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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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.
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 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    |
| 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 | NA    |
| ESR (mm/h)/CRP (mg/L) | 15/3.12 | 13/3.03 | NA    |
| AIDAI | 0 | 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.
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.

### 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) | 0.6 (0.5–1.3) | 0.004 |
| Knee cartilage          | 2.2±0.5       | 2.8±0.3    | 2.1±0.6   | 0.011 |
| Ankle cartilage         | 0.8±0.2       | 1.1±0.3    | 0.7±0.1   | 0.002 |
| Quadriceps tendon       | 4.5±0.9       | 5.3±0.8    | 4.3±1.0   | 0.041 |
| Superior patellar tendon | 2.0±0.4      | 2.7±0.7    | 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 |

**Table 2.** Ultrasonographic findings

- 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.
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]. Esched et al. [24] mentioned in their study that exertional leg pain and ankle enthesisopathy should be considered as the new features of spondyloarthritis 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 Yalcinkaya-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).

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Magni-Manzoni S, Malattia C, Lanni S, Ravelli A. Advances and challenges in imaging in juvenile idiopathic arthritis. Nat Rev Rheumatol 2012;8:329–36.
2. Tok F, Demirkaya E, Ozçakar L. Musculoskeletal ultrasound in pediatric rheumatology. Pediatr Rheumatol Online J 2011;9:25.
3. Bugni Miorto e Silva V, de Freitas Tavares da Silva C, de Aquigar Vilela Mitraud S, Nely Vilar Furtado R, Esteves Hilarion MO, Natour J, et al. Do patients with juvenile idiopathic arthritis in remission exhibit active synovitis on joint ultrasound? Rheumatol Int 2014;34:937–45.
4. Spannow AH, Stenborg E, Pfeiffer-Jensen M, Herlin T. Ultrasound measurement of joint cartilage thickness in large and small joints in healthy children: a clinical pilot study assessing observer variability. Pediatr Rheumatol Online J 2007;5:3.
5. Spannow AH, Pfeiffer-Jensen M, Andersen NT, Herlin T, Stenborg E. Ultrasonographic measurements of joint cartilage thickness in healthy children: age- and sex-related standard reference values. J Rheumatol. 2010 Dec;37(12):2595–601.
6. Pradsgaard DØ, Firsgaard B, Spannow AH, Heuck C, Herlin T. Cartilage thickness of the knee joint in juvenile idiopathic arthritis: comparative assessment by ultrasonography and magnetic resonance imaging. J Rheumatol 2015;42:534–40.
7. Lanni S, Martini A, Malattia C. Heading toward a modern approach in juvenile idiopathic arthritis. Curr Rheumatol Rep 2014;16:416.
8. Lin C, Diab M, Milojivic D. Grey-scale ultrasound findings of lower extremity enthese in healthy children. Pediatr Rheumatol Online J 2015;13:14.
9. Jousse-Joulin S, Breton S, Cangemi C, Fenoll B, Bressolette L, de Parscau L, et al. Ultrasonography for detecting enthesis in juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:849–55.
10. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
11. Demirkaya E, Ozen S, Bilginer Y, Ayaz NA, Makay BB, Unsul E, et al. The distribution of juvenile idiopathic arthritis in the eastern Mediterranean: results from the registry of the Turkish Paediatric Rheumatology Association. Clin Exp Rheumatol 2011;29:111–6.
12. Haslam KE, McCann LJ, Wyatt S, Wakefield RJ. The detection of subclinical synovitis by ultrasound in oligoarticular juvenile idiopathic arthritis: a pilot study. Rheumatology (Oxford) 2010;49:123–7.
13. Barut K, Sahin S, Adrovic A, Sinoplu AB, Yucel G, Pamuk G, et al. Familial Mediterranean fever in childhood: a single-center experience. Rheumatol Int 2018;38:67–74.
14. Yalcinkaya F, Ozen S, Ozçakar ZB, Aktay N, Cakar N, Düzova A, et al. A new set of criteria for the diagnosis of familial Mediterranean fever in childhood. Rheumatology (Oxford) 2009;48:395–8.
15. Backhaus M, Burmester GR, Gerber T, Grassi W, Machold KP, Swen WA, et al; Working Group for Musculoskeletal Ultrasound in the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. Guidelines for musculoskeletal ultrasound in rheumatology. Ann Rheum Dis 2001;60:641–9.
16. Balint PV, Kane D, Wilson H, McNees IB, Sturrock RD. Ultrasonography of enthesal insertions in the lower limb in spondyloarthritis. Ann Rheum Dis 2002;61:905–10.
17. de Miguel E, Cobo T, Muñoz-Fernández S, Naredo E, Usón J, Acebes JC, et al. Validity of enthesis ultrasound assessment in spondyloarthritis. Ann Rheum Dis 2009;68:169–74.

18. Weiss PF, Colbert RA, Xiao R, Feudtner C, Beukelman T, DeWitt EM, et al. Development and retrospective validation of the juvenile spondyloarthritis disease activity index. Arthritis Care Res (Hoboken) 2014;66:1775–82.

19. Piram M, Koné-Paut I, Lachmann HJ, Frenkel J, Ozen S, Kuemmerle-Deschner J, et al; EUROFEVER, EUROTRAPS and the Paediatric Rheumatology International Trials Organisation (PRINTO) networks. Validation of the auto-inflammatory diseases activity index (AIDAI) for hereditary recurrent fever syndromes. Ann Rheum Dis 2014;73:2168–73.

20. Kerimoglu U, Hayran M, Ergen FB, Kirkpantur A, Turgan C. Sonographic evaluation of entheseal sites of the lower extremity in patients undergoing hemodialysis. J Clin Ultrasound 2007;35:417–23.

21. Ozkan F, Cetin GY, Inci MF, Bakan B, Yuksel M, Ekerbicer HC, et al. Increased enthesopathy in patients with familial Mediterranean fever: evaluation with a new sonographic enthesitis index. J Ultrasound Med 2013;32:325–32.

22. Tufan A, Mercan R, Tezcan ME, Kaya A, Bitik B, Ozturk MA, et al. Enthesopathy in patients with familial Mediterranean fever: increased prevalence in M694V variant. Rheumatol Int 2013;33:1933–7.

23. Yilmaz Ö, Kısacık B, Ozkan F, Güven G, Unlü EN, Pehlivan Y, et al. Does enthesopathy relate to M694V gene mutation in patients with Familial Mediterranean fever? Clin Rheumatol 2013;32:1593–8.

24. Eshed I, Rosman Y, Livneh A, Kedem R, Langevitz P, Ben-Zvi I, et al. Exertional leg pain in familial Mediterranean fever: a manifestation of an underlying enthesopathy and a marker of more severe disease. Arthritis Rheumatol 2014;66:3221–6.

25. Akar S, Soysal O, Balci A, Solmaz D, Gerdan V, Onen F, Tunca M, Akkoc N. High prevalence of spondyloarthritis and ankylosing spondylitis among familial Mediterranean fever patients and their first-degree relatives: further evidence for the connection. Arthritis Res Ther 2013;15:R21.

26. Akkoc N, Sari I, Akar S, Binicier O, Thomas MG, Weale ME, et al. Increased prevalence of M694V in patients with ankylosing spondylitis: additional evidence for a link with familial Mediterranean fever. Arthritis Rheum 2010;62:3059–63.

27. Cosan F, Ustek D, Oktu B, Duyaz-Tozkir J, Cakiris A, Abaci N, et al. Association of familial Mediterranean fever-related MEFV variations with ankylosing spondylitis. Arthritis Rheum 2010;62:3232–6.

28. Akkoc N, Gul A. Familial Mediterranean fever and seronegative arthritis. Curr Rheumatol Rep 2011;13:388–94.