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Introduction of an MR-based semi-quantitative score for assessing partial meniscectomy and relation to knee joint degenerative disease: data from the Osteoarthritis Initiative

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2]	ntroduction of an MR-based Semi-quantitative Score for Assessing Partial Meniscectomy
3	and Relation to Knee Joint Degenerative Disease:
4	Data from the Osteoarthritis Initiative

5Abstract

6**Objectives:** To develop an MR-based semi-quantitative meniscus scoring technique for 7postoperative assessment of the degree of meniscal resection, to test its reproducibility and to 8study the relationship between amount of resection and degenerative disease burden.

9Methods: We studied the right knee of 135 participants from the Osteoarthritis Initiative that 10underwent meniscal surgery an average of 14 years previously. The amount of meniscal resection 11was assessed on baseline 3.0T MRIs and calculated as meniscus resection score (MenRS) with a 12range of 0 to 18. Knee abnormalities at baseline and 48-month were graded using a modified 13Whole-Organ Magnetic Resonance Imaging Score (WORMS). Subjects were also stratified 14according to meniscal resection performed after injury versus without preceding injury. 15Statistical analysis included intra-class correlation coefficient (ICC) to determine reproducibility 16as well as regression models and partial correlations to correlate MenRS with WORMS 17outcomes.

18**Results:** ICC values for intra- and inter-observer reproducibility of MenRS were 0.980 and 190.977, respectively. Overall, the amount of meniscal resection showed a significant correlation 20with baseline WORMS grades: higher MenRS was associated with higher total WORMS grades 21(p=0.004), cartilage (p=0.004), and ligament (p<0.001) subscores. However, no significant 22association between MenRS and change in WORMS grades over 48 months was found. The

23relationship between MenRS and baseline WORMS grades did not change after adjusting for a 24reported history of knee injury.

25**Conclusions:** Postoperative assessment of knee following partial meniscectomy using the newly 26developed MenRS showed excellent reproducibility and significant cross-sectional correlation 27with WORMS gradings.

28

29Keywords

30Partial meniscectomy; Meniscus; Magnetic resonance imaging; Knee osteoarthritis

31

32Key Points

331. The newly developed semi-quantitative MR-based meniscal resection score demonstrated

34excellent reproducibility.

352. A significant correlation between the amount of meniscal resection measured using the 36newly developed score and the degree of overall knee joint degenerative disease and cartilage 37defects was found.

38

39Abbreviations

40BMI = body mass index 41DESS = dual echo at steady state 42ICC = intra-class correlation coefficient 43KL = Kellgren-Lawrence 44MenRS = Meniscus Resection Score 45OA = Osteoarthritis 46OAI = Osteoarthritis Initiative 47WORMS = Whole-Organ Magnetic Resonance Imaging Score 48WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index 49

50Introduction

51Conservative treatment for meniscal tears [1]-[2], has been advocated over meniscectomy to 52reduce the risk of knee osteoarthritis (OA) [3-5]. However, partial meniscectomy is to some 53extent unavoidable [6] and is still commonly performed in the Western World with an incidence 54of 300 per 100,000 people annually [7].

A large number of predictive factors for the development of knee OA after meniscectomy A large number of predictive factors for the development of knee OA after meniscectomy for the amount of meniscus removed remaining the strongest predictor [8] with the amount of meniscus removed remaining the strongest predictor [8] Number of the amount of meniscus removed remaining the strongest predictor [9] and age at Saurgery [10]. When comparing different meniscectomy techniques, partial meniscectomy has syshown significantly better radiologic and functional outcomes than subtotal and total 60meniscectomy [11-13]; the benefits of more conservative meniscectomies were also highlighted 61by biomechanical evidence that joint stress on articular cartilage increased proportionally to the 62amount of meniscus resected [14-16]. Furthermore, Englund et al noted that the type of meniscal 63tears (degenerative or traumatic tears) may have confounded the association of the degree of 64resection with radiographic and symptomatic osteoarthritis [17; 18].

To the best of our knowledge, few studies have documented the amount of meniscal 66resection in clinical practice, thus the exact effect of various size of resection on subsequent OA 67risk remains unknown. Hede et al calculated the percentage of removed meniscal surface on 68postoperative drawings which were made to indicate the area excised from each meniscus, and 69found it to be inversely related to knee joint function [12]. A quantitative MRI method has been 70validated to determine the reduction in meniscal volume after meniscectomy [19; 20]; however, 71manual segmentation of the meniscus is a time-consuming process, limiting its potential to be 72used in large clinical studies [21].

To date, MR imaging is the standard technique to analyze the postoperative appearance of 74the resected meniscus [22], detect meniscal deficiencies [23; 24] and reveal OA-associated 75abnormalities [25; 26]. Thus, the purpose of our study was (1) to develop an MR-based semi-76quantitative scoring approach to assess the degree of meniscal resection (meniscus resection 77score, MenRS), (2) to evaluate its reproducibility, (3) to correlate the MenRS with the 78degenerative disease burden both cross-sectionally and longitudinally.

79

80Methods

81This study utilized data from the Osteoarthritis Initiative (OAI; https://oai.epi-ucsf.org/), a 82longitudinal multi-center study of 4796 subjects aimed at identifying risk factors for knee OA. 83Informed consent was obtained from all participants; the study was compliant with the Health 84Insurance Portability and Accountability Act and was approved by the local institutional review 85boards of all participating centers.

86

87Subjects

Subjects with meniscal surgery of the right knee were selected from the OAI, excluding 89individuals with endstage OA of the right knee at baseline (baseline Kellgren-Lawrence (KL) 90grade higher than 3) and a history of rheumatoid arthritis. Individuals with multiple meniscal 91surgeries or ACL reconstruction were also excluded. The remaining subjects were categorized 92into 2 groups according to their reported history of preceding knee injury (badly enough to limit 93ability to walk for at least two days). For subjects with preceding knee injury, the follow-up 94question "Was this meniscal surgery performed to repair an injury episode?" was also part of the 95selection and needed to be answered as "yes". To obtain a clear association of knee injury and 96meniscal surgery, we included only subjects who had meniscal surgery within 2 years after an 97episode of knee injury [8; 10]. In total, 158 subjects with preceding knee injury and 73 without 98were selected.

⁹⁹ During the image analysis, 23 subjects showed severe meniscal deformity of the right 100knee, such as root or flap tears, severe extrusion or maceration. Since this would limit the 101meniscus scoring [27] and may have an independent impact on accelerating knee degeneration 102[28; 29], these subjects were excluded from the analysis. Subjects with bilateral meniscectomy of 103the right knee were also excluded due to the small number (n=3). To validate the score, we used 104the contralateral meniscus of the left knee as a reference [20; 30] and therefore excluded 70 105subjects with meniscectomy or meniscal deformity with or without tears of the left knee at 106baseline. Using the above criteria, a total of 95 subjects with preceding injury and 40 without 107were selected as shown in Figure 1. All subjects had undergone meniscal surgery on average14 108years (median 9 years, range 0-59 years) before baseline assessment and then were followed over 109an additional 48 months.

110

111 MR imaging

MR images were obtained at the four different clinical sites of the OAI with cross 113calibrated 3.0-T imagers (Trio, Siemens) using quadrature transmit-receive coils (USA 114Instruments). Images obtained with the following three sequences were analyzed: *(a)* coronal 2D 115intermediate-weighted (IW) turbo spin-echo (TSE) sequences [repetition time (TR)/echo time 116(TE), 3700 milliseconds (ms)/29ms]; *(b)* sagittal 2D IW TSE sequences with fat suppression 117(TR/TE, 3200ms/30ms); and *(c)* sagittal 3D dual-echo steady-state (DESS) sequences 118(TR/TE/flip angle, 16.3ms/4.7ms/25°). More details are available in the OAI MR protocol [31].

120Meniscus resection score (MenRS)

A consensus training session was performed by three musculoskeletal radiologists (D.S., 122J.N. and T.M.L.) to calibrate and standardize readings. Subsequently, the amount and location of 123meniscal resection were scored on baseline MR images of the right knee by a radiologist (D.S.). 124As shown in Figure 2, a zone classification system modified from Cooper et al [32] was used. 125Each meniscus was divided into radial and circumferential zones, each comprising one-third of 126the meniscus. Radial zones were referred to as A, B, and C for the medial meniscus (from 127posterior to anterior) and D, E, and F for the lateral meniscus (from anterior to posterior). The 128circumferential zones were 1 for the inner third, 2 for the middle third, and 3 for the outer third. 129The anterior and posterior horn were typically assessed in the sagittal plane of MR images, 130whereas the body of the meniscus was assessed in the coronal plane [33]. To avoid overlap 131between grades obtained in the different planes during our analyses we cross-referenced the 132grades using the thin section axial multi-planar reformatting of the sagittal 3D DESS sequence, 133which allows better assessment of shape and subdivisions of the entire meniscus [21].

To evaluate the amount of meniscus resected, each zone was graded either as 0 (no 135resection), 1 (< 50% of the area resected) or 2 (> 50% of the area resected) as shown in Figure 3 136and then summed across zones. The maximum value of MenRS for each meniscus was 18, which 137is consistent with near total meniscectomy. To validate the MenRS concerning the amount of 138meniscal resection, findings were compared with the contralateral meniscus, which was used as a 139reference [20; 30].

140

141

143WORMS grading

Baseline and 48-month follow-up images of the right knee were graded semi-145quantitatively to assess fairly early knee degenerative changes, using the modified Whole Organ 146Magnetic Resonance Imaging Score (WORMS) system [34]. To optimize reproducibility in the 147grading, all members in our group initially have to undergo a WORMS training. In this study, a 148trained radiologist (D.S.), blinded to subject characteristics, scored all MRIs under the 149supervision of a board certified musculoskeletal radiologist (T.M.L.). Cartilage defects were 150scored from 0 to 6, bone marrow edema pattern (BMEP) as well as subarticular cysts were 151scored from 0 to 3 in each of the same six regions (patella, trochlea, medial/lateral femur, and 152medial/lateral tibia). Other abnormalities including those of the ligaments and joint effusion were 153also graded. Since meniscal surgery was our predictor, we did not include meniscal lesions as 154one of the outcomes. We calculated sum scores combining all five imaging parameter categories 155as well as for each imaging category individually over all sub-regions of each knee.

156

157Reproducibility

Two radiologists (D.S., J.N.) independently graded meniscal resection in 20 randomly 159selected subjects to determine inter-reader reproducibility. After a 1-month interval, the grading 160was repeated to determine intra-reader reproducibility. Intra- and inter-reader reproducibility of 161the amount of meniscal resection were assessed by the intra-class correlation coefficients (ICCs) 162and the Bland-Altman plots.

163

164Statistical analyses

Statistical analyses were performed with STATA (Version 14; Stata, College Station, statistical analyses were performed with STATA (Version 14; Stata, College Station, using a two-sided, 0.05 level of significance. Subject characteristics were calculated to subjects with and without preceding injury. Between-group differences were to subject to assess the associations of MenRS with baseline WORMS to grades and change in WORMS grades (independent variable: MenRS, dependent variables: mean to subject with numeric dependent variables (i.e. total WORMS grades as to subject as a subject of subject variables (i.e. total WORMS grades as to subject as subject variables (i.e. the presence of effusion).

Since previous studies have highlighted that knee OA following meniscectomy is 176primarily found at the tibiofemoral joint [14; 35], four separate compartmental predictors were 177examined for cartilage defects, BMEP and subchondral cysts: index compartment (surgical 178tibiofemoral joint), contralateral compartment (nonsurgical tibiofemoral joint), femoral 179compartment (lateral and medial femur) and tibial compartment (lateral and medial tibia).

180 In a subsequent analysis, we examined whether the occurrence of a preceding injury 181confounded the relationship between MenRS and WORMS grades by including injury as a 182covariate. All analyses were adjusted for age at baseline, age at surgery, sex and baseline BMI.

183

184**Results**

185Subject characteristics

186 Subject characteristics are shown in Table 1. No significant differences were found between 187subjects with and without preceding injury except for the mean age at surgery, which was 188significantly higher in subjects without preceding injury compared to those with preceding injury 189(51.7±12.0 years vs 41.2±15.4 years, p<0.001).

190

191Validation using the contralateral side as a reference

Comparing the corresponding menisci of the resected right knee and the control left knee, 193differences in meniscal morphology were found in 96 of 135 menisci and all of these knees had a 194meniscal resection with MenRS=1-18. Even after review with the contralateral side no 195differences in meniscal morphology were found in 39 subjects. In these menisci, resection or 196debridement may have been minimal, which was not visualized with MRI, and therefore we 197scored them as MenRS=0. In these 39 subjects cartilage in the tibiofemoral compartment was 198found to be significantly less damaged at baseline than in those 96 subjects with meniscal 199resection grade 1-18 (2.31 ± 2.41 versus 4.79 ± 4.48 , coefficient: 2.94, p<0.001) but longitudinal 200change over 48 months was not significantly different (p>0.05).

201

202Scoring amount of meniscus resected

The amount and location of the resected meniscus, assessed with the proposed method on 204baseline MR images are demonstrated in Table 2. Of the 96 subjects with MenRS>0, the mean 205score in subjects with preceding injury was found to be significantly higher compared to those 206without preceding injury (7.83 ± 6.21 vs 5.01 ± 3.65, p=0.03). In addition, scores ranging from 20716 to 18, representing a resection of most meniscal tissue, were significantly more often present 208in subjects with preceding injury compared to those without preceding injury (16.8% vs 2.5%, 209p=0.02).

211Reproducibility

ICCs for intra- and inter-reader agreement of MenRS in the overall meniscus were 0.980 213(95% CI: 0.949, 0.992) and 0.977 (95% CI: 0.941, 0.991), respectively. In the Bland-Altman 214plots of intra- and inter-reader assessments, most of the values ranged within a mean difference \pm 2151.96 SD of -0.15 \pm 2.72 and -0.05 \pm 2.95, respectively (Figure 4). Furthermore, intra-reader ICCs of 216MenRS in anterior horn, body and posterior horn were 0.992, 0.968 and 0.966, while inter-reader 217ICCs were 0.998, 0.963 and 0.905. For WORMS gradings, the inter-reader reliability was good 218with ICCs of 0.876-0.919 for cartilage defects, BMEP and cysts, as assessed during the training. 219

220Association between amount of meniscus resected and degenerative disease burden

Significant associations were found between amount of meniscus resected and baseline 222WORMS grades, with higher MenRS being associated with higher WORMS grades (Table 3, 223Figure 5). The MenRS were significantly associated with total WORMS for all five MR imaging 224parameter categories (r=0.25, p=0.004), as well as separately for cartilage (r=0.25, p=0.004) and 225ligaments (r=0.32, p<0.001), but not for BMEP, subchondral cysts and joint effusion (odds ratio: 2261.01, 95% CI: 0.92-1.10, p=0.86).

In separate analyses of index and contralateral compartments, the MenRS showed 228significant correlations with baseline total WORMS, cartilage lesions and BMEP in the index 229compartment (r range 0.33-0.37, p \leq 0.001), while no or only weakly significant correlations were 230found in the contralateral compartment (r range 0.18-0.21, p range 0.049-0.09). With respect to 231the femoral and tibial compartments, the correlations between MenRS versus baseline cartilage 232lesions and BMEP were both statistically significant (femoral, r range 0.33-0.36, p<0.001; tibial, 233r range 0.43-0.49, p<0.001).

However, the MenRS was not significantly associated with changes in WORMS grades 235over 48 months, except for BMEP of the index compartment (r=-0.25, p=0.03). After further 236adjustment for preceding knee injury, the associations of MenRS with baseline WORMS and 237change in WORMS grades remained nearly the same (Supplemental Table). Assessing clinical 238features, the MenRS did not show significant associations with the baseline Western Ontario and 239McMaster Universities Osteoarthritis Index (WOMAC) scores as well as change in WOMAC 240scores over 48 months (linear regression, p-range =0.27-0.95).

241

242Discussion

243In this study, we developed an MR-based semi-quantitative scoring method to assess the amount 244of meniscus removed in patients that underwent meniscectomy. The score showed excellent 245intra- and inter-reader reproducibility and was significantly associated with severity of 246postoperative knee OA using cross-sectional WORMS analysis. However, there was no 247significant association between the MenRS and WORMS change scores between baseline and 24848-month. Furthermore, the association of MenRS with WORMS grades did not vary when 249further adjusted for preceding knee injury, though larger resections were found after previous 250injury.

Standard partial meniscus resection procedures like shaving or debridement make the Sizexact measurement of the resected meniscal volume challenging [20]. To date, two approaches been published for assessing meniscal resection. The International Society of Arthroscopy, SizeXact Committee recently proposed for surgeons SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after SizeXact calculate the percentage of resected meniscal surface area on a diagram created after 257(ICC=0.65) [36]. Bowers et al validated a quantitative MRI approach for detecting a decrease in 258meniscal volume due to partial resection [19; 20]. Nevertheless, the time required for meniscal 259segmentation by different techniques varied between 30 and 90 minutes [21; 34; 37]; and its 260validity in detecting a small amount of resection was questioned, especially for patients with 261meniscal hypertrophy [29].

The proposed scoring method offers a novel way to evaluate the degree of resection after 263meniscectomy using routine knee MRIs. The zone classification of meniscal resection in our 264method was based on Cooper's classification system that has been widely used to standardize 265description of meniscal tears and guide surgical treatment [32; 36]. Using the menisci of the 266contralateral knee as a reference our approach showed excellent performance. The evaluation of 267the amount of the resected meniscus on a 3-point scale for each zone was concise and simple 268with 5-7 minutes required for a musculoskeletal radiologist to score each knee. The comparison 269with the contralateral knee only added approximately 2 minutes.

The intra- and inter- reproducibility for the MenRS detected amount of resection per 271meniscus, and even per radial zone, were excellent. The MenRS showed significant positive 272associations with total WORMS as well as cartilage and ligament sub-scores, indicating that a 273larger amount of meniscal resection was associated with a higher number of knee osteoarthritic 274abnormalities. Biomechanical studies have repeatedly documented increases in contact stress and 275shear stress over articular cartilage, changes in pressure distributions and loss of joint stability 276with respect to the amount of meniscus resected [15; 38; 39]. These adverse effects potentially 277increase the susceptibility of cartilage to damage and place the knee at higher risk of OA 278development [40], in line with our findings. No significant correlations between MenRS versus 279BMEP and subchondral cysts were found. This may be related to the variability of BMEP over 280time and the strong association between BMEP and subchondral cysts as described previously 281[41; 42]. As expected, separate analyses showed that the MenRS was significantly associated 282with WORMS grades of the index compartment but not of the contralateral compartment.

When correlating MenRS with changes in WORMS scores over 48 months, no significant 284differences were shown in the majority of imaging parameter categories and compartments. 285However, these findings do not suggest that the amount of meniscal resection is not associated 286with the progression of knee OA after meniscectomy. Subjects in our study had undergone 287meniscal surgery an average of 14 years earlier. At baseline assessment, many subjects already 288had radiographic knee OA and substantial cartilage lesions. We hypothesize that progression of 289degenerative changes may occur soon after surgery and then plateau or decrease as the joint 290adjusts to the meniscal resection [5; 35].

Our findings confirmed the observation of Englund et al [17; 18] that subjects with 292preceding injury appeared to undergo meniscectomy at a younger age and had a higher rate of 293total resection compared to subjects without preceding injury. Several previous studies reported 294higher evidence of knee OA following resection of degenerative than traumatic meniscal tears 295[35; 43]. Conversely, Matsusue et al found no significant difference in clinical outcomes between 296patients with and without a history of trauma [3]. In our study, when determining the association 297of amount of meniscal resection and the severity of postoperative knee OA, we found no 298significant difference between subjects with and without preceding injury. These findings 299indicate that in patients with meniscal surgery the resection amount is likely the main risk factor 300for the subsequent knee joint degeneration, whereas the initial reason for meniscal resection 301seems to be subordinate. 302 Moreover, our proposed method could detect the part of the meniscus resected 303(lateral/medial, AH/body/PH). Subjects with a lateral meniscectomy sustained a significantly 304worse baseline WORMS outcomes in the global and index compartments when compared to 305those with medial meniscectomy. When investigating the association between side of resection 306and WOMAC scores, no significant differences were found between medial and lateral 307meniscus. However, the limited number of lateral meniscectomies in our study (baseline: n=14, 30848-month: n=10) should be noted.

Our study has several limitations. Firstly, surgical reports of meniscectomy were not 310available for participants in the OAI dataset due to the HIPAA compliance. However, to ensure 311accuracy on the information about the participants' meniscectomy, we used the self-reported 312questionnaires to identify participants with meniscectomy and moreover, all MRIs were 313reviewed thoroughly by a musculoskeletal radiologist for signs of meniscal surgery. Secondly, 314baseline MRI scans were acquired with long interval following surgery, potentially not capturing 315important imaging findings occurring directly after meniscectomy. Finally, preoperative MRIs 316are more readily available in clinical trials and would be helpful for further investigating the type 317of meniscal tears [17]. In our study, we utilized contralateral knee MRIs and found them to be a 318reliable reference. Of further note was that the index (right) knee showed significantly higher 319WOMAC scores both at baseline and 4-year FU when compared to the contralateral (left) knee, 320which was in line with previous studies finding that radiographic OA was substantially more 321frequent in the operated knee than in the contralateral knee [44, 45].

In conclusion, the described MR-based semi-quantitative scoring method is a concise and 323reproducible technique for assessing various degrees of partial meniscectomy and the score is 324significantly correlated with the severity of postoperative knee OA. Subjects had an increased 325risk of cartilage defects, BMEP and ligamentous abnormalities with increased meniscus 326resection, particularly in the index compartment.

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451 Table Legends

452Table 1. Subject characteristics

453

454**Table 2.** MR-based semi-quantitative scoring of amount and location of meniscus resected

456**Table 3.** Association of meniscus resection score with baseline WORMS and change in WORMS 457grades over 48 months ^a

458

459Figure legends

460Figure 1 Flowchart shows subject selection from OAI database.

461

462Figure 2 Zone classification of the meniscus for scoring amount of meniscus resected.

463

464**Figure 3** Grading amount of meniscus resected for each involved zone. Schematic drawings 465(left) and MR images (right) show grade 1 < 50% (A) and grade 2 > 50% (B) of the subregional 466volume resected in the inner third of the body of medial meniscus (zone B1) in the right knee. 467The resected meniscal tissues, cross-hatched in schematic drawings, are noted as truncated 468appearance (arrow) in the coronal 2D intermediate-weighted turbo spin-echo sequence and 469substance loss (arrow) in the axial multi-planar reformatting of the sagittal 3D dual-echo steady-470state sequence. The small MR images show the contralateral meniscus of the left knee which are 471used as a reference.

473**Figure 4** Bland-Altman plots showing (A) the difference between assessments by two readers,474and (B) the difference between two occasionally different assessments by one reader.475

476Figure 5 Sagittal intermediate-weighted turbo spin-echo fat-suppressed MR images of the left 477knee at baseline (A, D), the right knee at baseline (B, E) and the right knee over 48 months (C, 478F). A-C show the MR images of a 45-year-old woman who had a knee injury and then underwent 479medial partial meniscectomy (arrows) (meniscal resection with a score of 4 at the posterior horn) 480when she was 30 years old. D-F show the MR studies of a 57-year-old man who had no knee 481 and underwent partial meniscectomy (arrows) (meniscal resection with a score of 2 at the 482posterior horn) when he was 50 years old. The 45-year-old woman with a large amount of 483meniscal resection demonstrated a full-thickness focal cartilage defect at the medial tibia at 484baseline (thin arrows) (medial tibial cartilage WORMS grade 5); over 48 months, she developed 485BMEP at the medial tibia (*) (medial tibial BMEP grade 0 in B and 2 in C) and thinning of the 486cartilage at the medial femoral condyle (arrowheads) (medial femoral cartilage WORMS grade 0 487 in B and 3 in C). In contrast, only a partial thickness cartilage defect at the medial femur 488(arrowheads) was seen in the 57-year-old man with a relatively small amount of meniscal 489 resection and no progression was detected over 48 months (medial femoral cartilage WORMS 490grade 3 in B and C).