reliable method but involves ionizing radiation, which poses a significant problem for children (9, 10). MR imaging with in-phase and out-of-phase images is useful for the detection of hepatic fat. Recently, proton density fat fraction (PDFF) with MR imaging is chemical shift-based water and fat separation method. It has been used to quantify the fat in the liver accurately (11). Noninvasive quantitative assessment of steatosis plays a crucial role in the assessment and follow-up of patients with NAFLD. PDFF has been used as the noninvasive standard of reference for evaluating liver fat content and reflects the amplitude of the MR signal coming from proton nuclei in water and fat molecules (12, 13). Recent improve-

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ments in MR imaging have facilitated the estimation of PDFF through MR imaging—a current biomarker that has demonstrated robust correlation with 1H MR spectroscopy. PDFF MR imaging yields fat mapping of the entire liver parenchyma and could be performed using any MR imaging system. Notably, it is completely easy to interpret and clinically useful, especially given PDFF's excellent diagnostic accuracy, repeatability, and reproducibility (14, 15).

Several clinical studies have explored the correlation among ALT, aspartate aminotransferase (AST), other related factors, and hepatosteatosis in children with different radiological imaging techniques (16-18). Unlike other clinical studies, the purpose of our study was to evaluate liver fat fraction (LFF), AST and ALT levels in children who are overweight and obese by using a new MR technique called the PDFF MR imaging. To the best of our knowledge, our study is the first original research that evaluated the correlation between the LFF and AST and ALT levels in children who are overweight and obese by using PDFF MR images.

MATERIALS AND METHODS

Patients

Between June and November 2018, a total of 30 consecutive patients who were overweight and obese [based on the body mass index (BMI) z-scores] were referred from the pediatric nutrition department to our radiology clinic. Patients with any of the following criteria were excluded: claustrophobia (n=3) and steatogenic medication usage (n=2). Overall, 25 children, aged 9-17 years, met the inclusion criteria. Based on the BMI z-scores, children were divided into the following three groups: patients with BMI z-score between the 85-95th percentile (12 of 25 patients, 48%) were assigned to the overweight group, and those with BMI z-score above the 95th percentile (13 of 25 patients, 52%) were assigned to the obese group. Additionally, 12 healthy children (aged 10-17 years) with BMI z-score below 85th percentile were assigned to the control group.

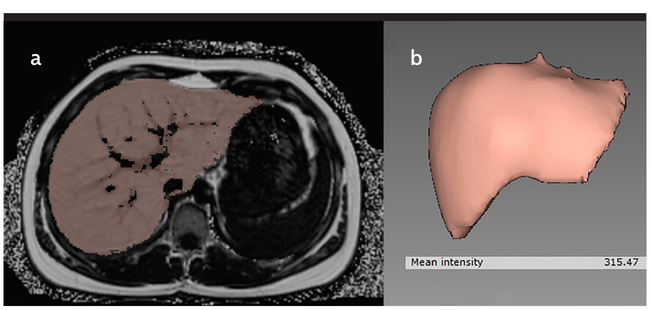

Figure 1. a, b. The PDFF MR image (a) and 3D volumetric image (b) of a 13-years-old boy. The whole liver selected with semiautomatic 3D volume measurement program. The mean intensity was 315.47 and it refers to 31.54 liver proton density fat fraction (b). This value was also calculated with semiautomatic 3D volume measurement program.

All procedures in the study were conducted per the ethical standards of the institutional and national research committees and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Approval for the study was granted by the Ethics Committee of Ataturk University School of Medicine. All children, as well as their parents, provided written informed assent.

MR Imaging Acquisition

All imaging was performed using the 3T MR scanner (Magnetom Skyra, Siemens Healthcare, Erlangen, Germany) in the supine position, with an 18-channel phased-array body coil centered over the upper abdomen. PDFF MR imaging was performed using the following sequences and parameters: a whole-liver volume acquisition with multi-echo volume interpolated breath-hold examination (VIBE) acquisition was performed using six-echo 3D spoiled-gradient-echo acquisition. Two-dimensional parallel acceleration was used to allow whole liver coverage in a single breath-hold. Parameters of this sequence were as follows: repetition time (TR)=9.5 ms; first echo time (TE)=1.22 ms with 6 echoes collected with ΔTE=1.23 ms; flip angle=5°; slice thickness=4 mm; field of view=43×35 cm; matrix=256×164 and acquisition time=20 seconds.

Image analysis

All PDFF MR images were analyzed on a 3D workstation (Syngo.via VB10B, Siemens Healthcare, Forchheim, Germany) by two radiologists with 5 (R.S) and 3 (B.P) years of experience, respectively, in abdominal imaging, who were blinded to all clinical data. Notably, the density value of tissues ranges from 0 to 1000 on PDFF MR images based on the fat content. Accordingly, tissues with 100% fat content have an intensity value of 1000, and tissues with 0% fat content have an intensity value of 0. The LFF was then calculated as 1/10 of the mean whole liver parenchymal intensity on 3D volume measurement workstation (Myrian Pro, Intrasense, France) (Figure 1).

Laboratory analysis

Fasting blood samples were obtained within 15 days of PDFF MR imaging examinations and analyzed at the Ataturk University School of Medicine Laboratory for AST and ALT levels. At the time of this study, the normal reference ranges of AST and ALT assays at the university lab was less than or equal to 35 U/L.

Statistical analysis

Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp.; Armonk, NY, USA). BMI z-score was computed for all children by using their height, weight, age, gender, and reference parameters provided by the Center for Disease Control and Prevention (19). Because the continuous and categorical variables were not normally distributed, the correlation between LFF and AST and ALT levels were examined using pairwise Spearman's correlations. Moreover, Spearman's correlation coefficients between LFF and AST and ALT levels were evaluated individually for all patients in the overweight and obese groups. When interpreting the strength of the correlation, the standard accepted definitions of none (r=0.0-0.1), weak (r=0.1-0.3), moderate (r=0.3-0.5), and strong (r=0.5-1.0) were used (20). One-way analysis of variance (ANOVA) test was employed to compare the volumetric measurements among the overweight, obese, and control groups. In addition, a receiver operating characteristic (ROC) analysis was conducted to evaluate the clinical utility of PDFF MR and its relationship with AST and ALT levels. A $p<0.05$ was considered statistically significant.

RESULTS

The overweight group comprised 12 patients [7 boys (58.3%), 5 girls (41.7 %)]. The mean age of the overweight group was 13.66±1.32 years (range: 12-16 years). The mean height of the overweight group was 153.11±13.53 cm (range: 136-178 cm). The mean weight of the overweight group was 58.22±13.33 kg (range: 40-80 kg). The mean BMI of the overweight group was 24.49±1.84 kg/m^2 (range: 21.62-27.18 kg/m^2).

The obese group comprised 13 patients [6 boys (45.5%), 7 girls (54.5 %)]. The mean age of the obese group was 12.27±2.14 years (range: 9-17 years). The mean height of the obese group was 155.63±10.30 cm (range: 138-170 cm). The mean weight of the obese group was 73±19.86 kg (range: 51-112 kg). The mean BMI of the obese group was 29.73±5.72 kg/m^2 (range: 21.22-43.75 kg/m^2).

The control group had 12 patients [5 boys (41.7 %), 7 girls (58.3 %)]. The mean age of the control group was 12.45±1.1 years (range: 10-16 years). The mean height of the control group was 150.68±12.82 cm (range: 134-173 cm). The mean weight of the control group was 33.21±12.41 kg (range: 29-48 kg). The mean BMI of the control group was 20.12±1.1 kg/m^2 (range: 18.53-22.23 kg/m^2). All the demographic findings for the overweight, obese, and control groups are summarized in Table 1.

The mean AST level in the overweight, obese, and control groups was 32.6±19.3, 37.4±24.3, and 30.2±11.6 IU/L, respectively. The mean ALT level in the overweight, obese, and control groups was 47.4±36.1, 54.8±35.8, and 40.1±14.6 IU/L, respectively (Table 1). No statistically significant difference was observed between the overweight

Table 1. The demographic details of the overweight, obese, and control groups.

	Mean Age	Mean weight (kg)	Mean height (cm)	Mean BMI (kg/m^2)
Overweight group (n=12)	13.66±1.32	58.22±13.33	153.11±13.53	24.49±1.84
Obese group (n=13)	12.27±2.14	73±19.86	155.63±10.30	29.73±5.72
Control group (n=12)	12.45±1.1	33.21±12.41	150.68±12.82	20.12±1.1

BMI: Body mass index

Table 2. The mean liver fat fraction (LFF) values, AST and ALT levels in overweight, obese, and control group patients.

	Overweight group	Obese group	Control group	p		
Mean LFF	190.41±106.8	171.2±126.8	85.8±13.1	1*	2#	3&
	(range: 24.36-335.2)	(range: 38.2-457.7)	(range: 42.4-134.4)	0.723	0.023	0.033
Mean AST levels	32.6±19.3 IU/L	37.4±24.3 IU/L	30.2±11.6 IU/L	1*	2#	3&
	(range: 11-89 IU/L)	(range: 9-99 IU/L)	(range: 10-55 IU/L)	0.963	0.774	0.707
Mean ALT levels	47.4±36.1 IU/L	54.8±35.8 IU/L	40.1±14.6 IU/L	1*	2#	3&
	(range: 10-186 IU/L)	(range: 9-220 IU/L)	(range: 15-67 IU/L)	0.792	0.678	0.721

1*: shows between overweight and obese group, 2#: shows between overweight and control group, 3&: shows between obese and control group. LFF: Liver fat fraction; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase and obese groups regarding the mean AST and ALT levels (p=0.963 and p=0.792, respectively). Furthermore, no statistically significant differences were observed among the overweight, obese, and control groups regarding the mean AST and ALT levels (Table 2).

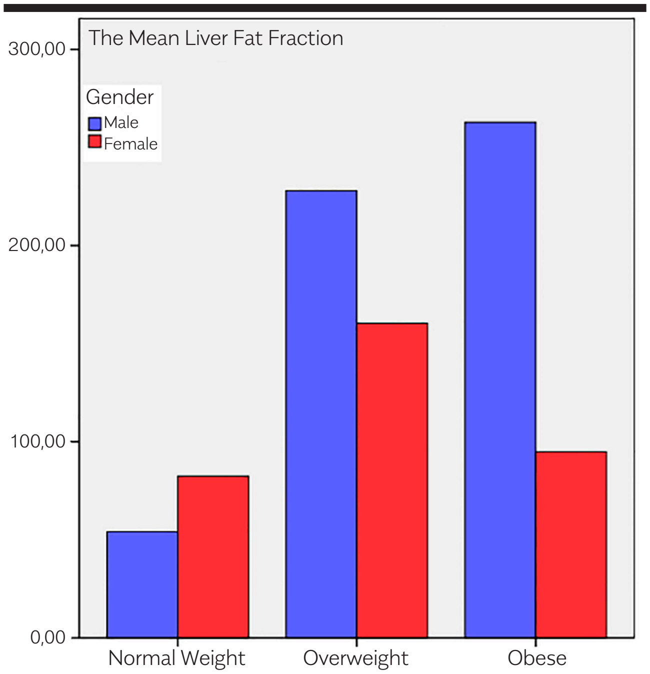

Figure 2. The mean liver fat fraction graphics of gender distribution in normal overweight, obese, and control groups. The mean LFF value of boys was significantly higher than girls in the obese group.

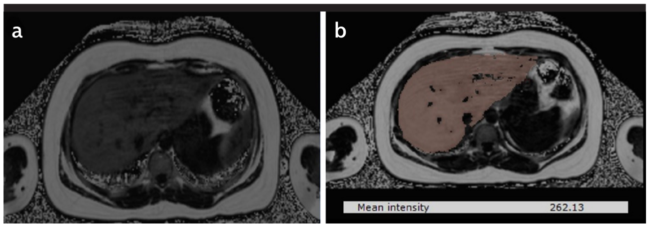

Figure 3. a, b. The PDFF MR image (a) and 3D volumetric image (b) of a 15-year-old girl. The PDFF MR image shows a bright liver parenchyma, indicating high liver fat fraction. The whole liver selected with semiautomatic 3D volume measurement program. The mean intensity was 262.13 and it refers to 26.21 liver proton density fat fraction (b). The AST level of the patient was 98 IU/L and the ALT level was 168 IU/L.

The mean LFF value for the overweight, obese, and control groups was 190.41±106.8, 171.2±126.8, and 85.8±13.1, respectively. The mean LFF value of the control group was significantly lower than the overweight and obese groups (p=0.023 and p=0.033, respectively). No statistically significant difference was detected between the overweight and obese groups regarding the mean LFF values (p=0.723, Table 1). The mean LFF values of each group exhibited different gender distribution patterns (Figure 2). The mean LFF value of girls was lower than boys in the overweight group, albeit not a statistically significant difference. The mean LFF value of boys was significantly higher than girls in the obese group (p=0.018, Table 3). The mean LFF value was higher in girls than boys in the control group, albeit without a statistically significant difference.

Among all overweight and obese groups, LFF and AST levels exhibited a strong correlation (r=0.716, p<0.001). Similarly, the LFF and ALT levels demonstrated a strong correlation (r=0.878, <0.001) (Figure 3). ROC analysis ascertained an optimal LFF threshold of 114 IU/L for predicting AST level (sensitivity=75%, specificity=89%). Furthermore, the ROC analysis ascertained an optimal LFF threshold of 114 IU/L for predicting ALT level (sensitivity=80%, specificity=90%, Figure 4).

When comparing between overweight and control groups, LFF and AST levels had no significant correlation (r=0.02,

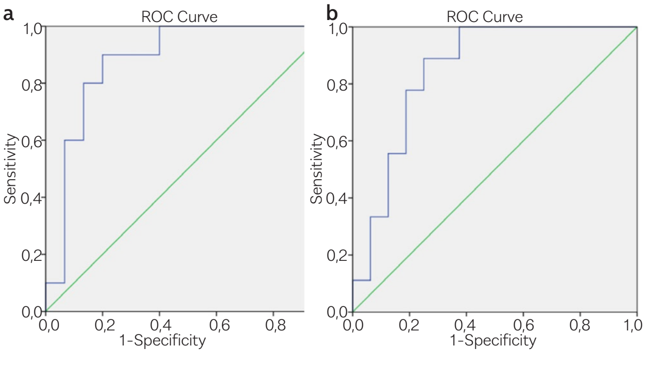

Figure 4. a, b. The ROC curves revealed optimal LFF threshold of 114 IU/L for predicting AST level (A, with sensitivity and specificity values) and optimal LFF threshold of 114 IU/L for predicting ALT level (B, with sensitivity and specificity values).

Table 3. The gender differences of mean liver fat fraction (LFF) values in overweight, obese, and control group patients.

	Overweight group (=12)			Obese group (n=13)			Control group (n=12)		
	Male (n=7)	Female (n=5)	p	Male (n=6)	Female (n=7)	p	Male (n=5)	Female (n=7)	p
Mean LFF	227.92±82.99	160.4±122.97	0.381	262.92±126.5	94.83±62.88	0.018	77.8±12.35	88.6±13.31	0.439

LFF: Liver fat fraction

p=0.677). Moreover, the LFF and ALT levels demonstrated a weak correlation (r=0.15, p=0.409). Among all obese and control groups, LFF and AST levels had no significant correlation (r=0.05, p=0.654). Similarly, the LFF and ALT levels demonstrated no significant correlation (r=0.01, p=0.786).

DISCUSSION

Our study primarily focused on evaluating the correlation between LFF and AST and ALT levels in overweight and obese patient groups. Our results revealed a strong correlation between the mean LFF values and AST and ALT levels in overweight and obese groups. Furthermore, the mean LFF values of each group exhibited different gender distribution patterns.

Pediatric obesity is a common epidemic that is a risk factor for hypertension, diabetes, insulin resistance, and NAFLD. Navarro-Jarabo JM et al. (16) analyzed the prevalence of hepatic steatosis among the pediatric population within an area in southern Europe besides the variables associated with its development and severity. They performed multiple logistic regression analyses on 144 children, and it revealed factors associated with steatosis and the ALT level [odds ratio 1.08, 95% confidence interval (CI): 1.03-1.13]. In addition, they determined that a level of ALT<23.5 IU/L predicted the lack of severe steatosis with an area under the ROC curve of 0.805 (95% CI: 0.683-0.927). Unlike this study, we determined that ROC analysis ascertained an optimal LFF threshold of 114 IU/L for predicting ALT level with 80% sensitivity and 90% specificity. Moreover, we determined that the LFF and ALT levels had a strong correlation (r=0.878, p<0.001).

Nadeau et al. (21) reported a high prevalence of elevated ALT among children with type II diabetes mellitus. Thus, elevations in ALT may be a surrogate for fatty liver disease and an early indicator of looming diabetes. Burgert et al. (22) performed a study involving a multiethnic cohort of 392 adolescents who were obese. They revealed that the elevated ALT (>35 IU/L) was observed in 14% of adolescents, with a preponderance of male sex. In addition, they evaluated the hepatic fat fraction by using fast MR imaging and noted that 32% of adolescents had an increased hepatic fat fraction, which was associated with decreased insulin sensitivity and increased triglycerides. Our study revealed that the LFF and ALT levels demonstrated a strong correlation, and the mean LFF values of the obese group exhibited a male sex predominance. Therefore, we believe that hepatic steatosis could be a core feature of metabolic syndrome.

Nevertheless, the conventional liver serum parameters, such as ALT and AST that are elevated in most chronic and acute liver diseases, cannot be the ideal markers for liver injury in NAFLD. Thus, the quantification of hepatosteatosis is a crucial issue because it provides useful information regarding disease severity. The histopathological analysis is the primary method of quantifying hepatic steatosis, albeit with potential disadvantages. Moreover, it is not feasible to perform a liver biopsy to evaluate patients during each follow-up visit. Therefore, imaging modalities are commonly preferred for this purpose. US is an initial screening method for evaluating hepatosteatosis because it is economical and widely available (23-26). The sensitivity and specificity values of US in determining hepatosteatosis reportedly vary. Despite the reported accuracy values, US has limited clinical use for the quantification of hepatosteatosis (9, 27, 28). Idilman et al. (9) determined the utility of PDFF measurements in quantifying liver fat content in patients with NAFLD and compared their results with liver biopsy findings. They observed a close correlation between PDFF and liver biopsy for the quantification of hepatosteatosis (*r*=0.82). Furthermore, they emphasized that PDFF measurement through MR imaging provided a non-invasive and accurate estimation of the presence, as well as the grade of hepatosteatosis in patients with NAFLD. Therefore, we performed PDFF MR imaging in our study to evaluate and perform volumetric measurements of visceral and subcutaneous fat.

Nonetheless, our study had some limitations. First, our patient cohort was relatively small. Therefore, future studies with larger samples are necessary to confirm our results. Second, we did not correlate the LFF with biopsy. Nevertheless, the PDFF measurement exhibited an excellent diagnostic accuracy in quantifying steatosis compared with liver biopsy results. Tang et al. (29) evaluated the diagnostic performance of estimating PDFF through MR imaging to evaluate hepatic steatosis in patients with NAFLD with a centrally scored histopathologic validation as the reference standard in 77 patients who had NAFLD and liver biopsy. They determined that the whole liver PDFF MR imaging was systematically higher, with higher histologic steatosis grade and significantly correlated with the histologic steatosis grade. Because of these advantages of PDFF MR imaging technique, we performed PDFF MR imaging modality in normal, overweight, and obese groups and determined the visceral and subcutaneous fat through PDFF MR images in our study. Third, we did not perform any correlation analysis between US grading of hepatosteatosis and LFF values. Therefore, future studies with larger samples, including children of different ages and sex, are warranted to explore this aspect further.

In conclusion, we evaluated the correlation between LFF and AST, ALT levels obtained using PDFF MR images in children who were overweight and obese. Notably, PDFF MR images can be a useful technique for volumetric measurements of liver fat. Thus, clinicians can easily use PDFF MR imaging alongside AST and ALT levels to treat hepatosteatosis and NAFLD. Our results indicated a strong correlation between LFF and AST, ALT values in children who are overweight and obese.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ataturk University School of Medicine (Decision no: 5/25, 07.06.2018).

Informed Consent: Written informed consent was obtained from the patients' parents who participated in this study.

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Conflict of Interest: The authors have no conflict of interest to declare.

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