THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2022.77632
Med Bull Sisli Etfal Hosp 2022;56(4):519–524

Original Research

Ultrasound Measurement of Femoral Cartilage Thickness in Patients with Familial Mediterranean Fever and its Relation to Amyloidosis and Other Disease Characteristics

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Abstract

Objectives: This study aimed to determine femoral cartilage thickness (FCT) in patients with familial Mediterranean fever (FMF) and healthy individuals and to assess the relationship of FCT with the development of amyloidosis and clinical features.

Methods: Patients diagnosed with FMF according to the Tel-Hashomer criteria and healthy controls were included in the study. FCT of both knees was measured with a 7–12 MHz linear probe in maximum knee flexion. Three midpoint measurements were obtained from each knee: Lateral femoral condyle (LFC), intercondylar area (ICA), and medial femoral condyle (MFC). The patients' clinic characteristics include disease duration, medications, comorbid conditions, amyloidosis, chronic renal failure (CRF), FMF gene mutation, arthritis, sacroiliitis, PRAS score, and Physical Activity Questionnaire Short Form score were recorded.

Results: A total of 46 patients with FMF (36 women) and 20 age-sex-body mass index-matched controls (14 women) were enrolled in this study. The patients and controls' mean age were 37±12.9 and 37.5±8.6 years, respectively. Amyloidosis occurred in 7 patients (15.2%), CRF in 3 (6.5%), and knee arthritis in 8 (17%). Disease activity was mild in 55.8%, moderate in 20.9%, and severe in 23.23% of the patients. The mean FCT in millimeter values in the FMF and control groups was as follows: On the right side, LFC 1.9±0.5 and 2±0.52, ICA 2.2±0.77 and 2.25±0.97, and MFC 2±0.47 and 2.25±0.72; on the left side, LFC 1.9±0.4 and 2.05±0.55, ICA 2.25±0.87 and 2.25±0.87, and MFC 1.85±0.5 and 2.25±0.6. Patients with FMF had decreased cartilage thickness at the lateral condyle of both knees ($p<0.05$) and medial condyle of the left knee ($p<0.05$) compared with controls. FCT measurements were similar in patients with or without arthritis, amyloidosis, and CRF ($p>0.05$). FCT scores were not different among the disease activity groups ($p>0.05$).

Conclusion: These findings suggest that patients with FMF have decreased FCT compared with controls, and there is no significant relationship between the FCT and amyloidosis and disease activity.

Keywords: Amyloidosis, Cartilage, Familial Mediterranean fever

Please cite this article as "Gezer HH, Erdem Gursoy D, Acer Kasman S, Baklacioglu HS, Duruoz MT. Ultrasound Measurement of Femoral Cartilage Thickness in Patients with Familial Mediterranean Fever and its Relation to Amyloidosis and Other Disease Characteristics. Med Bull Sisli Etfal Hosp 2022;56(4):519–524".

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Submitted Date: December 17, 2021 **Revised Date:** April 10, 2022 **Accepted Date:** April 20, 2022 **Available Online Date:** December 19, 2022

Familial Mediterranean fever (FMF) is the most common inflammatory disease characterized by recurrent attacks of fever and serositis. It is inherited as an autosomal recessive trait and caused by mutations of the Mediterranean fever (MEFV) gene that encodes the pyrin protein.[1] Pathogenic mutations in the MEFV gene cause gain of function of pyrin protein, resulting in increased activation of inflammasome and release of IL-1ß.[2]

Although the most common feature of the disease is abdominal pain and fever, the most important complication and a significant cause of death is amyloidosis, leading to chronic renal failure (CRF). Increased production of serum amyloid a protein in the liver and decreased elimination leads to accumulation of the protein in extracellular areas and the development of amyloidosis. Although the frequency of amyloidosis decreases with early diagnosis and colchicine treatment, it remains a significant problem.[3] In a multicenter study from Turkey, amyloidosis was seen in 8.6% of patients, particularly with male sex, delay in diagnosis, M694V genotype, arthritis, end-stage renal disease, and family history of amyloidosis.[4] Although amyloid deposition is mainly diagnosed with renal involvement, it may accumulate in many tissues.[3] Amyloid fibrils first reserve in the spleen, liver and kidneys, and then in several tissues such as the thyroid, testis, heart, adrenal glands, gastrointestinal system, and the nervous system, even in joints.[5]

Mutations appear to result in decreased phosphorylation of pyrin and gain of function, resulting in increased activation of the pyrin inflammasome and release of IL-1b.

Sonographic femoral cartilage thicknesses (FCT) was evaluated in various chronic rheumatic diseases and was shown to be thinner than healthy individuals.[6-8] In FMF, the most frequently involved joint is the knee, and even if there is no joint involvement, increased pro-inflammatory cytokines such as IL-1 and TNF alpha may cause destructive effects on the joint cartilage. In addition, amyloidosis, which develops with increased inflammatory cytokines, can accumulate in many places but the cartilage thickness and the effect of amyloidosis on cartilage have not been evaluated before, so we chose the knee joint, which is the most accessible and easy to evaluate joint to measure cartilage thickness. In the present study, we aimed to determine FCT in FMF patients and healthy individuals and to assess the relationship of FCT with the development of amyloidosis and clinical features.

Methods

Study Design and Patients

This cross-sectional study was conducted between October 2018 and April 2019 in the Department of Rheumatology, Marmara University, Istanbul. Forty-six patients with diagnoses of FMF according to the Tel-Hashomer criteria[9] were included in the study. Patients with knee trauma, operation, or other inflammatory diseases were excluded from the study. The control group had 20 healthy sex-, age, and body mass index (BMI)-matched subjects selected among hospital staff.

The study was approved by the Ethical Committee of Marmara University Medical School (09.2018.382) and was conducted in compliance with the Declaration of Helsinki. All patients were informed about the study procedure and gave written consent to participate.

Disease Characteristics

Demographic and clinical features including age, gender, education level, comorbidities, disease duration, medications, amyloidosis, attack features, and FMF gene mutations were recorded. Other clinical manifestations such as arthritis, arthralgia, erysipelas-like erythema, and protracted febrile myalgia were noted.

Laboratory measurements included erythrocyte sedimentation rate (ESR) (mm/h) and C-reactive protein (CRP) (mg/L).

FMF disease severity was assessed using the PRAS score of six conditions, including onset age of disease, the number of attacks per month, presence of acute or chronic arthritis, erysipelas-like erythema, amyloidosis, and colchicine dosages. Scores of 2–5 indicate mild disease, 6–10 show moderate severity, and 10 or more indicate severe disease.[10]

Physical activity was assessed using the International Physical Activity Questionnaire Short Form (IPAQ-SF), a validated patient-reported scale designed to measure physical activity.[11] IPAQ-SF consists of seven physical activity items into four categories (vigorous intensity, moderate intensity, walking, and sitting) during the past 7 days.[12] Scoring the IPAQ can be reported in categories (low activity levels, moderate activity levels, or high activity levels) or metabolic equivalent of task (MET) as a continuous variable. Values <600 MET-min/week were assessed as low, 600–3000 MET-min/week as moderate physical activity, and more than 3000 MET-min/week as high physical activity (www.ipaq.ki.se). Regular exercise was defined as aerobic or muscle-strengthening activities at least three 40 min per week.

Femoral Cartilage Measurements

The thickness of femoral cartilage (FCT) was measured by a 7–12 MHz linear probe (Logiq P5, GE, Medical Systems, USA) by the same physician (HHG) who is experienced in

musculoskeletal ultrasound and blinded to the patient's clinical data. The probe was placed axially on the suprapatellar knee area at maximum flexion while the patient was supine. Three midpoint measurements were obtained from each knee: Lateral femoral condyle, intercondylar area (ICA), and medial femoral condyle (MFC). The interval between the thin hyperechoic line at the synovial space/cartilage interface and the hyperechoic line at the cartilage-bone interface was scored as the cartilage thickness (Fig. 1). Each patient was scanned 3 times and the mean value of the score was recorded.

Sample Size

We calculated the sample size of the study based on a trial performed on Behçet disease. The MFC thickness of the left knee was 1.9±0.3 mm, while it was 2.2±0.4 mm in healthy controls, and the difference was significant ($p<0.05$).[7] While Type I error is 0.05 and test power is 0.80, the minimum sample size required in each group was determined as 18 by G-Power version 3.0.10 program.

Statistical Analysis

Categorical variables were presented as numbers and percentages, and continuous variables were presented as mean±standard deviation or median (interquartile range: IQR). The Kolmogorov–Smirnov test and histogram graphs were used to assess the distribution of continuous variables. The Student's t-test was used; otherwise, the Mann–Whitney U-test was used. Categorical variables were compared with the Chi-squared test or the Fisher's exact test. The Spearman's correlation coefficient was calculated for correlations. Data were processed using the Statistical Package for the Social Sciences software (SPSS, version 22 IBM Corporation, Armonk, NY, USA). $P<0.05$ was considered statistically significant.

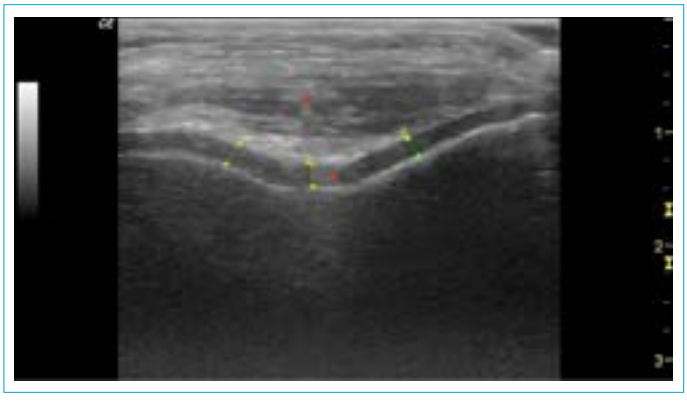

Figure 1. Ultrasonographic measurement of the femoral cartilage thicknesses at three sites (lateral, intercondylar and medial condyles). F femur, *Femoral cartilage.

Results

Demographic and Clinical Data

A total of 46 patients with FMF were included in this study. Of this group, 36 (78.3%) were female, and the mean age was 37±12.9 years. Knee arthritis was present in 8 patients (17%), hip arthritis in 1 (2.25), arthralgia in 21 (45.7%), and erysipelas-like erythema in 6 (13%).

Of the 46 patients, 23 had available gene analysis, of which five had M694 homozygous mutations, and two had V726A homozygous mutations. Other patients had other single or compound heterozygous mutations (Table 1).

Seven patients (15.2%) had AA amyloidosis, of which two were treated with IL-1i, two were anti-TNFi, and one was azathioprine. All patients used colchicine; only three patients used another preparation (colchicine opocalcium or colchicine lirca) due to inadequate response or intolerance to colchicine preparation used in Turkey. Three patients had a CRF due to amyloidosis. The clinical characteristics of the patients and healthy subjects are presented in Table 1. The patient and control groups were similar in age, gender, and BMI.

Mean FCT values of the FMF patients and controls are shown in Table 2. Patients with FMF had decreased cartilage thickness at the lateral condyle of both knees ($p<0.05$) and medial condyle of the left knee ($p<0.05$) compared with controls.

FCT was similar in patients with or without arthritis, amyloidosis, and CRF ($p>0.05$) (Table 3). Likewise, there was no difference in terms of IL-1 treatment ($p>0.05$).

Table 1. Demographic and clinical characteristics of FMF patients and controls

	FMF (n=46)	Controls (n=20)	p
Age, years	37±12.9	37.5 ±8.6	0.93
Gender (female/male)	36 (78.3%)	14 (70%)	0.47
BMI, kg/m^2	25.8±4.9	26.2±5.1	0.87
FMF gene mutation, n			
M694V homozygous	5	-	-
V726A homozygous	2	-	-
M694V/any	7	-	
M680I/any	2		
V726A/any	1		
Other	6		
PRAS			
Mild	24 (55.8%)		
Moderate	9 (20.9%)		
Severe	10 (23.3%)		

BMI: Body mass index, Data are presented as mean (±) and n (%).

Table 2. Comparison of the femoral cartilage thickness measurements (mm) between FMF and controls

	FMF (n=46)	Controls (n=20)	p*
Right			
LFC	1.9 (0.5)	2 (0.52)	0.042
ICA	2.2 (0.77)	2.25 (0.97)	0.356
MFC	2 (0.47)	2.25 (0.72)	0.146
Left			
LFC	1.9 (0.4)	2.05 (0.55)	0.048
ICA	2.25 (0.87)	2.25 (0.87)	0.398
MFC	1.85 (0.5)	2.25 (0.6)	0.004

LFC: Lateral femoral condyle, ICA: Intercondylar area, MFC: Medial femoral condyle, data are presented as median (IQR), *Mann–Whitney U-test.

Table 3. Comparison of the femoral cartilage thickness measurements (mm) between patients with amyloidosis and without amyloidosis

	Amyloidosis+(n=7)	Amyloidosis-(n=39)	p*
Right			
LFC	1.8 (0.4)	1.9 (0.5)	0.63
ICA	2.6 (0.8)	2.1 (0.7)	0.19
MFC	2 (0.65)	2 (0.4)	0.21
Left			
LFC	2.1 (0.7)	1.9 (0.35)	0.47
ICA	2.5 (0.4)	2.2 (0.9)	0.2
MFC	2.2 (0.95)	1.8 (0.5)	0.45

LFC: Lateral femoral condyle, ICA: Intercondylar area, MFC: Medial femoral condyle, data are presented as median (IQR) *Mann–Whitney U-test.

The mean PRAS score was 6.12±3. Disease activity was mild in 55.8%, moderate in 20.9%, and severe in 23.23% of the patients. FCT scores were not different among the three disease activity groups (p>0.05). There was no correlation between PRASS score and FCT (Table 4).

Of 46 patients, 7 (15.2%) were doing regular exercise. FCT scores did not differ in patients with and without regular exercise (p>0.05). The median MET score reflecting IPAQ-SF was 2192 (IQR: 3481), with 15.9%, 47.7%, and 36.4% of patients having low, moderate, and high physical activity, respectively. According to these physical activity groups, FCT scores were not different (p>0.05).

Table 4. Correlations of PRASS score and femoral cartilage thickness measurements

	R-LFC	R-ICA	R-MFC	L-LFC	L-ICA	L-MFC
PRASS						
Spearman' rho	−0.236	0.024	−0.007	−0.069	−0.192	−0.122
p	0.142	0.883	0.968	0.674	0.235	0.453

R-LFC: Right lateral femoral condyle, R-ICA: Right intercondylar area, R-MFC: Right medial femoral condyle, L-LFC: Left lateral femoral condyle, L-ICA: Left intercondylar area, L-MFC: Left medial femoral condyle.

There was no significant correlation among FCT scores and age, BMI, symptom duration, and acute-phase reactants (ESR and CRP) in patients with FMF (p>0.05).

Discussion

To the best of our knowledge, this is the first study to evaluate FCT in adult FMF patients and its associations with amyloidosis and other disease characteristics. The present study showed that the femoral cartilage in patients with FMF is significantly thinner than healthy controls, but cartilage thickness is not associated with amyloidosis and disease activity state. The lateral FCT on both sides and the medial cartilage thickness on the left side were significantly thinner than healthy population. Even if the mean of the right medial FCT is thinner than controls, the difference was not significant. One of the reasons for this may be that it is frequently affected in osteoarthritis, especially in the dominant extremity due to the load on the medial side. Another reason may be the low number of patients.

Many studies have published similar results concerning decreased FCT in several rheumatic diseases, including Behçet disease, scleroderma, and ankylosing spondylitis (AS).[6,7,13] On the contrary, cartilage thickness was similar between healthy subjects and patients with psoriatic arthritis.[14] Even in a study evaluating cartilage thickness in several joints in children with FMF, cartilage was thicker than controls.[15] Although there is no difference in systemic lupus erythematosus (SLE), decreased cartilage thickness has been reported in patients with SLE using steroids.[8] The thinner cartilage thickness seen in patients with FMF may also lead to early prevention in terms of early osteoarthritis. In rheumatic diseases, proteolytic enzymes increase with the deterioration of the balance between the anabolic and catabolic processes in cartilage. In joint diseases such as RA, the inflamed synovium secretes TNF-α and IL-1, which also cause the increase of proteinases, prostaglandins, and nitric oxide from chondrocytes. Increased matrix metalloproteinase (MMPs) degrades the cartilage collagens and proteoglycans.[16] MMP-3 levels were significantly higher in inflammatory rheumatic diseases such as RA, psoriatic arthritis, polymyalgia rheumatica, and crystal arthritis.[17] Similarly, in a study of pediatric patients with FMF, MMP-3, a direct effector of cartilage and synovial damage, was higher in FMF, especially in those with arthritis.[18] Although abdominal pain and fever are the most common symptoms in FMF, arthritis may develop in approximately 21–77% of patients.[19] The joint attacks are usually monoarticular, tran-

sient, and involve large joints such as the knee, ankle, and hip.[3] Our study found that 17% of our patients developed knee arthritis, but cartilage thickness was similar in those with and without arthritis. This may be partially explained by the non-erosive pattern of arthritis in FMF. Despite the recurrent arthritis attacks, erosion in the joints is not expected. In rare cases, patients present with hip arthritis may cause destructive arthritis.[3]

IL-1 stimulates the synthesis and activity of matrix metalloproteinases, and other enzymes involved in cartilage destruction are increased in patients with FMF both in attack and attach-free periods. Moreover, IL-1 is also responsible for releasing mediators such as nitric oxide and prostaglandins, responsible for cartilage destruction.[20,21] Consequently, IL-1, the target cytokine in FMF pathogenesis and treatment goal, also has an essential function in cartilage destruction and may have decreased cartilage thickness. Although these cytokines are expected to increase with disease activity, we did not find any difference between disease activity and cartilage thickness in our patients. Similarly, in a study with AS, no correlation was found between FCT and BASDAI scores, indicating disease.[13]

Our study found no significant association between amyloidosis and cartilage thickness. Deposition of amyloid in multiple systems, including articular tissue, occurs primarily in patients with AL amyloidosis, multiple myeloma, and transthyretin amyloidosis. In these diseases, amyloid deposits may affect the synovium, ligament, tendon, and articular cartilage. A systematic review showed amyloid deposition during orthopedic surgeries, including carpal tunnel syndrome, osteoarthritis, spinal stenosis, and rotator cuff tears.[22] Furthermore, localized amyloid deposits can be localized in the articular cartilage, especially in patients with osteoarthritis.[23] In an autopsy study, amyloid deposits were found more frequently in the articular cartilage than in the synovium and were associated with osteoarthritic changes.[24] Biopsy studies on cartilage involvement in patients with AA amyloidosis are insufficient, but scintigraphy studies are available. In a study of all amyloid types with serum amyloid P component scintigraphy, non-specific uptake in joints was present in 13% of AA amyloidosis, all known with arthritis.[25] In our results, the presence of arthritis and the amyloidosis did not seem to have any effect on cartilage measurements.

Factors that have been shown to affect cartilage thickness in healthy individuals are age and exercise. In a cross-sectional study, younger age and physical activity were associated with thicker cartilage thickness.[26] However, in our study, age and physical activity were not effective on cartilage thickness. This may be explained by the small sample size or by most patients being physically inactive.

Although this is the first study to evaluate cartilage thickness in FMF and its relationship with amyloidosis and disease activity, the most prominent limitation is the small sample size of patients with amyloidosis. In larger patient groups, amyloidosis and cartilage thickness can be evaluated more clearly.

Conclusion

Our study revealed that patients with FMF have decreased FCT compared with controls, and there is no significant relationship between the FCT and amyloidosis and disease activity.

Disclosures

Ethics Committee Approval: The study was approved by the Ethical Committee of Marmara University Medical School (09.2018.382) and was conducted in compliance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – H.H.G., D.E.G., S.A.K.; Design – H.H.G., H.S.B., M.T.D.; Supervision – M.T.D.; Materials – H.H.G., D.E.G., S.A.K., H.S.B.; Data collection – H.H.G., D.E.G., S.A.K., M.T.D.; Analysis – H.H.G., H.S.B.; Literature search – D.E.G., S.A.K.; Writing – H.H.G.; Critical review – H.H.G., D.E.G., S.A.K., H.S.B., M.T.D.

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