Journal of Pediatric Academy

Original Article

Year: 2022 Volume: 3 Issue: 1
Doi: 10.51271/jpea-2022-168

Can Point Shear Wave Elastography be Used as an Indicator of Metabolic Complications in Overweight Children and Adolescents? Evaluation of Subcutaneous Adipose Tissue

Author(s)

Zehra Filiz Karaman[1], Nihal Hatipoğlu[2]

Affiliation(s)

[1]Erciyes University Medical Faculty, Department of Radiology, Division of Pediatric Radiology, Kayseri, Turkey
[2]Erciyes University Medical Faculty, Department of Pediatrics, Division of Pediatric Endocrinology, Kayseri, Turkey

Article Information

Article Type: Original Articles
Article Group: Pediatric Radiology

Received: 17.03.2022
Accepted: 04.04.2022
Available Online: 25.04.2022

Cite this article as: *Karaman ZF, Hatipoğlu N. Can Point Shear Wave Elastography be Used as an Indicator of Metabolic Complications in Overweight Children and Adolescents? Evaluation of Subcutaneous Adipose Tissue. J Pediatr Acad 2022; 1: 20-25.*

Abstract

This study aims to search the association of obesity, metabolic parameters, and abdominal subcutaneous white adipose tissue (scWAT) stiffness in children and adolescents using ultrasound point shear wave elastography (p-SWE). One hundred and forty overweight or obese children referred to as overweight were included in the study group. Thirty-two lean children, referred to as leans, were included in the control group. In all individuals, scWAT shear wave speed (SWS) was measured with p-SWE. ScWAT stiffness was compared between the two groups. The association of anthropometric, metabolic factors and scWAT stiffness is determined. Weight, body mass index, body mass index-standard deviation score, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, fasting insulin were significantly higher in the overweight group ($p<0.05$). ScWAT SWS was significantly different between the groups ($p=0.006$) The median value of scWAT SWS was 1,5 m/s (range; 0.9-3.8), 1.23 m/s (range; 0.7-3.1) for leans and overweight, respectively. In leans, no significant difference was found between boys and girls for scWAT SWS ($p=0.094$). In overweight, a significant difference was found for scWAT SWS between boys and girls ($p=0.022$). The scWAT stiffness is lower in overweight than leans. Gender has a pivotal role in scWAT stiffness. If supported with future long-time follow-up studies, p-SWE may be compatible with assessing subcutaneous adipose tissue changes related to obesity and metabolic complications in childhood and adolescence.

Keywords: Obesity, adipose tissue fibrosis, childhood, shear wave elastography

Correspondence: Zehra Filiz Karaman, Erciyes University Medical Faculty, Department of Radiology, Division of Pediatric Radiology, Kayseri, Turkey
E-mail: dr.fkaraman@gmail.com

Introduction

Childhood obesity is a significant health problem in industrialized countries.[1] The prevalence rates for obesity and overweight are reported as 9.8% and 23.2%, respectively, in Turkish children.[2]

In obesity, adipose tissue mass increases depending on adipose cells' expansion and new adipose cells' genesis.[3] An increase in adipose tissue mass is associated with adipose tissue inflammation and eventually fibrosis, which plays a leading role in metabolic dysfunction. Like other fibrotic diseases, increased production and accumulation of extracellular matrix (ECM) proteins are in charge of adipose tissue fibrosis.[4,5] ECM can be reshaped to adapt to normal fluctuations in adipocyte size,in healthy adipose tissue. However, in fibrotic adipose tissue, ECM cannot be dynamically remodeled to accommodate excess lipid storage.[6] This inability of adipocytes to enlarge may beat a path for ectopic deposition of fat into the liver and other organs, thus promoting metabolic complications.[7]

Highlights

- Subcutaneous white adipose tissue (sc WAT) stiffness was significantly lower in overweight than lean children
- Gender has a pivotal role in scWAT stiffness.
- Future long-time follow-up studies are needed to reveal the relationship of subcutaneous adipose tissue changes and obesity-metabolic complications in childhood and adolescence.

Assessment of subcutaneous white adipose tissue (sc WAT) fibrosis may provide valuable clues to determine the metabolic complications in obesity. ScWAT morphology and fibrosis can be determined through surgical biopsies.[8] Unfortunately, this procedure can only be used for experimental purposes because it is challenging to apply and repeat. Therefore, noninvasive techniques are needed. Currently, there are no noninvasive techniques in practical use that simply characterize scWAT fibrosis. Adipose cell hypertrophy, inflammation, and fibrosis may affect tissue hardness as observed in the liver. Recently, ultrasound elastography techniques have emerged to detect liver and other parenchymal tissue hardness.[9-15] Based on these circumstances, an ultrasound elastography technique called shear wave elastography (SWE) is used to search for scWAT fibrosis in the current study.

With the growing obesity epidemic, screening adipose tissue fibrosis can give usefull information about patient outcomes and therapeutic options. The present study aimed to search the association of obesity, metabolic parameters, and abdominal scWAT stiffness in children and adolescents using ultrasound p-SWE.

Material and Method

Study Population

This study was carried through the Department of Pediatric Radiology and the Department of Pediatric Endocrinology. One hundred seventy-two cases who were 8-18 years old were included in the study. The study and control group were defined according to the body mass index-standard deviation score (BMI-SDS) of individuals. One hundred and forty of them were overweight and obese children which were referred as overweight and included in the study group. Thirty- two of them were leans and included in the control group. Children under eight years old were excluded because of the short duration of obesity to develop metabolic complications.

Ethical Aspects

The local ethics committee approved the study. Written consent was obtained from patients and/or their parents.

Clinical and Laboratory Findings

Body mass index (BMI) is calculated by dividing weight by the square of the height. BMI-SDS was calculated according to growth charts using sex and age. [16] Individuals were grouped as leans (BMI-SDS < +1SD), overweight (+1SD < BMI-SDS ≤ +2SD), and obese (BMI-SDS > +2SD).[17] In this study, all of those with BMI-SDS > +1 SD (overweight and obese) were categorized as overweight.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting blood glucose, fasting insulin, homeostatic model assessment-insulin resistance (HOMA-IR), triglycerides concentrations, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT) were recorded for all participants. The following formula was used for calculating HOMA-IR: fasting plasma glucose (mg/dL) × fasting plasma insulin (IU/mL)/405.[18] These parameters were obtained within a week before or after the elastography measurements. The radiologist was blinded to the metabolic parameters of individuals.

Conventional Ultrasound Evaluation and p-SWE Measurements

All ultrasound examinations were performed by a single radiologist with 18 years of experience in abdominal ultrasonography and two years in SWE. Acuson S3000, Helix Evolution Ultrasound System (Siemens) with a 9L4 linear transducer is used for the examinations.

Shear wave elastography (SWE) is one of the ultrasound elastography techniques, using shear wave speed (SWS) to determine tissue hardness. During the real-time B mode ultrasound imaging, localized transient displacements in the tissue forming the shear waves are generated by applying a short duration acoustic push pulse The velocity of shear waves is recorded. In point shear-wave elastography (p-SWE), a region of interest (ROI) box is put on the interested body areas for elastography measurements. The measurement is expressed either in m/s or kPa, which are changeable during the examination. The square root of tissue elasticity is proportional to SWS which directly relates to tissue hardness.[19-21] This means that the harder the tissue, the faster the shear wave spreads. Extracellular matrix components, primarily fibrotic deposits (i.e., collagen), are known as the main factors affecting tissue hardness.[22]

Grayscale ultrasonography and elastography measurements were performed in the supine position. The transducer was put on the right side of the patient's abdomen, approximately 5 cm laterally from the umbilicus, where abdominal scWAT is at its maximum thickness. Firstly, scWAT thickness was measured and recorded in millimeters. Then, elastography measurements were performed and recorded in m/s. P-SWE was used for elastography measurements with an ROI of 1.0 x 0.5 cm (**Figure 1**). To average the effect of scWAT heterogeneity, SWE measurements were performed on multiple sites neighboring each other. Measurements were obtained during superficial breathing to avoid invalid measurements. The mean of 10 valid measurements for scWAT SWS was recorded. The screen displayed ''xxx,'' when the measurements were invalid. So, such measurements were repeated. The exam duration time was approximately five minutes. The intraobserver agreement expressed as interclass correlation coefficient was 0.96 for p-SWE measurements (95 % CI, 0.95-0.97; p <0.001), demonstrating that the p-SWE measurements had perfect agreement reproducibility.

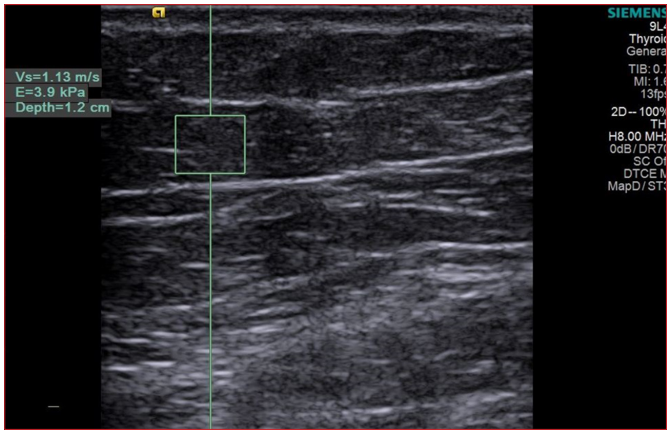

Figure 1. A 10-year-old overweight boy. P-SWE measurement of subcutaneous adipose tissue with an ROI

Statistical Analysis

Analyses were performed with SPSS IBM Statistics Version 22.0. The Shapiro-Wilk test was used to confirm the normality of distribution for quantitative data. Two independent groups were compared by t-test or Mann-Whitney U for normally distributed data and non-normally distributed data, respectively. Test values were expressed as the mean ± SD. Pearson correlation was used for normally distributed data, and Spearman correlation was used for non-normally distributed data. Correlation analyses were performed for lean boys, lean girls, overweight boys, and overweight girls separately. The interclass correlation coefficient was used for reliability measurements. Differences were regarded as significant at p<0,05.

Results

The age of overweight children enrolled in this study was between 8 and 18 (mean; 12.93 ± 2.52). Fifty-nine of them were boys, and 81 of them were girls. The age of lean children was between 8 and 17 (mean; 13.06 ± 2.58). Eight of them were boys, and 24 of them were girls. The leans and overweight subjects were compared in terms of age, gender, anthropometric, metabolic parameters, scWAT thickness, and scWAT SWS. No significant differences were found between the two groups for age, gender, height, fasting glucose, triglycerides level, AST, and HOMA-IR. Weight, BMI, BMI-SDS, SBP, DBP, fasting insulin, ALT, scWAT thickness were significantly different between the groups. Also, scWAT SWS was significantly different between the groups (p=0.006). The median value of scWAT SWS was 1.5 m/s (range; 0.9-3.8) and 1.23 m/s (range; 0.7-3.1) for leans and overweight, respectively (**Table 1**).

Table 1
Comparison of demographic, anthropometric, metabolic, and laboratory parameters of leans and overweight

	Leans Median (range)	Overweight Median (range)	p
Gender			0.072
Girls	24	81	
Boys	8	59	
Age	13.2 (8-17.4)	3.4 (8.1-18)	0.830
Weight (kg)	46.5 (22.1-83)	73.2 (29.5- 127)	<0.001
Height (cm)	156 (121.5-183.5)	156,5 (117.3-188)	0.58
BMI (kg/m2)	18.9 (14.1-26.2)	28 (18.7-42.8)	<0.001
BMI-SDS	-0.55 (-2.48-1)	2.5 (1.1-4.2)	<0.001
SBP (mmHg)	100 (90-110)	110 (90-140)	0.013
DBP (mmHg)	60 (50-80)	70 (50-90)	0.010
Triglycerides (mg/dl)	98 (28-149)	105 (41-391)	0.062
HDL cholesterol (mg/dl)	52.0 (39-78)	44.0 (28.4-86)	0.001
Fasting glucose (mg/dl)	84.5 (61-95)	87.0 (65-106)	0.388
Fasting insulin (µIU/ml)	9.1 (4.4-15.8)	15.5 (1.4-76.4)	0.012
HOMA-IR	1.85 (0.91-12.4)	3.6 (0.3-17)	0.201
AST (IU/L)	23.5 (17-40)	22.0 (10-84)	0.98
ALT (IU/L)	14 (5-62)	19 (6-158)	<0.001
ScWAT thickness (mm)	13.7 (5-33)	38.0 (9.5-75.0)	<0.001
ScWAT SWS (m/s)	1.5 (0.9-3.8)	1.23 (0.7-3.1)	0.006

BMI, body mass index; BMI-SDS, body mass index-standard deviation score; SBP, Systolic blood pressure; DBP, Diastolic blood pressure; HDL cholesterol, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HOMA-IR, homeostatic model assessment-insulin resistance; ScWAT, subcutaneous white adipose tissue; SWS, Shear wave speed

ScWAT thickness and scWAT SWS were compared according to gender in leans and overweight. In leans, no significant difference was found between boys and girls for scWAT thickness and SWS. In overweight, no significant difference was found for scWAT thickness between boys and girls. However, a significant difference was found for scWAT SWS between boys and girls in overweight (p=0.022). The median value of SWS was 1,36 m/s (range; 0.71-3.07), 1.12 m/s (range; 0.70-3.04) for overweight boys and overweight girls respectively (**Table 2**, **Figure 2**).

Table 2
Comparison of scWAT thickness and SWS in leans and overweight according to gender

	Leans			Overweight		
	Boys	Girls	p	Boys	Girls	p
ScWAT thickness (mm) Median (range)	11.7 (5-22.7)	14.9 (4.9-33)	0.254	39.0 (9.5-75)	38.0 (18.30-75)	0.47
ScWAT SWS (m/s) Median (range)	1.66 (1.25-3.80)	1.37 (0.86-2.22)	0.094	1.36 (0.71-3.07)	1.12 (0.70-3.04)	0.022

ScWAT, subcutaneous white adipose tissue; SWS, Shear wave speed

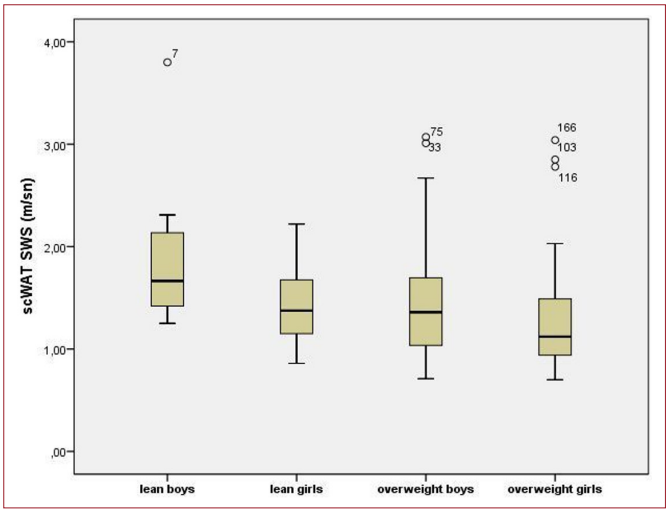

Figure 2. Box-plot showing scWAT SWS of lean boys, lean girls, overweight boys, overweight girls

Correlation analysis was performed between SWS, demographic and laboratory parameters for leans and overweight according to gender. For lean boys, SWS showed no correlation with anthropometric, metabolic, laboratory parameters, and scWAT thickness. For lean girls, SWS showed a relatively strong negative correlation with BMI (r=-0.678 p<0.001), BMI-SDS (r=-0.499 p=0.013), SBP (r=-0.638 p=0.035), DBP (r= -0.695 p=0.018), a relatively strong positive correlation with HDL cholesterol (r=0.616 p=0.033) and a strong negative correlation with scWAT thickness (r= -0.815 p<0.001). For overweight boys, SWS showed a weak positive correlation with ALT and a moderate negative correlation with scWAT thickness. For overweight girls, SWS showed a weak negative correlation with fasting glucose and scWAT thickness (**Table 3**).

Table 3.
The results of correlation analysis between SWS and anthropometric, metabolic, laboratory parameters in overweight boys and girls

	SWS for overweight boys (m/s)	SWS for overweight girls (m/s)
Fasting glucose (mg/dl)		-0.231 0.039
ALT (IU/L)	0.279 0.037	
scWAT thickness (mm)	-0.364 0.005	-0.288 0.009

The first line is r value, the second line is p value for all parameters. ALT, alanine aminotransferase; ScWAT: subcutaneous white adipose tissue; SWS, Shear wave speed

Discussion

Adipose tissue fibrosis has a critical and complicated role in obesity and metabolic dysfunction. The development of adipose tissue fibrosis is associated with some cell types, cellular pathways, or environmental factors, but the inclusionary cause is obesity.[6,23-25] Adipocytes, adipocyte progenitors, myofibroblasts, and fibroblasts are in charge of the production of ECM. Another prominent participant in the development of fibrosis is hypoxia. Hypoxia occurs when adipocytes reach the diffusion limit of oxygen due to lipid accumulation—long-term hypoxia agglomerates macrophages to the area. Also, mast cells contribute to the development of fibrosis by promoting collagen production. It was shown that obese subjects had more pericellular fibrosis accompanied by accumulation of macrophage and mast cells compared with normal-weight subjects. Despite all this information, the association between obesity and adipose tissue fibrosis is complex and is not entirely understood. The prevalence of adipose tissue fibrosis increases with severe obesity, but not all obese patients develop tissue fibrosis.[6]

Depending on the studies,[5,26-29] reporting a close association between obesity and adipose tissue fibrosis and the effects of fibrosis on tissue stiffness,[9-13] it may be anticipated that being overweight may potentially increase scWAT stiffness, in the current study. However, the results showed contradistinction with this expectancy. ScWAT stiffness was significantly lower in overweight than leans. Despite the greater adipose tissue thickness, lower SWS in overweight may be explained by the 'adipose tissue expandability' concept,[30] which states that adipocytes' capacity to expand for lipid storage differs in individuals. It also states that lipid storage capacity is a more determinative factor of obesity-associated metabolic complications than the amount of adipose tissue fibrosis. Patients with higher storage capacity compared with others may have fewer metabolic complications. Short-term exposure to obesity or its complications, might be an explanatory factor for the lower tissue stiffness in overweight children which potentially may affect the development or maintenance of fibrosis in adipose tissue. Charmaine S.T. et al.[31] determined the immunohistochemistry of subcutaneous adipose cells and ECM markers in children. They reported that overweight children had significantly less total collagen staining compared to normal-weight children. Also, they said that the percentage of total collagen was inversely associated with the BMI Z score. In their study, Walker et al.[32] observed a trend in decreasing collagen ratio in obese children compared with leans. These two studies' findings are supporting the lower adipose tissue stiffness in overweight children in the current study.

When SWS was evaluated according to gender, there was no difference in the leans. Conversely, it was interesting to see that girls' SWS values were significantly lower than boys in overweight. This may be explained by the fact that girls gain more fat mass during puberty and less muscle than boys.[33] The 'adipose tissue expandability concept' may also have a role in this situation, with increased lipid capacity of adipocytes causing less tissue stiffness.

After this stage of the study, the correlation analysis between scWAT SWS and the other parameters was performed separately according to gender. There were negative relationships between SWS and BMI, BMI-SDS, SBP, DBP, scWAT thickness, and a positive relationship between SWS and HDL cholesterol in lean girls (**Table 3**). In overweight girls, all these relationships disappeared, and weak negative correlations were seen between SWS and fasting glucose, scWAT thickness. In overweight boys, a weak positive correlation was seen between SWS and ALT. There are few studies[34,35] using elastography to assess scWAT fibrosis in adults and children. Sasso et al.[34] in their study, reported a negative correlation between SWS and total body fat

mass, cholesterol and a positive correlation between total body lean mass, fasting glycemia, fasting insulin, and HOMA-IR. Abdennour et al.[35] in a study in morbidly obese adults, assessed scWAT stiffness and compared the values with immunohistochemistry (IHC) evaluated scWAT fibrosis. They found that scWAT stiffness was positively associated with scWAT IHC fibrosis. They also reported that SWS correlated positively with fasting glycemia, insulin, HbA1c, fat-free mass, and negatively with body fat and HDL cholesterol. In the current study, BMI and BMI-SDS were used to evaluate body fat instead of measuring total body fat. BMI is reported as having a high discriminatory power to identify body fat.[36] The negative correlations between SWS and weight, BMI, BMI-SDS in lean girls, in the current study were similar to their results. It was intriguing not to see a relationship between SWS and anthropometric factors in overweight while seeing in lean girls. Although the reason for this result is unknown, further long-time follow-up studies are needed to elucidate the relation of scWAT SWS and anthropometric, metabolic parameters as the duration of obesity increases.

This study has significant limitations. One of them is the lack of scWAT biopsy for histological confirmation. However, it was impossible to achieve histologic samples as there was no indication. The second limitation is the short duration of obesity in children and adolescents to see the effects of anthropometric and metabolic parameters on scWAT properties. The lack of knowledge of fat mass may be another limitation. A more comprehensive examination of body composition (waist circumference, BMI, fat-free mass, fat mass) in future studies may give more apparent findings.

This is the first study searching the association of anthropometric, metabolic parameters, and scWAT stiffness in children using p-SWE, to our knowledge.

Conclusion

Stiffness of scWAT was found lower in overweight than in leans, and gender had a pivotal role in scWAT stiffness. If supported with future long-time follow-up studies, p-SWE can be compatible with assessing subcutaneous adipose tissue changes related to obesity and metabolic complications in childhood and adolescence.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Conflict of Interest: There are no conflicts of interest in connection with this paper, and the material described is not under publication or consideration for publication elsewhere.

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Ethics Committee (Date: 20.01.2021, Decision No: 2021/63)

Financial Disclosure: The authors have no conflicts of interest to declare.

Informed Consent: Informed consent was obtained from the parents of the patients.

References

1. Ogden CL, Carroll MD, Curtin LR, Lamb MM, Flegal KM. Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA.* 2010; 303: 242-249. [CrossRef]
2. Çelmeli G, Çürek Y, Arslan Gülten Z, et al. Remarkable increase in the prevalence of overweight and obesity among school age children in Antalya, Turkey, between 2003 and 2015. *J Clin Res Pediatr Endocrinol.* 2019; 11: 76-81. [CrossRef]
3. Verboven K, Wouters K, Gaens K, et al. Abdominal subcutaneous and visceral adipocyte size, lipolysis and inflammation relate to insulin resistance in male obese humans. *Sci Rep.* 2018; 8: 4677. [CrossRef]
4. Gustafson B, Gogg S, Hedjazifar S, Jenndahl L, Hammarstedt A, Smith U. Inflammation and impaired adipogenesis in hypertrophic obesity in man. *Am J Physiol Endocrinol Metab.* 2009; 297: E999-E1003. [CrossRef]
5. Mariman EC, Wang P. Adipocyte extracellular matrix composition, dynamics and role in obesity. *Cell Mol Life Sci.* 2010; 67: 1277-1292. [CrossRef]
6. DeBari MK, Abbott RD. Adipose tissue fibrosis: mechanisms, models, and importance. *Int J Mol Sci.* 2020; 21: 6030. [CrossRef]
7. Duval C, Thissen U, Keshtkar S, et al. Adipose tissue dysfunction signals progression of hepatic steatosis towards nonalcoholic steatohepatitis in C57BL/6 mice. *Diabetes.* 2010; 59: 3181-3191. [CrossRef]
8. Mutch DM, Tordjman J, Pelloux V, et al. Needle and surgical biopsy techniques differentially affect adipose tissue gene expression profiles. *Am J Clin Nutr.* 2009; 89: 51-57. [CrossRef]
9. Berná-Serna JD, Sánchez-Jiménez R, Velázquez-Marín F, et al. Acoustic radiation force impulse imaging for detection of liver fibrosis in overweight and obese children. *Acta Radiol.* 2018; 59: 247-253. [CrossRef]
10. Kwon YD, Ko KO, Lim JW, Cheon EJ, Song YH, Yoon JM. Usefulness of transient elastography for non-invasive diagnosis of liver fibrosis in pediatric non-alcoholic steatohepatitis. *J Korean Med Sci.* 2019; 34: e165. [CrossRef]
11. Garcovich M, Veraldi S, Di Stasio E, et al. Liver stiffness in pediatric patients with fatty liver disease: diagnostic accuracy and reproducibility of shear-wave elastography. *Radiology.* 2017; 283: 820-827. [CrossRef]
12. Herrmann E, de Lédinghen V, Cassinotto C, et al. Assessment of biopsy-proven liver fibrosis by two-dimensional shear wave elastography: An individual patient data-based meta-analysis. *Hepatology.* 2018; 67: 260-272. [CrossRef]
13. Castera L, Friedrich-Rust M, Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology.* 2019; 156: 1264-1281.e4. [CrossRef]
14. Sağlam D, Demirbaş F, Bilgici MC, Yücel S, Çaltepe G, Eren E. Can point shear wave elastography be used as an early indicator of involvement?: evaluation of the pancreas and liver in children with cystic fibrosis. *J Ultrasound Med.* 2020; 39: 1769-1776. [CrossRef]
15. Yucel S, Ceyhan Bilgici M, Kara C, et al. Acoustic radiation force impulse quantification in the evaluation of thyroid elasticity in pediatric patients with Hashimoto thyroiditis. *J Ultrasound Med.* 2018; 37: 1143-1149. [CrossRef]
16. Demir K, Özen S, Konakçı E, Aydın M, Darendeliler F. A comprehensive online calculator for pediatric endocrinologists: ÇEDD Çözüm/TPEDS Metrics. *J Clin Res Pediatr Endocrinol.* 2017; 9: 182-184. [CrossRef]
17. WHO. World Health Organization (WHO) BMI-for-age (5-19 years) Growth Chart 2007. Accessed June 20, 2019 [CrossRef]
18. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia.* 1985; 28: 412-419. [CrossRef]
19. Zhai L, Palmeri ML, Bouchard RR, Nightingale RW, Nightingale KR. An integrated indenter-ARFI imaging system for tissue stiffness quantification. *Ultrason Imaging.* 2008; 30: 95-111. [CrossRef]

20. Guzmán-Aroca F, Reus M, Berná-Serna JD, et al. Reproducibility of shear wave velocity measurements by acoustic radiation force impulse imaging of the liver: a study in healthy volunteers. *J Ultrasound Med.* 2011; 30: 975-979. *[CrossRef]*
21. Barr RG. Shear wave liver elastography. *Abdom Radiol (NY).* 2018; 43: 800-807. *[CrossRef]*
22. Mueller S, Sandrin L. Liver stiffness: a novel parameter for the diagnosis of liver disease. *Hepat Med.* 2010; 2: 49-67. *[CrossRef]*
23. Sun K, Park J, Gupta OT, et al. Endotrophin triggers adipose tissue fibrosis and metabolic dysfunction. *Nat Commun.* 2014; 5: 3485. *[CrossRef]*
24. Spencer M, Yao-Borengasser A, Unal R, et al. Adipose tissue macrophages in insulin-resistant subjects are associated with collagen VI and fibrosis and demonstrate alternative activation. *Am J Physiol Endocrinol Metab.* 2010; 299: 1016-1027. *[CrossRef]*
25. Muir LA, Neeley CK, Meyer KA, et al. Adipose tissue fibrosis, hypertrophy, and hyperplasia: Correlations with diabetes in human obesity. *Obesity (Silver Spring).* 2016; 24: 597-605. *[CrossRef]*
26. Divoux A, Tordjman J, Lacasa D, et al. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. *Diabetes.* 2010; 59: 2817-2825. *[CrossRef]*
27. Buechler C, Krautbauer S, Eisinger K. Adipose tissue fibrosis. *World J Diabetes.* 2015; 6: 548-553. *[CrossRef]*
28. Lackey DE, Burk DH, Ali MR, et al. Contributions of adipose tissue architectural and tensile properties toward defining healthy and unhealthy obesity. *Am J Physiol Endocrinol Metab.* 2014; 306: 233-246. *[CrossRef]*
29. Muir LA, Neeley CK, Meyer KA, et al. Adipose tissue fibrosis, hypertrophy, and hyperplasia: Correlations with diabetes in human obesity. *Obesity (Silver Spring).* 2016; 24: 597-605. *[CrossRef]*
30. Virtue S, Vidal-Puig A. Adipose tissue expandability, lipotoxicity and the Metabolic Syndrome--an allostatic perspective. *Biochim Biophys Acta.* 2010; 1801: 338-349. *[CrossRef]*
31. Tam CS, Tordjman J, Divoux A, et al. Adipose tissue remodeling in children: the link between collagen deposition and age-related adipocyte growth. *J Clin Endocrinol Metab.* 2012; 97: 1320-1327. *[CrossRef]*
32. Walker RW, Allayee H, Inserra A, et al. Macrophages and fibrosis in adipose tissue are linked to liver damage and metabolic risk in obese children. *Obesity (Silver Spring).* 2014; 22: 1512-1519. *[CrossRef]*
33. Wells JC. Body composition in childhood: effects of normal growth and disease. *Proc Nutr Soc.* 2003; 62: 521-528. *[CrossRef]*
34. Sasso M, Liu Y, Aron-Wisnewsky J, et al. AdipoScan: a novel transient elastography-based tool used to non-invasively assess subcutaneous adipose tissue shear wave speed in obesity. *Ultrasound Med Biol.* 2016; 42: 2401-2413. *[CrossRef]*
35. Abdennour M, Reggio S, Le Naour G, et al. Association of adipose tissue and liver fibrosis with tissue stiffness in morbid obesity: links with diabetes and BMI loss after gastric bypass. *J Clin Endocrinol Metab.* 2014; 99: 898-907. *[CrossRef]*
36. Alves Junior CA, Mocellin MC, Gonçalves ECA, et al. Anthropometric indicators as body fat discriminators in children and adolescents: a systematic review and meta-analysis. *Adv Nutr.* 2017; 8: 718-727. *[CrossRef]*