BJR
© 2021 The Authors. Published by the British Institute of Radiology
https://doi.org/10.1259/bjr.20210237

Received: 17 February 2021 | Revised: 04 August 2021 | Accepted: 23 August 2021

Cite this article as:
Bayramoglu Z, Akyol Sari ZN, Koker O, Adaletli I, Eker Omeroglu R. Shear wave elastography evaluation of liver, pancreas, spleen and kidneys in patients with familial mediterranean fever and amyloidosis. *Br J Radiol* 2021; **94**: 20210237.

FULL PAPER

Shear wave elastography evaluation of liver, pancreas, spleen and kidneys in patients with familial mediterranean fever and amyloidosis

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Objectives: Amyloid deposits in a visceral organ can contribute to tissue stiffness that could be measured with shear wave elastography (SWE). We aimed to investigate changes in organ stiffness in conjunction with laboratory parameters in patients with Familial Mediterranean Fever (FMF) and amyloidosis.
Methods: This prospective study included 27 FMF patients, 11 patients with amyloidosis, and 38 healthy controls. Median shear wave elasticity values of the liver, spleen, both kidneys, and pancreas on SWE were compared among study and control groups. The mean values of CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) were compared by the *t*–test and the median of SAA (serum amyloid A protein) was compared with the Mann–Whitney *U* test between FMF groups with and without amyloidosis. Spearman's correlation analysis was performed to reveal the association between stiffness values and laboratory parameters.
Results: The median liver, spleen, kidney, and pancreas elasticity values were significantly higher in the FMF group with amyloidosis compared to control subjects. The median kidney stiffness values in the FMF group with or without amyloidosis were significantly higher compared to control subjects. Median liver stiffness values in FMF patients with amyloidosis were significantly higher than FMF patients without amyloidosis. There were statistically significant positive correlations between the CRP (p = 0.001, r = 0.56), ESR (p = 0.001, r = 0.61), and SAA (p = 0.002, r = 0.53) levels with spleen stiffness, and CRP (p = 0.006, r = 0.48) and ESR (p = 0.001,r = 0.61) levels with pancreas stiffness, and ESR (p = 0.004, r = 0.51) levels with the left kidney stiffness.
Conclusion: SWE could be a potential tool for noninvasive follow-up of FMF patients and also amyloid deposition.
Advances in knowledge: Both acute inflammation and amyloidosis in the FMF patients could increase organ stiffness.

INTRODUCTION

Amyloidosis is an extracellular accumulation of amyloid protein that has an abnormal fibrillary structure. Primary amyloidosis is also known as amyloid light-chain (AL) amyloidosis and is caused by the production of abnormal components of antibodies that form amyloid deposits that cause damage within affected organs. It is seen spontaneously or often associated with multiple myeloma and often related to kidney failure. Secondary AA amyloidosis is the most common type worldwide and a complication of long-term chronic infectious or inflammatory disorders due to the oversynthesized serum amyloid A protein (SAA) as an acute-phase reactant along with the proinflammatory cytokines.[1] Commonly involved organs with AA amyloidosis are kidneys, liver, spleen, adrenal glands, gastrointestinal system, myocardium, and peripheral nerves.[2] Proteinuria and renal involvement constitute the initial manifestations of systemic amyloidosis followed by hepatosplenomegaly, adrenal insufficiency, and malabsorption.[2] Proteinuria ≥ 0.5 g/24 h and alkaline phosphatase value >1.5× upper limit of normal are major criteria for renal and hepatic involvement with amyloidosis, respectively.[2]

After the development of clinical suspicion in the diagnosis of AL amyloidosis, serum and urine protein electrophoresis are examined. Protein electrophoresis with immunofixation method may accidentally give normal results in 25% of patients.[3] Sensitivity up to 99% has been reported with the serum free light chain assay test for

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the diagnosis of AL amyloidosis.[4] However, in the presence of pathological results, abdominal fat pad, rectum, or bone marrow biopsies are required.[5] Histopathological examination demonstrates the amyloid accumulation with Congo red positive material revealing apple-green birefringence.[6] Unless the type of amyloidosis is established, the appropriate treatment cannot be determined. The leading causes of secondary (reactive AA) amyloidosis are chronic inflammatory diseases such as Familial Mediterranean Fever (FMF), rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and chronic infectious diseases such as tuberculosis, bronchiectasis, and osteomyelitis. In a study evaluating the relationship between laboratory findings and histopathological findings in RA patients, significantly increased SAA values were found in those with a diagnosis of biopsy-confirmed amyloidosis compared to those with normal results.[7]

FMF is an autosomal recessive disorder that generally affects Turks, Arabs, Armenians, and presents with attacks of aseptic polyserositis and fever. Increased SAA levels are found in FMF patients compared to controls, and in the case of homozygous or compound heterozygous mutations compared to single heterozygous mutations.[8] The M694V homozygosity and heterozygosity were found to be associated with increased risk of AA amyloidosis development in FMF patients.[9] High triggering receptors expressed on myeloid cells-1 activation levels were found in a recent study in FMF patients diagnosed with amyloidosis despite normal SAA values.[10] There is no definitively accepted biochemical test that detects the development of amyloidosis in FMF patients with high specificity. Distribution of a radiolabeled serum amyloid P component to the visceral amyloid deposits rapidly after intravenous injection presents a 100% diagnostic sensitivity in AA amyloidosis.[11]

Given the negative aspects of invasive procedures and radiation exposure, studies on non-invasive diagnostic methods have come to the fore. Hepatomegaly, absence of segment IV atrophy, heterogeneous parenchyma, periportal involvement of the liver, and low signal intensity on T_1- and T_2 weighted magnetic resonance images increase the suspicion of hepatic amyloidosis in patients with chronic inflammatory processes.[12] High signal intensity on T_1 weighted images and low signal intensity on T_2 weighted images support the splenic involvement with amyloidosis.[13] Enlarged kidneys in the early phase and amyloid contracted kidneys in the advanced stages of amyloidosis are seen with increased echogenicity on ultrasound.[14] Increased myocardial stiffness by intrinsic cardiac elastography[15] and increased hepatic stiffness by shear wave elastography (SWE)[16] have been demonstrated in amyloidosis. The evaluation of salivary glands with SWE during acute episodes of FMF and the process of amyloidosis was associated with the increased stiffness.[17] However, there is a lack of data regarding the quantitative evaluation of tissue stiffness due to the amyloid accumulation in several abdominal organs of children by SWE. SWE could be used to confirm the presence/absence of disease in the liver, spleen, pancreas, and kidney and therefore be an alternative to nuclear medicine-based studies or biopsy. In addition, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and SAA values change with acute or chronic inflammation, SAA values are also used as a follow-up parameter to predict the development of amyloidosis.[7] However, there are insufficient data on how changes in these parameters take place during an FMF acute attack and the development of chronic inflammation-induced amyloidosis in FMF patients.

This study aims to evaluate alterations of tissue stiffness in solid abdominal organs in FMF either with or without amyloidosis compared to healthy subjects. Additionally, we aim to compare the CRP, SAA, and ESR among FMF patients with or without proven amyloidosis. To the best of our knowledge, this is the first study to evaluate tissue elasticity in patients with FMF and amyloidosis in conjunction with laboratory parameters.

METHODS AND MATERIALS

This prospective study was performed between January 2019 and May 2021. The local ethics committee approved the study (File number: 2017/1182). Informed consent was obtained from the legal guardians of participants.

Patients

This study employed 27 pediatric patients (15 male, 12 female; mean age: 13.4 ± 4.82 years) diagnosed with FMF based on positive mutation analysis results, increased serum inflammatory markers, pertinent clinical history, and response to treatment with colchicine and 11 patients (7 male, 4 female; mean age: 17.81 ± 7.56 years) having a histopathological diagnosis of renal amyloidosis secondary to FMF. Due to the different age range of the study groups, we created a control group that includes controls covering a similar range (n = 38; 20 male, 18 female; mean age 15.12 ± 5.58 years). We reviewed FMF patients in the pediatric rheumatology outpatient clinic and amyloidosis patients who were under follow-up in the rheumatology department with histopathologically proven renal amyloidosis due to FMF. Healthy subjects were selected from individuals without any symptoms or disease that may involve the liver, spleen, kidney, and pancreas of their own or their first-degree relatives.

Clinical and laboratory findings

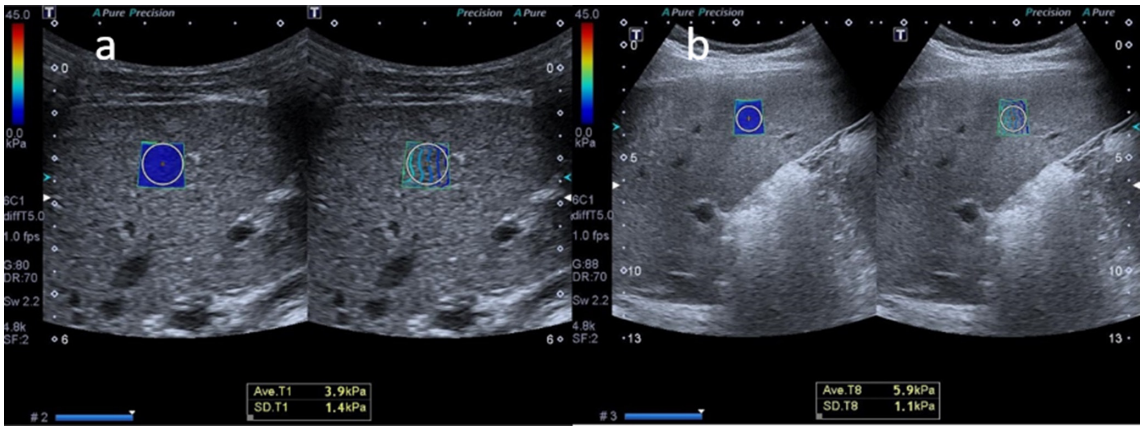
The genetic analysis of FMF patients, parameters regarding height and weight, presence of acute attack within the previous year, the duration of the disease and treatment, SAA, CRP, and ESR levels were recorded for both study groups.

Shear wave elastography (SWE) evaluation

SWE (dynamic elastography) is a non-invasive method used to measure tissue stiffness, providing quantitative and qualitative data about the elasticity of various tissues. Shear waves are generated using focused acoustic radiation force causing tissue displacement in the transverse plane which is calculated using a speckle tracking algorithm. Shear wave velocities are related to shear modulus and Young's modulus expressing the relationship between material density and shear wave velocity (G (shear modulus) = $\rho\ cs^2$ (ρ = material density, cs: shear-wave velocity). The tissue elasticity is measured in kiloPascals (kPa) or as shear wave velocity (meters/second; m/s).[18] SWE is more objective due to quantitative data without the need for compression compared

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Figure 1. SWE evaluations of the liver in a 10-year-old male patient with FMF (a) and 24-year-old male patient with amyloidosis (b). The ROI was selected at the right hepatic lobe with the intercostal approach. The ROI was placed away from the major vessels and the liver capsule. Optimal paralel propagation lines were obtained with a breath-hold. FMF, Familial Mediterranean Fever; ROI, region of interest; SWE, shear wave elastography.



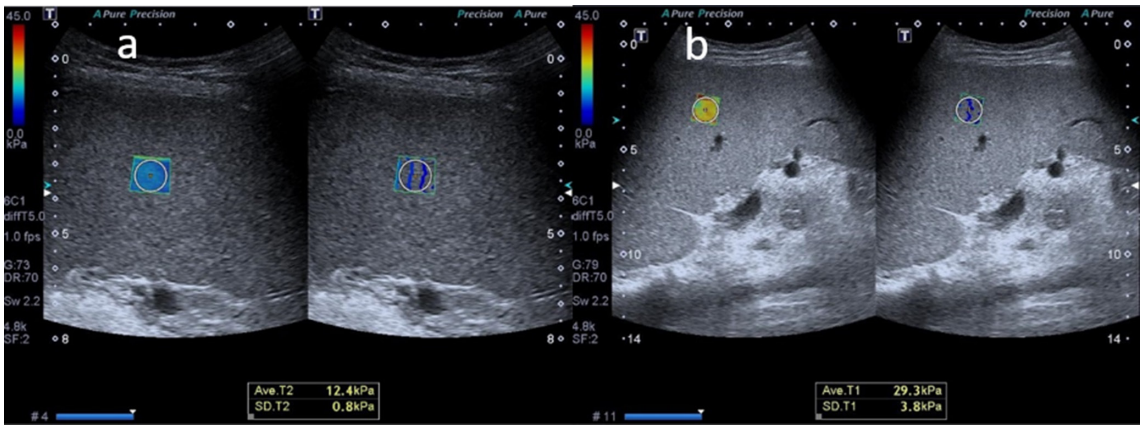
to the strain elastography. Changes in tissue stiffness due to inflammation, infection, storage diseases, and neoplasia can be followed up with SWE.

SWE examinations of liver, spleen, pancreas, and bilateral kidneys were performed simultaneously during the week of blood tests. Grayscale ultrasound and SWE assessments were performed with the consensus of a pediatric radiologist with more than 9 years of ultrasound and 2 years of SWE experience and a radiologist with 3 years of pediatric radiology experience using an 8–10 MHz convex transducer (Canon Aplio 500 Platinium; Japan) to measure tissue stiffness in the liver, kidneys, spleen, and pancreas. Cooperative subjects allowing consents for participation (N = 38 patients and 38 controls) and providing breath-hold along with optimal propagation maps on SWE were included. Patients were fasted for 4 hours. The liver, spleen, and pancreas elasticity of all control and study subjects were examined. In two patients with amyloidosis native kidney elasticity could not be evaluated because of previous renal transplant.

Any heterogeneity within the parenchyma, contour lobulation, organomegaly, and biliary or urinary dilatation were exclusion criteria for control subjects. Median elasticity values for each organ were recorded as shear wave elasticity (kPa). Five different acquisitions of elasticity within a region of interest that were 10 mm in diameter for liver, spleen, and kidneys were obtained and median elasticity values were recorded for statistical purposes.

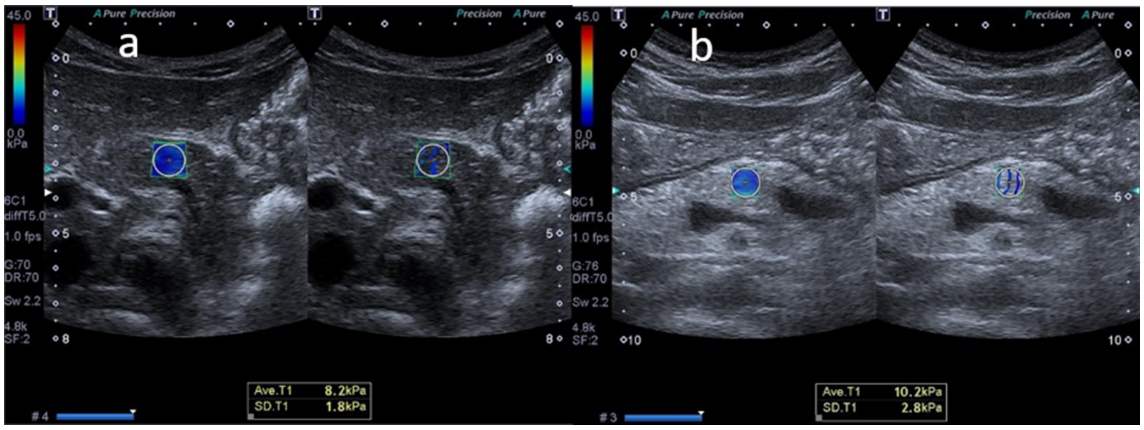
Liver SWE evaluations were performed in patients in the left lateral decubitus position. The liver parenchyma at the right hepatic lobe were achieved via the intercostal approach. During the breath-hold, the circle-shaped ROIs were placed within the parenchyma away from the vessels and 3 cm away from the liver capsule (Figure 1). Splenic SWE evaluation was performed in patients in the right lateral decubitus position. Parenchymal elasticity was examined within the ROI placed to the central portion of the spleen during the breath-hold (Figure 2).

Figure 2. SWE evaluations of the spleen in a 10-year-old female patient with FMF (a) and 23-year-old male patient with amyloidosis (b). The ROI was placed in the midportion of the spleen with the intercostal approach. The ROI was placed away from the major vessels. Optimal paralel propagation lines were obtained with a breath-hold. FMF, Familial Mediterranean Fever; ROI, region of interest; SWE, shear wave elastography



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Figure 3. SWE evaluations of the pancreas in an 11-year-old male patient with FMF (a) and a 23-year-old male patient with amyloidosis (b). Three acquisitions of SWE were performed from the pancreas head, corpus, and tail. A region of interest that was 10 mm in diameter was placed to the pancreas and optimal paralel propagation lines were obtained with breath-hold. FMF, Familial Mediterranean Fever; SWE, shear wave elastography



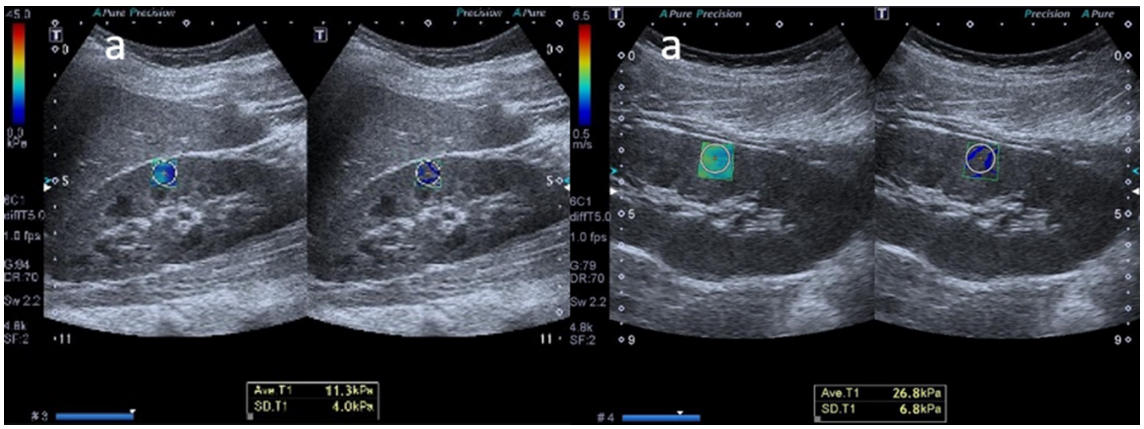
Pancreatic SWE evaluation was performed in patients in the supine and also right lateral decubitus positions within the ROI measuring 10 mm in diameter placed in the central portion of the parenchyma (Figure 3). Three measurements obtained from ROIs within the central portion of the head, corpus, and tail of the pancreas were averaged and the median elasticity values for the whole pancreas was recorded. The measurements were taken as previously described.[19]

Renal SWE evaluation was performed in a prone position during breath-hold. We imaged the kidneys in the longitudinal section. We obtained SWE measurements from the renal cortex in the interpolar region and the ROIs were placed away from the pelvis and medulla for each kidney (Figure 4). Renal stiffness measurements were taken with the previously described method.[19] Median elasticity values were used for statistical analysis.

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS v. 21.0, SPSS Inc.). Descriptive analysis of quantitative variables was expressed as mean ± standard deviation and median with interquartile range (IQR). Normality in the distribution of quantitative data was checked by the Kolmogorov–Smirnow test paying attention to skewness and kurtosis. Age, height, and weight of the control and study groups were compared with the ANOVA or the Kruskal–Wallis test. Treatment and disease duration along with attack numbers in FMF patients with and without amyloidosis were compared with the Mann–Whitney *U* test. Kruskal–Wallis analysis was performed for comparison of organ stiffness among three groups and the Mann–Whitney *U* test was performed for two-group comparisons for organ stiffness as the post-hoc analysis. The Mann–Whitney *U* or Student's *t*-test was used to compare the CRP, ESR,

Figure 4. SWE evaluations of the right kidney in an 11-year-old female patient with FMF (a) and the left kidney in a 24-year-old male patient with amyloidosis (b). SWE measurements were obtained on the longitudinal plan providing the paralel propagation lines from the periphery to the central portion of the kidney away from the medulla and pelvis. FMF, Familial Mediterranean Fever; SWE, shear wave elastography.



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Table 1. Auxological parameters of the study and control subjects, and medication status of the FMF patients with or without amyloidosis

	FMF without amyloidosis (n:27)	FMF with amyloidosis (n:11)	Control group (n:38)	
	Mean ± Std. Dev./Median (IQR)	Mean ± Std. Dev./ Median (IQR)	Mean ± Std. Dev./ Median (IQR)	*p*
Age (years)	13.4 ± 4.82	17.81 ± 7.56	15.12 ± 5.58	0.029[a]
Weight (kg)	47.08 ± 17.28	54.4 ± 14.9	47.21 ± 14.52	0.28[a]
Height (cm)	152 (135–167)	167 (147.5–170)	154 (123–187)	0.19[b]
Colchicine treatment duration (years)	3 (2.5–5.5)	5 (1.75–7.25)		0.72
Disease duration (years)	5 (3–8.5)	6 (3.75–8.25)		0.62
Number of attacks per year	2 (1.5–2)	2 (1.75–2.25)		0.67

FMF, Familial Mediterranean Fever; IQR, interquartile range.
p values obtained with the Mann–Whitney *U* test for comparison of the treatment and disease duration, and attack numbers in FMF patients with and without amyloidosis patients.
[a]*p* values by ANOVA test.
[b]*p*-value by the Kruskal–Wallis test.

and SAA among FMF patients with and without amyloidosis. Spearman's correlation analysis was performed to evaluate the relationship between elasticity parameters and ESR, CRP, and SAA levels in the study group. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Descriptive statistics including of the age, numbers of attacks within the previous year, duration of the disease, and treatment with colchicine are given in Table 1. No significant differences were found in the number of attacks within the previous year, the duration of the disease, and medication with colchicine between the FMF with and without amyloidosis patients. Amyloidosis patients were older than the FMF patients without proven amyloidosis. No significant differences were found between the mean weights and the median heights of the study and control subjects. The mean age of the control subjects was higher than the FMF patients without amyloidosis and lower than the FMF patients with amyloidosis ($p = 0.029$).

The median hepatic, splenic, renal, and pancreas stiffness values are given in Table 2. The median hepatic ($p = 0.008$), splenic ($p = 0.008$), right ($p = 0.007$) and left kidney ($p = 0.001$), and pancreas ($p = 0.018$) stiffness values in FMF patients with amyloidosis was significantly higher than control subjects. The median right ($p = 0.02$) and left renal ($p = 0.002$) stiffness values were significantly

Table 2. Median stiffness values of liver, spleen, kidneys, and pancreas in each group along with three-group and two-group comparisons

	FMF without amyloidosis Group 1	FMF with amyloidosis Group 2	Control group Group 3		
	Median (IQR)	Median (IQR)	Median (IQR)	*p*	
Liver stiffness (kPa)	6.11 (5.47–6.95)	7.55 (6–8.12)	6.77 (5.9–7.4)	**0.029**[a]	**Group 1 *vs* 2: 0.03** Group 1 *vs* 3: 0.78 **Group 2 *vs* 3:0.008**
Spleen stiffness (kPa)	16.35 (14.02–18.07)	17.95 (15.77–20.45)	16.4 (15–18.7)	**0.032**[a]	Group 1 *vs* 2: 0.13 Group 1 *vs* 3:0.25 **Group 2 *vs* 3:0.008**
Right kidney stiffness (kPa)	18.45 (15.67–20.37)	19.1 (15.07–28.82)	14.2 (13.8–16.8)	**0.016**[a]	Group 1 *vs* 2: 0.84 **Group 1 *vs* 3:0.02** **Group 2 *vs* 3:0.007**
Left kidney stiffness (kPa)	19.05 (16.57–21.8)	19.9 (15.57–29.07)	16.4 (15.2–17.5)	**0.035**[a]	Group 1 *vs* 2: 0.49 **Group 1 *vs* 3:0.002** **Group 2 *vs* 3:0.001**
Pancreas stiffness (kPa)	10 (8.45–11.22)	11.25 (10.7–13.87)	9.2 (8.6–10.2)	0.002[a]	Group 1 *vs* 2: 0.06 Group 1 *vs* 3: 0.65 **Group 2 *vs* 3: 0.018**

IQR, interquartile range.
Bold *p* values represent statistically significant results
[a]*p* values were obtained with the the Kruskal–Wallis test and the post-hoc analysis was performed with the Mann–Whitney *U* test.

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Table 3. Frequencies of abnormal laboratory parameters and comparisons of the mean/median values among FMF patients with and without amyloidosis

	FMF without amyloidosis			FMF with amyloidosis			*p*
	Frequency (%)		Mean ± Std. Dev./ Median (IQR)	Frequency (%)		Mean ± Std. Dev./ Median (IQR)	
CRP (mg/L)	Normal	52	12.8 ± 3.9	Normal	25	32.5 ± 2.12	**0.02**
	Increased	48		Increased	75		
ESR (mm/h)	Normal	32	28.44 ± 18.5	Normal	25	102.5 ± 31.81	**0.03**
	Increased	68		Increased	75		
SAA (mg/L)	Normal	20	8 (6–57)	Normal	30	26 (24–85)	**0.004**[a]
	Increased	80		Increased	70		

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FMF, Familial Mediterranean Fever; IQR, interquartile range; SAA, serum amyloid A protein.
Bold *p*-values represent statistically significant results
[a]*p* values by the t-test/Mann-Whitney U test.

higher in FMF patients without amyloidosis compared to the control subjects. No significant differences in the median renal, splenic, and pancreatic stiffness were found between the FMF patients with and without amyloidosis.

Statistically significant differences in mean CRP (p = 0.02), ESR (p = 0.03) values and median SAA (p = 0.004) values were recorded between FMF with and without amyloidosis patients. Tables 3 and 4Spleen stiffness values were modestly correlated with CRP (p = 0.001, r = 0.56), ESR (p = 0.001, r = 0.61), and SAA (p = 0.002, r = 0.53) values. Pancreas stiffness values were also modestly correlated with CRP (p = 0.006, r = 0.48) and ESR (p = 0.001, r = 0.61) levels. Left kidney stiffness values were also weakly correlated with ESR (p = 0.004, r = 0.51) levels.

DISCUSSION

In this study, we investigated intra-abdominal solid organ stiffness values in FMF and FMF induced amyloidosis compared with healthy controls. Organ stiffness by SWE increases in the case of FMF and also development of amyloidosis. As far as we know, this is the first study in children investigating organ elasticity in FMF and also amyloidosis patients. Stiffness values tend to show modest positive correlation with CRP, ESR, and SAA levels. SWE could be a promising quantitative follow-up modality in FMF patients with acute inflammation and FMF-induced amyloidosis.

Table 4. Spearman's correlation analysis of organ stiffness with laboratory parameters

Compared parameters	*p*	r
Liver stiffness CRP	0.069	0.32
Spleen stiffness CRP	0.001	0.56
ESR	0.001	0.61
SAA	0.002	0.53
Pancreas stiffness CRP	0.006	0.48
ESR	0.001	0.61
SAA	0.07	0.34
Right kidney stiffness ESR	0.068	0.32
Left kidney stiffness ESR	0.004	0.51

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SAA, serum amyloid A protein.

Histopathological evaluation is a gold-standard method for the diagnosis of amyloidosis, but requires invasive biopsy which is not preferred in children and is associated with a risk of bleeding. SWE is a non-invasive, quantitative imaging modality revealing mechanical and viscoelastic tissue properties *in vivo*. Ultrasound SWE has the potential to diagnose hepatic fibrosis, cholestasis, inflammation, and hepatitis.[20–22] Detection of amyloidosis by SWE has been demonstrated in an adult patient.[16] No comparable case series were encountered in the literature. Increased stiffness values by transient elastography in amyloidosis could be due to the increased rigidity of the liver due to amyloid deposition with or without fibrosis.[23] CRP, ESR, and SAA levels are commonly abnormal laboratory parameters in the amyloidosis group and poorly correlated with stiffness values.

In our study, increased stiffness in the presence of amyloidosis was detected in liver, spleen, kidney, and pancreas. Considering that only renal biopsies of patients with histopathologically diagnosed amyloidosis are available, elevated stiffness of liver, pancreas, and spleen are likely to be due to the amyloid deposition, and an increase in stiffness being a means of non-invasive detection of amyloidosis. However, renal stiffness was elevated in FMF patients with and without histopathologically proven amyloidosis compared to the control subjects. Therefore, kidneys could be more likely to be affected by inflammatory changes.

Both point-SWE and 2D-SWE are operator-independent and quantitative techniques that measure tissue stiffness. On 2D-SWE, shear waves are generated by using acoustic radiation force impulse propagating perpendicularly to the ultrasound pulse. Shear modulus is calculated based on tissue displacement and depends on tissue density and shear wave speed.[18] Shear wave speed (1–14 m/sn) and shear wave elasticity (1–210 kPa)

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show a linear correlation and they are interchangeable. Focused ultrasound beams are used in the target tissue in a single location in point-SWE.

Normal values of liver stiffness in healthy pediatric individuals have been depicted between 5.69 ± 0.92 kPa and 6.58 ± 1.46 kPa from newborns to children over 10 years old.[24] Depicted hepatic elasticity values are affected by the type/model of ultrasound devices and probes, underlying pathological conditions, and respiratory status.[24] Hepatic stiffness values for FMF patients and healthy controls were within this reference range adjusted for healthy children but amyloidosis patients revealed stiffness values over the reference ranges depicted for children and adults (<6.2 kPa).[25]

Normal spleen shear wave velocity values in children were revealed as 2.25 m/s in children aged 8.1 ± 4.7 years by acoustic radiation force impulse imaging.[26] No comparable data regarding shear wave elasticity of pediatric spleen was found. However, the given shear wave velocity value of 2.25 m/s corresponds to 28.9 kPa with our device which is much higher than observed in our control and study groups. Shear wave elasticity and velocity measurements depend on the device, probe, and respiratory status. In the current study, splenic elasticity in amyloidosis patients was higher compared to control subjects. Portal hypertension and amyloid accumulation in the spleen may contribute to increased spleen stiffness. Significant but poor positive correlations of spleen stiffness with ESR, SAA, and CRP suggesting a role of the chronic inflammation in the observed increased stiffness. The correlations of inflammatory markers such as ESR and CRP with arterial stiffness have been investigated in rheumatoid arthritis and systemic lupus erythematosus.[27,28] Our study only demonstrated a modest association of inflammatory markers with solid organ stiffness in children. However, there are studies reporting an increase in tissue stiffness of intra-abdominal solid organs in chronic infectious diseases.[22] It should be kept in mind that organ volume may increase due to non-amyloid factors and thus tissue stiffness may increase. 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.[29] Therefore, increase in the tissue stiffness may not be specific for amyloidosis but sensitivefor infectious and inflammatory disorders.

Pancreas tissue properties in FMF patients have been evaluated by diffusion-weighted MRI and have revealed no differences compared to healthy children.[30] Similarly, we did not found a difference in pancreatic stiffness of healthy subjects and children with uncomplicated FMF. However, pancreatic stiffness was higher in FMF-induced amyloidosis compared to healthy children. Additionally, pancreatic stiffness was weakly correlated with CRP and ESR values. Normal pancreas stiffness by SWE has been depicted as 8.75–9.35 kPa in children aged 3–18 years old.[31] Although FMF patients revealed higher pancreas elasticity values than control subjects, the difference failed to reach statistical significance in patients without histopathologically proven amyloidosis. On the other hand, there were statistically significant differences in pancreatic stiffness in FMF patients with amyloidosis compared to healthy subjects.

The anisotropic morphology of the kidneys owing to the direction of the collecting tubules requires axis-dependent evaluation for optimal comparisons. Therefore, we obtained all measurements by placing the ROI at the peripheral cortex and middle 1/3 of both kidneys on the anterolateral aspect and the longitudinal plan compatible with the paralel direction of the shear waves with the collecting tubules. Based on our comparisons, renal stiffness in FMF subjects was higher than in the control groups. Changes in the renal stiffness would be an early finding on SWE during the follow-up of patients with chronic inflammatory diseases. SWE evaluation was superior to renal length and cortical thickness assessment in the detection of adult chronic kidney disease.[32] Kidney stiffness values have also been correlated with the degree of renal insufficiency.[32] To the best of ourknowledge, there are no published data on renal SWE examination in children with renal insufficiency or amyloidosis.

This is a study of intra-abdominal solid organ elasticity examination in children with FMF. Although the disease and treatment durations are similar in FMF with and without amyloidosis groups, the mean ages were higher in the FMF group with amyloidosis possibly due to later diagnosis. There are several limitations of our study. First, the study groups were of different age ranges due to the rare incidence of amyloidosis complications in children younger than 18 years old. Therefore, we could not compare the stiffness values in FMF patients with and without amyloidosis groups properly. Although we used a control group with subjects including both children and also young adults, there were significant differences in mean ages of the study and control groups. Second, the examinations were performed with the consensus of the pediatric radiologist and in our institute (Istanbul Medical Faculty) with the same device, probe, approach, and breath-hold status but interobserver comparisons have not been presented. Third, the number of patients with amyloidosis was limited. Finally, since we did not have data on histopathological grading in patients diagnosed with amyloidosis, the histopatholgical severity of the disease could not be compared with the degree of increase in organ stiffness. Also, the time intervals between the biopsy and SWE evaluation were variable. 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.

CONCLUSION

Stiffness evaluation of solid intra-abdominal organs could be a promising, non-invasive, and quantitative follow-up modality in chronic inflammatory diseases with or without amyloidosis.

CONTRIBUTORS

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. Additionally, there are no conflicts of interest in connection with this paper, and the material described is not

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underpublication or consideration for publication elsewhere. No financial support was taken during the paper was preparing.

INFORMED CONSENT

Written informed consent was obtained from all individual participants included in the study.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional Ethics committee (File number: 2017/1182) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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