Non-invasive Evaluation of Liver Involvement of Children with Cystic Fibrosis by Shear-Wave Elastography

Kistik Fibrozisli Çocuklarda Karaciğer Tutulumunun Shear-Wave Elastografi ile Non-invaziv Değerlendirilmesi

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ABSTRACT

Objective: Hepatobiliary complications commonly occur in cystic fibrosis with increasing prevalence due to longer life expectancies and widespread screening efforts. Shear-wave elastography is a novel noninvasive method that involves application of local mechanical compression on soft tissue using focused ultrasonography and acquiring strain images that show tissue response. We aimed to compare abdominal ultrasonography and Shear-wave elastography and also clinical and laboratory findings of children with cystic fibrosis prospectively.

Material and Methods: This study is a prospective study conducted in thirteen cystic fibrosis patients followed between February 2018 and March 2019. The severity of cystic fibrosis-related liver disease was categorized according to international criteria. Elastography measurement was performed in the same session with the evaluation of the liver by abdominal ultrasonography in the patients. The liver stiffness measurements were compared with clinical data, biochemistry parameters and ultrasound findings.

Results: Measurements were performed in thirteen cystic fibrosis children (three boys, ten girls). The median kiloPascal value of liver stiffness measurements with shear-wave elastography is 6.36 (IQR 5.40-10.80). The median liver stiffness measurement in subjects without cystic fibrosis-related liver disease was 6.30 (IQR 5.26-16.18) kiloPascals (n=5); The median liver stiffness measurement in subjects with cystic fibrosis-related liver disease was 6.46 (IQR 5.43-10.80) kiloPascals. While no significant correlation was found between kiloPascal values and age, gender, AST, ALT, hemoglobin A1c values, a strong positive correlation was found between cystic fibrosis-related liver disease and hemoglobin A1c and ALT values (r=0.702, p=0.007; r=0.761, p=0.003, respectively).

Conclusion: Cystic fibrosis-related liver disease has a significantly varying disease burden, its prevalence is increasing, and its early recognition is crucial for treatment and follow-up. Although there are no clear range values determined for children in tissue stiffness measurements in Shear-wave elastography, clinical and other laboratory and imaging methods and follow-up and evaluation are important.

Key Words: Children, Cystic Fibrosis, Liver, Shear-Wave Elastography

ÖZ

Amaç: Kistik fibrozis dünyada beyaz ırkın en sık görülen genetik hastalığıdır. Kistik fibroziste ortalama yaşam beklentisi arttığından komplikasyonlar ve yönetimi daha önem kazanmıştır. Shear-wave elastografi, odaklanmış ultrasonografi kullanılarak yumuşak doku üzerinde lokal mekanik kompresyon uygulanmasını ve doku tepkisini gösteren gerinim

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Conflict of Interest / *Çıkar Çatışması*: On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles. Approval was obtained for the study from Ankara Pediatrics Hematology Oncology Training and Research Hospital, Clinical Research Ethics Committee (26.02.2018- 2018-031).

Contribution of the Authors / Yazarların katkısı*: *ERYILMAZ POLAT S: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***HIZAL M:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***ÖZSEZEN B:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***TUĞCU GD:*** Organizing, supervising the course of progress and taking the responsibility of the research/study. ***ALIMLI AG:*** Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results. ***CİNEL G:*** Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

How to cite / *Atıf yazım şekli* : Eryılmaz Polat S, Hızal M, Özsezen B, Tuğcu GD, Alımlı AG and Cinel G. Non-invasive Evaluation of Liver Involvement of Children with Cystic Fibrosis by Shear-Wave Elastography. Turkish J Pediatr Dis 2023;17:363-368.

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Received / Geliş tarihi : 31.03.2023
Accepted / Kabul tarihi : 03.04.2023
Online published : 15.06.2023
Elektronik yayın tarihi
DOI:10.12956/tchd.1274367

görüntülerinin elde edilmesini içeren yeni, invaziv olmayan bir yöntemdir. Bu çalışmada kistik fibrozisli çocukların abdominal ultrasonografi ve Shear-wave elastografi ile klinik ve laboratuvar bulgularını prospektif olarak karşılaştırmayı amaçladık.

Gereç ve Yöntemler: Bu çalışma, Şubat 2018 ile Mart 2019 tarihleri arasında takip edilen on üç kistik fibrozis hastasında gerçekleştirilen prospektif bir çalışmadır. Kistik fibrozis ile ilişkili karaciğer hastalığının şiddeti uluslararası kriterlere göre kategorize edildi. Hastalarda karın ultrasonografisi ile karaciğerin değerlendirilmesi ile aynı seansta elastografi ölçümü yapıldı.

Bulgular: Toplam on üç kistik fibrozisli çocuk değerlendirildi. Shear-wave elastografi ile karaciğer sertliği ölçümlerinin median değeri 6.36 (IQR 5.40-10.80) kiloPaskal'dı. Kistik fibrozise bağlı karaciğer hastalığı olmayan deneklerde medyan karaciğer sertliği ölçümü 6.30 (IQR 5.26-16.18) kiloPaskal (n=5)'di; Kistik fibrozis ilişkili karaciğer hastalığı olan kişilerde medyan karaciğer sertliği ölçümü 6.46 (IQR 5.43-10.80) kiloPaskal olmuştur. kiloPascal değerleri ile yaş, cinsiyet, AST, ALT, HbA1c değerleri arasında anlamlı bir ilişki bulunmazken, kistik fibrozis ilişkili karaciğer hastalığı ile hemoglobin A1c ve ALT değerleri arasında güçlü bir pozitif korelasyon bulundu (sırasıyla r=0.702, p=0.007; r=0.761, p=0.003).

Sonuç: Kistik fibrozis ile ilişkili karaciğer hastalığı, önemli ölçüde değişen bir hastalık yüküne sahiptir, prevalansı artmaktadır ve erken tanınması tedavi ve takip için çok önemlidir. Shear-wave elastografide doku sertliği ölçümlerinde çocuklar için belirlenmiş net bir aralık değerleri olmamakla birlikte klinik ve diğer laboratuvar ve görüntüleme yöntemleri ile takip ve değerlendirme önemlidir.

Anahtar Sözcükler: Çocuklar, Kistik fibrozis, Karaciğer, Shear-wave elastografi

INTRODUCTION

Cystic fibrosis (CF) is a monogenic disease thought to affect at least 100,000 people worldwide. Mutations in cystic fibrosis transmembrane conductance regulator (CFTR), the gene encoding the epithelial ion channel that normally transports chloride and bicarbonate, lead to impaired mucus hydration and clearance. Since the discovery of the most common CFTR mutation (Phe508del), more than 2000 mutations have been identified in CFTR (1). Clinical information is available on an increasing number of detected CFTR mutations, variants with variable clinical outcomes, and variants that cause CF that are not definitively disease-causing. The prognosis in CF has improved markedly with modern multidisciplinary care, improvement of respiratory complications, and modulatory therapies. As a result, non-pulmonary complications are becoming increasingly important. Cystic fibrosis liver disease (CFLD) is the third leading cause of death in people with cystic fibrosis. It is estimated that between 20 and 40% of all CF patients have cystic fibrosis-related diabetes (CFRD) (2). CFLD generally has two phenotypes: focal biliary cirrhosis, which begins early in life and leads to multilobular cirrhosis, or obliterative portal venopathy, which occurs later in life (1-3). In an international study on severe CFLD (cirrhosis and portal hypertension (PHT)), the prevalence was reported as 3-5%; 94% of patients were diagnosed before the age of 20 (3). Early detection of CFLD is difficult due to the lack of a reliable screening tool; liver function tests and ultrasonographic changes may not be sufficient. Non-invasive diagnostic methods are needed to identify those at higher risk of developing liver disease in children with CF and to predict which of these patients will develop CFLD. Ultrasound (US) elastography is a non-invasive imaging modality that has been used to assess tissue stiffness (TS) in the clinical setting for approximately 3 decades. Two-dimensional shear wave elastography (2D-SWE) is a new technique. In the US device, acoustic radiation force is automatically generated by the probe and applied to the tissue at certain frequencies and intensities. In this way, it allows the evaluation of TS both quantitatively and qualitatively (4). Today, life expectancy has increased with the newly developed diagnosis and treatment methods in CF. Since it is a chronic disease that requires long-term follow-up, there is an important need to develop easy-to-apply and non-invasive methods that predict liver complications. It has been found that elastography can significantly predict liver fibrosis in adult patients, but there are not enough studies on elastography in pediatric patients. The aim of this study is to measure liver parenchymal changes with shear wave elastography (SWE) in pediatric patients with CF and to evaluate them together with clinical, laboratory and US results.

MATERIALS and METHODS

Prospective analysis of liver stiffness measurements (LSM) with SWE and abdominal US of liver findings of patients diagnosed and followed up with CF between February 2018 and March 2019 in the Pediatrics Hematology Oncology Training and Research Hospital, Ankara Health Sciences University, Department of Pediatric Pulmonology were performed. Approval was obtained for the study from Ankara Pediatrics Hematology Oncology Training and Research Hospital, Clinical Research Ethics Committee (26.02.2018- 2018-031). The patients' SWE and abdominal US results were compared to their clinical, laboratory and microbiological results. Medical records were used to acquire demographic, clinical, laboratory, and radiological information on the patients. Blood was drawn from all patients prior to imaging and a routine liver panel was analyzed. The panel included, among others: Alanine aminotransaminase (ALT), aspartate aminotransaminase (AST), alkaline phosphatase (ALP), bilirubin, gamma-glutamyl transpeptidase (GGT), international normalized ratio (INR). All patients gave written informed consent. The cystic fibrosis-related liver involvements of the patients were classified according to international guidelines (5,6). Patients without CFLD were defined by no evidence of liver disease on examination, imaging, or laboratory evaluations, and non-prescribed ursodeoxycholic acid (UDCA). Patients classified as CFLD without portal hypertension met at least one

of the following criteria: persistent AST, ALT, GGT 2 times the upper limit of normal or intermittent elevations of these values, or steatosis (histological determination) or fibrosis (histological determination); cirrhosis without cholangiopathy and portal hypertension, with ultrasonographic abnormalities incompatible with cirrhosis/liver involvement; or the use of UDCA. CFLD with cirrhosis/PHT was defined as demonstration of cirrhosis and PHT based on clinical examination/imaging, histology, and laparoscopy. SWE performance was evaluated by a pediatric radiologist with 6-MHz and 9-MHZ point SWE and 9-MHz 2D-SWE. LSM results in the cases were reported in kiloPascal (kPa). The validity of the measurements was evaluated by the device. Simultaneous abdominal US evaluations of the patients were performed by the same pediatric radiologist. The descriptive statistics of the study were shown as number, percentage, median and interquartile range (IQR). Statistical analysis was evaluated in SPSS 23 package program.

RESULTS

Thirteen pediatric CF patients were included in the study and patient characteristics are shown in Table I. 10 patients were female (76.9%) and 3 were male (23%). The mean age of the patients was 5.4 (0.7-16). Patients had a mean body weight of 18.6 (6.4–35.5) kg, mean height of 105.2 (55–143) cm and a mean body mass index (BMI) of 16 (12.9–19.2) kg/m^2. All patients had CFTR genetic test results, Phe508del mutation was the most common (n=8, 61.5%). In the abdominal US of the patients, hepatomegaly was found in 1 patient (7.6%), hepatosteatosis and hepatomegaly were found in 2 patients (15.3%), while the others were evaluated as normal (76.9%). ALT and AST were >1.3 times the upper limit of normal range in 4 (30.7%) and 5 (38.5%) of subjects, respectively. Total and direct bilirubin values of all patients were within normal ranges. Five (38.5%) patients were classified as without CFLD and 8 (61.5%) subjects as CFLD without PHT. There was no patient with CFLD with PHT. Twelve patients (92%) had pancreatic insufficiency and were receiving pancreatic enzyme replacement therapy. None of the patients with CF had endocrine pancreatic insufficiency. Three patients had a history of meconium ileum. Due to the small age of the sample group, pulmonary function tests could be performed in 4 (30%) patients. The mean pulmonary function forced expiratory volume in 1 second (FEV1) of the patients was 53% (n=4). None of the patients had cirrhosis US criteria or ascites.

The median kPa value of the patients was 6.36 (IQR 5.40-10.80). In comparisons between patients, there was no statistically significant difference between kPa values in patients with Phe508del mutation, liver involvement, elevated AST/ALT, and patients with and without elevated hemoglobin A1c (HBA1c) (p=0.222; p=0.833; p=0.284; p=0.940, respectively). While no significant correlation was found between kPa values and age, gender, AST, ALT, HbA1c values, a strong positive correlation was found between CFLD and hemoglobin A1c (HbA1c) and ALT values (r=0.702, p=0.007; r=0.761, p=0.003, respectively). One patient has hepatomegaly and normal liver function tests and the patient's Kpa value was 6,36; two patients with elevated liver function tests and hepatosteatosis had Kpa values of 5.15 and 19.3; 1 patient with elevated liver function tests had a Kpa of 6.38. Abdominal US and liver function tests of other patients were normal.

Table I: Summary of the distribution of demographic and clinical variables of patients (n=13).

Clinical Variable	Number (n), (%), Mean +/- SD
Age at LSM (year)	5.4±2.5 years
Sex	
Male	76.9
Female	23
Laboratory Findings	
ALT	34.2 U/L (10–67)
>1.3 times the ULN ALT	30.7
AST	44.6 U/L (21–87)
>1.3 times the ULN AST	38.4
GGT	23.8 U/L (7–110)
HBA1c	5.4 (4.4-6.5)
BMI	16 kg/m^2 (12.9–19.2)
CF-related diabetes	n= 4, (30.7)
Ursodeoxycholic acid therapy	n= 7, (53.8)
Chronic *P. aeruginosa* infection	n= 7, (53.8)
deltaF508 mutation	n= 8, (61.5)
Stage of liver disease	
CFnoLD	n= 5, (38.4)
CFLD	n= 8, (61.5)
Hepatic steatosis	n= 2, (15.3)
Hepatomegaly	n= 3, (23)
kPa values	
CFnoLD	n=5, 7.79 (5.2-13.53)
CFLD	n=8, 9.23 (4.1-20.2)

ALT: *alanine aminotransferase,* ***AST:*** *aspartate aminotransferase,* ***BMI:*** *body mass index,* ***CFLD:*** *cystic fibrosis liver disease,* ***CFnoLD:*** *cystic fibrosis with no evidence of liver disease,* ***GGT:*** *gamma-glutamyl transferase,* ***HBA1c:*** *hemoglobin A1c,* ***kPa:*** *kiloPascal,* ***LSM:*** *liver stiffness measurement,* ***P. aeruginosa:*** *Pseudomonas aeruginosa,* ***SD:*** *standard deviation,* ***UNL:*** *upper limit of normal range.*

DISCUSSION

Hepatic involvement is an important cause of mortality and morbidity in patients with CF. Many factors play a role in the etiology of CFLD. Detection and staging of CFLD poses challenges in clinical practice due to the lack of specific diagnostic tools, but identifying children at risk of developing CFLD is of clinical importance for CF patient management. CFLD is usually asymptomatic and CFLD screening includes physical examination, biochemical evaluations and US, with further studies added as needed (7). The guidelines recommend

annual monitoring of liver enzymes in all patients with CF. If abnormal and there are persistent unexplained elevations in liver enzymes, US and liver biopsy may be considered (8). Liver biopsy is still used as the most valid standard for the evaluation of liver fibrosis. However, it is an invasive procedure that can cause serious complications (9). Non-invasive diagnostic methods are needed to identify and evaluate patients at risk of developing liver disease (10). Therefore, researchers focused on the evaluation of non-invasive methods for the evaluation of liver fibrosis. One of these methods is elastography, which measures TS or elasticity. These include transient elastography (TE or FibroScan) and 2D-SWE. 2D-SWE is an integrated US method that provides a color map of liver elasticity values simultaneously with real-time visual imaging (4). This study evaluated the ability of 2D-SWE to detect CFLD in pediatric CF patients. In our clinical practice, we needed more sensitive noninvasive methods to detect and evaluate CFLD in children, and we used and evaluated SWE as a screening method for CFLD in our patients to gain more experience.

US detection of CFLD is difficult and non-specific unless it is at an advanced stage (11). 2D-SWE is a promising new tool to detect hepatic fibrosis indirectly by measuring liver stiffness and has been shown to be useful in adult CF patients and different chronic liver diseases (11,12). In a study of 125 children with CF with SWE, the LSM was 8.1 kPa (IQR = 6.7–11.9) in CFLD; It was found to be 6.2 kPa (IQR = 5.6–7.0; $p<0.0001$) in CFnoLD and 5.3 kPa (IQR = 4.9–5.8; $p<0.0001$) in healthy controls. LSM was significantly higher in CFLD and cystic fibrosis with no evidence of liver disease (CFnoLD) than in controls (11). Other studies have evaluated LSM using SWE in healthy control children and have shown median values ranging from 5.5 kPa to 7.4 kPa (13-15). Several TE studies have reported higher LSM in CFLD compared to CFnoLD children (8, 16, 17). A meta-analysis of TE suggested a cut-off point of 5.95 kPa for increased liver stiffness (18). A meta-analysis of 12 studies evaluated 550 children with chronic liver disease and established a cut-off point of 9.4 kPa to predict significant liver disease (11,19). In our study, the median LSM in patients with CFnoLD was 6.30 (IQR 5.26-16.18); was similar to that reported for CFnoLD by other groups using TE. In our study, the median LSM for CFLD was 6.46 (IQR 5.43-10.80) kPa, and it was lower than the studies using TE (11,17,19). Other studies with TE have reported much higher median LSM values between 14 and 15.1 kPa. These differences between measurements may be due to differences in patients' CFLD severity and study designs (8,16). In our study, there was no statistically significant difference in kPa values between patients without CFLD and patients with CFLD, but the study sample was small. Also, none of the subjects with CFLD in our study had PHT or cirrhosis. Monitoring serial LSM for changes over time may be a more useful strategy for detecting early fibrosis and categorizing LSM values in CFLD. More data and studies are needed to predict accurate thresholds that are disease specific, according to age and BMI. A study in children and young adults with CF showed a correlation between liver stiffness measurement (LSM) and the presence and severity of liver disease (8). Taken together, all these results confirm that SWE is a reliable and reproducible non-invasive method to detect advanced fibrosis in children with CFLD, and that advanced liver disease with cirrhosis shares common LSM features across different diagnostic groups.

One of the advantages of LSM over biopsy is that it allows monitoring of liver disease progression. This study could not evaluate the progression of liver disease using SWE, as CFLD development and progression to fibrosis are variable in patients with CF. Relatively less data are available on 2D-SWE and pediatric references are lacking. Although the specificity of TE was good (87%), its sensitivity was found to be quite low (55%) (18).

No specific biomarker was convincingly associated with kPa values in our study, but the fact that some children have already been treated with UDCA may explain the lack of evidence in this regard. Despite the lack of validated reference ranges, numerical results in kPa may be useful on an individual basis in monitoring disease progression. One study showed that liver stiffness increased over time and that the worsening slope detected by elastography and longitudinal measurements could predict CFLD (20). This is an important aspect of the potential of these methods in patient-based clinical evaluation. With non-invasive elastography methods, a clear distinction cannot be made between PHT and liver fibrosis. Limitations include the lack of reference values for children for the 2D SWE method and the lack of validation and standardization for different techniques.

Many factors play a role in the etiology of CFLD. Studies have linked CFLD with genotype, history of meconium ileus, malnutrition, CFRD, and male gender (21-24). Fluctuations in transaminase levels may occur in CF patients due to respiratory tract infections, multiple drug use, nutrition and complications (5). Studies have shown that male gender, Pseudomonas aeruginosa, Phe508del homozygosity, history of meconium ileus, and CFRD are important independent risk factors for cirrhosis in CF patients (2). Hemodynamic changes as a result of advanced cirrhosis can exacerbate ventilation-perfusion mismatch and cause hypoxia. One study showed that hypoxic conditions favored the growth of resistant Pseudomonas aeruginosa strains (25, 26). The role of UDCA in the treatment of CFLD is controversial; In a recent cohort study and systematic review by the Cochrane collaboration, it was found that the use of UDCA did not change the incidence of severe CFLD (24, 27). In a retrospective study of a large group of patients with CF, previous use of UDCA in the last 20 years did not change the incidence of severe CFLD (24). CFRD is a common and serious complication of CF that usually occurs after the second decade of life. One study showed that patients with CFLD have a more than 11-fold increased risk of developing CFRD compared with individuals without CFLD (28). In our study, a strong positive correlation was found between CFLD and HbA1c values,

which is consistent with the literature (r=0.761). Other studies have also shown this relationship (7,24,28,29). Therefore, earlier screening of patients with CFLD for CFRD should be considered. In addition, longitudinal follow-up of these patients with the 2D SWE method will be important.

The most important limitation of the study is the small sample size due to the small number of patients. However, the study design reflects a population of subjects reflecting clinical practice and patient distributions in a CF center. Another limitation is the lack of histological evaluations of CFLD patients. However, there was no CFLD with cirrhosis/PHT in the patient group. kPa and FEV1 values could not be compared since most of the patients were under 6 years of age.

As with other liver diseases and systemic diseases with liver involvement, there is a need for markers that allow accurate assessment of the severity of liver disease as well as the detection of fibrosis in CF. Noninvasive differentiation and recognition of necroinflammation from fibrosis plays an important role in this area. In addition, disease-specific cut-off values need to be applied for all diagnostic tools presented.

More research involving different chronic liver diseases is needed for a better understanding of SWE. This is particularly important for CF because the clinical course of the disease and liver involvement are not the same for all mutations. Because this method is not established, comparison of published studies and interpretation of measured values is difficult.

CONCLUSION

This study provides evidence that SWE may be a useful, non-invasive tool for assessing liver disease in patients with CF. Measurement of SWE with TS in patients with CF may guide further management regarding the timing of assessment of CFLD development in patients. Prospective studies with a larger population are needed to detect liver involvement in the early period in patients with CF and to calculate the cut-off values of SWE in this patient group. Longitudinal follow-up of the patients will be more meaningful to evaluate the effectiveness of SWE.

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