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Accuracy Rate of Shear Wave Elastography in Detecting the Liver Fibrosis in Overweight and Obese Children with Hepatosteatosis

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What is already known on this topic?

- *Liver biopsy is the gold standard for the detection and staging of liver tissue damage.*
- *Liver biopsy is an invasive technique, has risks of complications, and cannot be repeated frequently during follow-up.*
- *Many new invasive techniques have been developed to evaluate liver tissue.*

What does this study adds on this topic?

- *In obese and overweight patients, elastography values are higher than in healthy subjects as well as patients with liver fibrosis.*

ABSTRACT

Objective: The aim of this study was to compare the accuracy rate of liver stiffness calculated by shear wave elastography with liver biopsy results in obese and overweight children.

Materials and Methods: Obese and overweight children between 3 and 18 years of age, who had hepatic steatosis and a healthy control group were included in this study. A blood sample was obtained for laboratory tests and shear wave elastography was performed for all subjects. Liver biopsies were performed only in patients with hepatosteatosis, providing permission for biopsy, and for whom the biopsy procedure was not contraindicated.

Results: A cohort of 142 children (78 overweight/obese and 64 healthy) was included in this study. Shear wave elastography values were significantly higher in the patient group as compared to the control group (34.0 vs. 8.2 kPa; $P < .001$). Obese children had higher elastography values compared to non-obese children (50.2 vs. 23.7 kPa, $P < .001$). No correlation was detected between fibrosis score and elastography values. Elastography increased with increasing weight (correlation coefficient: 0.334, $P = .003$) and body mass index (correlation coefficient: 0.364, $P = .001$).

Conclusion: In obese and overweight patients, elastography values are higher than in healthy subjects as well as patients with liver fibrosis. Disease-specific cut-off, mean, and normal reference range values should be defined with large-scale studies to improve interpretation of elastography values. Our results are contradictory in the determination of liver fibrosis with shear wave elastography in obese and overweight patients, thus further research with a larger patient population is recommended.

Keywords: Pediatric, obesity, liver, fibrosis

INTRODUCTION

In recent decades, the prevalence of pediatric overweight and obesity has dramatically increased worldwide.[1] In 2019, 38 million children under the age of 5 were announced to be overweight or obese.[2] With this significant rise in pediatric overweight and obesity, nonalcoholic liver diseases have become one of the most frequently seen chronic liver diseases in the pediatric population.[3] Nonalcoholic fatty liver disease (NAFLD) means the accumulation of fat in the liver without excessive alcohol intake or without other known pathologies in the liver causing hepatic steatosis[4]; it is a disease spectrum ranging from simple steatosis (fat infiltration in the liver) to nonalcoholic steatohepatitis (NASH). Steatosis might be a simple steatosis without any inflammation in the liver tissue or a NASH is defined by

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hepatocellular inflammation leading to fibrosis and cirrhosis.[5,6] The gold standard for the detection of liver tissue damage and for diagnosing NAFLD is the liver biopsy.[7] Since biopsy is an invasive process with risks of bleeding and infection, it is not the first choice for patients and physicians. Furthermore, liver biopsy cannot be repeated frequently during the follow-up period of the patients. As a result, in recent years, reliable and noninvasive techniques have been developed to evaluate liver stiffness.[8] Among those techniques, Shear Wave Elastography (SWE) is the most recently developed ultrasound technique that provides quantitative results about the fibrosis of the tissue. For the measurement of liver stiffness, the results obtained with SWE may be considered better than transient elastography[9]; therefore, SWE has been widely used in the recent years.[10] SWE is a useful tool for different diseases other than hepatosteatosis and liver stiffness, one of which is the measurement of renal cortical stiffness. The assessment of cortical stiffness by SWE is a simple, inexpensive, noninvasive method to predict contrast-induced acute kidney injury.[11] Another use of SWE is to assess muscular abnormalities related to systemic sclerosis.[12]

With this prospective study, we compared the liver biopsy findings and liver fibrosis calculated by the SWE method in obese and overweight children with simple steatosis or steatohepatitis.

MATERIALS AND METHODS

Patient Selection

This study was a single-center, prospective, cross-sectional study conducted in the Pediatric Gastroenterology Unit between 01.03.2015 and 01.09.2015 in accordance with the principles of the Helsinki Declaration. The ethical approval was obtained from the ethics committee of İstanbul University Cerrahpaşa Faculty of Medicine (number: 83045809/604.01/02-41284, date: 10.02.2015). Obese (body mass index [BMI] >95th percentile) and overweight (BMI >85th percentile) children between 3 and 18 years of age, who had hepatic steatosis determined by liver ultrasonography (US), were included as the patient group. Age- and sex-specific percentiles were used in the determination of obesity and overweight according to the reference standards for the growth of Turkish children.[13] Patients receiving treatment for obesity or hepatosteatosis, as well as patients with other diseases that might cause hepatosteatosis, were excluded. A control group, which consisted of healthy children (64 healthy subjects) who were not obese or overweight and consented to provide blood samples, was also included. A total of 78 subjects were included in the patient group. Following a physical examination, a blood sample was taken from all subjects for the biochemical analysis. A physical examination was performed for hepatomegaly, splenomegaly, and collateral findings of chronic liver disease. Before the SWE examination, a grayscale US examination and specific blood tests were performed for all subjects at baseline to exclude other diseases (hepatitis B, hepatitis C, coeliac disease, autoimmune hepatitis) that might cause hepatosteatosis. We performed blood tests for metabolic diseases, blood lipid levels, viral hepatitis antibodies, and so on. Liver biopsy was performed only in patients with hepatosteatosis and elevated liver enzymes for more than 6 months with unknown etiology, who provided permission for biopsy, and for those patients in whom the biopsy procedure was not contraindicated (n = 32). A US-guided intercostal percutaneous liver biopsy was obtained from the right lobe of the liver. Liver fibrosis was evaluated in a blinded manner according to the Brunt scoring system and scored from F0 to F4 where F0 was no fibrosis, F1 was perisinusoidal/pericellul ar fibrosis, F2 was perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis, F3 was perisinusoidal/pericellul ar fibrosis and portal fibrosis with focal or extensive bridging fibrosis, and F4 was cirrhosis.[14]

Ultrasonography and Shear Wave Elastography

All radiologic examinations were done by the same radiologist who was blinded to the laboratory tests and clinical examination results of the subjects. We used the Aixplorer ultrasound system (Super Sonic Imagine, Aix-en-Provence, France) with the SC6-1 convex abdominal broadband probe. Measurements were performed after 4 hours of fasting while the subjects were in the supine position. A region of interest (ROI) of 2 cm was selected on the liver parenchyma that was free of large vessels to avoid artifacts. Three measurements from the right lobe of the liver and 2 measurements from the left lobe of the liver were obtained. For each patient, 2-dimensional color-coded real-time elasticity values were displayed on the screen, and tissue stiffness was recorded in kilopascals (kPa) (Figures 1 and 2).

Statistical Analysis

The Statistical Package for Social Sciences statistical software for Windows (Version 20.0, IBM corp., Armonk, NY, USA) was used for the analysis. Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as the mean and standard deviation and as the median and interquartile range (IQR) where appropriate. The chi-square test was used to compare categorical variables between the groups. The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test and

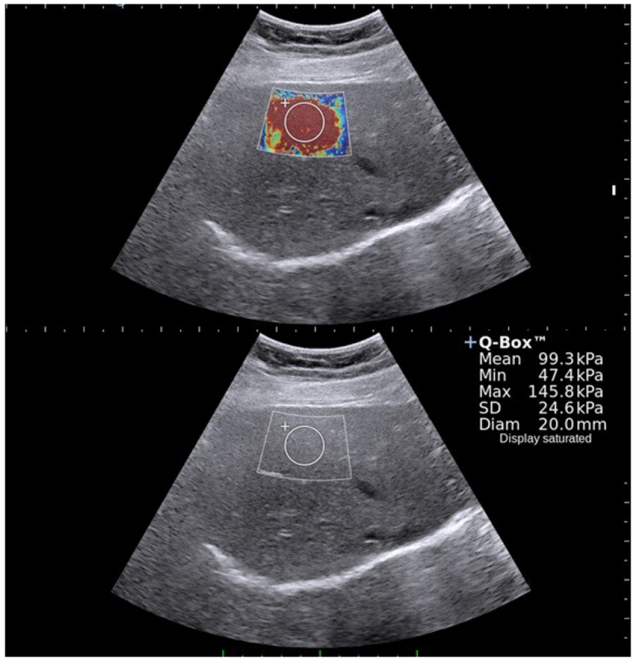

Figure 1. Two-dimensional shear wave elastography measurement of the liver of a patient with hepatic steatosis. Diam, diameter of the white circle; SD, standard deviation.

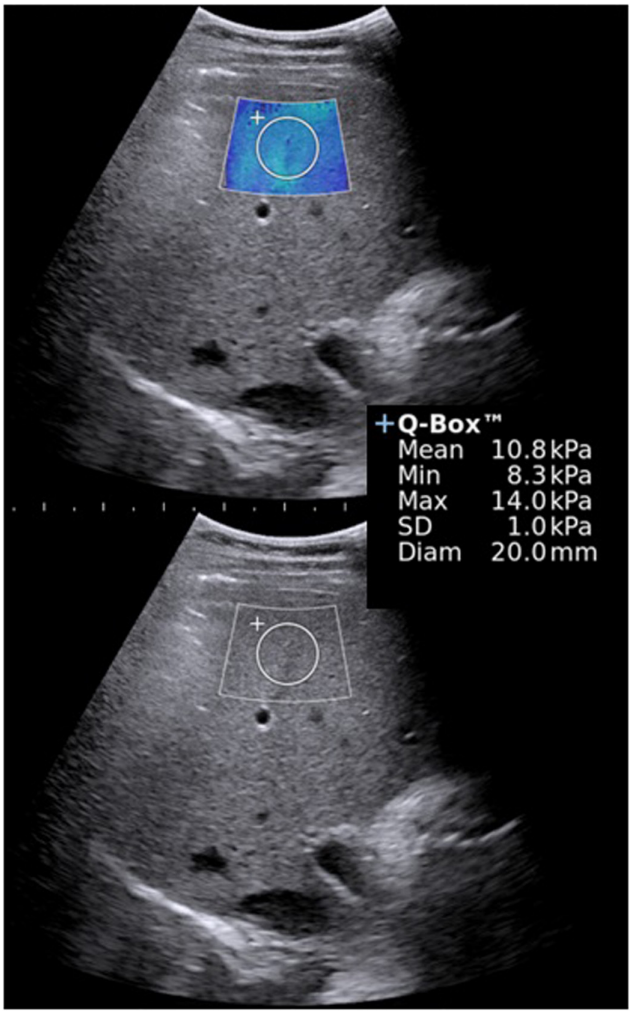

Figure 2. Two-dimensional shear wave elastography measurement of the liver in a patient in control group. Diam, diameter of the white circle; SD, standard deviation.

graphically (i.e., using a histogram, Q-Q plot, and box plot). Student's *t*-test or the Mann–Whitney *U* test was used for the comparison of continuous variables between two groups. One-way ANOVA or the Kruskal–Wallis test was used for the comparison of continuous variables between more than 2 groups. For normally distributed data, regarding the homogeneity of variances, Tukey and Games-Howell tests were used for multiple comparisons of groups. For nonnormally distributed data, the Bonferroni-adjusted Mann–Whitney *U* test was used for multiple comparisons of groups. To evaluate the correlations between measurements, the Pearson correlation coefficient or Spearman rank correlation coefficient was used depending on whether the statistical hypotheses were fulfilled or not. The significant statistical level was 0.05.

RESULTS

The study was completed with 78 overweight/obese children (34 females, 44 males) with hepatosteatosis (patient group) and 64 healthy children (control group, 29 females, 35 males). The mean BMI was higher in the overweight/obese patients than in the healthy controls (28.9 vs. 18.9 kg/m^2; $P < .001$).

Table 1. Shear Wave Elastography Values of the Groups (Overweight/Obese and Control)

	Group		
	Overweight/Obese	**Control**	***P***
SWE (kPa), mean ± SD	34.0 ± 33.7	8.2 ± 2.3	**<.001**[a]
Median (IQR)	17.5 (10.9-50.7)	7.6 (6.9-9.1)	
Sex			.837[d]
Male	44 (56%)	35 (54%)	
Female	34 (44%)	29 (46%)	

[a]Mann–Whitney *U* test; [b]Student's *t*-test; [c]Kruskal–Wallis test; [d]chi-square test.
IQR, interquartile range; kPa, kilopascal; SD, standard deviation; SWE, shear wave elastography; US, ultrasonography.

The mean SWE values were significantly higher in the overweight/obese patients than in the healthy controls (34.0 vs. 8.2 kPa; $P < .001$), suggesting liver stiffness in overweight/obese children (Table 1).

Furthermore, our data revealed that obesity has an effect on SWE values since obese children had higher elastography values than nonobese children (50.2 vs. 23.7 kPa, $P < .001$). Liver biopsy results were available for 32 children (19 males, 13 females) in the patient group. However, we could not detect a correlation between biopsy results and SWE values since we observed a decreasing trend in the SWE values while the level of fibrosis increased in the patient group (Table 2).

Table 2. SWE Values According to Sex, Physical Examination of the Liver, Biopsy Results, and Grade of Hepatosteatosis

		SWE (kPa)		
		Mean ± SD	**Median (IQR)**	***P***
Patient	Sex			.111[a]
	Male (n = 44)	27.7 ± 28.3	15.8 (9.8-35)	
	Female (n = 34)	42.0 ± 38.6	33.1 (13.1-64.9)	
Control	Sex			.382[b]
	Male (n = 35)	7.9 ± 1.8	7.5 (6.9-8.6)	
	Female (n = 29)	8.4 ± 2.7	7.9 (7-9.3)	
Liver–physical examination				.189[a]
Normal (n = 58)		36.2 ± 31.7	19.3 (10.6-57.3)	
Abnormal (n = 20)		27.8 ± 39.2	14.1 (11-30.6)	
Biopsy				.343[c]
Not performed (n = 46)		32.2 ± 36.0	15.3 (9.6-42.3)	
F0 (n = 9)		45.0 ± 31.0	51 (15.2-64.9)	
F1 (n = 17)		39.2 ± 33.5	31.1 (12.7-51.6)	
F2 (n = 3)		19.2 ± 11.1	13.9 (11.8-31.9)	
F3 (n = 3)		14.3 ± 3.1	14 (11.3-17.5)	
US grade of hepatosteatosis				.636[c]
Low (n = 51)		35.5 ± 37.8	15.3 (9.7-62.4)	
Moderate (n = 17)		32.5 ± 29.2	18.8 (13.3-48.6)	
High (n = 10)		29.4 ± 16.5	31.5 (14.4-36.5)	

[a]Mann–Whitney *U* test; [b]Student's *t*-test; [c]Kruskal Wallis test; [d]chi-square test.
F0, no fibrosis; F1, perisinusoidal/pericellular fibrosis; F2, perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis;
F3, perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis; F4, cirrhosis; IQR, interquartile range; kPa, kilopascal;
SD, Standard deviation; SWE, shear wave elastography; US, ultrasonography.

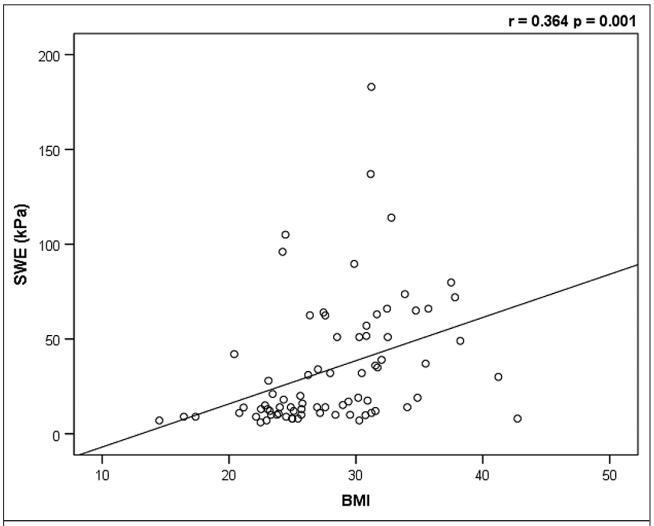

Figure 3. Correlations between elastography and BMI. BMI, body mass index; SWE, shear wave elastography.

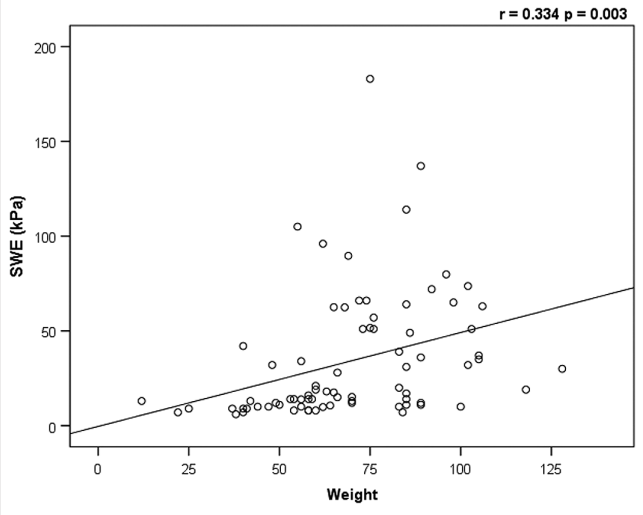

Figure 4. Correlations between elastography and weight. SWE, shear wave elastography.

Shear wave elastography values according to sex, physical examination of the liver, biopsy results, and grade of hepatosteatosis are presented in Table 2. No difference was detected between the sexes in terms of liver stiffness. Additionally, after categorizing the subjects according to the physical examination findings, biopsy results, or grade of hepatosteatosis, the data did not reveal any statistically significant differences in the groups (Table 2).

Statistically significant correlations were found in SWE values, with weight and BMI values (Figures 3 and 4). The results indicated that SWE value increased with increasing weight (poor positive correlation coefficient: 0.334, $P = .003$) and BMI (poor positive correlation coefficient: 0.364, $P = .001$). A significant difference was detected in the biopsy findings and the sex when classified according to the Brunt scoring, and our results showed that most of the females in the patient group had no fibrosis (F0, 54%), whereas most of the males had F1 fibrosis ($P = .034$, Table 3).

Table 3. Distribution of Liver Fibrosis Stages According to Demographic Characteristics

	Biopsy				
	F0	F1	F2	F3	*P*
Age (years), mean ± SD	14.8 ± 2.7	13.7 ± 2.2	13.7 ± 1.9	13.6 ± 2.9	.689[a]
Sex (*n*) (%)					
Male	2(11%)	12(63%)	2(11%)	3(16%)	**.034**[b]
Female	7 (54%)	5 (38%)	1 (8%)	0 (0%)	
BMI (kg/m^2), mean ± SD	29.6 ± 4.7	30.3 ± 5.4	27.7 ± 5.7	28.3 ± 2.2	.827[a]

[a]One-way ANOVA; [b]chi-square test.
BMI, body mass index; F0, no fibrosis; F1, perisinusoidal/pericellular fibrosis; F2, perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis; F3, perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis; F4, cirrhosis; SD, standard deviation.

DISCUSSION

In our study, we evaluate the accuracy rate of liver stiffness with liver biopsy results in obese and overweight children. Our study results showed statistically significant differences between SWE values of healthy children and overweight/obese children with hepatosteatosis. Similar results were obtained in other studies conducted in overweight and obese children with chronic liver disease and it was reported that SWE values were significantly higher in these patient groups. However, the numerical SWE values varied between these studies. Compared to our study, Tutar et al[15] reported a similar SWE value in their control group; however, the mean SWE value was higher in our overweight/obese patients than in their patient group (34.0 vs. 18.4 kPa). In another study conducted by Mărginean et al[16] the mean SWE values obtained from the control (3.73 kPa) and the patient (3.84 kPa) groups were found to be lower than those of our control group. Mjelle et al[17] evaluated 242 healthy children to establish reference values for 2 different SWE methods (2-dimensional SWE and point SWE) and reported median liver stiffness values of 3.3 (range: 2.7-4.3) and 4.1 (range: 3.6-4.7) kPa for 2-dimensional SWE and point SWE, respectively. Although Bailey et al[18] also found a statistically significant difference between the SWE values of both groups, their results could not be compared with ours since they reported SWE values in m/s. Reasons for obtaining different results between these studies may be associated with methodological factors such as obtaining measurements using different devices at different depths or may be related to patient characteristics. Similar to the results obtained from patients with chronic liver disease, conflicting results have been reported regarding the correlation between liver fibrosis and SWE values in obese patients and patients with NASH. Although there are studies supporting that liver fibrosis can be detected by SWE,[8,15,16,19,20] there are also studies reporting that the level of fibrosis cannot be determined by SWE[15] or that liver stiffness is not associated with hepatic steatosis.[21] In our study, SWE values of obese patients were much higher than controls, but it was observed that these values did not reflect the degree of liver fibrosis. We considered possible reasons for this outcome. SWE examination in obese patients is technically difficult due to the thickness of the subcutaneous adipose tissue and fatty tissue of the liver may also affect the speed of ultrasound waves and provide higher SWE values.[22] Unsatisfactory biopsy

specimens may also be considered another potential reason. There is a positive correlation between weight, BMI, and SWE values. Bailey et al[18] found similar results and mentioned that SWE values were significantly associated with age in normal-weight children and with BMI in obese children. In line with our results, they did not report a sex difference in terms of liver stiffness. Furthermore, Trout et al[23] reported that SWE values are significantly correlated with BMI; however, there are contradictory reports as well.[24,25] In our study, no correlation was detected between fibrosis score and SWE values. This may be due to both the small number of patients undergoing biopsy (indicated in the Discussion section) and the fact that most of the patients undergoing biopsy had F1 fibrosis.

Our study has several limitations. First, we detected an age difference between the control and patient groups. Having older patients compared to the control group may have negatively affected our study results. Second, our sample size was considerably small when compared to published reports. And the third is the differences in the number of patients, and control groups are the limitations of the study.

CONCLUSION

As mentioned in many reports, SWE is a safe, sensitive, and non-invasive examination method for demonstrating liver fibrosis. Various mean values and normal reference ranges were found in many studies conducted in patient groups with chronic liver disease and fibrosis. Disease-specific SWE cutoff, mean, and normal reference range values should be defined with large-scale studies to improve the interpretation of SWE values. In obese and overweight patients and patients with NASH, SWE values are higher than those in healthy subjects as well as in patients with liver fibrosis. We found contradictory results in the determination of liver fibrosis with SWE in obese and NASH patients, thus further research with a larger patient population is recommended.

Ethics Committee Approval: This study was approved by Ethics Committee of İstanbul University (Approval No: 83045809/604.01/02-41284, Date: 10.02.2015).

Informed Consent: Written informed consent was obtained from the patients' parents who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

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