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Original Article PEDIATRICS

Evaluation of the thicknesses of cartilage and enthesis in familial Mediterranean fever and enthesitis-related arthritis

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ABSTRACT

OBJECTIVE: Subclinical inflammation is still a controversial issue in inflammatory diseases. There is no reliable, easy, and cheap inflammation marker in daily clinical practices currently. This study aims to predict clinical remission using cartilage and tendon thicknesses.

METHODS: Eleven patients with Familial Mediterranean Fever (FMF) who had musculoskeletal involvement before and 11 patients with Enthesitis-Related Arthritis (ERA) were included in this study. They were on remission with clinical and laboratory evaluations for at least three months. Demographic and clinical features of the subjects, including age, sex, body mass index, disease duration, age at onset, medical treatment, and laboratory evaluations, were all noted. Healthy children of the same age were included as the control group. The thicknesses of the bilateral knee, second metacarpophalangeal and ankle joints cartilages, quadriceps, superior and inferior patellar, and the Achilles tendons were measured with a linear probe. A total of 198 joint and 264 tendon thicknesses were measured.

RESULTS: The thicknesses of metacarpophalangeal, knee, and ankle cartilages were higher in the FMF group than in the others. In the FMF group, the quadriceps tendon thickness was higher than in the ERA group, and the superior patellar tendon thickness was higher than in the control group ($p<0.05$).

CONCLUSION: According to our preliminary findings, an increased thickness of the cartilage and tendon in FMF patients may be an indicator of subclinical inflammation. Increased thickness of the enthesis in FMF patients may also indicate that enthesitis-related arthritis will also develop in the future.

Keywords: Cartilage thickness; child; enthesis thickness; inflammation.

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Musculoskeletal ultrasound (MSUS) indicates that the detection of joint effusion, synovitis, tenosynovitis, enthesitis and the evaluation of cartilage and bone erosions [1]. The tendon insertion sites of the large joints are excellent targets for US imaging because their superficial location can easily be evaluated with high-frequency transducers. The appearance of tendon fibres, tendon thickness, the presence of vascularity within the tendon, as well as the enthesis can be imaged [2, 3]. Musculoskeletal ultrasound (MSUS) can also be used as a guidance for aspiration, biopsy, and intra-articular treatment [2]. There are significant differences in the evaluation of

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growing children when compared to adults. The amount of physiological fluid, cartilage thickness, and appearance of epiphysis differ according to age and sex. The evaluation of pathological changes becomes more difficult with physiological changes. The first US study in the pediatric age group was a comparison of the cartilage thickness measurements of 11 healthy children performed by skilled and non-skilled investigators in 2007 [4]. The measurements of cartilage thickness according to age and sex in healthy children were published, and studies continued with cartilage and entheseal measurements of the patients with juvenile idiopathic arthritis [5–9].

Enthesitis-related arthritis (ERA) is defined by the International League of Associations with Rheumatology (ILAR) criteria in the JIA subgroup. Arthritis and enthesitis last longer than six weeks in children under the age of 16, or arthritis or enthesitis plus two of the following: tenderness on sacroiliac joint or inflammatory back pain, HLA-B27 positivity, the onset of arthritis in boys older than six, anterior uveitis, family history of ankylosing spondylitis, ERA, sacroiliitis with inflammatory bowel disease (IBD), or anterior uveitis in at least one first-degree relative [10]. The definition of Juvenile Spondyloarthropathy (JSpA) is used instead of ERA. The incidence of ERA is 15–20% in JIA cases and has a peak onset at the age of 12. Sixty percent of the patients are boys. The distribution rate of ERA is 18.9%, and HLA-B27 positivity is 63.3% in Turkish ERA patients [11]. The pathological MSUS findings, which could not be detected by physical examination, were particularly striking [12]. A more objective measure, such as the US is extremely useful for enthesitis, where the pain is the primary physical examination finding and is considered as an indicator of active inflammation. Power Doppler US has been used to detect enthesitis in JIA as it was proved to be more sensitive than physical examination [2, 3].

Familial Mediterranean fever, which is an auto-inflammatory disease, presents acute and mostly non-degenerative arthritis. It was reported that 40.7% of the children with FMF were diagnosed with articular symptoms in Turkey [13]. Of these patients, 63.2% had M694V and 20% had other exon 10 mutations. Of the children with articular symptoms of FMF, 8% had chronic arthritis and 39.1% of these patients were diagnosed with ERA [13].

The disease remission is determined according to the active joint findings and improvement in acute phase reactants in routine clinical practice. Subclinical inflammation is still a controversial issue in both FMF and JIA. There is currently no reliable, easy, and cheap inflammation marker in clinics.

This study aimed to predict clinical remission using cartilage and tendon thicknesses. We evaluated the cartilage and tendon thicknesses of patients with FMF and ERA in the remission period.

MATERIALS AND METHODS

Eleven FMF patients who previously had musculoskeletal involvement and 11 ERA patients were included in this study. They were on remission with clinical and laboratory evaluations for at least three months. The patient groups had no growth disorder, obesity, and other chronic diseases. The ILAR criteria were used for the diagnosis of ERA [10]. The Yalçınkaya-Ozen children FMF classification criteria based on clinical findings were used for the diagnosis of FMF [14]. The healthy children of the same age were included as a control group. All patients and control group were in the same body mass index. The US measurements of the bilateral knee, second metacarpophalangeal (MCP), and ankle joints cartilage, quadriceps, superior and inferior patellar and Achilles tendons were measured with a linear probe (7–12 MHz Logiq P5, GE Medical Systems, USA). The measurement locations and techniques were determined according to the guidelines of EULAR and other studies [4, 15–17]. The US scans were performed by a pediatric rheumatologist who had three years of US experience and was blinded to clinical information regarding FMF, ERA, the control groups, and disease activity. A total of 198 joint and 264 tendon thickness measurements were performed. The clinical and laboratory information was obtained from medical records. Demographic and clinical features of the subjects, including age, sex, body mass index, disease duration, age at onset, medical treatment, and laboratory evaluations, were all noted. The remission was defined by the Juvenile Spondyloarthritis Disease Activity Index (JSpADA) in ERA patients and the Auto Inflammatory Disease Activity Index (AIDAI) in patients with FMF [18, 19].

The necessary institutional and ethical approvals were obtained at the beginning of this study following the Helsinki declaration (05.12.2014/657). The children and their parents were informed about this study, and their participation was voluntary. A written consent form was completed by each participant.

Table 1. Demographic features of the patients

	Control (n=11)	FMF (n=11)	ERA (n=11)	p
Age	11.18±2.22	12.45±2.87	13.81±2.31	0.061
The age of diagnosis (year)		9.33±4.22	12.3±2.06	0.149
Sex (F/M)	8/3	7/4	3/8	0.070
BMI (kg/m²)	18–24	18–24	18–24	NA
HLAB27 positivity			7+	NA
MEFV Mutations		M694V Homozygous: 6 M694V Heterozygous: 2 E148Q Heterozygous: 1 No mutations:2		NA
Affected joints before the remission		Knee: 3, ankle: 2, hip: 2	Knee: 5, ankle: 5, sacroiliac: 2	NA
Affected enthesis before the remission		Achille: 3	Achille: 8 Quadriseps: 4 Patella: 3	NA
ESR (mm/h)/CRP (mg/L)		15/3.12	13/3.03	NA
AIDAI		0		NA
JSpADAS		0	0	NA
Treatments		Colchicine: 11, Mtx: 1	Mtx: 11 ETA:1	NA

BMI: Body mass index; Mtx: Methotrexate; ETA: Etanercept; JSpADAS: Juvenile Spondyloarthritis Disease Activity Index; AIDAI: Auto-Inflammatory Disease Activity Index; NA: Not applied.

Statistics

Statistical analysis was performed using SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as percentages, means, and standard deviations if they were normally distributed and as median (min–max) if they were abnormally distributed. In the comparison of the groups, those with normal distribution were assessed using the Anova and those with abnormal distribution using the Kruskal Wallis test. $P<0.05$ was considered to be statistically significant.

RESULTS

There were eleven children in each group. The mean ages were 11.18±2.22, 12.45±2.87, and 13.81±2.31 in the control, FMF, and ERA groups, respectively. The age of diagnosis was 9.33±4.22 in the FMF group and 12.3±2.06 in the ERA group. The BMI index was 18–24 in all groups. The age, duration of disease, gender, and BMI did not show differences between the groups statistically ($p>0.05$). The AIDAI was calculated as 0 in patients with FMF. The JSpADA was calculated as 0 in ERA patients. The distribution of MEFV mutations was M694V homozygous in six patients. The articular involvements, laboratory findings, and treatments are given in Table 1.

Median thickness was 1.2 (0.7–1.9) mm in MCP cartilage, 2.8±0.3 mm in knee cartilage, and 1.1±0.3 mm in ankle cartilage in the FMF group, which were higher than in others ($p<0.005$). The mean thickness of the quadriceps tendon in the FMF group was 5.3±0.8 mm, which was higher than in the ERA group. The superior patellar tendon thickness was 2.7±0.7 mm, which was higher than in the control group ($p<0.05$) (Table 2 and Fig. 1).

DISCUSSION

We investigated the cartilage and entheseal thicknesses in patients with ERA and FMF who were on clinical remission. In this study, we found that MCP, knee, and ankle joint cartilage were thicker in FMF patients than in both the control and ERA groups. Moreover, increased cartilage thickness was detected in previously unaffected joints. To our knowledge, this study is the first study to investigate cartilage thickness in FMF patients with arthritis. Pradsgaard et al. [6] reported that the cartilage thickness decreased in systemic and polyarticular JIA

Table 2. Ultrasonographic findings

	Control (n=11)	FMF (n=11)	ERA (n=11)	p
MCP cartilage	0.7 (0.5–0.1)	1.2 (0.7–1.9)[ab]	0.6 (0.5–1.3)	**0.004**
Knee cartilage	2.2±0.5	**2.8±0.3**[ab]	2.1±0.6	**0.011**
Ankle cartilage	0.8±0.2	**1.1±0.3**[ab]	0.7±0.1	**0.002**
Quadriceps tendon	4.5±0.9	**5.3±0.8**[b]	4.3±1.0	**0.041**
Superior patellar tendon	2.0±0.4	**2.7±0.7**[a]	2.4±0.3	**0.016**
Inferior patellar tendon	2.2±0.2	2.6±0.6	2.3±0.2	0.129
Achilles tendon	3.8±0.7	4.4±0.6	3.9±0.6	0.081

a: Significant difference from the control group; b: Significant difference from the ERA group. The parameters with normal distribution were expressed as mean±SD, and the parameters with abnormal distribution were expressed as median (minimum–maximum). The measurements are given in mm.

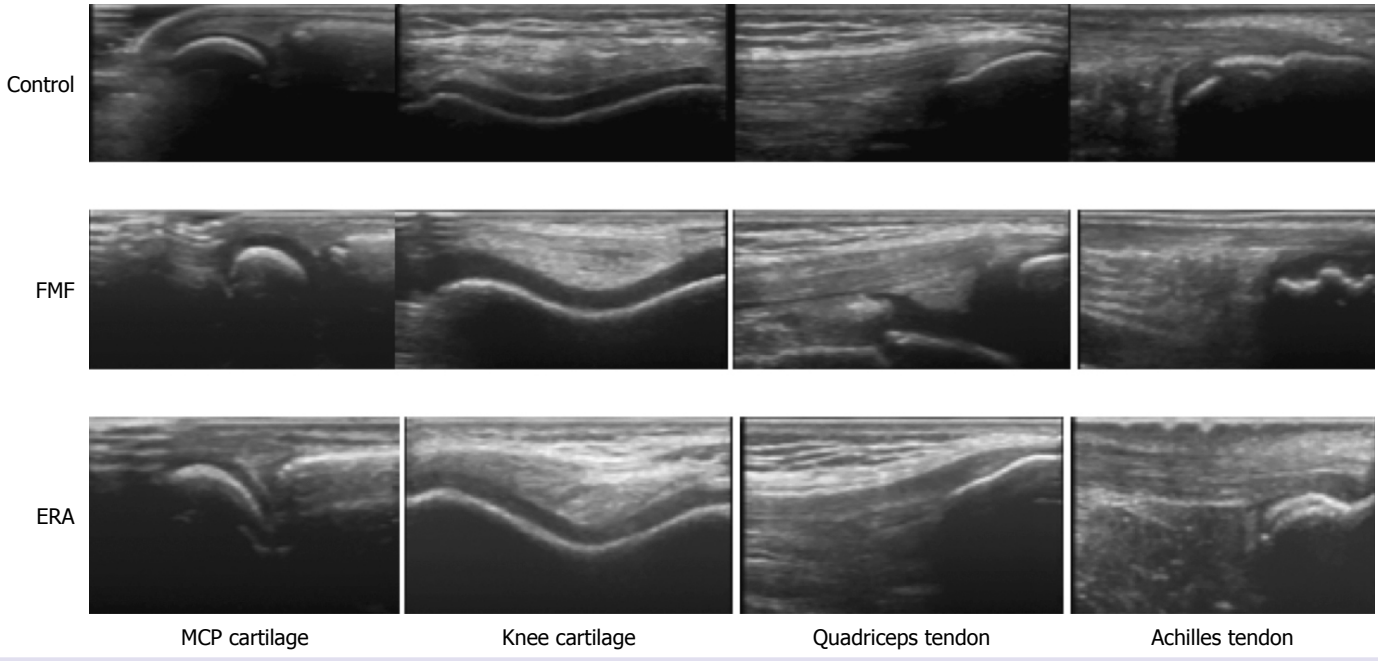

Figure 1. Ultrasonographic appearances of cartilage and enthesis.

patients in the inactive period compared to the other JIA types. The authors claimed that the severity of the illness was more influential than the duration of the illness on changes in cartilage. Inflammation severity may lead to degenerative arthritis and a decrease in cartilage thickness. The cartilage thicknesses of our ERA patients were not different from those of the control group.

We detected an increase in entheseal thicknesses in our patients with FMF. Entheseal thickness was detected higher in adult patients with FMF than in the control group in various studies [20–24]. Enthesopathy, which is an important finding of spondyloarthritis, was detected in FMF [22]. Especially FMF patients carrying M694V have a high rate of concomitant ankylosing spondylitis [25]. It was indicated that both of the diseases had a common inflammatory pathway like IL-1. Tufan et al. [22] claimed that dysregulation of the IL-1 pathway by M694V mutation might lead individuals to be prone to developing enthesopathy. In another study, Kerimoglu et al. [20] claimed that synovitis and inflammation due to amyloid deposition might first result in enthesophyte formation and then erosion. We routinely investigated the development of amyloid in our patients with urine analysis; proteinuria was not detected in patients with FMF

involved in this study. As mentioned above, an inflammatory pathway may cause an increase in the thickness of enthesis and cartilage. Subclinical inflammation is still a controversial issue in inflammatory disease. There is currently no reliable, easy, and cheap inflammation marker in daily practices. We suggested that the increase in both enthesis and cartilage thicknesses may be an indication of subclinical inflammation in patients with FMF.

Juvenile SpA develops at a rate of 39.1% in FMF patients [13]. Meanwhile, the M694V allele frequency significantly increased in patients with AS [25–28]. Eshed et al. [24] mentioned in their study that exertional leg pain and ankle enthesopathy should be considered as the new features of spondyloarthropathy in patients with FMF. An increase in enthesis thicknesses in our FMF patients may suggest that SpA may develop in the future.

The limited number of patients and the single operator are major limitations of our study. Although all 11 patients with FMF were diagnosed according to Yalçınkaya-Ozen [14] FMF classification criteria, three of them had not significant MEFV mutations. A homogeneous patient group will provide accurate and more beneficial information. This is the preliminary study of cartilage and enthesis thickness in children. In further studies, cartilage and tendon thicknesses may be compared in active and inactive periods of the diseases. We compared patients with FMF who had articular involvement with the ERA and control groups, which is the significance of our study. Our results will shed light on future pediatric MSUS studies.

Conclusion

The increased thicknesses of cartilage and tendon in FMF patients may be indicators of subclinical inflammation. An increased enthesis thickness in FMF may suggest that jSpA can also develop in the future.

Ethics Committee Approval: The institutional and ethical approvals were obtained at the beginning of the study following the Helsinki declaration (date: 05.12.2014, number: 657).

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