Tibial coverage, meniscus position, size and damage in knees discordant for joint space narrowing – data from the Osteoarthritis Initiative

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Running title: JSN-related tibial coverage by meniscus

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ABSTRACT

INTRODUCTION: Meniscal extrusion is thought to be associated with lesser coverage of the tibial surface, but it is currently not known which specific (quantitative) proportion the tibial plateau is covered at different stages of radiographic knee osetoarthritis. We compared quantitatve and semiquantitative measures of meniscus morphology in painful knees with discordant medial joint space narrowing (mJSN) status,

METHODS: A sample was drawn from the first half (2678 cases) of the Osteoarthritis Initiative cohort with bilateral frequent pain, OARSI mJSN grades 1-3 in one, no-JSN in the contra-lateral, and no lateral JSN in either knee. Segmentation and three-dimensional quantitative analysis of the tibial plateau and meniscus, and semiquantitative evaluation of meniscus damage (MOAKS) was performed using coronal 3Tesla MR images (MPR DESSwe and IW-TSE images). Contra-lateral knees were compared using paired t-tests (between-knee, within-person design).

RESULTS: 60 participants fulfilled the inclusion criteria (43 with unilateral mJSN1;17 with unilateral mJSN2/3). Medial tibial plateau coverage was 36±9% in mJSN1 vs. 45±8% in contralateral no-JSN knees, and was 31±9% in mJSN2/3 vs. 46±6% in no-JSN knees (each $p<0.001$). mJSN knees showed greater meniscus extrusion and damage (MOAKS), but no significant difference in meniscus size (e.g. volume). No significant differences in lateral tibial coverage, lateral meniscus morphology or meniscus position were observed between mJSN and no-JSN knees.

CONCLUSIONS: Knees with medial JSN showed substantially less medial tibial plateau coverage by the meniscus. The lesser degree of mechanical protection may be a reason for greater rates of cartilage loss in JSN knees found in other studies.

Key Words: Meniscus, Joint Space Narrowing, Radiographic Osteoarthritis,

Magnetic Resonance Imaging, Tibial Coverage

Introduction

Reduction in radiographic joint space width (JSW) (= joint space narrowing [JSN]) is a diagnostic feature that is commonly used to classify knees as having advanced structural osteoarthritis (OA) [1], and it has been shown that JSN predicts further structural deterioration of the knee, specifically femorotibial cartilage loss [2-6] Further, there is evidence for a relationship between JSN and pain[7].

The meniscus is a fibrocartilage structure positioned between the tibial plateau and distal femoral knee cartilages, with all three structures being known to make up the radiographic joint space [8]. The meniscus transmits a substantial proportion of the forces across the femorotibial joint [9-11], and keeps the forces encountered by the cartilage and subchondral bone in reasonable limits, by distributing loads and reducing knee joint contact stress [10-13]. Meniscus damage is frequent in the general population, occurs more often in the medial than in the lateral meniscus, and its prevalence increases with more severe JSN [14]. Further, meniscal damage is known to be associated with meniscal extrusion [15-18]. Although meniscal extrusion is thought to be associated with lesser coverage of the tibial plateau and hence less mechanical protection of the articular surface, it is currently not known which specific (quantitative) proportion the tibial plateau is covered by the meniscus at different stages of knee OA, i.e. in knees with different grades of JSN.

Only few studies have quantitatively evaluated the position (extrusion) of the meniscus in two dimensions in one or more image slices [8,19-24]. More recently, a 3D technique was proposed that permits fully quantitative morphometric analysis of the meniscus (including tibial plateau coverage, meniscus position, and meniscus size [e.g. volume, height, etc,]) [25]. The aim of the current study therefore was to compare quantitative measures of the meniscus, specifically tibial plateau coverage, in painful knees with discordant medial JSN (mJSN) status, using a between-knee, within-person study design [3,7,26,27]. In particular, we aimed to stratify observations for participants with mild and advanced (unilateral) mJSN, to evaluate whether only medial or also lateral meniscus morphology is affected by mJSN, and to characterize meniscus damage in these knees using the novel MOAKS grading system [28]

Methods

Study participants

The subsample analyzed in the current study was drawn from the first half (2678 cases) of the OA Initiative (OAI) cohort (baseline clinical data 0.2.1; http://www.oai.ucsf.edu/datarelease/). [26]. The OAI is a multi-center, population-based longitudinal cohort study, targeted at identifying risk factors associated with the onset and progression of knee OA, and at characterizing biomarkers of the disease. Participants in the OAI cohort were between 45 and 79 years old at baseline and included a diversity of ethnic backgrounds. Participants with rheumatoid or other inflammatory arthritis, bilateral end stage knee OA, inability to walk without aids, or MRI contra-indications were excluded. Informed consent was obtained from all participants and the study was approved by the local ethics committees.

The subcohort for the current study was selected specifically to permit a between-knee, within-person comparison of painful knees with mJSN vs. painful knees without mJSN or lateral JSN [26]. Briefly the subjects fulfilled the following inclusion criteria:

- Body mass index (BMI) >25 kg/m^2
- Frequent knee pain (i.e., pain on most days in at least one month in the past 12 months) in both knees
- mJSN OARSI grades 1-3 in one knee [29,30] and no mJSN in the other (contra-lateral) knee
- No lateral JSN in either knee

The primary selection was based on the radiographic readings performed at the OAI clinical sites and was complemented by either central OAI readings (when available at the time point of participant selection) or by consensus evaluation of two experienced readers (A.G and D.H.) [3,26]. Compared to a previous study with n=73 participants [26], the current study excluded three participants with infrequent pain in the no-JSN knee, three participants with some degree of lateral JSN, and seven in whom the meniscus could not be segmented due to severe destruction (1=mJSN1, 3=mJSN2 , 3=mJSN3). Finally, 60 participants were included in the analysis.

MR images and segmentation

MR images were acquired for each knee with a 3 Tesla Magnetom Trio magnet (Siemens Erlangen, Germany) and quadrature transmit-receive knee coils (USA Instruments, Aurora, OH)[31,32]. For the current study, the coronal multi-planar reconstruction of the sagittal double echo steady state sequence with water excitation was used (DESSwe: reconstructed slice thickness=1.5mm, in-plane resolution 0.37mm x 0.7mm, interpolated to 0.37mm x 0.37mm) [33,34]. Meniscus segmentation and morphometry from the DESS has been shown to yield acceptable inter-observer reliability and good agreement with measurements made from a coronal intermediate-weighted turbo spin echo (IW-TSE) sequence [35]. The advantage of the DESS, however, is that it provides greater spatial resolution and better delineation of the tibial plateau cartilage surface area and also has been validated for accurately depicting the tibial cartilage [33].

Quantitative analysis

All images underwent initial quality control (K.B.). Manual segmentation of the medial and lateral tibial plateau area (i.e. the area of cartilage surface, including denuded areas of subchondral bone = ACdAB [25 36]), and the surfaces of the medial and lateral meniscus (tibial, femoral and external – Fig. 1) was performed by a single experienced operator (K.B.). Segmentation and quantitative analysis was performed using dedicated image analysis software (Chondrometrics GmbH, Ainring, Germany [25 36]. Segmentation was started anteriorly and was ended posteriorly in the first/last image in which both the tibial cartilage and the menisci could be reliably identified. Internally, the borders of the menisci were defined by the internal margin of the cartilage surfaces of the medial and lateral tibia, respectively, because these are continuous with the transverse and menisco-femoral ligaments and because no intrinsic anatomical demarcation could be used to separate these structures. The size of the tibial plateau and of the total meniscus surface (i.e. the sum of the tibial, femoral and external surface), the meniscus volume, mean and maximal meniscus thickness, and the mean and maximal meniscus width were computed from the segmentations [25]. Meniscus position relative to the tibial plateau was measured by determining the percentage of tibial plateau covered by meniscus. The mean and maximal extrusion distance of the meniscus were measured as the distance between the external margin of the tibial plateau area and that of the tibial meniscus area (Fig. 1). A further measure of extrusion was the (relative, percent) area of the tibial meniscus surface not covering the tibial plateau. The mean and maximal overlap distance between the meniscus and tibial plateau were computed using the distance between the external margin of the tibial plateau and the internal margin of the meniscus (i.e. the intersection of its tibial and femoral area (Fig. 1). Please note that a more negative value indicates a more “internal” position relative to the external border of the tibial plateau [25,36]. In addition to the above 3D measures, meniscus width, extrusion and overlap distance were also determined for the central five slices, to more specifically evaluate the meniscus body. Measures in this region also were shown to display superior inter-observer reproducibility [35] and sensitivity to between-knee differences of pain frequency [37].

Semi-quantitative analysis

Semi-quantitative MR readings of meniscal integrity and position were performed by an experienced musculoskeletal radiologist (A.G.) using the MOAKS scoring system [28] based on fat-suppressed sagittal and non-fat-suppressed coronal IW-TSE images [31]. Meniscus morphology (damage) was evaluated for the medial and lateral meniscus in the anterior and posterior horn and the meniscus body and divided into 7 different grades (0=normal; 1=signal change; 2=radial tear; 3= horizontal tear; 4=vertical tear; 5=complex tear; 6=partial maceration; 7=complete maceration). The maximum grade observed in any of the three regions was used, summarizing grade 2-5 lesions as meniscus tears, and grade 6 or 7 lesions as maceration. Meniscal root tears were defined as being present (=1) or absent (=0). Meniscus position (extrusion) was also classified, with grade 0 representing<2mm; grade 1 representing 2-2,9mm; grade 2 representing 3-4,9mm, and grade 3 representing > 5mm extrusion.

Statistical analysis

Mean values and standard deviations (SDs) were determined for all quantitative measures of meniscus position and size in knees with and without mJSN. Participants were stratified based on mJSN grade; mJSN2 and mJSN3 were combined due to the small number of the latter (see below). Hence, mJSN1 knee were compared vs. contralateral no-JSN knees, and mJSN2/3 vs. contralateral no-JSN knees, using 95% confidence intervals (CIs). Because statistical comparisons were performed between knees of the same subjects, differences were tested using paired t-tests. Medial tibial plateau coverage by the medial meniscus was considered the primary, and the mean overlap distance between the external tibial plateau margin and the internal meniscus margin the co-primary anlaysis. Measures of meniscus extrusion were considered secondary analyses. All other quantitative measures were viewed as exploratory. p-values <0.01 were considered significant

The maximum (semi-quantitative) MOAKS morphology score across the entire meniscus (anterior horn, posterior horn and meniscus body) was computed and compared between mJSN1 vs. contralateral no-JSN knees, and between mJSN2/3 vs. contralateral no-JSN knees using a Wilcoxon signed rank test. Differences between mJSN1 vs. mJSN2/3 knees were evaluated using Mann-Whitney U-test. The same statistical testing procedures as above were applied to MOAKS extrusion scores.

Results

Demographics

The sample included 22 men and 38 women. The mean age was 61.3±9.2 years, the body height 1.66 ± 0.96 m, the body weight 86.6 ± 13.0 kg, and the BMI 31.3 ± 3.9 kg/m^2. Of the 60 mJSN knees, 43 knees were grade 1, 14 grade 2, and 3 grade 3. As per inclusion/exclusion criteria, no lateral JSN was present.

Medial meniscus tibial plateau coverage

Knees with mJSN grade 1 had less medial tibial plateau coverage (36.0±8.8%) than contra-lateral noJSN knees (45.1±8.4%; Table 1). Knees with mJSN grade 2/3 also had less medial tibial plateau coverage (31.3±9.3%) than contra-lateral noJSN knees (46.2±6.1%; Table 2). The relative position of the internal margin of the meniscus compared with the external margin of the tibial plateau (mean overlap distance) showed less negative values (less coverage) in mJSN1 and mJSN2/3 vs. contra-lateral noJSN knees (Table 1&2). Similar relationships were observed for the maximum overlap distance, and for the overlap distance in the central five slices (Tables 1 & 2).

Medial meniscus extrusion

The mean extrusion of the entire medial meniscus was greater in mJSN vs. noJSN knees (mJSN1: 3.45±1.46 vs. 2.11±1.51mm; mJSN2/3: 4.62±1.23 vs. 2.50± 1.29mm; Tables 1&2) and so was the mean extrusion in the central five slices (mJSN1: 3.09±1.81 vs. 1.84±1.26mm; mJSN2/3: 4.10±1.85 vs. 1.79±1.32mm; Tables 1 & 2). Further the medial meniscus surface area extruding the tibial plateau was significantly greater in mJSN than in noJSN knees (mJSN1: 27±11 vs. 16±8.1%; mJSN2/3: 36±16 vs. 16±7.3%) and so was the maximum extrusion across the meniscus (Tables 1&2).

Other quantitative measures of the medial and lateral meniscus

Measures of meniscus size did not show significant differences between mJSN vs. contralateral noJSN knees (Tables 1 & 2). The only exception was the meniscus width, which was significantly smaller in mJSN than in the noJSN knees (entire meniscus and central 5 slices; Table 1 & 2).

No significant differences in any of the quantitative measures of lateral meniscus position or size were observed in mJSN vs. contra-lateral noJSN knees (Tables 1 & 2).

Semi-quantitative results

The average maximum lesions score in the medial meniscus was significantly greater ($p<0.001$) in mJSN 1 than in contra-lateral noJSN knees (mean 3.3 vs. 1.7; median 3 vs. 1), and also tended to be greater ($p=0.021$) in mJSN 2/3 than in noJSN knees (mean 3.9 vs. 2.0; median 5 vs. 1). The mean average score in the lateral meniscus was similar between mJSN and contra-lateral noJSN knees (mJSN1: 0.7 vs. 0.8, $p=0.7$; mJSN 2/3:1.1 vs. 0.5, $p=0.31$).

The presence of meniscus tears (MOAKS 2-5) and maceration (MOAKS 6-7) for the medial and lateral meniscus in different subgroups is shown in Table 3. 65% of the mJSN1 knees and only 37% of the noJSN knees had any medial meniscus damage (MOAKS 2-7); 65% of the mJSN 2/3 knees had any damage vs. 44% of the noJSN knee, with mJSN 2/3 knees displaying a high percentage (47%) of partial or complete maceration (Table 3). The frequency of lateral meniscus tears was not significantly different between mJSN and noJSN knees (mJSN1: 16 vs. 21%, $p=0.51$; mJSN 2/3 24 vs. 12%, $p=0.36$). There was no maceration observed in any lateral meniscus.

The mean average extrusion score in the medial meniscus was greater in mJSN than in noJSN knees (mJSN1: 1.3 vs. 0.9, p=0.003; mJSN 2/3, p=0.001). The mean average score in the lateral meniscus was the same in mJSN 1 as in noJSN knees (0.3 vs. 0.3; p=1.0), and was not significantly different between mJSN 2/3 and noJSN knees (0.4 vs. 0.2; (p=0.37).

Meniscal root tears were observed in three knees with mJSN 2/3, in one with mJSN1, and in one knee with noJSN.

Discussion

The current study is the first to report three-dimensional quantitative measures, specifically tibial plateau coverage, and semi-quantitative measures using MOAKS, of the medial and lateral meniscus at different radiographic stages of knee OA, specifically in painful knees with and without radiographic JSN. The study aimed to directly compare knees with mJSN vs. contralateral knees without JSN using a between-knee, within-person study design. Key results are that medial tibial plateau coverage is substantially lower in mJSN than in (contra-lateral) no-JSN knees. Medial meniscus extrusion and morphology lesion scores were greater in mJSN than in noJSN knees, whereas no differences in meniscus size (e.g. volume, thickness) were detected between contralateral knees. Further, no differences were observed in quantitative measures of the lateral meniscus.

A limitation of this study is its moderate sample size, particularly of knees with mJSN2/3, although knees were selected from a very large sample. This is because KOA often is a bilateral disease and knees rarely are discordant by 2 or more JSN grades, when both being frequently painful. Further, in some knees (mostly with mJSN 2/3) the meniscus could not be segmented due to complete maceration. Nevertheless, highly significant differences were identified between mJSN vs. no-JSN knees in tibial plateau coverage and extrusion. The strength of the study is the choice of a between-knee, within-person comparison [3,7,26,27], which eliminates between-person confounding, such as differences in sex, age, weight, height, body mass index, occupation/physical activity levels, and others. For instance, differences in medial meniscus position and extrusion have been reported between men and women [24,38]. The between-knee, within-person also involves greater statistical efficiency, by allowing one to apply a paired test approach.

Another limitation is that segmentation of the meniscus was done using only coronal (but not sagittal) MRI. Coronal images are ideal for evaluating the meniscal body and meniscus extrusion of the body in external direction, but preclude measurement of anterior extrusion [24], because of the partial volume effects in this region with coronal slices. However, the coronal protocol was shown to display satisfactory intra-observer [25,36,37] and inter-observer reproducibility [35], and the primary outcome to be studied was tibial plateau coverage, which can be adequately measured using the coronal protocol. A further strength is that coverage by the meniscus was measured for the entire medial and lateral tibial plateau and was not confined to one or several (central) slices. A 3T DESSwe sequence was used for meniscus segmentation which is not used to clinically evaluate the meniscus, but has been validated for the purpose of cartilage measurement [33,34] and delineates the cartilage surface (the segmentation of which is required to measure coverage and extrusion) with high spatial resolution. Further, quantitative meniscus measurements obtained from the 3T DESSwe have shown satisfactory agreement with those from the IWTSE, which is commonly used for the clinical evaluation of the meniscus [35].

The prevalence of medial meniscus damage found in (painful) mJSN knees in our study (approx. 65%) agrees well with the prevalence rate observed in knees with frequent symptoms and radiographic evidence of knee osteoarthritis (Kellgren Lawrence grade 2 or higher) reported in a large population based study [14]. Our measures of medial meniscus extrusion in mJSN knees (central 5 slices) also are in good agreement with similar measurements of Vanwanseele et al [22] in a cohort of subjects with predominantly (82%) medial knee OA (3.86 mm), and our extrusion results in the medial meniscus of no-JSN knees with those of Hwang et al. in subjects with end-stage lateral knee OA (2.5 mm in women, 1.7 mm in men). However, our measures of mean medial meniscus extrusion in the central 5 slices of mJSN knees are somewhat smaller than those reported by Jung et al. [23]for the medial meniscus body in knees with varus OA (6.1 mm).

The observation that knees with mJSN show greater medial meniscus extrusion than those without confirm previous comparisons made using two-dimensional measurement in single MRI slices between subject knees with and without mJSN [19,39]. However, we did not find consistent difference in meniscus size or signs of meniscus hypertrophy [23] between mJSN and no-mJSN knees.

The medial tibial plateau coverage by the medial meniscus in the no-JSN knees in our current study (approx. 45%) is somewhat smaller than that previously described in a healthy reference cohort of men and women (50%), whereas the lateral tibial plateau coverage in the current study is identical to the healthy reference subjects (58%)[38]. As the no JSN knees in the current study displayed frequent pain and were contra-lateral to knees with advanced medial radiographic OA, they can be assumed to be at an early state of (medial) knee osteoarthritis, which appears to be associated with an reduction by approx.. 5% of medial tibial plateau coverage (from 50 to 45%). Knees with mJSN1, in contrast, displayed a much larger reduction in of medial tibial plateau coverage to 36%, and those with mJSN 2/3 to only 31%. These between-knee differences are much larger than those previously observed between painful vs. (contra-lateral) painless knees (41% vs. 44% medial plateau coverage) with the same JSN status [37]. The dramatic reduction in medial tibial plateau coverage by the medial meniscus in knees with medial radiographic JSN very likely is associated with substantially reduced mechanical protection of the medial tibial plateau cartilage. Although this needs to be further explored in longitudinal studies, it is plausible that the greater mechanical stress acting on the cartilage in JSN knees with less medial tibial plateau coverage may explain why knees with (medial) radiographic JSN show much greater rates of (medial) femorotibial cartilage loss than osteoarthritis knees without JSN [3-6] [2].

In conclusion we find that knees with mJSN show substantially less tibial plateau coverage of the medial meniscus, more medial meniscus extrusion, and greater medial meniscus lesion scores, but no general difference in meniscus size (e.g. volume), compared with contralateral no-JSN knees in the same person. No significant differences in lateral tibial plateau coverage and lateral meniscus position, size and lesions scores were, however, detected between knees with and without mJSN. The substantially lesser degree of medial tibial plateau coverage and protection in knees with mJSN may provide a mechanical reason why other studies found greater rates of medial femorotibial cartilage loss in knees with radiographic JSN than in those without.

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AUTHOR'S CONTRIBUTION

All authors have made substantial contributions to (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted. Specific contributions are:

(1) the conception and design of the study: KB, AG, OB, DH, FE

(2) acquisition of data: CK

(3) analysis and interpretation of data: KB, AG, WW, OB, CK, DH, ME, HR, FE

(4) Drafting the article: KB, FE

(5) Revising the article critically for important intellectual content: KB, AG, WW, OB, CK, DH, ME, HR, FE

(6) Final approval of the version submitted: KB, AG, WW, OB, CK, DH, ME, HR, FE

(7) Statistical expertise: WW, FE

(8) Obtaining of funding: KB

(9) Collection and assembly of data: KB, WW

KB takes responsibility for the integrity of the work as a whole, from inception to finished article. KB was involved in conception and design of the study, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, and final approval of the article.

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The funding sources took no active part of influence on the analysis of the data and in drafting or revising the article. The manuscript received the approval of the OAI Publications Committee based on a review of its scientific content and data interpretation.

DECLARATION OF POTENTIALLY COMPETING INTERESTS

Katja Bloecker, Martin Englund, Herbert Resch and Kent Kwoh have no competing interests

Ali Guermazi is President and co-owner of the Boston Core Imaging Lab (BICL), a company providing MRI reading services to academic researchers and to industry. He provides consulting services to Novartis, Genzyme, Stryker, MerckSerono and AstraZeneca.

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REFERENCES

1. 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;34:645-87.

2. Le Graverand MP, Buck RJ, Wyman BT, Vignon E, Mazzuca SA, Brandt KD et al . Change in regional cartilage morphology and joint space width in osteoarthritis participants versus healthy controls: a multicentre study using 3.0 Tesla MRI and Lyon-Schuss radiography. Ann Rheum Dis 2010;69:155-62.

3. Eckstein F, Benichou O, Wirth W, Nelson DR, Maschek S, Hudelmaier M et al . Magnetic resonance imaging-based cartilage loss in painful contralateral knees with and without radiographic joint space narrowing: Data from the Osteoarthritis Initiative. Arthritis Rheum 2009;61:1218-25.

4. Eckstein F, Le Graverand MP, Charles HC, Hunter DJ, Kraus VB, Sunyer T et al . Clinical, radiographic, molecular and MRI-based predictors of cartilage loss in knee osteoarthritis. Ann Rheum Dis 2011;70:1223-30.

5. Wirth W, Buck R, Nevitt M, Le Graverand MP, Benichou O, Dreher D et al . MRI-based extended ordered values more efficiently differentiate cartilage loss in knees with and without joint space narrowing than region-specific approaches using MRI or radiography--data from the OA initiative. Osteoarthritis Cartilage 2011;19:689-99.

6. Eckstein F, Nevitt M, Gimona A, Picha K, Lee JH, Davies RY et al . Rates of change and sensitivity to change in cartilage morphology in healthy knees and in knees with mild,

moderate, and end-stage radiographic osteoarthritis: Results from 831 participants from the osteoarthritis initiative. Arthritis Care Res (Hoboken) 2010;63:311-9.

7. Neogi T, Felson D, Niu J, Nevitt M, Lewis CE, Aliabadi P et al . Association between radiographic features of knee osteoarthritis and pain: results from two cohort studies. BMJ 2009;339:b2844. doi: 10.1136/bmj.b2844.:b2844.

8. Hunter DJ, Buck R, Vignon E, Eckstein F, Brandt K, Mazzuca SA et al . Relation of regional articular cartilage morphometry and meniscal position by MRI to joint space width in knee radiographs. Osteoarthritis Cartilage 2009;17:1170-6.

9. Krause WR, Pope MH, Johnson RJ, Wilder DG. Mechanical changes in the knee after meniscectomy. J Bone Joint Surg Am 1976;58:599-604.

10. Walker PS, Erkman MJ. The role of the menisci in force transmission across the knee. Clin Orthop Relat Res 1975;184-92.

11. Chivers MD, Howitt SD. Anatomy and physical examination of the knee menisci: a narrative review of the orthopedic literature. J Can Chiropr Assoc 2009;53:319-33.

12. Kurosawa H, Fukubayashi T, Nakajima H. Load-bearing mode of the knee joint: physical behavior of the knee joint with or without menisci. Clin Orthop Relat Res 1980;283-90.

13. Englund M. The role of biomechanics in the initiation and progression of OA of the knee. Best Pract Res Clin Rheumatol 2010;24:39-46.

14. Englund M, Guermazi A, Gale D, Hunter DJ, Aliabadi P, Clancy M et al . Incidental meniscal findings on knee MRI in middle-aged and elderly persons. N Engl J Med 2008;359:1108-15.

15. Rennie WJ, Finlay DB. Meniscal extrusion in young athletes: associated knee joint abnormalities. AJR Am J Roentgenol 2006;186:791-4.

16. Choi CJ, Choi YJ, Lee JJ, Choi CH. Magnetic resonance imaging evidence of meniscal extrusion in medial meniscus posterior root tear. Arthroscopy 2010;26:1602-6.

17. Lee DH, Lee BS, Kim JM, Yang KS, Cha EJ, Park JH et al . Predictors of degenerative medial meniscus extrusion: radial component and knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2011;19:222-9.

18. Crema MD, Roemer FW, Felson DT, Englund M, Wang K, Jarraya M et al . Factors Associated with Meniscal Extrusion in Knees with or at Risk for Osteoarthritis: The Multicenter Osteoarthritis Study. Radiology 2012;264:494-503.

19. Gale DR, Chaisson CE, Totterman SM, Schwartz RK, Gale ME, Felson D. Meniscal subluxation: association with osteoarthritis and joint space narrowing. Osteoarthritis Cartilage 1999;7:526-32.

20. Hunter DJ, Zhang YQ, Tu X, LaValley M, Niu JB, Amin S et al . Change in joint space width: hyaline articular cartilage loss or alteration in meniscus? Arthritis Rheum 2006;54:2488-95.

21. Hunter DJ, Zhang YQ, Niu JB, Tu X, Amin S, Clancy M et al . The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis. Arthritis Rheum 2006;54:795-801.

22. Vanwanseele B, Eckstein F, Smith RM, Lange AK, Foroughi N, Baker MK et al . The relationship between knee adduction moment and cartilage and meniscus morphology in women with osteoarthritis. Osteoarthritis Cartilage 2010;

23. Jung KA, Lee SC, Hwang SH, Yang KH, Kim DH, Sohn JH et al . High frequency of meniscal hypertrophy in persons with advanced varus knee osteoarthritis. Rheumatol Int 2010;30:1325-33.

24. Hwang SH, Jung KA, Lee WJ, Yang KH, Lee DW, Carter A et al . Morphological changes of the lateral meniscus in end-stage lateral compartment osteoarthritis of the knee. Osteoarthritis Cartilage 2012;20:110-6.

25. Wirth W, Frobell RB, Souza RB, Li X, Wyman BT, Le Graverand MP et al . A three-dimensional quantitative method to measure meniscus shape, position, and signal intensity using MR images: a pilot study and preliminary results in knee osteoarthritis. Magn Reson Med 2010;63:1162-71.

26. Eckstein F, Wirth W, Hunter DJ, Guermazi A, Kwoh CK, Nelson DR et al . Magnitude and regional distribution of cartilage loss associated with grades of joint space narrowing in radiographic osteoarthritis--data from the Osteoarthritis Initiative (OAI). Osteoarthritis Cartilage 2010;18:760-8.

27. Benichou OD, Hunter DJ, Nelson DR, Guermazi A, Eckstein F, Kwoh K et al . One-year change in radiographic joint space width in patients with unilateral joint space narrowing: data from the Osteoarthritis Initiative. Arthritis Care Res (Hoboken) 2010;62:924-31.

28. Hunter DJ, Guermazi A, Lo GH, Grainger AJ, Conaghan PG, Boudreau RM et al . Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage 2011;19:990-1002.

29. Altman RD, Gold GE. Atlas of individual radiographic features in osteoarthritis, revised. Osteoarthritis Cartilage 2007;15 Suppl A:1-56.

30. Altman RD, Hochberg M, Murphy WA, Jr., Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3 Suppl A:3-70.

31. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage 2008;16:1433-41.

32. Schneider E, NessAiver M, White D, Purdy D, Martin L, Fanella L et al . The osteoarthritis initiative (OAI) magnetic resonance imaging quality assurance methods and results. Osteoarthritis Cartilage 2008;16:994-1004.

33. Eckstein F, Hudelmaier M, Wirth W, Kiefer B, Jackson R, Yu J et al . Double echo steady state magnetic resonance imaging of knee articular cartilage at 3 Tesla: a pilot study for the Osteoarthritis Initiative. Ann Rheum Dis 2006;65:433-41.

34. Wirth W, Nevitt M, Hellio Le Graverand MP, Benichou O, Dreher D, Davies RY et al . Sensitivity to change of cartilage morphometry using coronal FLASH, sagittal DESS, and coronal MPR DESS protocols--comparative data from the Osteoarthritis Initiative (OAI). Osteoarthritis Cartilage 2010;18:547-54.

35. Siorpaes K, Wenger A, Bloecker K, Wirth W, Hudelmaier M, Eckstein F. Interobserver reproducibility of quantitative meniscus analysis using coronal multiplanar DESS and IWTSE MR imaging. Magn Reson Med 2012;67:1419-26.

36. Bloecker K, Wirth W, Hudelmaier M, Burgkart R, Frobell R, Eckstein F. Morphometric differences between the medial and lateral meniscus in healthy men - a three-dimensional analysis using magnetic resonance imaging. Cells Tissues Organs 2012;195:353-64.

37. Wenger A, Englund M, Wirth W, Hudelmaier M, Kwoh K, Eckstein F. Relationship of 3D meniscal morphology and position with knee pain in subjects with knee osteoarthritis: a pilot study. Eur Radiol 2012;22:211-20.

38. Bloecker K, Englund M, Wirth W, Hudelmaier M, Burgkart R, Frobell RB et al . Size and position of the healthy meniscus, and its correlation with sex, height, weight, and bone area- a cross-sectional study. BMC Musculoskelet Disord 2011;12:248.

39. Adams JG, McAlindon T, Dimasi M, Carey J, Eustace S. Contribution of meniscal extrusion and cartilage loss to joint space narrowing in osteoarthritis. Clin Radiol 1999;54:502-6.

Fig. 1: Coronal Reformat DESS MRI: Showing the medial and lateral meniscus on the medial and lateral tibial plateau with segmentation of: FA=femoral meniscus area, TA=tibial meniscus area, EA=external meniscus area, ACdAB= articular surface of the medial tibial plateau area

Figure 2: 3D reconstruction of the medial (right) and lateral (left) meniscus; a) meniscal thickness (Th), overlap distance (OvD) and width (Wid) are marked; b) both menisci (turquoise) covering the tibial plateau (ACdAB; purple), Tibial (TA), femoral (FA) and external (EA) surface areas are marked, as well as the total surface area of the meniscus (TOT A); meniscal extrusion (Ex) and the uncovered tibial surface area of the meniscus (TA.uncovp) are indicated schematically.

Figure 3: Coronal IW-TSE MRI of the Left Knee: showing a meniscus grade 3 tear (arrow), scored using the MOAKS system

Figure 4: Bar graph showing the tibial plateau coverage by the medial meniscus in contra-lateral knees with and without JSN 1 and 2/3.

Table1: Knees with medial joint space narrowing (mJSN) grade 1 vs contralateral knees without JSN: Tibial coverage, meniscus position and meniscus size

Medial meniscus	mJSN Mean ± SD	no JSN Mean ± SD	Diff # Mean	[95% CI]	p-value
Tibial plateau coverage					
ACdAB.Covp [%]	36.0 ± 8.75	45.1 ± 8.36	-9.14	[-12-2-(-6.08)]	<0.001
OvD.Me [mm]	-9.01 ± 2.13	-11.3 ± 2.57	2.26	[1.56-2.96]	<0.001
OvD.Max [mm]	-2.43 ± 1.69	-3.88 ± 1.92	1.44	[0.85-2.03]	<0.001
OvD.c5 [mm]	-4.08 ± 2.31	-6.79 ± 3.20	2.71	[1.90-3.51]	<0.001
Meniscus extrusion					
Ex.Me [mm]	3.45 ± 1.46	2.11 ± 1.51	1.34	[0.92-1.76]	<0.001
Ex.Max [mm]	7.05 ± 1.84	6.60 ± 1.48	0.45	[-0.04-0.94]	0.068
Ex.c5 [mm]	3.09 ± 1.81	1.84 ± 1.26	1.25	[0.76-1.74]	<0.001
TA.uncovp [%]	26.5 ± 11.4	16.3 ± 8.11	10.2	[6.84-13.6]	<0.001
Meniscus size					
Wid.Me [mm]	8.13 ± 1.50	9.24 ± 1.57	-1.11	[-1.54-(-0.68)]	<0.001
Wid.Max [mm]	14.1 ± 2.68	16.3 ± 3.15	-2.21	[-3.02-(-1.41)]	<0.001
Wid.c5 [mm]	7.39 ± 2.20	9.39 ± 2.94	-1.76	[-2.58-(-0.95)]	<0.001
Th.Me [mm]	2.67 ± 0.502	2.72 ± 0.532	-0.05	[-0.15-0.06]	0.399
Th.Mav [mm]	6.63 ± 1.52	6.44 ± 1.32	0.18	[-0.18-0.54]	0.318
V [mm^3]	1930 ± 747	2112 ± 871	-182	[-330-(-34.1)]	0.017
TOTA [mm^2]	1470 ± 371	1553 ± 412	-83.5	[-148-(-18.9)]	0.013

Lateral meniscus	mJSN Mean ± SD	no JSN Mean ± SD	Diff # Mean	[95% CI]	p-value
Tibial plateau coverage					
ACdAB.Covp [%]	57.2 ± 5.61	57.8 ± 5.21	-0.59	[-2.38-1.20]	0.510
OvD.Me [mm]	-15.9 ± 2.58	-16.1 ± 2.16	0.12	[-0.28-0.52]	0.559
OvD.Max [mm]	-8.70 ± 2.28	-8.60 ± 2.17	-0.10	[-0.50-0.29]	0.600
OvD.c5 [mm]	-9.95 ± 2.42	-9.89 ± 2.45	-0.06	[-0.51-0.40]	0.798
Meniscus extrusion					
Ex.Me [mm]	-1.41 ± 1.99	-1.31 ± 1.86	-0.11	[-0.62-0.41]	0.681
Ex.Max [mm]	7.24 ± 1.81	7.49 ± 2.01	-0.25	[-0.86-0.36]	0.409
Ex.c5 [mm]	-0.50 ± 1.19	-0.28 ± 1.13	-0.21	[-0.53-0.11]	0.183
TA.uncovp [%]	3.90 ± 4.20	4.45 ± 3.97	-0.54	[-1.80-0.71]	0.386
Meniscus size					
Wid.Me [mm]	8.85 ± 1.41	8.99 ± 1.26	-0.14	[-0.42-0.15]	0.348
Wid.Max [mm]	12.7 ± 1.96	12.7 ± 1.61	-0.02	[-0.45-0.41]	0.912
Wid.c5 [mm]	10.6 ± 2.21	10.7 ± 2.17	-0.12	[-0.62-0.38]	0.628
Th.Me [mm]	2.64 ± 0.445	2.62 ± 0.392	0.02	[-0.06-0.10]	0.627
Th.Mav [mm]	6.60 ± 1.05	6.61 ± 1.05	-0.01	[-0.22-0.20]	0.929
V [mm^3]	1964 ± 652	2001 ± 602	-36.9	[-148.2-74.4]	0.508
TOTA [mm^2]	1509 ± 334	1536 ± 303	-26.9	[-84.4-30.7]	0.351

SD: standard deviation; # mean of the pairwise differences (may deviation from difference between group means); ACdAB.Covp: area of cartilage surface covered with meniscus in percent; Ex.Me: mean external extrusion; Ex.Max: maximal external extrusion; OvD.Me: mean overlap distance; OvD.Max: maximal overlap distance. Note that a positive value for meniscal extrusion indicates an "external" position relative to the external border of the tibial plateau. whereas a negative value indicates an "internal" position relative to the external border. A more negative value for the overlap distance indicates a more internal position of the inner margin of the meniscus; TA.uncovp: tibial area of the meniscus not covering the tibial plateau in percent; TOT A: sum of all three surface areas of the meniscus; V: volume of the meniscus; Th.Me: mean thickness of the meniscus; Th.Mav: average thickness of the meniscus; Wid.Me: mean width of the meniscus; Wid.max: maximal width of the meniscus; Ex.c5: mean extrusion in the central 5 slices; Wid.c5: mean width in the central 5 slices; OvD.c5: mean overlap distance in the central 5 slices

Table 2: Position and Size of the medial (MM) and lateral meniscus (LM) in mJSN grade 2/3 vs no-mJSN

Medial meniscus	mJSN	no JSN	Diff #		
	Mean ± SD	Mean ± SD	Mean	[95% CI]	p-value
Tibial plateau coverage					
ACdAB.Covp [%]	31.3 ± 9.29	46.2 ± 6.14	-14.8	[-21.6-(-8.03)]	<0.001
OvD.Me [mm]	-7.76 ± 2.40	-10.8 ± 1.44	3.08	[1.54-4.62]	0.001
OvD.Max [mm]	-1.79 ± 1.54	-3.71 ± 1.42	1.91	[0.80-3.03]	0.002
OvD.c5 [mm]	-3.46 ± 1.81	-5.95 ± 2.43	2.50	[1.01-4.00]	0.003
Meniscus extrusion					
Ex.Me [mm]	4.62 ± 1.23	2.50 ± 1.29	2.12	[1.06-3.18]	0.001
Ex.Max [mm]	7.86 ± 1.61	7.25 ± 1.39	0.61	[-0.53-1.74]	0.273
Ex.c5 [mm]	4.10 ± 1.85	1.79 ± 1.32	2.31	[1.01-3.62]	0.002
TA.uncovp [%]	36.4 ± 15.6	16.2 ± 7.28	20.2	[10.1-30.3]	0.001
Meniscus size					
Wid.Me [mm]	8.25 ± 1.22	8.96 ± 1.02	-0.72	[-1.44-0.002]	0.051
Wid.Max [mm]	14.1 ± 2.33	16.4 ± 2.74	-2.31	[-4.07-(-0.54)]	0.014
Wid.c5 [mm]	7.88 ± 2.08	8.46 ± 1.94	-0.58	[-1.93-0.76]	0.373
Th.Me [mm]	2.88 ± 0.397	2.68 ± 0.340	0.20	[-0.05-0.44]	0.103
Th.Mav [mm]	7.09 ± 1.13	6.58 ± 0.712	0.51	[-0.16-1.18]	0.128
V [mm^3]	2037 ± 574	2031 ± 526	6.37	[-343-356]	0.970
TOTA [mm^2]	1507 ± 294	1547 ± 265	-40.6	[-232-151]	0.660

Lateral meniscus	mJSN	no JSN	Diff #		
	Mean ± SD	Mean ± SD	Mean	[95% CI]	p-value
Tibial plateau coverage					
ACdAB.Covp [%]	62.2 ± 6.77	58.8 ± 5.99	3.43	[-1.79-8.66]	0.183
OvD.Me [mm]	-17.1 ± 1.93	-16.2 ± 2.20	-0.90	[-2.51-0.71]	0.253
OvD.Max [mm]	-10.2 ± 2.45	-9.48 ± 2.65	-0.68	[-2.60-1.23]	0.459
OvD.c5 [mm]	-11.9 ± 2.44	-10.7 ± 2.80	-1.25	[-3.25-0.75]	0.204
Meniscus extrusion					
Ex.Me [mm]	-1.62 ± 1.44	-1.38 ± 1.74	-0.24	[-1.46-0.98]	0.683
Ex.Max [mm]	7.36 ± 1.76	7.06 ± 1.08	0.30	[-0.73-1.32]	0.548
Ex.c5 [mm]	-0.716 ± 0.90	-0.476 ±1.13	-0.24	[-1.08-0.60]	0.554
TA.uncovp [%]	3.34 ± 2.79	3.89 ± 3.92	-0.55	[-3.06-1.96]	0.648
Meniscus size					
Wid.Me [mm]	9.60 ± 1.52	9.07 ± 1.20	0.54	[-0.46-1.53]	0.269
Wid.Max [mm]	14.2 ± 2.42	13.4 ± 2.01	0.78	[-0.86-2.41]	0.330
Wid.c5 [mm]	12.6 ± 2.41	11.4 ± 2.64	1.15	[-0.74-3.04]	0.214
Th.Me [mm]	2.65 ± 0.279	2.59 ± 0.322	0.05	[-0.11-0.22]	0.495
Th.Mav [mm]	6.45 ± 0.930	6.47 ± 0.969	-0.02	[-0.44-0.41]	0.934
V [mm^3]	1953 ± 519	1877 ± 532	76.3	[-231-384]	0.606

TOTA [mm^2]	1503 ± 310	1462 ± 273	41.2	[-128-211]	0.615

Abbreviations see Table 1.

Table 3: Semi-quantitative evaluation of the medial meniscus morphology and extrusion according to the MOAKS grading system

	JSN 1 knees		JSN 2/3 knees	
	mJSN	no JSN	mJSN	no JSN
Morphology:				
Grade 0/1	34.9%	62.8%	35.3%	52.9%
Grade 2-5	32.6%	30.2%	17.6%	35.3%
Grade >6	32.6%	7.0%	47.1%	11.8%
Extrusion body				
Grade 0	30.2%	37.2%	5.6%	52.9%
Grade 1	20.9%	39.5%	17.6%	17.6%
Grade 2	34.9%	20.9%	35.3%	23.5%
Grade 3	14.0%	2.3%	41.1%	5.88%

Morph: meniscus morphology: 1= signal change; 2= radial tear; 3= horizontal tear; 4= vertical tear; 5= complex tear; 6= partial maceration; 7= complete maceration; Ex.total: extrusion in the total meniscus: 0:< 2mm; 1: 2-2.9mm; 2: 3-4.9mm; 3:> 5mm; Ex.body: extrusion in the meniscus body; Root tear: meniscus root tear: 1= present