Determining the effects of excess weight on renal cortical stiffness in children and adolescents with point Shear Wave Elastography

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Abstract

Aim: To determine the early effects of excess weight on renal cortical stiffness in children and adolescents using point shear wave elastography (pSWE). Materials and methods: One hundred and forty-six overweight and obese children (43.2% male; mean age, 12.6±2.9 years: range 4.3-18) and 48 lean children (27.1% male: mean age, 12.4±3.4: range 4.8-18.9) were included in the study and control group, respectively. pSWE measurements of the two kidneys were performed. The mean value of shear wave velocity was compared between groups. Results: The mean shear wave velocity was 2.79±0.53 m/s for the control subjects and 3.09±0.59 m/s for the overweight-obese subjects. The differences between the two groups were statistically significant (p=0.001). There was no correlation between shear wave velocity and age or depth. A positive correlation was found between shear wave velocity and body mass index, body mass index-standard deviation score. Conclusion: Renal cortical stiffness was higher in children with excess weight than in lean children. This study is the first attempt at applying pSWE to investigate the early adverse effects of excess weight.

Keywords: shear wave elastography; kidney; children; adolescent; excess weight

Introduction

Childhood obesity has become a global health problem. The prevalence rates for obese and overweight individuals were 9.8% and 23.2%, respectively in the Turkish population [1].

Excess weight is known to be an important risk factor for renal function alteration. The association of obesity and progressive renal damage was reported in many studies [2-6]. The rate of end-stage renal disease (ESRD) was found to increase from 10/100 000 person-years in normal weight [body mass index (BMI), 18.5–24.9 kg/m²] persons to 108/100 000 person-years in extreme obese persons (BMI, ≥40 kg/m²) [7]. Vivante et al found that obesity had a six-fold higher risk for ESRD development among approximately 1.2 million 17-year-old adolescents followed up for 25 years [8].

Insulin resistance or diabetes mellitus, cardiovascular diseases and hypertension were recognized as important factors for chronic kidney disease (CKD). Obesity itself, even in the absence of the above-mentioned risk factors, was correlated with CKD development [9]. Overweight and obesity are associated with an altered renal hemodynamic profile that predisposes an individual to chronic renal damage [10]. Obesity-related glomerulopathy was associated with focal segmental glomerulosclerosis. Podocyte alterations, renal interstitial abnormalities, mesangial expansion and glomerulomegaly are the typical histological changes found in renal parenchyma in obese patients [11]. In children with severe obesity, albuminuria and decreased estimated glomerular filtration rate were reported to be early kidney disorders [12].

Early diagnosis of obesity-related kidney pathology is essential to prevent chronic renal damages. Renal biopsy is the gold standard in assessing histological changes; [13] however, being an invasive method with
complications, it cannot be indicated in patients without clinical and laboratory evidence of renal damage. Thus, non-invasive methods are needed for determining the adverse renal effects of excess weight.

Ultrasoundography (US) is a non-invasive, safe and easily applicable renal imaging method in children [14]. However, conventional US does not diagnose kidney diseases until the size or echotexture of the kidneys change. Point Shear Wave Elastography (pSWE), a recently developed US technique, assesses the elastic properties of tissues. During real-time B mode imaging, a region of interest (ROI) is placed on the kidney parenchyma and a short duration acoustic push pulse is applied, generating localized transient displacements in the tissue forming the shear waves. The measurement is displayed either in m/s (shear wave velocity) or kPa (elasticity modulus or Young's modulus) [15,16]. SWE has been used in evaluation of renal tissue stiffness in vesicoureteral reflux (VUR), ureteropelvic junction obstruction (UPJO), hydronephrosis, CKD, and kidney allografts [17-20].

The present study aims to determine the relation of excess weight and renal parenchymal stiffness in children and adolescents and to assess the applicability of pSWE in determining the early parenchymal changes of kidneys associated with excess weight.

**Materials and methods**

This study is a single-center study approved by the Ethics Committee of our university. Children’s parents signed the informed consent according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

**Study population**

The study was carried out by the Department of Pediatric Radiology and the Department of Pediatric Metabolism and Nutrition. One hundred and ninety-four cases were included in the study: 146 with overweight or obese (study group) and 48 with normal weight (control group). The study group and control group were identified according to their body mass index-standard deviation score (BMI-SDS).

BMI was calculated by dividing weight by the square of the height. BMI-SDS was calculated according to growth charts using age and sex [21]. Individuals were categorized as lean (BMI-SDS < +1SD), overweight (+1SD < BMI-SDS ≤ +2SD) and obese (BMI-SDS > +2SD) [22]. BMI was expressed as kg/m² and BMI-SDS was summarized by percentiles. Subjects with diabetes, hypertension, nephrolithiasis, hydronephrosis, renal parenchymal diseases, or high serum urea nitrogen and creatinine were excluded.

**Conventional US and pSWE**

All US investigations were performed by a single radiologist with 18 years of experience in abdominal ultrasonography and two years in SWE, using Acuson S3000, Helx Evolution Ultrasound System (Siemens) with a 6C1 convex transducer. First, the kidneys were evaluated using conventional US (size, renal parenchymal echotexture, pelvicalyceal system and nephrolithiasis) followed by pSWE measurements, which were performed with the patient in supine position for the right kidney and in lateral decubitus position for the left kidney. Measurements were obtained during breath-holding or superficial breathing and in the longitudinal plane for each kidney 2-8 cm from the skin. The ROI (1.0x0.5 cm) was placed in the middle third of the cortex as similarly as possible for all individuals. Five valid measurements were performed for each kidney and the mean value of all ten measurements of both kidneys was recorded. In invalid measurements, the screen displayed “xxx,” and such measurements were repeated. The entire exam duration time was approximately 10 minutes.

To assess the intraobserver variability, pSWE measurements of all individuals were used.

**Statistical analysis**

Statistical analysis was performed with SPSS IBM Statistics Version 22.0. The Shapiro Wilk test was used to confirm the normality of distribution for continuous variables. The Mann-Whitney U test, Kruskal Wallis, and post hoc analysis were used to compare the groups’ continuous variables. Values were expressed as the mean ± standard deviation (SD) and range (minimum to maximum). The Spearman correlation was used for correlation analysis. Interclass correlation coefficient was used for reliability measurement. Differences were regarded as significant at p < 0.05.

**Results**

All subjects in the study and control group were compared for demographic parameters (Table I). The mean SWV for the control subjects was 2.79±0.53 (2.58±0.52 for males, 2.87±0.51 for females, p=0.09). The mean SWV for the study group was 3.09±0.59 (3.09±0.60 for males, 3.08±0.59 for females, p=0.95). A significant difference was found between the control and study groups for SWV (p=0.001).

There was no correlation between SWV and depth, age and gender. BMI and BMI-SDS showed a positive correlation with SWV (r=0.244; p=0.001, r=0.193; p=0.09, respectively).

After splitting the study group into subgroups of overweight (32 children) and obese (114 children) the mean
SWV values were compared with the lean individuals. The mean SWV of the overweight group and the obese group were higher than the lean group, 2.96±0.71 m/s and 3.12±0.55 m/s, respectively. However, the difference was statistically significant only in the obese group (p=0.002) and not in the overweight group (p=0.592).

The intraobserver agreement for the right and left kidneys, which is expressed as interclass correlation coefficient, was 0.70 (95% CI, 0.61–0.78; p<0.001) and 0.74 (95% CI, 0.67–0.81; p<0.001), respectively. The results demonstrated that the shear wave velocity measurements had substantial agreement reproducibility.

Discussions

Excess weight has been closely associated with renal damage. Obesity and overweight accounts for adverse renal effects, making them candidates to become the main renal risk factor eventually [10]. The early diagnosis of adverse renal effects of excess weight is essential for preventing progressive renal damage.

In the present study, the effects of excess weight on renal cortical stiffness were evaluated in children and adolescents using pSWE. Renal cortical stiffness was significantly higher in children with excess weight compared to lean children. When the children with excess weight were classified into subgroups of overweight and obese, it was demonstrated that renal cortical stiffness of obese volunteers was higher than in those who were overweight; however, the difference was not significant. The renal cortical stiffness of volunteers who were overweight was higher than in the lean group. Nevertheless, the difference was not significant. Renal cortical stiffness of obese volunteers was significantly higher than in the lean group. These results demonstrate that the more excess weight there is, the more renal cortical stiffness occurs.

Grass et al [23] evaluated kidneys of healthy children and reported a positive correlation between SWV and age, weight and body height, while there was no correlation between SWV and BMI, gender and depth. Lee et al [24], reported a positive correlation between SWV and age upon conducting a study on 202 healthy children’s kidneys. Habibi et al [18] reported no correlation between SWV and age, sex and BMI. Bota et al [25] reported that only age and gender were significantly correlated with renal SWV. Horster et al [26] evaluated liver stiffness in healthy volunteers with transient elastography and reported that an increase of 1 cm in depth caused a decrease of 0.132 m/s in the SWV. In the current study, no correlation was found between SWV and age, gender and depth but BMI and BMI-SDS were positively correlated with SWV.

Lee et al [24] reported that the mean SWV values for the right and left kidneys were 2.10 m/s and 2.33 m/s, respectively. They performed the examination with a 4-9 MHz linear probe in children younger than five years and a 1-4 MHz convex probe for children older than five years. They obtained the measurements from the middle section of the kidneys in axial view in supine position. Goya et al [27] found an SWV of 2.39 and 2.37 m/s for the healthy right and left kidneys, respectively. They performed the measurements from the upper, middle, and lower poles in supine and lateral decubitus position. Uçar et al [17] found that the SWV of healthy kidneys was 2.09. They obtained the measurements lying on the side from the upper, middle, and lower poles. In the current study, the mean SWV value for the control subjects was 2.79±0.53 m/s, which is relatively high compared with the literature. The measurements were obtained from the middle third of the cortex in the supine position for the right kidney and in the lateral decubitus position for the left kidney.

The differences of SWE techniques and ultrasound units may play a role in the heterogeneity of the results of all these studies. The parts of the kidney in which the measurements were realized and the angle of ROI are important factors, which may also be responsible for the variations of the results as SWV is affected by the plane of acquisition due to anisotropy. The complex structure of the kidney is the cause of anisotropy. The kidney parenchyma is formed by the cortex and the medulla. Spherical glomeruli and proximal and distal tubules are settled in the cortex, whereas the tubules perpendicular to the
capsule are settled in the medulla. The SWV is affected by the structural differences between these two parts. The longitudinal arrangement of the tubules in the medulla accounts for the higher SWV. When the ultrasound beam is sent parallel to the medullary structures, the shear waves perpendicularly pass through vascular and tubular interfaces, decreasing the speed, resulting in lower SWV. When the ultrasound beam is perpendicular to the main pyramid axis, shear waves do not intervene with interfaces that increase speed, resulting in higher SWV [28,29]. The measurements obtained from the upper and lower poles are more prone to the effects of anisotropy as it is difficult for these regions to place ROI parallel to the tubular system. It is recommended to place the ROI on the middle cortex as this location allows the exclusion of the medulla and sinus [30]. We carefully measured SWV precisely at the same place of the middle third of the cortex to reduce the effect of anisotropy.

There are conflicting results about the alterations of SWV values for damaged renal parenchyma in literature. Bilgici et al. [31] and Hu et al. [32] reported that SWV values decrease with chronic renal failure compared to healthy paediatric kidneys. Takata et al [33] found decreased SWV values in chronic renal failure; however, in their study, no significant difference was observed between the kidneys with early-stage renal parenchymal disease and the kidneys with end-stage renal disease. Habibi et al. [18] showed that SWV values in the kidneys with UPJO are statistically lower compared to healthy ones. Goya et al [27] reported decreased SWV values in renal scars compared with healthy kidneys. Apart from the studies mentioned above that found a negative correlation between SWV values and renal parenchymal damage or fibrosis, there are contrary studies. Moon et al [34] reported a positive correlation between SWV and fibrosis in rat kidneys. Kim et al [20] found increased SWV in transplanted kidneys with subclinical rejection even with a normal renal resistive index. Ucar et al [17] observed an increased renal cortical stiffness in children with vesicoureteral reflux (VUR) in the areas with scar formation. Bruno et al [35] reported increased renal cortical SWV in VUR even without scar formation. Another study by Goya et al [36] that evaluated diabetic nephropathy showed that SWV of the kidney in patients with type 2 diabetes (2.88±0.59 m/s) was significantly higher than that for the control subjects (2.35±0.39 m/s). They showed that the SWV of the kidneys was increased even in the first stage of diabetic nephropathy. They suggested that tubulointerstitial fibrosis and sclerosis in vessels and the glomerulus are in charge of the increased renal stiffness in patients with Type 2 diabetes. Another study evaluating [37] the kidneys’ renal cortical stiffness in Type 2 diabetes with grade 3-4 diabetic nephropathy showed that SWV was also higher than that in the control subjects. Saglam et al [38] evaluated the effects of Type 1 diabetes on renal cortical elasticity. They did not find any significant difference in SWV between patients with Type 1 diabetes and healthy subjects. In the current study, the mean SWV of the patients with excess weight was significantly higher than the healthy control subjects.

The contradictions may be related to the fact that kidney stiffness measurements are not affected only by fibrosis but also by anisotropy, vascularization and hydro-nephrosis. Asano et al [39] claimed that hypoperfusion and decrease in glomerular filtration rate are the factors causing decreased cortical stiffness in ESRD. The report by Liu et al [40] supports this study, showing a correlation between renal blood flow and renal stiffness. They observed that when they gradually decreased the renal blood flow in mice, the stiffness value decreased. Also, they observed that renal stiffness increased after ligating the renal vein. Based on these results, they claimed that increased hydrostatic pressure might lead to increased stiffness.

We found that renal cortical stiffness was higher in children with obesity compared with lean children. This result may indicate that the effects of histological changes, rather than hypoperfusion, were at the forefront for the alterations in SWV for the volunteers in this study. Already all the volunteers in the study had normal GFR values. However, it should not be forgotten that renal perfusion and glomerular filtration rate are significant factors. Alterations in these factors may disrupt the balance on the renal cortical stiffness and change the SWV values.

There are significant limitations of the current study. It was impossible to achieve histologic samples because there is no indication for renal biopsy in children with excess weight. Another limitation is that the ROI sometimes included the adjacent tissues since the dimension of the ROI is constant in pSWE and the organ size is smaller in children compared with adults. Some of the measurements may be performed close to the renal capsule that may increase SWV compared with deeper areas [41]. Anisotropy could result in intraobserver variation due to the complex architecture; however, it was impossible for us to completely eliminate the anisotropy.

To our knowledge, this is the first study evaluating the effects of excess weight on renal cortical stiffness with pSWE in children.

In conclusion, renal cortical stiffness is significantly higher in children with excess weight than in lean children. We have made a first attempt at applying pSWE to
investigate the early adverse effects of excess weight on kidneys. It may be a foundation for further research that may clarify the applicability of ultrasound elastography to assess the adverse effects of excess weight on kidneys.

**Conflict of interest:** none

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