Acta Clin Croat 2023; 62:19-24

doi: 10.20471/acc.2023.62.01.03

Original Scientific Paper

ULTRASONOGRAPHIC EVALUATION OF FEMORAL CARTILAGE THICKNESS IN PARTICIPANTS WITH ASYMPTOMATIC HYPERURICEMIA: A CASE-CONTROL STUDY

İlker Fatih Sari[1], Fazıl Kulakli[1], Nurçe Çilesizoğlu Yavuz[1], İlker Ilhanli[2] and Canan Çelik Içen[1]

[1]Giresun University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Giresun, Turkey; [2]Ondokuz Mayıs University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Samsun, Turkey

SUMMARY – The aim was to evaluate the effect, if any, of asymptomatic hyperuricemia on distal femoral cartilage thickness through musculoskeletal ultrasonography. A total of 66 participants were evaluated in this prospective, controlled study, including 33 asymptomatic hyperuricemic patients who presented at our outpatient clinic between January and April 2020, and 33 normouricemic subjects matched for age, gender and body mass index. Participants with systemic diseases affecting uric acid level such as chronic renal failure, psoriasis, gout, etc., participants using drugs that can affect uric acid level, and those with knee complaints were excluded from the study. Cartilage thickness measurements were taken using musculoskeletal ultrasonography from the right medial condyle, right lateral condyle, right intercondylar area, left medial condyle, left lateral condyle and left intercondylar area. Distal femoral cartilage thickness was lower in all measurement areas in the asymptomatic hyperuricemia group than in the normouricemic group ($p<0.05$ all). No correlation was noted between uric acid levels and cartilage thickness in all measurement areas in either the asymptomatic hyperuricemic or normouricemic group ($p>0.05$ all). We think that distal femoral cartilages seem to be thinner in participants with asymptomatic hyperuricemia. Longitudinal studies are needed to determine whether asymptomatic hyperuricemia will lead to knee osteoarthritis in individuals, although we believe that people with asymptomatic hyperuricemia should be informed accordingly in order to prevent development of potential knee osteoarthritis.

Key words: *Asymptomatic hyperuricemia; Femoral cartilage; Osteoarthritis; Cartilage thickness; Ultrasound*

Introduction

Asymptomatic hyperuricemia refers to serum uric acid levels >6.5 mg/dL in women and >7 mg/dL in men without signs of crystal deposition disease[1]. It is believed that chronic exposure to high serum uric acid levels may trigger a low-level inflammatory process due to the accumulation of monosodium urate crystals without the development of gout[2], and due to hyperuricemia, these crystals may cause interleukin (IL)-1β production, resulting in cartilage damage[3].

Osteoarthritis (OA) is a chronic disease that is common worldwide, and that is characterized by loss of articular cartilage, especially in weight-bearing joints, and changes in subchondral bone. There are lo-

Correspondence to: *İlker Fatih Sarı, MD*, Giresun University Faculty of Medicine, Department of Physical Medicine and Rehabilitation, Giresun, Turkey
E-mail: ilker_fatihsari@hotmail.com

Received May 12, 2021, accepted April 12, 2022

cal (history of injury, malalignment, muscle weakness, etc.) and systemic (age, female gender, race, genetic susceptibility, inflammatory diseases, obesity, etc.) risk factors associated with OA[4], but besides these, researchers have also identified potential biological relationships among uric acid, gout and OA[5,6]. A previous study identified a relationship between asymptomatic hyperuricemia and radiological knee and symptomatic knee forms of OA[7].

Ultrasonographic (US) imaging, in addition to being inexpensive, easily applicable and appropriate for dynamic imaging, has been shown to be effective in evaluating distal cartilage structure of the femur, and previous studies have used US to measure distal femoral thickness in some clinical situations[8-12]. There have to date, however, been no studies evaluating distal femoral cartilage thickness through US measurement in patients with asymptomatic hyperuricemia.

In the present study, we hypothesized that distal femoral cartilage thickness may be decreased in individuals with asymptomatic hyperuricemia, and so we aimed to determine whether a relationship exists between uric acid levels and cartilage thickness measured using an easy approach such as US.

Patients and Methods

This case-control study included a total of 66 participants, comprising 33 (22 women and 11 men) patients who presented to the Physical Medicine and Rehabilitation outpatient clinic between January and April 2020 for any reason other than knee joint complaints, and that were found to have asymptomatic hyperuricemia, and 33 healthy normouricemic participants (20 women and 13 men) matched to the asymptomatic hyperuricemia group by age, gender and body mass index (BMI). G Power 3.1 software was used to calculate the required sample size. Based on a power of 80% and two tailed 5% level of significance, we calculated that the total sample size required was 56[8]. Ethical approval for the study was obtained from the Ethics Committee of the authors' affiliated institutions (decision number KAEK 103). All participants signed an informed consent form before participating in the study.

The clinical and demographic characteristics of the patients, which included age, weight, height, BMI, physical activity status, smoking and alcohol use, and systemic diseases were recorded. Regular physical activity was defined as moderate-intensity physical activity for at least 30 minutes at least 3 days a week[8]. After 12 hours of fasting, uric acid levels measured by spectrophotometry from venous blood were recorded, with the results expressed in mg/dL. A level of >6.5 mg/dL in women and >7 mg/dL in men was accepted as hyperuricemia.

Excluded from the study were any participants with conditions that may lead to elevated blood levels of uric acid, those with gout, knee joint complaints, previous knee surgery or a history of knee trauma, those with chronic renal failure, history of inflammatory disease, conditions such as serious organ disease, cancer, severe heart failure, chronic liver disease or hemophilia, psoriasis, and those using medications that could decrease or increase uric acid levels. Subjects with hyperechoic enhancement of the superficial margin of the hyaline cartilage (double contour sign) or intraarticular tophi in US evaluation were also excluded, as it can be a sign of gouty arthritis. In addition, detailed physical examination of the patients was performed, and participants with a limited knee range of motion, crepitation, quadriceps atrophy, and decreased patellar motion were excluded from the study, even though they did not have active complaints.

Ultrasonographic measurements were taken bilaterally using a linear probe (3-13 MHz MyLabSix; Esaote Biomedica, Italy) within 2 days of blood collection, by a blind investigator (author) with no knowledge of the patients' results. Distal femoral cartilage measurements were taken with the patient in supine position and the knees at maximum flexion (Fig. 1). The probe was placed axially on the upper edge of the patella, and cartilage

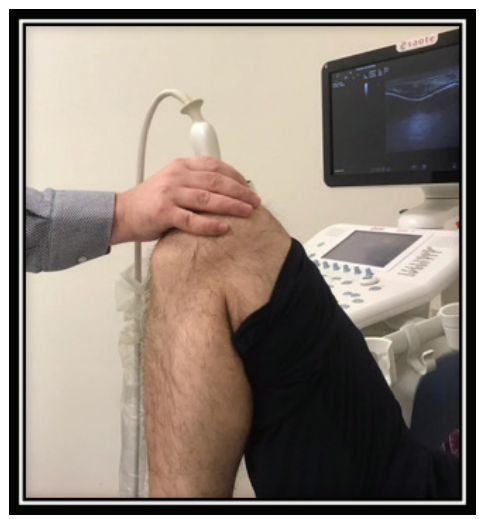

Fig 1. The patient and probe positioning during ultrasonographic measurements.

thickness measurements were taken from the right medial condyle, right lateral condyle, right intercondylar area, left medial condyle, left lateral condyle and left intercondylar area. Cartilage thickness was interpreted as the distance between the thin hyperechoic line at the synovial space/cartilage interface and the sharp hyperechoic line at the cartilage-bone interface[13] (Fig. 2).

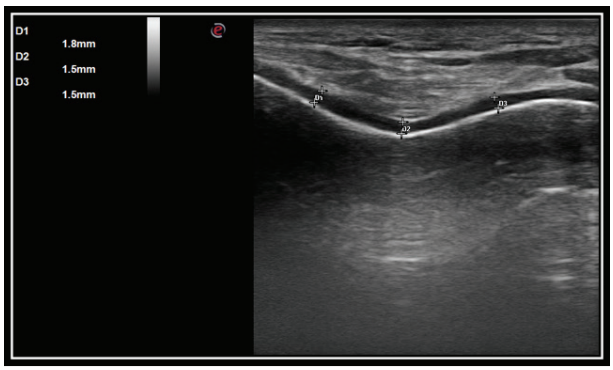

Fig 2. Ultrasonographic image (suprapatellar axial view) showing right femoral distal cartilage measurements (D1 right lateral condyle, D2 right intercondylar area, D3 right medial condyle).

Statistical analysis

Study data were uploaded into a computer and analyzed using IBM SPSS Statistics (Version 21.0. Armonk, NY: IBM Corp.). Data were expressed as mean ± standard deviation (SD) and percentages. Since the assumption of normality was met, an independent sample t-test as a parametric test was used to compare numerical data of the two groups (age, BMI, distal femoral cartilage thickness), while categorical data (gender, level of education, smoking, alcohol consumption, regular physical activity, systemic diseases) were compared using the χ^2-test or Fisher exact test. The correlation between uric acid levels and femoral cartilage thickness was assessed using Pearson's correlation test, since the assumption of normality was met. A p value of <0.05 was considered statistically significant.

Results

The study included 66 patients, i.e., 33 hyperuricemic patients and 33 normouricemic subjects, mean age 59.38±11.45 (60-91) years. There was no statistically significant difference according to age, gender, smoking, regular physical activity, and rates of hypertension and diabetes mellitus between the two groups (p>0.05 all) (Table 1).

As shown in Table 2, the values of distal femoral cartilage thickness measurement were statistically significantly lower in all measurement areas in the asymptomatic hyperuricemia group when compared to the control group (p<0.05 all).

There was no correlation between uric acid levels and distal femoral cartilage thickness in either the asymptomatic hyperuricemic or normouricemic group (p>0.05 all).

Discussion

The design and performance of the present study was based on the hypothesis that cartilage thickness values may be lower in subjects with asymptomatic hyperuricemia than in normouricemic individuals, that the distal femoral cartilage thickness is statistically thinner in patients with asymptomatic hyperuricemia than in normouricemic subjects; however, no correlation was established between uric acid levels and cartilage thickness in these groups. A remarkable feature of the present study is that it was the first to assess distal femoral cartilage thickness using the US method, which is inexpensive, easily applicable, and allows dynamic imaging in patients with asymptomatic hyperuricemia.

Hyperuricemia is a metabolic condition that is necessary for the development of gout as one of the more common forms of arthritis, while asymptomatic hyperuricemia refers to high blood levels of uric acid in the absence of gout and symptoms. The treatment of asymptomatic hyperuricemia is controversial. The chance of developing gout or urolithiasis in people with hyperuricemia is fairly low in clinical practice[14]. In the United States, the prevalence of hyperuricemia is 21.4%, while the prevalence of gout is 3.9%[15]. It is believed that there is an increased risk of hypertension, chronic kidney disease, cardiovascular disease and insulin resistance syndrome in chronic hyperuricemia without crystal deposition[14].

The relationship between gout and OA is well known. It is believed that monosodium urate crystals are likely to cause cartilage damage by increasing the levels of IL-1β[3], although it is not known exactly whether such a situation exists in asymptomatic hyperuricemia. Silent urate crystals have been identified in up to 30% of patients with asymptomatic hyperuricemia using advanced imaging methods, and may also cause predisposition to degenerative arthritis, leading to direct mechanical damage to the joint[2]. Wang *et al.* report a higher prevalence of both symptomatic and radiograph-

Table 1. Clinical characteristics of all studied subjects

		Asymptomatic hyperuricemia (N=33) Mean ± SD	Normouricemia (N=33) Mean ± SD	p-value
Age (years)		60.55±11.14	58.21±11.80	0.412
BMI (kg/m^2)		29.80±3.04	28.05±4.12	0.055
Serum urate (mg/dL)		7.28±0.74	4.81±0.93	<0.001
		n (%)	n (%)	
Sex:	Female	22 (66.7)	20 (60.6)	0.609
	Male	11 (33.3)	13 (39.4)	
Education:	No literacy	6 (18.2)	5 (15.2)	0.928
	Primary-secondary School	19 (57.6)	19 (57.6)	
	High school-university	8(24.2)	9 (27.3)	
Occupation:	Housewife	14(42.4)	14 (42.4)	0.891
	Retired	8 (24.2)	10 (30.3)	
	White colored	5 (15.2)	5 (15.2)	
	Blue colored	6 (18.2)	4 (12.1)	
Smoking:	Yes	7 (21.2)	10 (30.3)	0.398
	No	26 (78.8)	23 (59.7)	
Alcohol use:	Yes	1 (3.0)	1 (3.0)	1.000
	No	32 (97.0)	32 (97.0)	
Doing exercise:	Yes	5 (15.2)	2 (6.1)	0.427
	No	28 (84.8)	31 (93.9)	
Hypertension:	Yes	19 (57.6)	18 (54.5)	0.804
	No	14 (42.4)	15 (45.5)	
DM	Yes	8 (24.2)	4 (12.1)	0.202
	No	25 (75.8)	29 (87.9)	

BMI = body mass index; DM = diabetes mellitus; SD = standard deviation

ic knee OA in patients over the age of 60 years, in those with asymptomatic hyperuricemia, and in the non-obese. Based on this finding, it was concluded that high uric acid levels may be involved in the pathogenesis of OA, and may play a role in the course of more painful and/or more severe disease[7]. A retrospective study involving 4,685 patients established a positive correlation between elevated uric acid levels and the radiological appearance of osteophytes in women, but not in men[16], although it is not known whether the patients with hyperuricemia in this study had asymptomatic hyperuricemia. In a previous study involving 50 participants of a similar age, including 25 patients with involved gout and asymptomatic hyperuricemia, and a control group of 25 individuals, knee OA was detected in 68% of the gout patients, 52% of asymptomatic patients, and 28% of the

Table 2. Comparison of femoral cartilage thickness measurements (millimeter)

	Asymptomatic hyperuricemia (n=33) Mean ± SD	Normouricemia (n=33) Mean ± SD	p-value
RLC	1.69±0.40	1.99±0.36	0.002
RIA	1.83±0.50	2.36±0.50	<0.001
RMC	1.81±0.51	2.22±0.40	<0.001
LMC	1.81±0.54	2.12±0.40	0.009
LIA	1.87±0.58	2.22±0.49	0.011
LLC	1.72±0.48	1.98±0.38	0.017

RLC = right lateral condyle; RIA = right intercondylar area; RMC = right medial condyle; LMC =: left medial condyle; LIA = left intercondylar area; LLC = left lateral condyle

control group[6]. While the abovementioned studies were based on a diagnosis of radiographic and symptomatic knee OA rather than the thickness of femoral cartilage, it was not possible to evaluate radiographic knee OA in the present study due to the inclusion of patients without knee complaints. Considering that OA starts from the cartilage in the pathogenesis of the disease, and that cartilage thickness is affected even though it is not symptomatic, the distal femoral cartilage thickness was measured and found to be lower in the asymptomatic hyperuricemic group.

In the present study, no correlation was established between uric acid levels and cartilage thickness in the asymptomatic hyperuricemia or normouricemic patient groups. However, the cartilage thickness was found to be lower regardless of the uric acid level, when the uric acid level exceeded a certain value, as occurs in asymptomatic hyperuricemia. We believe that this may be attributable to the accumulation of monosodium urate crystals, which do not cause active inflammation, in the joints of individuals with asymptomatic hyperuricemia, causing cartilage damage and thus a decrease in cartilage thickness. Supporting this idea, a previous study identified a double counter image, which is indicative of accumulated monosodium urate crystals in joints, in six (25%) of 24 patients with asymptomatic hyperuricemia evaluated by US[17]. This finding supports the suggestion that asymptomatic hyperuricemia may cause crystal deposition in joints without any complaints.

The present study had some limitations. First, the uric acid levels were measured only once, although these levels may change over time. Second, the study also included patients without knee complaints and clinical findings in which no radiological imaging or functional assessment of the knee was performed. In addition, the joints of the participants other than the knee, such as the hip and hand, were not evaluated radiologically. Detailed physical examination of the patients was performed and the participants did not want to be exposed to x-ray from the joint without complaints. Therefore, radiological imaging was not performed. Accordingly, the extent to which the difference in cartilage thickness between the two groups affected functionality was not evaluated. Nonetheless, the findings of the present study should be considered significant and noteworthy.

Conclusion

According to this study, distal femoral cartilage is thinner in people with asymptomatic hyperuricemia. Future longitudinal studies may consider evaluating whether OA develops in these patients. We believe that patients with asymptomatic hyperuricemia should be considered at risk of the development of OA, and should be informed about the necessary protective measures to prevent its development.

References

1. Takir M, Kostek O, Ozkok A, Elcioglu OC, Bakan A, Erek A, *et al*. Lowering uric acid with allopurinol improves insulin resistance and systemic inflammation in asymptomatic hyperuricemia. J Investig Med. 2015;63(8):924-9. 10.1097/JIM.0000000000000242
2. Yip K, Cohen RE, Pillinger MH. Asymptomatic hyperuricemia: is it really asymptomatic? Curr Opin Rheumatol. 2020;32(1):71-9. 10.1097/BOR.0000000000000679
3. Martinon F, Pétrilli V, Mayor A, Tardivel A, Tschopp J. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;9;440(7081):237-41. 10.1038/nature04516.

4. Sharma L. Local and systemic risk factors for incidence and progression of osteoarthritis. In: Hochberg MC, Smolen JS, Gravallese EM, Weinblatt ME, Silman AJ, Weisman MH, editors. Rheumatology. Philadelphia: Elsevier; 2019. p. 1513-21.
5. Neogi T, Krasnokutsky S, Pillinger MH. Urate and osteoarthritis: evidence for a reciprocal relationship. Joint Bone Spine. 2019;86(5):576-82. 10.1016/j.jbspin.2018.11.002
6. Howard RG, Samuels J, Gyftopoulos S, Krasnokutsky S, Leung J, Swearingen CJ, *et al*. Presence of gout is associated with increased prevalence and severity of knee osteoarthritis among older men: results of a pilot study. J Clin Rheumatol. 2015;21(2):63-71. 10.1097/RHU.0000000000000217
7. Wang S, Pillinger MH, Krasnokutsky S, Barbour KE. The association between asymptomatic hyperuricemia and knee osteoarthritis: data from the third National Health and Nutrition Examination Survey. Osteoarthr Cartil. 2019;27(9):1301-8. 10.1016/j.joca.2019.05.013
8. Malas FU, Kara M, Aktekin L, Ersöz M, Ozçakar L. Does vitamin D affect femoral cartilage thickness? An ultrasonographic study. Clin Rheumatol. 2014;33(9):1331-4. 10.1007/s10067-013-2432-y
9. Akkaya S, Akkaya N, Ozcakar L, Kılıç A, Sahin F, Atalay NS, *et al*. Ultrasonographic evaluation of the femoral cartilage thickness after unilateral arthroscopic partial meniscectomy. Knee Surg Sports Traumatol Arthrosc. 2013;21(5):1104-10. 10.1007/s00167-012-2081-8
10. Öztürk GT, Malas FÜ, Yildizgören MT, Baki AE, İnal EE, Batmaz İ, *et al*. Ultrasonographic assessment of the femoral cartilage thickness in patients with pes planus: a multicenter study by TURK-MUSCULUS. Am J Phys Med Rehabil. 2015;94(7):568-72. 10.1097/PHM.0000000000000214
11. Batmaz İ, Sarıyıldız MA, Çilesizoğlu N, Karkucak M, Yazmalar L, Serdar ÖF, *et al*. Ultrasonographic evaluation of femoral cartilage thickness in patients with psoriatic arthritis. J Back Musculoskelet Rehabil. 2016;29(4):703-8. 10.3233/BMR-160672
12. Kara M, Okur A, Serin Hİ. Ultrasonographic evaluation of femoral cartilage thickness in patients with polycystic ovary syndrome. Acta Clin Croat. 2019;58(1):103-6. 10.20471/acc.2019.58.01.13
13. Özçakar L, Tunç H, Öken Ö, Ünlü Z, Durmuş B, Baysal Ö, *et al*. Femoral cartilage thickness measurements in healthy individuals: learning, practicing and publishing with TURK-MUSCULUS. J Back Musculoskelet Rehabil. 2014;27(2):117-24. 10.3233/BMR-130441
14. Paul BJ, Anoopkumar K, Krishnan V. Asymptomatic hyperuricemia: is it time to intervene? Clin Rheumatol. 2017;36(12):2637-44. 10.1007/s10067-017-3851-y
15. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. Arthritis Rheum. 2011 Oct;63(10):3136-41. 10.1002/art.30520
16. Ding X, Zeng C, Wei J, Li H, Yang T, Zhang Y, *et al*. The associations of serum uric acid level and hyperuricemia with knee osteoarthritis. Rheumatol Int. 2016;36(4):567-73. 10.1007/s00296-015-3418-7
17. Bhadu D, Das SK, Wakhlu A, Dhakad U. Articular cartilage of knee and first MTP joint are the preferred sites to find double contour sign as an evidence of urate crystal deposition in asymptomatic hyperuricemic individuals. Acta Reumatol Port. 2018;43(4):264-8. PubMed PMID: 30641534.

Sažetak

ULTRAZVUČNA PROCJENA DEBLJINE FEMORALNE HRSKAVICE U OSOBA S ASIMPTOMATSKOM HIPERURICEMIJOM: ISTRAŽIVANJE S KONTROLNOM SKUPINOM

I. Fatih Sari, F. Kulakli, N. Çilesizoğlu Yavuz, I. Ilhanli i *C. Çelik Içen*

Cilj istraživanja bio je procijeniti učinak, ako postoji, asimptomatske hiperuricemije na debljinu distalne femoralne hrskavice pomoću mišićno-koštanog ultrazvuka. U ovom prospektivnom kontroliranom istraživanju sudjelovalo je ukupno 66 osoba, uključujući 33 bolesnika s asimptomatskom hiperuricemijom koji su došli u našu ambulantu između siječnja i travnja 2020. godine i 33 osobe s normouricemijom podjednake dobi, spola i indeksa tjelesne mase. Isključene su bile osobe sa sistemskim bolestima koje utječu na razinu mokraćne kiseline, kao što su kronično bubrežno zatajenje, psorijaza, giht itd., osobe koje uzimaju lijekove koji mogu utjecati na razinu mokraćne kiseline te oni s tegobama u koljenu. Debljina hrskavice mjerena je pomoću mišićno-koštanog ultrazvuka u desnom medijalnom kondilu, desnom lateralnom kondilu, desnom interkondilarnom području, lijevom medijalnom kondilu i lijevom interkondilarnom području. Debljina distalne femoralne hrskavice bila je niža na svim mjernim mjestima u skupini osoba s asimptomatskom hiperuricemijom u usporedbi sa skupinom osoba s normouricemijom ($p<0,05$ sve). Nije zabilježena korelacija između razina mokraćne kiseline i debljine hrskavice ni na jednom mjernom mjestu niti u skupini s asimptomatskom hiperuricemijom niti u skupini s normouricemijom ($p<0,05$ sve). Smatramo da su distalne femoralne hrskavice tanje u osoba s s asimptomatskom hiperuricemijom. Potrebna su longitudinalna istraživanja kako bi se utvrdilo hoće li asimptomatska hiperuricemija dovesti do osteoartritisa koljena kod tih osoba, ali vjerujemo da osobe s asimptomatskom hiperuricemijom treba primjereno obavijestiti kako bi se spriječio razvoj mogućeg osteoartritisa koljena.

Ključne riječi: *Asimptomatska hiperuricemija; Femoralna hrskavica; Osteoartritis; Debljina hrskavice; Ultrazvuk*