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

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

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Introduction
Childhood obesity is a significant health problem in industrialized countries. The prevalence rates for obesity and overweight are reported as 9.8% and 23.2%, respectively, in Turkish children. In obesity, adipose tissue mass increases depending on adipose cells’ expansion and new adipose cells’ genesis. 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. 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. 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. Assessment of subcutaneous white adipose tissue (scWAT) fibrosis may provide valuable clues to determine the metabolic complications in obesity. ScWAT morphology and fibrosis can be determined through surgical biopsies. 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. 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 useful 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. Individuals were grouped as leans (BMI-SDS < +1SD), overweight (+1SD < BMI-SDS ≤ +2SD), and obese (BMI-SDS > +2SD). 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. 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. 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.
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.

**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>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of demographic, anthropometric, and laboratory parameters of leans and overweight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Lean Boys Median (range)</td>
</tr>
<tr>
<td>Girls</td>
<td>24 (8-18)</td>
</tr>
<tr>
<td>Boys</td>
<td>18 (8-22)</td>
</tr>
<tr>
<td>Age</td>
<td>13.2 (8.17-14.7)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>46.5 (22.1-83)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156 (121.5-183.5)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>18.9 (14.1-26.2)</td>
</tr>
<tr>
<td>BMI-SDS</td>
<td>-0.55 (-2.48-1)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>100 (90-110)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>60 (50-60)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>98 (28-149)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>52.0 (39-78)</td>
</tr>
<tr>
<td>Fasting glucose (mg/dl)</td>
<td>84.5 (61-95)</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>9.1 (4.4-15.8)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.85 (0.91-12.4)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>23.5 (17-40)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>14 (5-62)</td>
</tr>
<tr>
<td>ScWAT thickness (mm)</td>
<td>13.7 (5-35)</td>
</tr>
<tr>
<td>ScWAT SWS (m/s)</td>
<td>1.5 (0.9-3.8)</td>
</tr>
</tbody>
</table>

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>
<thead>
<tr>
<th>Table 2</th>
<th>Comparison of scWAT thickness and SWS in leans and overweight according to gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean Boys</td>
<td>Lean Girls</td>
</tr>
<tr>
<td>ScWAT thickness (mm) Median (range)</td>
<td>11.7 (5-22.7)</td>
</tr>
<tr>
<td>ScWAT SWS (m/s) Median (range)</td>
<td>1.66 (1.25-3.80)</td>
</tr>
</tbody>
</table>

**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.
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 BMI-SDS, SBP, DBP, scWAT thickness, and a positive correlation with BMI (r= -0.678 p<0.001), BMI-SDS, SBP, DBP, scWAT thickness, and a positive correlation with BMI (r= -0.678 p<0.001). For overweight girls, SWS showed a weak positive correlation with ALT and scWAT thickness. For overweight boys, SWS showed a weak positive correlation with ALT and scWAT thickness. For overweight girls, SWS showed no correlation with anthropometric, metabolic, laboratory parameters and scWAT thickness. For overweight 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.32 The ‘adipose tissue expandability concept’ may also have a role in this situation, with increased lipid capacity of adipocytes causing less tissue stiffness.

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.32 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 total body fat.
mass, cholesterol and a positive correlation between total body lean mass, fasting glycemia, fasting insulin, and HOMA-IR. Abdenour 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 lean, 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.

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