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Cartilage thickness at the posterior aspect of the medial condyle is thicker in medial femorotibial osteoarthritic knees compared to non-osteoarthritic knees: a tri-dimensional quantitative analysis

Student

Bergqvist Louise

Tutor

Dr Omoumi Patrick

Dpt of Radiodiagnostic and Interventional Radiology

Co-tutor

Pr Dr Meuli Reto

Dpt of Radiodiagnostic and Interventional Radiology

Expert

Pr Dr Jolles-Haeberli Brigitte

Dpt of Musculoskeletal Medicine (DAL)

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Abstract

Objective

1. To test, through tri-dimensional analysis, whether cartilage thickness at the posterior aspect of the medial and lateral condyles differs in medial femorotibial OA knees compared to matched non-OA knees.
2. To determine the locations of thickest cartilage at posterior aspects of femoral condyles.

Design

Two groups of non-OA (n=40) and severe medial femorotibial OA (n=40) patients of over 50 years of age, matched for gender, age and bone morphometric parameters, with radiographs and CT arthrograms of the knee, were randomly selected retrospectively. CT arthrograms were segmented to measure the mean cartilage thickness, the maximal cartilage thickness and the location of maximal cartilage thickness in a region of interest at the posterior aspect of the condyles.

Results

For the medial condyle, mean and maximum cartilage thicknesses were statistically significantly higher in OA knees compared to non-OA knees (1.66 vs. 1.46mm, $p=0.012$ and 2.53 vs. 2.13mm, $p=0.0006$ respectively). The thickest cartilage was located in the half most medial aspect of the medial condyle for both groups. For the lateral condyle, no statistically significant difference between non-OA and OA knees was found ($p\geq 0.16$).

Conclusions

Cartilage at the posterior aspect of the medial condyle, but not the lateral condyle is statistically significantly thicker in OA knees compared to matched non-OA knees. The thickest cartilage was located in the half most medial aspect of the posterior medial condyle. These results will serve as the basis for future research to determine whether the thicker cartilage corresponds to cartilage hypertrophy due to reparative processes in reaction to OA.

Keywords

Osteoarthritis; cartilage morphology; quantitative; tri-dimensional; CT arthrography

I. Introduction

Osteoarthritis (OA) is a chronic disease of the joint that clinically presents with symptoms such as pain, stiffness and loss of function of a joint. It may develop in any joint, but is most commonly found in knees, hips, hands, feet and spinal vertebrae joints.

i. Prevalence of OA:

OA is common. In 2005, nearly 27 million adults in the US had some form of OA(1). In 1987, the Framingham Osteoarthritis Study found that the age-standardized prevalence for radiographic knee OA was 19% among adults age ≥ 45 . The Johnston County Osteoarthritis Project in 2007 accounted for about 28% African Americans and Caucasians age ≥ 45 with radiographic knee OA (1-3). However, the prevalence of symptomatic knee OA which is defined by radiographic OA **with** pain, aching or stiffness in the joint, is lower: around 7 % of adults age ≥ 45 in the Framingham Study had symptomatic knee OA; in the Johnston County Project it was more, 17% of adults age ≥ 45 . Furthermore, knee OA prevalence is rising: the Framingham Study showed that over the past 20 years prevalence of symptomatic knee OA has risen by 4,1% and 6% in women and men respectively(3).

ii. Burden of OA: economic burden and burden of disease

Due to its high prevalence, OA represents a high economical and societal burden. OA costs arise from pain-relieving medication, physician visits, hospitalizations and surgery but also from indirect costs such as lost wages, lost productivity and home care for patients physically impaired by OA.

In 1997, a research including data from 5 industrialized countries on the economic costs of musculoskeletal disorders, among which OA was the most common, showed that the costs of OA accounted for 1% to 2.5 % of the gross national product of these countries (4).

OA also significantly reduces quality of life. Of the 291 conditions in the Global Burden of Disease 2010 study, hip and knee OA ranked 11th highest in terms of YLDs. In terms of DALYs, hip and knee OA ranked 38th below cardiovascular and circulatory disease and epilepsy. In comparison, in 1990, it ranked 49th (5).

iii. Risk factors for OA

OA has a multifactorial etiology with both environmental and genetic risk factors. Risk factors for OA are classically divided into individual systemic factors, and joint-related local factors. Individual factors are age, sex, ethnicity and genetics and also obesity, diet and bone metabolism. Local risk factors have an impact on one specific joint. They include muscle strength, physical activity, joint injury, joint malalignment such as a varus or valgus knee and leg length inequality (3, 6).

Risk factors for the onset of OA are not necessarily the same as those fueling the progression of joint damage. Joint injury, joint malalignment and synovitis or effusion are risk factors for the progression of OA (7). Bone density is another one; indeed some research show that osteoporosis might protect to a certain extent from getting osteoarthritis, but that it increases the chances of progression of joint damage if one already has OA (8).

Most of these risk factors can in fact be acted upon. Therefore, prevention of obesity and injuries for instance is an important tool in order to diminish the number of patients who ultimately will need treatment for OA (8).

iv. Treatment of OA

There is no existing cure for osteoarthritis. The goal of OA treatment is reduction of pain and maintenance or even improvement of physical function, as well as preventing progression of the disease; all this in order to preserve quality of life.

There are three treatment modalities: non-pharmacological, pharmacological and surgical. Non-pharmacological treatment strategies include weight reduction, exercise but also pacing of activities, and joint protection (9). Pharmacological treatment is mainly pain-relieving medication such as NSAIDs and paracetamol. Strong opioids are prescribed to patients not responding to NSAIDs. Glucosamine sulphate, chondroitin sulphate and hyaluronic acid are symptomatic slow-acting drugs used to treat OA although their effectiveness is still debated. Intra-articular injections of corticosteroids have proven to efficiently treat acute inflammatory exacerbations (9, 10). For patients with severe pain and functional impairment, and not responding to conservative care, the last treatment option is surgery. It includes interventions such as osteotomy, joint fusion, joint distraction and joint replacement (9, 11).

As researchers acquire a better understanding of the pathophysiological mechanisms of OA, new therapeutic agents acting on recently discovered biomolecular pathways are tested.

These new drugs are called disease-modifying drugs. Other innovative techniques are regenerative therapies such as autologous chondrocyte cell or mesenchymal stem cell implantation/transplantation (12).

v. Etiopathogenesis of OA

One central feature of OA is the degeneration of joint cartilage. But OA is not as much a degenerative joint disease as a failed response to cope with an excessive mechanical stress on the joint (13). Chondrocytes act as mechano-sensors and chemo-sensors and respond to variations in the environment by altering their metabolism (11). The balance between catabolic and anabolic activities ultimately ends up favoring catabolism. Cartilage matrix breakdown products trigger the release of destructive proteolytic enzymes from synovial cells and macrophages thus fueling the catabolic process (11). Catabolic products activate inflammatory pathways; therefore, low-grade synovitis can be found in OA joints (14). Inflammatory mediators in their turn drive catabolic pathways, inhibit matrix synthesis and promote cell death, creating a vicious circle of cartilage degradation and inflammation (11, 15).

Furthermore, OA does not only involve cartilage but the joint in its entirety; for instance, OA is also associated with increased bone turnover and bone proliferative changes (8, 14, 16).

vi. Role of imaging in OA

Imaging is used for two main purposes in OA: firstly, as a diagnostic means. By detecting and quantifying cartilage tissue loss, imaging serves as a biomarker of the disease. This is mainly done using radiography. Secondly, new methods and technical improvements in imaging such as MRI and injected MR- and CT-arthrography have allowed to gain a better understanding of the pathophysiological processes in osteoarthritic joints.

Radiography is the gold standard for image-based diagnosis of OA. Radiographic signs such as osteophytes, subchondral cysts, sclerosis and joint space narrowing are detected and used in the Kellgren-Lawrence classification system, the reference for grading OA severity (17). Despite being a cheap and simple diagnostic means, radiography has its shortcomings: it lacks sensitivity and specificity in detecting OA-damage to articular tissue and its sensitivity to longitudinal change is also poor (18).

MRI offers a more global view of the joint pathology thanks to its ability to assess structures such as cartilage, ligaments, menisci, synovium, capsular structures, fluid collections and

bone marrow. Pre-radiographic pathologic changes can be detected, and with computational MRI biochemical features of joint tissues can be explored. Within research, MRI is the most used modality of imaging and has directly participated in shifting the view of OA from a disease of the cartilage to a disease of the joint as a whole (18, 19).

In MR-arthrography and CT-arthrography contrast agents are injected into the joint space. These are more invasive techniques but the high spatial resolution and multiplanar acquisition modality allow a better detection of cartilage lesions (18, 20, 21). With the highest spatial resolution and highest contrast between bone and cartilage, CT-arthrography is the most accurate technique (18, 22, 23).

vii. Cartilage loss and preserved cartilage in OA

Cartilage thinning is a central hallmark in knee OA. Quantifying cartilage thickness and its evolution is a compelling factor in the diagnostic procedure, the identification of risk factors for structural disease progression and the assessment of the clinical impact of disease modifying drugs (24).

Recent MRI studies measuring cartilage thickness account for important temporal and spatial variations in knee cartilage thickness. Indeed, OA knees can temporarily undergo cartilage thickening in the early stages of the disease. It has been shown that in knees with Kellgren/Lawrence grade 2 (KLG 2) but not KLG 3, cartilage thickness is increased compared to knees with KLG 0; it is probably due to swelling induced by water increase when the collagen matrix ruptures (25, 26). Also changes in cartilage thickness vary greatly throughout the total cartilage surface (25, 27-31). For instance, the rate of cartilage thinning is higher in central, weight-bearing subregions (29).

Interestingly, a recent research using CT-arthrography found that cartilage thickness at the non-weight-bearing posterior aspect of the medial condyle of the knee was increased in OA knees (KLG ≥ 2) compared to non-OA knees (28). This is worth some attention since it may point to possible reparative properties of cartilage, challenging the classical definition of OA being a one-way phenomenon towards destruction of cartilage and cartilage tissue loss.

However, in this previous study showing thicker cartilage in OA knees, cartilage thickness was manually measured at a single focal point, on the midsagittal plane of each condyle. Since cartilage thickness is known to vary throughout the articular surface, this finding of thicker cartilage could be due to a methodological bias. Furthermore, determining the location of thickest cartilage in these posterior areas could enhance our understanding of

morphological differences related to OA and provide a basis for future analyses, including histobiological assays.

Therefore, in the current study we aimed:

1. To test, through tri-dimensional analysis, whether cartilage thickness at the posterior aspect of the medial and lateral condyles differs in medial femorotibial OA knees compared to matched non-OA knees.
2. To compare the location of the thickest cartilage between non-OA and OA knees within the posterior aspect of the condyles showing differences in cartilage thickness.

II. Methodology

i. Patient population

From a set of 607 patients with knee radiographs and CT arthrograms performed over a one-year period for the diagnostic work-up of knee pain, we retrospectively and randomly selected two groups of non-OA (n=40) and severe medial femorotibial OA (n=40) patients of more than 50 years of age, matched for gender (sex ratio males/females=13/27 vs. 19/21 respectively, $p=0.82$), age (61.5 (95%CI [59.6-63.5]) vs. 64.2 (95%CI [60.8-67.6]) years respectively, $p=0.17$) and bone morphometric parameters (biepicondylar femoral diameter = 8.0 (95%CI [7.8-8.2]) vs. 8.1 (95%CI [7.9-8.3]) cm respectively, $p=0.34$; mediolateral tibial diameter = 7.2 (95%CI [7.0-7.4]) vs. 7.3 (95%CI [7.2-7.5]) cm respectively, $p=0.33$). Any knees presenting imaging signs of the following conditions were excluded from the initial set of examinations: previous bone fractures, previous knee surgery (including knee replacement procedures, ligamentoplasty, cartilage repair procedures) or poor image quality. The sample size was determined based on previously published data (28). Due to limited MR capacities at our institution, CTA is commonly used for diagnostic work-up of clinical suspicion of menisco-cartilaginous pathology.

ii. Imaging protocol

Radiography

Knee radiographs were obtained immediately before the arthrographic examinations and included lateral and postero-anterior (PA) weight-bearing views, following the Lyon-Schuss protocol (32).

CT arthrography

10 mL of ionic contrast material (meglumine ioxaglate and sodium ioxaglate, Hexabrix 320 (320 mg of iodine per millimeter); Guerbet, Aulnay-sous-bois, France) were injected into the knee joint with fluoroscopic guidance using a lateral approach. The knee was then actively mobilized to allow diffusion of the contrast material in the joint cavity.

CT arthrograms were performed on a 40-detector row CT scanner (Somatom Definition AS; Siemens Healthcare, Forchheim, Germany). Patients were positioned supine, with extension of the knee. Previously described acquisition parameters were optimized for the knee joint: tube voltage 120 kVp; reference tube current-time product 350 mAs with the application of a dose modulation protocol (Care Dose 4D; Siemens Healthcare); detector configuration, 16x0.6 mm; collimation 0.6 mm; pitch 0.85; gantry rotation time 1s. The following image reconstruction parameters were used: field-of-view (FOV) 15x15 cm; matrix 512²; section thickness/increment 0.6/0.3 mm; bone convolution kernel (U70u).

All acquired data were systematically archived on a picture archiving and communication system (PACS) workstation (Carestream Client version 13; Carestream Health, Rochester, NY, USA).

iii. Image analysis

Radiographs

One fellowship-trained radiologist with 4 years of experience in musculoskeletal radiology retrospectively graded the femorotibial joints on the PA radiographs according to the Kellgren/Lawrence scale of radiographic OA. The medial, lateral and patellofemoral compartments were graded separately and the final K/L grade of the knee was defined as the worse grade of all three compartments. OA knees were defined by a K/L grade ≥ 2 in any compartment and non-OA knees by K/L grade < 2 in all compartments (33). The reader was blinded to CTA findings while analyzing the radiographs.

CT arthrograms

Three untrained readers analyzed the CT arthrograms. They were blinded to radiographic findings but not to CT signs of OA.

iv. Imaging post-processing

The CT images were segmented semi-manually to reconstruct tri-dimensional mesh models of the femoral bones and cartilages (34). Anatomically-standardized cartilage thickness maps were then calculated based on the distance between the bone and cartilage models (34, 35). Two regions of interest (ROI) corresponding to the posterior aspect of each condyle were identified in each thickness map, as indicated in Figure 1, and the mean cartilage thickness, the maximal cartilage thickness and the location of the point of maximal cartilage thickness were determined for each ROI (35). The ROIs were defined independently for each condyle as the areas of the thickness maps passed the most posterior point of each condyle (Figure 1). CT post-processing was done using a custom-designed software (TiProScope, Lausanne, Switzerland).

III. Statistical analysis

The chi-square test was used to compare the distribution of males and females between non-OA and OA knees. For continuous variables, the one-sample Kolmogorov-Smirnov test was used to test whether data samples were normally distributed. A Student's t-test for independent samples was performed to test for a difference between continuous variables when the distribution was normal, and a Mann-Whitney test when the sample data were not normally distributed. All statistical analyses were performed using Matlab (MATLAB Release 2014b, The MathWorks, Inc., Natick, Massachusetts, United States) and an alpha-level of 5% was considered for all tests.

IV. Results

Table 1 shows the mean cartilage thickness and the maximum cartilage thickness at the posterior aspect of the medial and lateral condyles in OA and non-OA knees. There is a statistically significant difference between OA and non-OA knees at the posterior aspect of the medial condyle, with higher mean and maximal cartilage thickness in OA knees compared to non-OA knees ($p=0.012$ and $p=0.0006$ respectively). This significant difference is not found in the posterior aspect of the lateral condyle ($p=0.27$ and $p=0.16$).

	Mean cartilage thickness			Maximum cartilage thickness		
	Non-OA	OA	P-value	Non-OA	OA	P-value
Medial	1.46 (0.3)	1.66 (0.38)	0.012	2.13 (0.41)	2.53 (0.57)	0.0006
Lateral	1.26 (0.31)	1.34 (0.34)	0.27	1.99 (0.49)	2.16 (0.54)	0.16

Table 1. Mean cartilage thickness and maximum cartilage thickness at the posterior aspect of the medial and lateral condyles in non-OA and OA knees. Data are mean (standard deviation) cartilage thicknesses for the 40 knees per group, expressed in mm. Significant differences are indicated in red.

Figure 1 shows the points of thickest cartilage in the predefined posterior ROI. The points of thickest cartilage were located in the medial aspect of the posterior medial condyle with no statistical difference between OA and non-OA knees.

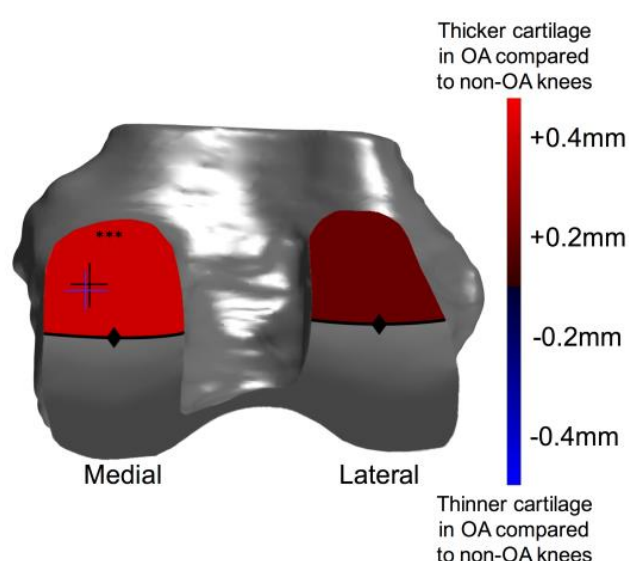


Figure 1 Illustration of the regions of interest (ROI) at the posterior aspect of the medial and lateral femoral condyles. These ROI of subchondral bone passed the most posterior point of each condyle (black diamonds) were determined on the tri-dimensional anatomically-standardized model, and all morphometric analyses in this study were performed in these ROI. The ROI are color-coded according to the differences in mean cartilage thickness between the non-OA and OA knees (*: $p<0.05$; **: $p<0.01$; ***: $p<0.001$). The location of the points of thickest cartilage for the medial condyle is also represented using crosses indicating the mean and standard deviation of the locations of thickest cartilage (black cross: non-OA knees; blue cross: OA knees). The femur in this figure corresponds to the average femur obtained after anatomical-standardization.

V. Discussion

This study focuses on the posterior aspect of the lateral and medial condyles of the knee. In our results, we find that in the medial condyle, mean as well as maximal cartilage thickness were statistically significantly higher in the severe femorotibial OA population compared to the non-OA population. This confirms tri-dimensionally what has been demonstrated in previous research in a bi-dimensional fashion (28). Furthermore, the location of the point of thickest cartilage is in the medial half of the medial condyle for both OA and non-OA knees.

These findings contradict the widely accepted theory that OA is a degenerative disease where joint cartilage thickness diminishes throughout its course. One explanation is that most studies up to now have focused on cartilage thickness in weight-bearing areas of the knees and not so much on non-weight bearing areas such as the posterior aspects of knee condyles (25, 27-31).

Further work is needed in order to understand the mechanisms underlying cartilage thickening in non weight-bearing cartilage areas. Previous studies have found cartilage swelling in early stages of knee OA (25, 26, 36, 37), however in our study all knees of the OA sample population were at an advanced stage of OA thus making this explanation less likely. Another hypothesis is that an anabolic state is triggered in OA knees as part of the disease process with mediators stimulating cartilage growth; however the pro-anabolic effect of OA would not be found in weight-bearing areas where mechanical destruction still exceeds cartilage growth, but only in non-weight-bearing areas such as the posterior aspect of the condyles where mechanical tear practically only occurs in a squatting position. Further studies are needed in order to find potential mediators responsible for or active in the triggering of this pro-anabolic state. Isolating those mediators would open the way to novel, potentially cartilage-regenerating, therapies.

The mean and maximal cartilage thickness is higher at the posterior aspect of the medial femoral condyle but not of the lateral femoral condyle. This can have a certain number of explanations. First the potentially pro-anabolic state generated by OA with mediators stimulating cartilage growth might be a strictly local process not extending to the whole joint. And the knees in the OA group were selected for OA in the medial compartment of the knee regardless of whether the lateral compartment had radiologic signs of OA or not. Previous studies show that cartilage in the lateral compartment of the knee becomes thinner in OA knees with KLG $\geq$ 2 (28). This might be due to the fact that the lateral and medial compartments of the knee are not under the same type of wearing process. The posterior

aspect of the lateral condyle more exposed to mechanical tears (38). The cartilage in knees with lateral compartment OA might also thicken due to a pro-anabolic state triggered by OA but it would be balanced or outbalanced by the mechanical tearing processes at work in that specific region of the knee.

In the second part of this research we also defined the points of thickest cartilage for both patient groups. They are located in the medial part of the posterior aspect of the medial condyle for both the OA and the non-OA group. This provides a specific target area to study the impact of novel therapeutic means for OA.

There are several limitations to this study. First, due to its retrospective nature, we could not monitor all inter-personal variables potentially influencing cartilage thickness in the knee. Our two populations were matched for age, sex and size of the bones, features that have been previously described as correlating with cartilage volume (38-42), but not for instance for testosterone levels in the blood which has also been described as having an impact on cartilage volume (41). Second, the state of one patient's cartilage was taken at one point in time, however a longitudinal follow-up would be necessary in order to prove that cartilage does indeed thicken with time. Third, the definition of OA in this study was a radiological one, results may be different if a clinical definition of OA was used; however since the radiological definition of OA does not take into account cartilage at the posterior aspect of the condyles, it avoids selection bias.

In conclusion, this study showed in a tri-dimensional fashion that cartilage at the posterior aspect of the medial femoral condyle of the knee is thicker in OA knees than in non-OA knees. Furthermore, the thickest point of cartilage is located in the medial half of the posterior aspect of the medial condyle of the knee.

VI. References

1. Lawrence RC, Felson DT, Helmick CG, Arnold LM, Choi H, Deyo RA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part II. Arthritis and rheumatism. 2008;58(1):26-35.
2. Litwic A, Edwards MH, Dennison EM, Cooper C. Epidemiology and burden of osteoarthritis. Br Med Bull. 2013;105:185-99.
3. Neogi T, Zhang Y. Epidemiology of osteoarthritis. Rheum Dis Clin North Am. 2013;39(1):1-19.
4. Bitton R. The economic burden of osteoarthritis. Am J Manag Care. 2009;15(8 Suppl):S230-5.
5. Cross M, Smith E, Hoy D, Nolte S, Ackerman I, Fransen M, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. Annals of the rheumatic diseases. 2014;73(7):1323-30.
6. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. Best Pract Res Clin Rheumatol. 2014;28(1):5-15.
7. Bruyere O, Cooper C, Arden N, Branco J, Brandi ML, Herrero-Beaumont G, et al. Can we identify patients with high risk of osteoarthritis progression who will respond to treatment? A focus on epidemiology and phenotype of osteoarthritis. Drugs Aging. 2015;32(3):179-87.
8. Dieppe PA, Lohmander LS. Pathogenesis and management of pain in osteoarthritis. Lancet. 2005;365(9463):965-73.
9. Bijlsma JW, Berenbaum F, Lafeber FP. Osteoarthritis: an update with relevance for clinical practice. Lancet. 2011;377(9783):2115-26.
10. Yu SP, Hunter DJ. Managing osteoarthritis. Aust Prescr. 2015;38(4):115-9.
11. Abramson SB, Attur M. Developments in the scientific understanding of osteoarthritis. Arthritis Res Ther. 2009;11(3):227.
12. Zhang W, Ouyang H, Dass CR, Xu J. Current research on pharmacologic and regenerative therapies for osteoarthritis. Bone Res. 2016;4:15040.
13. Brandt KD, Dieppe P, Radin EL. Etiopathogenesis of osteoarthritis. Rheum Dis Clin North Am. 2008;34(3):531-59.
14. Loeser RF, Goldring SR, Scanzello CR, Goldring MB. Osteoarthritis: a disease of the joint as an organ. Arthritis and rheumatism. 2012;64(6):1697-707.
15. Sellam J, Berenbaum F. The role of synovitis in pathophysiology and clinical symptoms of osteoarthritis. Nat Rev Rheumatol. 2010;6(11):625-35.
16. Teichtahl AJ, Wluka AE, Wijethilake P, Wang Y, Ghasem-Zadeh A, Cicuttini FM. Wolff's law in action: a mechanism for early knee osteoarthritis. Arthritis Res Ther. 2015;17:207.

17. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthritis. *Annals of the rheumatic diseases*. 1957;16(4):494-502.
18. Hayashi D, Roemer FW, Guermazi A. Imaging for osteoarthritis. *Ann Phys Rehabil Med*. 2016;59(3):161-9.
19. Roemer FW, Crema MD, Trattnig S, Guermazi A. Advances in imaging of osteoarthritis and cartilage. *Radiology*. 2011;260(2):332-54.
20. Wyler A, Bousson V, Bergot C, Polivka M, Leveque E, Vicaud E, et al. Comparison of MR-arthrography and CT-arthrography in hyaline cartilage-thickness measurement in radiographically normal cadaver hips with anatomy as gold standard. *Osteoarthritis and cartilage*. 2009;17(1):19-25.
21. Waldt S, Bruegel M, Ganter K, Kuhn V, Link TM, Rummeny EJ, et al. Comparison of multislice CT arthrography and MR arthrography for the detection of articular cartilage lesions of the elbow. *Eur Radiol*. 2005;15(4):784-91.
22. Schmid MR, Pfirrmann CW, Hodler J, Vienne P, Zanetti M. Cartilage lesions in the ankle joint: comparison of MR arthrography and CT arthrography. *Skeletal Radiol*. 2003;32(5):259-65.
23. Omoumi P, Rubini A, Dubuc JE, Vande Berg BC, Lecouvet FE. Diagnostic performance of CT-arthrography and 1.5T MR-arthrography for the assessment of glenohumeral joint cartilage: a comparative study with arthroscopic correlation. *Eur Radiol*. 2015;25(4):961-9.
24. Eckstein F, Wirth W. Quantitative cartilage imaging in knee osteoarthritis. *Arthritis*. 2011;2011:475684.
25. Buck RJ, Wirth W, Dreher D, Nevitt M, Eckstein F. Frequency and spatial distribution of cartilage thickness change in knee osteoarthritis and its relation to clinical and radiographic covariates - data from the osteoarthritis initiative. *Osteoarthritis and cartilage*. 2013;21(1):102-9.
26. Hellio Le Graverand MP, Buck RJ, Wyman BT, Vignon E, Mazzuca SA, Brandt KD, et al. Subregional femorotibial cartilage morphology in women--comparison between healthy controls and participants with different grades of radiographic knee osteoarthritis. *Osteoarthritis and cartilage*. 2009;17(9):1177-85.
27. Omoumi P, Michoux N, Thienpont E, Roemer FW, Vande Berg BC. Anatomical distribution of areas of preserved cartilage in advanced femorotibial osteoarthritis using CT arthrography (Part 1). *Osteoarthritis and cartilage*. 2015;23(1):83-7.
28. Omoumi P, Michoux N, Roemer FW, Thienpont E, Vande Berg BC. Cartilage thickness at the posterior medial femoral condyle is increased in femorotibial knee osteoarthritis: a cross-sectional CT arthrography study (Part 2). *Osteoarthritis and cartilage*. 2015;23(2):224-31.
29. Wirth W, Hellio Le Graverand MP, Wyman BT, Maschek S, Hudelmaier M, Hitzl W, et al. Regional analysis of femorotibial cartilage loss in a subsample from the Osteoarthritis Initiative progression subcohort. *Osteoarthritis and cartilage*. 2009;17(3):291-7.

30. Wirth W, Benichou O, Kwok CK, Guermazi A, Hunter D, Putz R, et al. Spatial patterns of cartilage loss in the medial femoral condyle in osteoarthritic knees: data from the Osteoarthritis Initiative. *Magn Reson Med*. 2010;63(3):574-81.
31. Jorgensen DR, Lillholm M, Genant HK, Dam EB. On Subregional Analysis of Cartilage Loss from Knee MRI. *Cartilage*. 2013;4(2):121-30.
32. Guermazi A, Burstein D, Conaghan P, Eckstein F, Hellio Le Graverand-Gastineau MP, Keen H, et al. Imaging in osteoarthritis. *Rheum Dis Clin North Am*. 2008;34(3):645-87.
33. Felson DT, McAlindon TE, Anderson JJ, Naimark A, Weissman BW, Aliabadi P, et al. Defining radiographic osteoarthritis for the whole knee. *Osteoarthritis and cartilage*. 1997;5(4):241-50.
34. Koo S, Gold GE, Andriacchi TP. Considerations in measuring cartilage thickness using MRI: factors influencing reproducibility and accuracy. *Osteoarthritis and cartilage*. 2005;13(9):782-9.
35. Favre J, Scanlan SF, Erhart-Hledik JC, Blazek K, Andriacchi TP. Patterns of femoral cartilage thickness are different in asymptomatic and osteoarthritic knees and can be used to detect disease-related differences between samples. *Journal of biomechanical engineering*. 2013;135(10):101002-10.
36. Calvo E, Palacios I, Delgado E, Ruiz-Cabello J, Hernandez P, Sanchez-Pernaute O, et al. High-resolution MRI detects cartilage swelling at the early stages of experimental osteoarthritis. *Osteoarthritis and cartilage*. 2001;9(5):463-72.
37. Hunter DJ, Niu JB, Zhang Y, LaValley M, McLennan CE, Hudelmaier M, et al. Premorbid knee osteoarthritis is not characterised by diffuse thinness: the Framingham Osteoarthritis Study. *Annals of the rheumatic diseases*. 2008;67(11):1545-9.
38. Ogino S, Huang T, Watanabe A, Iranpour-Boroujeni T, Yoshioka H. Magnetic resonance imaging of articular cartilage abnormalities of the far posterior femoral condyle of the knee. *Acta radiologica*. 2010;51(1):52-7.
39. Eckstein F, Winzheimer M, Westhoff J, Schnier M, Haubner M, Englmeier KH, et al. Quantitative relationships of normal cartilage volumes of the human knee joint--assessment by magnetic resonance imaging. *Anatomy and embryology*. 1998;197(5):383-90.
40. Hudelmaier M, Glaser C, Hohe J, Englmeier KH, Reiser M, Putz R, et al. Age-related changes in the morphology and deformational behavior of knee joint cartilage. *Arthritis and rheumatism*. 2001;44(11):2556-61.
41. Cicuttini FM, Wluka A, Bailey M, O'Sullivan R, Poon C, Yeung S, et al. Factors affecting knee cartilage volume in healthy men. *Rheumatology*. 2003;42(2):258-62.
42. Nishimura K, Tanabe T, Kimura M, Harasawa A, Karita K, Matsushita T. Measurement of articular cartilage volumes in the normal knee by magnetic resonance imaging: can cartilage volumes be estimated from physical characteristics? *Journal of orthopaedic science : official journal of the Japanese Orthopaedic Association*. 2005;10(3):246-52.