Original Article

Shear Wave Elastography Evaluation of Kidneys in Children with Familial Mediterranean Fever

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Abstract

Background and Aim: Familial Mediterranean fever (FMF) is an autosomal recessive disorder. Typical clinical manifestations are self-limiting attacks of recurrent fever, abdominal pain, arthralgia, and chest pain due to aseptic polyserositis. Renal involvement is common in FMF patients. Shear wave elastography (SWE) is a noninvasive method that provides the measurement of tissue stiffness. In this study, we aimed to show that SWE can be used as an adjunctive method for evaluating renal involvement in children with FMF. **Materials and Methods:** Our study group consists of 79 pediatric FMF patients and 79 control individuals. The study was planned prospectively. The variables, such as age, height, weight, and body mass index (BMI) of the patient and control groups, were kept in a similar way in order not to be affected by the differences. The right and left kidney sizes, parenchymal thicknesses, and SWE values in both groups were compared. The parenchymal stiffness degrees of the kidneys were quantified by shear modulus values in kilopascals. **Results:** In our study, no statistically significant difference was found between the control and patient groups in terms of the right and left kidney longitudinal dimensions, transverse dimensions, and parenchymal thicknesses. When the kidneys were evaluated in terms of the right and left kidney stiffness values, the stiffness values in the patient group were significantly higher in both kidneys compared with those in the control group ($P < 0.001$). **Conclusions:** SWE can be a noninvasive quantitative imaging method that can be used to evaluate kidney involvement by detecting changes in kidney stiffness in children with FMF.

Keywords: *Familial Mediterranean fever, kidney, shear wave elastography, ultrasound*

Introduction

Familial Mediterranean fever (FMF) is an autosomal recessive disorder that generally affects Turks, Arabs, and Armenians. Typical clinical manifestations are self-limiting attacks of recurrent fever, abdominal pain, arthralgia, and chest pain due to aseptic polyserositis.[1,2] There are different sets of diagnostic criteria: Tel HaShomer, Yalçınkaya-Özen, and the most recently created Eurofever/PRINTO (Paediatric Rheumatology International Trials Organisation).[3-5] Although genetic analysis of the FMF gene (MEFV) provides supportive evidence for diagnosis, it is still recommended to diagnose patients clinically.[6-8] Despite different gene mutations, all FMF patients are at high risk of amyloidosis regardless of these mutations. In patients with FMF, the serum amyloid A protein (SAA) levels increase and accumulate in various organs, especially the kidneys.[9]

Gray-scale ultrasound (US) imaging is used to evaluate the size, echogenicity, parenchymal thickness, and pelvicalyceal structures of the kidneys. In diffuse renal

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diseases, increased echogenicity may be seen in the renal parenchyma. However, increased echogenicity is usually seen in advanced disease and the definition of this finding can be subjective.[10,11] For this reason, it is necessary to find a method that is affected by subjective factors as little as possible and gives enough information about the kidney parenchyma for the evaluation of the kidneys.[12]

Shear wave elastography (SWE) is a noninvasive method that provides both qualitative and quantitative measurements of tissue stiffness.[13-15] The method is based on the principle of the measurement of velocity of the shear wave. The SWE technique can provide two measurement modes simultaneously, namely, Young's modulus (YM; unit: kPa) and shear wave velocity (SWV; unit: m/s). The tissue elasticity is measured in kilopascals (kPa) or as shear wave velocity (meters/second; m/s).[16]

Although there are several SWE studies in children,[12-15] studies using SWE for evaluating the changes that may occur in the kidneys of FMF patients are very limited in the literature.[17] SWE could be a promising quantitative follow-up modality in FMF patients for the early diagnosis of subclinical changes in the kidney tissue. US SWE has the potential to diagnose hepatic fibrosis, cholestasis, inflammation, and hepatitis.[18-20] The aim of this study was to evaluate whether there is renal involvement by measuring tissue stiffness with SWE in children with FMF.

To our knowledge, this is the first study performed with a large group of patients to evaluate tissue elasticity in patients with FMF.

Materials and Methods

This prospective study was performed between January 2017 and December 2021. The local ethics committee approved the study (File Number: 2017/1182). Informed consent forms were obtained from the legal parents of all participants. In this study, the kidney size, parenchymal thickness and echoes, and kidney stiffness values of children with FMF disease and completely healthy children in the control group were compared.

Patients

In this study, 79 children diagnosed with FMF disease, constituting the patient group, and 79 completely healthy individuals, constituting the control group, were included. Tel HaShomer criteria and Yalçınkaya-Özen criteria were used for the diagnosis of FMF. Of the following criteria, the first three are major criteria and the second three are minor criteria: a) recurrent febrile episodes accompanied by serositis; b) AA-type amyloidosis in the kidney; c) response to continuous colchicine therapy; d) recurrent febrile episodes; e) erysipelas-like erythema; and f) FMF in a first-degree relative. Two major criteria, or one major criterion and two minor criteria, were required for a "definite" diagnosis, and one major criterion and one minor criterion were required for a "probable" diagnosis.[3] The control group consisted of healthy children who did not have any kidney disease in themselves or their first-degree relatives, followed by family medicine.

Clinical and laboratory findings

In this study, age, gender, weight, height, and body mass index (BMI) parameters of both the control and FMF groups were recorded. BMI was calculated with the formula kg/m2. Additionally, in the FMF group, age at diagnosis, disease duration, presence of attacks in the last year, genetic mutations in the MEFV gene, and acute-phase reactants, such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) that were obtained during the same week with renal ultrasonography, were recorded.

Gray-scale US and SWE evaluation

Gray-scale US and SWE measurements were performed by a radiologist with at least six years of elastography experience. Measurements were conducted with the LOGIQ E9XDclear, GE Healthcare, Milwaukee, WI, ultrasonography device using the C1-6-DXD clear 1–6 MHz convex probe. Cooperative subjects allowing consent for participation in SWE were included. Renal US and SWE evaluations were performed in a prone position during breath hold. Participants fasted for 4 hours. Participants were allowed to rest for at least 20 minutes before measurement. A routine US examination was performed bilaterally on the kidneys, measuring the long and transverse diameters of the kidneys, kidney parenchymal thicknesses, and observing and recording the kidney parenchymal echogenicity. We regarded the renal parenchymal echoes, which were higher than the liver or spleen echoes, as the parenchymal echo enhancement.[21]

SWE examinations of bilateral kidneys were performed simultaneously during the week of blood tests in FMF patients. The elasticity of the bilateral kidneys of the patient and control subjects was examined.

We obtained SWE measurements from the renal cortex in the interpolar region in the longitudinal section. The regions of interest (ROIs) were placed away from the pelvis [Figure 1]. Five different acquisitions of elasticity with ROI that were 10 mm in diameter for kidneys were obtained with homogeneous color filling in at least 80% of the measurement box. The tissue

elasticity is calculated in kilopascals (kPa). The average of five different values was taken as the median stiffness value. The median kidney stiffness value, interquartile range (IQR), and IQR/median ratio were calculated for each patient. Patients with an IQR/median ratio of more than 30% were excluded from the study. Median elasticity values were used for statistical analysis. Renal stiffness measurements were performed as previously mentioned in the literature.[22]

Patients with FMF disease who did not want to participate in the study, who could not cooperate during the US examination, who could not hold their breath during the examination, and who had any renal or systemic disease in addition to FMF disease were not included in the patient group.

Having any renal or systemic disease during the examination, the presence of any infectious disease during the examination, the kidneys not being in their normal location or of normal size, pronounced contour lobulation, and parenchymal heterogeneity were exclusion criteria for the control subjects.

Results

Our study consisted of 79 healthy individuals, 50 (63.3%) females, 29 (36.7%) males, and 51 (64.6%) females and 28 (35.4%) males (79 patients) were diagnosed with FMF. There was no statistically significant difference in the proportions of gender between the control and FMF groups (P = 0.868). There was no statistically significant difference between the control and FMF groups in terms of age, height, weight, and BMI. The distribution between the groups is shown in Table 1. Including diagnosis age, number of patients who had attacks within the previous year, duration of the disease, and CRP–ESR values of FMF patients are given in Table 2.

When the kidneys were evaluated with gray-scale US examination, no statistically significant differences were found between the kidneys' longitudinal and transverse dimensions, kidney parenchyma thicknesses, and kidney echogenicity between the right and left kidneys in either the FMF group or the control group. There were no statistically significant differences in longitudinal dimensions, transverse dimensions, and parenchyma thicknesses between the control and FMF groups [Table 3]. Renal echogenicity was completely normal in both groups.

When the kidneys were evaluated with SWE, no statistically significant differences were found between the right and left kidneys in terms of stiffness values in either the FMF group or the control group. However, stiffness values in the FMF group were found to be significantly higher in both the right and left kidneys compared with the control group (P < 0,001). The kidney stiffness values of both groups are given in Table 4.

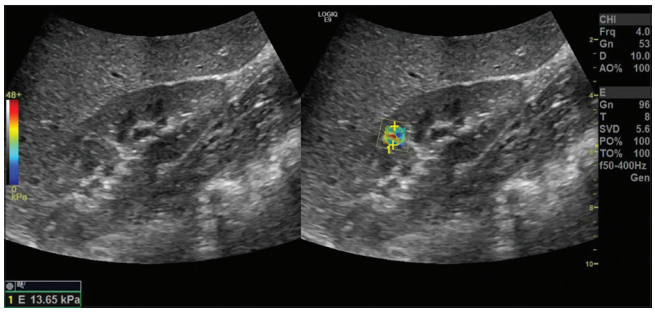

Figure 1: SWE evaluations of the right kidney in a 123-month-old male patient with FMF. SWE measurements were obtained on the longitudinal plan. The ROI was placed in the central portion of the kidney away from the pelvis

Discussion

Despite many studies on the application of elastography in studying kidney stiffness influencing factors,[23,24] differences in stiffness of different kidney parts,[25] fibrosis assessment after renal transplantation,[26,27] and renal tumors, its application in the pediatric kidney has rarely been reported.[28-30] Sohn *et al*.'s[30] study indicated that children with severe hydronephrosis had hardened renal parenchyma. In an animal experiment, Derieppe *et al*.[31] found that renal injury would result in increased stiffness level. Bayramoglu *et al*.,[17] however, recently studied various organs using SWE in pediatric patients with FMF and amyloidosis. In that study, they found that the SWE values obtained from the kidneys

Table 1: Age, height, weight, and BMI values of the control and FMF patient groups

	Mean±Std. Dev			*P*
	Total	Groups		
		Control (*n*=79)	FMF (*n*=79)	
Age (month)	125,35±39,06	125,95±44,94	124,75±32,43	0,847
Height (cm)	1,39±0,14	1,38±0,14	1,4±0,14	0,446
Weight (kg)	38,06±13,23	37,38±12,46	38,75±14,12	0,681
BMI (kg/m^2)	19,12±4,12	19,25±4,14	19±4,16	0,814

Independent-samples *t*-test was used. Pearson's Chi-square test was used. BMI: body mass index; FMF: familial Mediterranean fever.

in patients with FMF were significantly higher than in the control group. However, SWE measurements were made in different organs and the patient group was limited. Bayramoglu *et al*.[17] studied a very small group of patients with FMF with or without amyloidosis. They stated that further investigations with larger sample sizes are needed to determine normal shear wave elasticity (kPa) and velocity (m/s) values of solid organs in children and changes in organ stiffness during pathological conditions.

As far as we know, there is no study in the literature with a large number of patients showing the changes that may occur in the kidney parenchyma in children with FMF disease with SWE. Our study is the first study conducted in a large patient group using SWE in children with FMF disease. It is focused solely on evaluating changes that may occur in the kidneys. In our study, we did not find a significant difference between the SWE values between the right and left kidneys in either the control group or the FMF group. However, we found that SWE values were significantly increased in both kidneys in FMF patients compared with the control group ($P < 0.001$). The results of our study are very close to the results of Bayramoglu *et al*.[17]Increased stiffness values by SWE in FMF could be due to the increased rigidity of the renal parenchyma due to amyloid deposition, although it is not always clinically or biochemically apparent. Histopathological evaluation is the gold standard method for the diagnosis of amyloidosis but requires an invasive biopsy, which is not preferred in children and is associated with a risk of bleeding.

Kidneys in children develop and grow continuously with age. Bin Xu *et al*.[12] concluded that renal parenchymal stiffness increases with age in healthy individuals and SWE values increase with age. Lee *et al*.[28] also reached similar results in their study. As mentioned in these studies, we kept the age, gender, height, and weight of the patient and control groups similar to prevent differences in SWE values that may be caused by age and gender. In our study, there were no statistically significant differences between the control and FMF groups in terms of age, gender, height, and body weight.

Table 2: Clinical and laboratory findings of FMF patients

Disease duration (month)	9–132		
Age of diagnosis (month)	27–174		
	n		**%**
Number of patients who had attacks within the previous year	21		26,5
CRP (mg/dL)	43	54.4	Normal
	36	45,6	Increased
ESR (mm/h)	47	59,4	Normal
	32	40,6	Increased

CRP: C-reactive protein, reference range (0–5); ESR: erythrocyte sedimentation rate, reference range (0–20); FMF: familial Mediterranean fever

Table 3: Kidneys' longitudinal diameter, transverse diameter, and parenchymal thickness values in the control and FMF patient groups

	Mean±Std. Dev			P_1
	Total	Groups		
		Control	FMF	
Right kidney longitudinal diameter (mm)	97,09±11,69	96,82±11,38	97,37±12,05	0,771
Left kidney longitudinal diameter (mm)	96,75±11,09	96,89±10,61	96,61±11,62	0,875
P_2		0,903	0,144	
Right kidney transverse diameter (mm)	34,55±5,35	34,65±5,82	34,46±4,87	0,824
Left kidney transverse diameter (mm)	33,66±6,85	34,22±6,73	33,1±6,96	0,308
P_2		0,501	0,035	
Right kidney parenchymal thickness (mm)	12,38±1,93	11,98±1,94	12,38±1,94	0,811
Left kidney parenchymal thickness (mm)	11,31±1,43	12,23±1,44	12,2±1,44	0,798
P_2		0,237	0,237	

P_1: independent-samples *t*-test was used. P_2: paired-samples *t*-test was used. FMF: familial Mediterranean fever.

Table 4: Kidneys' stiffness values in the control and FMF patient groups

	Mean±Std. Dev.			P_1
	Total	Groups		
		Control	FMF	
Right kidney stiffness (kPa)	16,52±2,15	15,29±1,89	17,75±1,64	<0,001
Left kidney stiffness (kPa)	16,32±2,15	14,98±1,48	17,67±1,86	<0,001
P_2		0,115	0,699	

P_1: independent-samples *t*-test was used. P_2: paired-samples *t*-test was used. FMF; familial Mediterranean fever.

Bin Xu *et al*.[12] investigated pediatric glomerular disease and normal kidneys with SWE and showed that there was no marked difference in the renal long diameter between the patient group and the control group. Only 23 cases (21.90%) in the disease group were considered to have changes in the renal cortical echo. However, there was a significant difference in the SWE measurement when compared with the control group, indicating that SWE is beneficial in the early diagnosis of pediatric glomerular disease compared with conventional US.[12]

In our study, no significant differences were found in kidney sizes and parenchyma thickness using US in children with FMF disease when compared with healthy children. Moreover, renal echogenicity was evaluated as normal in all children with FMF disease. However, although the kidneys were observed to be completely normal on US, kidney SWE values were found to be significantly higher in the FMF group than in the control group. Our results show that US is not useful in the diagnosis and follow-up of FMF disease, and US is unnecessary in childhood FMF patients. It strongly supports the fact that the evaluation of the kidneys with SWE is very effective in the diagnosis and follow-up of patients and that it can show the changes that may occur in the kidneys by providing quantitative values. It is thought that changes in the treatment protocols can be made, especially if the kidney SWE values continue to increase in the follow-up examinations.

Due to the anisotropic morphology of the kidneys, axis-dependent evaluation is required for optimal examination. Therefore, we obtained all measurements as described in the literature by placing the ROI at the peripheral cortex and middle 1/3 of both kidneys on the anterolateral aspect and the longitudinal plan.[28]

There are studies in the literature reporting that chronic infectious diseases cause an increase in tissue stiffness in solid organs.[20,32] In addition, increased tissue stiffness in infectious diseases has been reported in the examination of superficial tissues with SWE in diseases, such as acute lymphadenitis.[33] Therefore, the increase in tissue stiffness may not always be specific to amyloid deposition. In infectious and inflammatory diseases, they can cause tissue stiffness similar to amyloidosis. In our study, patients with an additional chronic disease or infection during the examination were therefore not included in the study in either the control group or FMF group.

There are several limitations to our study. First, laboratory values, such as CRP and ESR, are known only in the FMF group. Therefore, a comparison with the control group could not be made. However, the control group consists of clinically normal individuals, and these individuals did not have any complaints during the examination. No disease was mentioned in the previous routine follow-ups of these children. For ethical reasons, blood samples could not be obtained from clinically normal children. Second, in our patient group, the diagnosis was mainly based on clinical manifestations, and some diagnostic criteria were used for an exact evaluation.[3-5] Although histopathological evaluation is the gold standard in the diagnosis of renal amyloidosis, it is not recommended in children due to the risk of complications. So, no patient underwent a kidney biopsy; therefore, a histopathological diagnosis was not available. Third, since the histopathological diagnosis of the patients was not available, the correlation between the histopathological severity of the disease and the SWE values could not be evaluated.

Conclusion

SWE is a noninvasive quantitative method used to detect renal involvement and to follow up on the progression of renal involvement in pediatric FMF patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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