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Investigation of Hepatic and Splenic Shear-wave Elastography Findings in Patients with Familial Mediterranean Fever

Ailevi Akdeniz Ateşi Hastalarında Karaciğer ve Dalak Shearwave Elastografi Bulgularının İncelenmesi

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ÖZ

Amaç: Ailevi Akdeniz Ateşi (AAA), iç organları etkileyebilen otoinflamatuar multisistemik bir hastalıktır. Bu çalışma, AAA'nın karaciğer ve dalak üzerindeki etkisini shear wave elastografisi (SWE) kullanarak değerlendirmeyi amaçlamaktadır.
Araçlar ve Yöntem: Çalışmamıza Tel-Hashomer kriterlerine göre AAA tanısı alan, 18 yaş ve üzeri, amiloidoz gelişmemiş, karaciğer ya da dalak dokusunu etkileyen herhangi bir durumu olmayan hastalar dahil edilmiştir. Elektronik tıbbi kayıtlar retrospektif olarak incelenmiştir. Shear wave elastografi incelemesi en az beş yıllık SWE deneyimi olan bir radyolog tarafından yapıldı. Shear wave elastografi bulguları AAA olguları ve sağlıklı grup arasında karşılaştırıldı.
Bulgular: Yaş ortalaması 32.3 yıl olan 51 AAA olgusu (25 kadın, 26 erkek) ile yaş ortalaması 36.9 yıl olan 14 sağlıklı birey (4 kadın, 10 erkek) incelendi. En sık görülen semptom ateş olup vakaların %98'inde görülürken, %64.7'sinde M694V gen mutasyonu vardı. Hasta ve kontrol grubunun ortalama SWE değerleri arasında anlamlı bir fark bulunmadı. Karaciğer sertliği ve yaş arasında hafif pozitif bir korelasyon olduğunu saptadık (r=0.319, p=0.023). Hastalık başlangıç yaşı, hepatik sertlik (r=0.474, p=0.001) ve hepatik velosite (r=0.386, p=0.007) ile koreleydi.
Sonuç: Ailevi Akdeniz Ateşi hastalarını takip etmek için non-invaziv yöntemler konusunda bir fikir birliği bulunmamaktadır. AAA'de dahil olmak üzere enflamatuar hastalıklardan etkilenen solid organlarda SWE ölçümlerinin kantitatif ve rutin olarak uygulanması için daha fazla çalışma yapılması gerekmektedir.

Anahtar Kelimeler: inflamasyon; otoinflamatuvar hastalık; sonoelastografi

ABSTRACT

Purpose: Familial Mediterranean Fever (FMF) is an autoinflammatory multisystemic disorder that may impact internal organs. This study aims to evaluate the impact of FMF on the liver and spleen utilizing shear wave elastography (SWE).
Materials and Methods: Our study included patients diagnosed with FMF according to the Tel-Hashomer criteria, aged ≥18 years, who did not have AA amyloidosis or any conditions affecting liver or spleen tissue. Electronic medical records were examined retrospectively. A radiologist with a minimum of five years of expertise in shear wave elastography conducted the procedure. Shear wave elastography results were compared between patients with FMF and healthy controls.
Results: We examined fifty-one cases of FMF (25 females, 26 males) with a mean age of 32.3 years, alongside 14 healthy persons (4 females, 10 males) with a mean age of 36.9 years. The predominant symptom was fever, observed in 98% of cases, whereas 64.7% had the M694V gene mutation. No significant difference was seen between the mean SWE values of FMF cases and the control group. A positive connection between hepatic stiffness and age was identified (r=0.319, p=0.023). The age at disease onset exhibited a correlation with hepatic stiffness and velocity (r=0.474, p=0.001; r=0.386, p=0.007, respectively).
Conclusion: A consensus on non-invasive methods to follow up patients with FMF is lacking. Further studies are necessary for the quantitative and routine application of SWE measurements in solid organs affected by inflammatory disorders, including FMF.

Keywords: autoinflammatory disease; inflammation; sonoelastography

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INTRODUCTION

Familial Mediterranean fever (FMF), which is the first described and most common autoinflammatory disease, usually affects Turks, Arabs, Armenians, and non-Ashkenazi Jews. There is a clear geographical clustering of the disease, and FMF originated from Middle Eastern countries.[1] FMF is characterized by recurrent episodes, including fever, serositis, and skin and joint inflammation that last 1-3 days and cease spontaneously. Patients with FMF are asymptomatic between episodes. The frequency and type of attacks can be variable depending on the individual.[2] The prevalence of FMF is 1/1000 in Turkey, and can rise to 1/395 in Central Anatolia.[3] The MEFV gene, which is situated on the short arm of chromosome 16 (16p13.3), is the most significant component in the pathophysiology of FMF. The MEFV gene encodes the 'pyrin' protein and is inherited as autosomal recessive. The association between the MEFV gene and FMF was first described in 1997.[4] Apart from the MEFV gene, other genetic factors (such as the MICA and SAA-1 genes) and environmental factors also take part in the pathogenesis of FMF.[5-9]

Colchicine is the cornerstone of FMF treatment. Colchicine leads to a decrease in the frequency and intensity of attacks, amyloidosis, renal failure, and mortality.[10] Anti-interleukin-1 agents are recommended for treating patients with colchicine-resistant FMF because interleukin-1 is the pivotal cytokine in FMF pathogenesis.[11] However, subclinical systemic inflammation continues in 30% of FMF cases. Chronic systemic inflammation in FMF patients increases complications such as normochromic normocytic anemia, growth retardation, decreased bone density, increased risk for infertility, and cardiovascular diseases.[12]

The primary predictor of prognosis and most prevalent FMF consequence is secondary amyloidosis (AA-type).[13] AA-amyloidosis is caused by the extracellular accumulation of an insoluble fibrillar protein named serum amyloid-A (SAA), especially in internal organs. So, AA-amyloidosis leads to organ dysfunction and failure. Patients with FMF having AA-amyloidosis are usually under 40 years of age and develop end-stage renal failure within five years after the initial diagnosis.[14] The diagnosis of amyloidosis is usually based on a renal biopsy, and currently, there is no accepted non-invasive test for follow-up or diagnosis. The early detection of AA-amyloidosis is essential for the effective management of FMF.

Elastography is an imaging method measuring tissue hardness.[15] Shear wave elastography (SWE) is a technique that uses very quick image sequences to develop a quantitative tissue stiffness map by perceiving shear wave (SW) waves, which are produced by applying transient mechanical impulses to the tissue under evaluation with a probe.[16] The hardness and elasticity of the tissue could be ascertained by measuring the velocity of the shear waves produced by the ultrasonic probe, and the speed of SW is higher in hard tissues.[17] Fibrosis causes tissue to become more rigid, which raises the shear wave velocity.[18]

Currently, there is increasing evidence for SWE in the medical literature. Published studies investigated the utilizability of SWE in solid organ parenchymal diseases or musculoskeletal injuries.[19-21] In this research, we aimed to investigate the effects of FMF on the liver and spleen without amyloidosis by examining splenic and hepatic SWE findings.

MATERIALS and METHODS

Patients' Selection

This study was approved by the Hatay MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (dated 24.10.2022 and numbered 09). The patients gave us their informed written consent.

Our research was a case-based retrospective study. A total of 65 participants; 51 patients with FMF and 14 participants as a control group were enrolled in the study. The study included patients who were referred to our rheumatology department between October 2022 and January 2023, were older than 18 years old, fulfilled the Tel-Hashomer classification criteria,[22] and did not develop amyloidosis. Exclusion criteria were having secondary amyloidosis, another systemic condition affecting the liver or spleen (e.g., non-alcoholic steatohepatitis, viral hepatitis), metabolic disorders including obesity, diabetes mellitus, and chronic liver and spleen diseases like cirrhosis. We also excluded patients who were pregnant or lactating. The control group consisted of adult admissions to the internal

medicine department without a history of chronic diseases or metabolic conditions.

Data Collection

Electronic patient files were retrospectively scanned. Baseline demographic, laboratory, clinical, and treatment data were noted. Our study included biochemical measures, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum amyloid-A (SAA), full urinalysis, spot urine protein, and creatinine. The patients' biochemical tests were carried out as part of a normal assessment upon admission. Blood tests are regularly assessed in routine visits during six-month period rheumatology visits. A shear wave elastography examination was conducted during admission for routine examination by a musculoskeletal radiologist. All patients and the control group adhered to legal procedures prior to the examination.

We used the LOGIQ E9 (GE Healthcare, Wauwatosa, WI, USA), a 1-6 MHz convex probe (XDClear C1-6-D) for grayscale and SWE evaluation. Pressure on the probe was avoided during measurement. Measurements were performed in the lateral decubitus position with breath holding (the left decubitus position was used for liver and the right decubitus position was used for spleen measurements). Individuals who could not hold their breath and could not obtain optimal measurements were excluded from the study. In each patient, 3 separate measurements of mean velocity (m/s) and mean stiffness (kPa) were taken by using a 0.8 mm diameter ROI (region of interest). The stiffness and velocity values from each measurement were taken, and the average of these 3 measurements was used for the study. SWE values and grayscale were taken from the recorded data at the time of the first inspection.

Statistical Analysis

Data analysis was conducted using the statistical package program, Statistical Package for the Social Sciences (SPSS), version 22.0. For descriptive statistics, the highest and lowest values, standard deviation, frequency (%), and mean value were utilized. The Shapiro-Wilk test was used to determine if the data were ordinarily distributed. Two distinct groups' worth of non-normally distributed quantitative data were analyzed using the Mann Whitney U test. The independent and qualitative data were analyzed using the chi-square test. Pearson Correlation analysis was used to assess the association between the SWE measurement values and the participants' ages as well as the patients' ages at disease onset. P-values less than 0.05 were regarded as significant in statistical studies.

RESULTS

We analyzed 65 participants; 78.5% of the participants were patients (n= 51; 25 females and 26 males), and 21.5% (n= 14; 4 females and 10 males) were in the control group. Among all participants, there were 29 females (44.6%) and 36 males (55.4%). The mean age was 32.33±10.57 years in the FMF group and 36.39±9.95 years in the control group. The mean body-mass index was 23.65±4.05 kg/m^2 in the FMF group and 24.75±2.96 kg/m^2 in the control group. Age, gender, and BMI were distributed uniformly in both the control group and the FMF patients (Table 1).

Table 1. Demographic data of patients and control group.

Variables	FMF group (n= 51)	Control group (n= 14)	p value
Age, mean±SD, years	32.33±10.57	36.39±9.95	0.893*
Male sex, n, (%)	26 (51%)	10 (71.4)	0.173**
Body-mass index, mean±SD, kg/m^2	23.65±4.05	24.75±2.96	0.347*

Abbrevations: FMF, Familial Mediterranean fever. *Student T test, **Chi-square test

In the FMF group, the mean age at disease onset was found to be 13.58±10.4 years (range 1-53 years). The most common clinical findings were fever in 98%, peritonitis in 86.3%, and arthritis in 66.7% of FMF cases. Pleuritis was present in 31.4%, erysipelas-like erythema in 17.6%, and pericarditis in 7.8% of FMF cases. The most common MEFV gene mutation was compound heterozygous with a rate of 39.2% (n=20). Homozygous MEFV gene mutations were detected as M694V (n=10), M680I (n=2), E148Q (n=1), and R202Q (n=1). Heterozygous mutations were M694V (n=11), E148Q (n=1) and V726A (n=1). Four cases had no mutation on the MEFV gene. The M694V mutation was present in 12 cases with compound heterozygous. As a result, M694V mutations were positive in 64.7% (n=33) of cases. The mean dosage of colchicine was

1.5 mg/day. Three patients were using Canakinumab treatment due to colchicine-resistant disease activity.

There was no significant difference between the patient and control groups' average SWE values (Table 2). Hepatic stiffness and age showed a weak positive correlation in the FMF group (r=0.319, p=0.023). In the control group, a high positive correlation was found between splenic velocity and age (r=0.721, p=0.004). Additionally, a weak positive correlation was found between the age of FMF onset and both hepatic stiffness and velocity in the patient group (r=0.474, p=0.001; r=0.386, p=0.007, respectively) (Table 3).

Table 2. Evaluation of SWE measurement results in patient and control groups.

Features		Median (kPa)	Min (kPa)	Max (kPa)	p*
Hepatic Stiffness	Patient	6.18	2.85	16.47	0.780
	Control	5.84	4.11	15.35	
Hepatic Velocity	Patient	1.40	0.96	2.08	0.655
	Control	1.37	1.14	2.08	
Splenic Stiffness	Patient	17.14	8.18	35.55	0.267
	Control	14.79	5.03	27.15	
Splenic Velocity	Patient	2.26	1.55	3.31	0.911
	Control	2.23	1.21	5.83	

Abbrevations: SWE, shear wave elastography; min, minimum; max, maximum *Mann-Whitney U test

Table 3: Relationship between participants' ages and the onset age of the disease with SWE values in the patient group.

Features		Hepatic Stiffness		Hepatic Velocity		Splenic Stiffness		Splenic Velocity	
		r*	p**	r*	p**	r*	p**	r*	p**
Age	Patient	0.319	0.023	0.248	0.080	-0.050	0.727	-0.159	0.264
	Control	0.095	0.747	0.065	0.824	0.147	0.616	0.721	0.004
Age at disease onset		0.474	0.001	0.386	0.007	2	0.988	-0.086	0.561

Abbrevations: SWE, shear wave elastography. * Correlation Coefficient **Pearson Correlational Analysis.

Table 4. Relationship between SWE value and laboratory findings.

Variables	Hepatic Stiffness		Hepatic Velocity		Splenic Stiffness		Splenic Velocity	
	r*	p**	r*	p**	r*	p**	r*	p**
Serum amyloid-A	0.017	0.906	0.060	0.684	0.141	0.333	0.141	0.332
Spot urine microprotein	-0.299	**0.049**	-0.308	**0.042**	-0.284	0.062	-0.243	0.111
Spot urine creatinine	-0.283	**0.049**	-0.242	0.094	-0.249	0.085	-0.204	0.159
Fibrinogen	0.158	0.2.79	0.104	0.478	0.046	0.753	0.009	0.949
Albumin	-0.114	0.424	-0.189	0.183	-0.076	0.594	-0.063	0.659
Total protein	-0.004	0.980	-0.039	0.790	-0.140	0.333	-0.104	0.471
BUN	0.218	0.128	0.204	0.156	-0.169	0.240	-0.139	0.337
Creatinine	-0.253	0.077	-0.300	**0.034**	-0.192	0.181	-0.175	0.223
CRP	0.002	0.990	0.044	0.761	0.134	0.347	0.123	0.391
ESR	0.286	**0.042**	0.285	**0.043**	0.082	0.567	0.055	0.701
SGPT	0.181	0.203	0.123	0.390	-0.048	0.737	-0.021	0.881
SGOT	0.025	0.863	-0.020	0.887	0.171	0.231	0.158	0.267
WBC	-0.207	0.144	-0.279	**0.047**	0.363	**0.009**	0.289	**0.040**
HGB	-0.088	0.537	-0.082	0.565	-0.096	0.502	-0.032	0.821
PLT	-0.078	0.586	-0.137	0.336	0.457	**0.001**	0.390	**0.005**

Abbreviations: SWE, shear wave elastography; BUN, blood urea nitrogen; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; SGPT, Serum Glutamic Pyruvic Transaminase; SGOT, Serum Glutamic-Oxaloacetic Transaminase; WBC, white blood count; HGB, haemoglobin; PLT, serum platelet count.
*Correlation Coefficient **Pearson Correlation Analysis

We detected a weak negative correlation was found between spot urine microprotein value and hepatic stiffness and velocity values (r=-0.299, p=0.049; r=0.308, p=0.042, respectively). Additionally, there was a weak negative correlation between spot urine creatinine and hepatic stiffness (r=0.283, p=0.049) and a weak negative correlation between creatinine value and hepatic velocity (r=0.3, p=0.034). There was a weak negative correlation between leukocyte count and hepatic velocity (r=-0.279, p=0.047) and a weak positive correlation between splenic stiffness and velocity values (r=0.009, p=0.040). Besides, we found a weak positive correlation between erythrocyte sedimentation rate and hepatic stiffness and velocity values (r=0.286, p=0.042; r=0.285, p=0.043, respectively) and a weak positive correlation between platelet count and splenic stiffness and velocity values (r=0.00, p=0.005) (Table 4).

DISCUSSION

In this study, we investigated the changes in tissue stiffness in the liver and spleen and compared these results between FMF patients and healthy subjects. Additionally, we compared the SWE values with the laboratory findings in cases of FMF. Our study is a contribution to the literature that evaluates tissue elasticity together with laboratory parameters in patients with FMF. The mean SWE values in our study did not show a significant difference between the FMF cases and the healthy control group. However, there was a weak positive correlation between age at FMF onset and hepatic stiffness and velocity in the patient group.

In a multicenter study conducted in 2014 in our country, the mean age at FMF onset was 15.7± 9.6 years,[23] whereas in our study, the mean age at disease onset was 13.58±10.4 years. In our study, the M694V mutation was present in 64.7% of the cases. The most common finding in Turkish FMF patients, as well as in our patients, was fever. There are very few studies in the literature that evaluate FMF cases by using SWE. Bayramoğlu Z. et al. examined the stiffness level of solid organs in 38 pediatric FMF patients and 38 healthy individuals in the control group. Compared to control participants, the FMF group with amyloidosis had significantly higher median values for elasticity of the liver, spleen, kidney, and pancreas. The relevant study found no difference in the median liver stiffness values between FMF patients without amyloidosis and the control group.[24] In this study, stiffness values tend to show a moderate positive correlation with CRP, ESR, and SAA levels. We also excluded patients with amyloidosis, as they could potentially explain the differences in our results. In our study, a weak positive correlation was found between ESR and hepatic stiffness and velocity values. Furthermore, a weak correlation was found between the leukocyte count and the velocity and stiffness of the spleen. However, an analysis of the mean SWE values of the patient and control groups revealed no significant difference. According to Aktı S et al., liver stiffness values were significantly higher in adults with FMF compared to the control group. They also didn't leave out patients who had secondary amyloidosis related to FMF.[25]

Kayalı et al. performed a study with 35 adult patients with FMF and 23 healthy control groups. Renal stiffness in FMF cases was found to be considerably higher ($p< 0.001$) than in the control group.[26] Among solid organs, the kidneys are the primary targets of FMF. Ozmen Z et al. reported a study with 79 pediatric FMF cases, and they found out kidney stiffness values were higher ($p<0.001$) than the healthy control group.[27] Urfalı M et al. found a significant increase in parotid gland, thyroid, and renal parenchymal stiffness, as well as arterial vascular resistance values, in 35 FMF patients. They also showed that tissue stiffness and vascular resistance values were higher ($p<0.001$) in the group with the M694V homozygous mutation.[28] Previous results could be affected by the M694V homozygous mutation, which is related and associated with more severe disease and an enhanced risk of amyloidosis.[29] Bayramoglu Z et al. found that during an acute attack, the salivary and thyroid glands' median shear wave elasticity and velocity values were significantly higher in pediatric FMF cases than in the healthy control group. Additionally, a significant correlation was spotted between the elasticity values of the parotid gland ($r=-0.4$, $p=0.04$) and thyroid glands ($r=-0.6$, $p=0.008$) and CRP, as well as a moderately negative correlation between serum amyloid-A and thyroid gland elasticity ($r=-0.58$, $p=0.018$).[30]

Acute phase responses such as ESR, CRP, and SAA are used to measure inflammatory activity in the follow-up of FMF cases. However, there is no predictive test for the development of amyloidosis. Amyloidosis is associated with a family history of the disease, end-stage renal failure, the M694V mutation (particularly homozygous), male gender, chronic arthritis, and delayed diagnosis in Turkish FMF patients; the incidence of amyloidosis is 8.6%.[31] Since amyloidosis is the main determinant of prognosis in FMF patients. Non-invasive measurement methods, such as SWE, hold great promise.

Despite unique results, our study has some limitations. We were unable to collect the desired number of patients and control group data due to the Kahramanmaras-centered earthquakes that occurred during the study period. Our study has a small number of patients and control groups. Lack of data regarding family history of amyloidosis or end-stage renal failure, the exclusion of FMF patients having secondary rheumatic disorders (such as seronegative

spondyloarthritis), and the absence of a patient group having AA-amyloidosis were the major limitations of our study.

In conclusion, we investigated the splenic and hepatic SWE findings in FMF cases and the control group. This study found a positive association between hepatic stiffness velocity and age at FMF onset. Our results should be supported by larger-scale research. Monitorization and follow-up are essential in patients with FMF because of amyloidosis-related solid organ involvement. The stiffness and velocity of solid organs could be useful parameters for non-invasive imaging techniques in inflammatory conditions.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

This study was approved by the Hatay MKU Tayfur Ata Sökmen Medical Faculty Clinical Research Ethics Committee (dated 24.10.2022 and numbered 09).

Authors' Contributions

Concept/Design: MMÇ, MP, AÇ. Data Collection and/or Processing: AÇ, MMÇ, MP. Data analysis and interpretation: MP, AK, AÇ. Literature Search: AK, AÇ, MMÇ. Drafting manuscript: AÇ, AK, MP.

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