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Direct Comparison of Fixed Flexion Radiography and MRI in Knee Osteoarthritis: Responsiveness Data from the Osteoarthritis Initiative

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Abstract

Objective—Minimum radiographic joint space width (mJSW) represents the FDA standard for demonstrating structural therapeutic benefits for knee osteoarthritis (KOA), but only shows moderate responsiveness (sensitivity to change). We directly compare the responsiveness of MRI-based cartilage thickness and JSW measures from fixed-flexion radiography (FFR) and explore the correlation of region-matched changes between both methods.

Methods—967 knees of Osteoarthritis Initiative participants with radiographic KOA were studied: 445 over one year with coronal FLASH MRI and FFR, and 375/522 over one/two years with sagittal DESS MRI and FFR. Standardized response means (SRM) of cartilage thickness and mJSW were compared using the sign-test.

Results—With FLASH MRI, SRM was −0.28 for medial compartment (MFTC) cartilage loss vs. −0.15 for mJSW, and −0.32 vs. −0.22 for the most sensitive MRI subregion (central MFTC) vs. the most sensitive fixed location JSW(X=0.25). With DESS MRI, one-year SRM was −0.34 for MFTC vs. −0.22 for mJSW and −0.44 vs. −0.28 for central MFTC vs. JSW(X=0.225). Over two years, the SRM was significantly greater for MFTC than for mJSW (−0.43 vs. −0.31, p=0.017) and for central MFTC than for JSW(X=0.225) (−0.51 vs. −0.44, p<0.001). Correlations between changes in spatially matched MRI subregions and fixed location JSW were not consistently higher (r=0.10–0.51) than those between non-matched locations (r=0.15–0.50).

Conclusions—MRI displays greater responsiveness in KOA than JSW FFR-based JSW, with the greatest SRM observed in the central medial femorotibial compartment. Fixed-location radiographic measures appear not capable of determining the spatial distribution of femorotibial cartilage loss.

Keywords

Sensitivity to change; Radiography; Fixed Flexion; Magnetic resonance imaging; Knee osteoarthritis

INTRODUCTION

Quantification of structural disease progression in knee osteoarthritis (OA) is of great importance for evaluating risk factors for OA progression [1–3] and for evaluating the response to pharmacological and non-pharmacological treatment. Magnetic resonance imaging (MRI)–based measurement of cartilage morphology (e.g. cartilage volume, thickness, and subregional thickness) has been suggested to be more sensitive to change than radiographic measures of progression (e.g. increase in joint space narrowing [JSN] scores and reduction in joint space width [JSW]), and hence to be a more powerful tool for identifying risk factors and for evaluating therapeutic intervention. MRI is considered to be more specific to (regional) cartilage loss [4,5] than radiography as there is evidence that JSW change is strongly associated with meniscal pathology [6–8]. Further, sensitivity to change in radiography critically depends on achieving optional medial tibia plateau alignment, which poses a considerable challenge in clinical studies [9–13].

The 1999 Food and Drug Administration (FDA) draft guidance, which has not been revised to date, considers radiographic JSW the reference standard for demonstrating benefits of therapeutic intervention in OA [14]. Recently, the Osteoarthritis Research Society International (OARSI) published a series of articles as a response to questions raised by the FDA for revising the 1999 draft guidance document [15]. As part of this OARSI FDA initiative[15], responsiveness to change and reliability of radiographic JSW in knee OA was reviewed using the standardized response mean (SRM = mean change/standard deviation [SD] of change) as a measure of responsiveness to change [13] An overall pooled SRM of 0.33 (95% confidence interval [CI] 0.26/0.41, positive SRM values defined as sensitivity to decrease in JSW) was reported for 43 estimates with variable follow-up (mean sample size = 100). Responsiveness (SRM) was 0.24 for studies with less than 1 year follow-up, 0.25 for those with 1–2 years of follow-up, and 0.57 for those with >2 years of follow-up. In parallel, the responsiveness of MRI was reviewed [16] and a pooled SRM for quantitative cartilage morphometry of the medial femorotibial compartment of −0.86 (95% CI −1.26/−0.46, negative SRM values defined as sensitivity to decrease in cartilage thickness) was reported from 31 estimates with variable follow-up (mean sample size = 92). Substantial differences in SRMs were noted between earlier (published before 2007) and more recent studies (2007 to 2009), and between different cartilage regions of the knee[16].

The direct comparability of SRMs between radiography and MRI from these reviews is limited, because both the cohort composition (radiographic stage of knee OA) and the follow-up time, which differ between studies, critically impact the observed rates of change and SRMs [17]. Only few studies have directly compared the rate of change and the sensitivity to change between radiography and MRI in the same knees and over the same observation period[18–20] and these have been conducted in rather small samples. Further, there have been recent innovations in the standardization of radiographic acquisition techniques [9–11], computerized and standardized (location-specific) JSW measurement of radiographs [21], MRI sequence and magnet development [11,22], and subregional measures of cartilage change with MRI [23–25], that have not been accounted for in the OARSI FDA initiative literature review, which included literature of up to 2009.

The objective of the current study therefore was to directly compare the responsiveness of minimum and location-specific JSW measures of standardized fixed-flexion radiographs (FFR) with compartment-level and subregional cartilage thickness measures obtained from 3Tesla MRI sequences in the medial compartment of the same knees selected from the Osteoarthritis Initiative (OAI). Specifically, we stratified the relative responsiveness of MRI versus FFR between different follow-up periods (one- and two years), radiographic disease stages (Kellegren Lawrence grades [26]), and MRI acquisition protocols (coronal FLASH, sagittal DESS). Further, we studied the correlation between location-specific JSW FFR measurements and anatomically corresponding subregional cartilage thickness change from MRI, to explore whether radiography is capable of assessing the spatial distribution of cartilage loss within the medial femorotibial joint space.

METHODS

Sample selection

OAI participants were aged 45 to 79 years at study start, had no contraindications to 3T MR imaging, had at most unilateral end-stage knee OA, had no rheumatoid or other inflammatory arthritis, and were able to walk without aids. Please see http://oai.epi-ucsf.org/datarelease/docs/StudyDesignProtocol.pdf for detailed inclusion and exclusion criteria of the OAI.

We used knees with definite radiographic OA (defined equivalent to a Kellgren and Lawrence grade [KLG] [26] >=2 as definite tibiofemoral osteophyte with or without joint space narrowing,) for which quantitative measurements of medial JSW (funded by the OAI for public use) and quantitative MRI measurements were available. Knees analysed at baseline and year one using coronal FLASH MRI were previously selected as part of a consortium-initiative of private sponsors focusing on knees at advanced stages of radiographic OA (please see [27,28] for a detailed description of the selection criteria). The analysis of knees using sagittal DESS MRI was funded by the OAI. Knees in the DESS sample were selected by the OAI coordinating center from the OAI progression subcohort to form a "core image assessment cohort" and included only knees with frequent symptoms and KLG 2 or 3 in site readings at baseline [17,28,29]. Baseline cartilage measurements for the FLASH sample, baseline and follow-up cartilage measurements for the DESS sample, and quantitative JSW measurements for both samples are available at http://oai.ucsf.edu/datarelease/. The analyses in the present study classified the baseline OA status of knees using the KL grades from the OAI-sponsored central radiographic readings[30] instead of the KL readings performed at the OAI clinical sites during enrollment.

A complete set of semi-quantitative radiographic readings at baseline [31], medial JSW measurements, and subregional cartilage thickness measurements (MRI) were available for a total of 1080 knees from the OAI progression subcohort (520 with FLASH MRI [baseline

and one year follow-up] and 560 with DESS MRI [baseline and two year follow-up, and 508 of these also with one-year follow-up]). Knees were excluded if the length of the observation periods differed by 45 days (one year follow-up, FLASH: n=75 or DESS sample: n=101) or by 90 days (two year follow-up, DESS sample: n=29) between radiography and MR imaging. When data on both knees from the same participant was available, the knee with the less severe KL grade or the left knee was excluded (DESS sample one/two year follow-up: n=8/9), because longitudinal changes in both knees of the same participant may not be independent. This selection resulted in a total of 967 knees (445 FLASH with one year, 522 DESS with two year, of which 375 DESS also had one year follow-up).

Imaging

As part of the OAI image acquisitions, bilateral FFR was performed annually using a SynaFlexer™ frame (Synarc, Inc., San Francisco, CA) [32–34]. The OAI knee MRI protocol included sagittal DESS (in-plane resolution: 0.37×0.46mm interpolated to 0.37×0.37mm, slice thickness: 0.7mm, repetition time: 16.3ms, echo time: 4.7ms, flip angle: 25°) and coronal FLASH MRI data (in-plane resolution: 0.31×0.31mm, slice thickness: 1.5mm, repetition time: 20ms, echo time: 7.57ms, flip angle: 12°), both with water excitation, that were acquired annually using 3 Tesla MRI scanners (Siemens Trio, Siemens, Erlangen, Germany) and quadrature transmit-receive knee coils [22,35]. The MR sequences were planned parallel to the long axis of the femoral diaphysis and either parallel (coronal FLASH) or perpendicular (sagittal DESS) to the line tangent to the posterior cortices of the femoral condyles [22,29].

Image analysis

The minimum JSW in the medial femorotibial compartment was measured in the digitized bilateral baseline, one, and two year follow-up FFRs using an automated software application [19,21,36]. In addition, fixed distance measures of the JSW were obtained between the external and internal border of the medial femorotibial compartment. To that end, the software automatically determined the tangent lines to the femoral condyles, which represented the x-axis (external to internal, internal = adjacent to the intercondylar notch) of the coordinate system. The medial and lateral borders of the knee were marked manually, perpendicular to this x-axis and tangential to the greatest prominence of the medial and the lateral femoral epicondyles (Figure 1). After normalization to the range between 0 (medial epicondyle) and 1 (lateral epicondyle), the x-axis was used to define the fixed locations, and JSW(x) measurements were performed between x=0.15 (external) and x=0.30 (internal) for the medial femorotibial compartment according to a coordinate system defined elsewhere[19]. The output was verified by an expert reader (JD), and corrected if needed. Because lateral JSW measurements were only available for parts of the cohort and because JSW measurements were reported to reliably measure the cartilage thickness in the medial but not in the lateral compartment [37], this study included only medial compartment measurements.

MRI-based cartilage thickness measurements were computed from segmentations of the weight-bearing femorotibial cartilage plates that were performed by fourteen experienced operators with blinding to the time of acquisition and to the baseline radiographic readings [38] (Figure 1). All segmentations underwent quality control by an expert reader and were corrected by the operators, if necessary. Cartilage thickness over the total area of subchondral bone (ThCtAB) was computed in the medial femorotibial cartilage plates (MT and cMF), the medial femorotibial compartment (MFTC=MT+cMF), and in 8 medial femorotibial subregions (5 in MT and 3 in cMF; Figure 1) [24]. In addition to the individual subregions (Figure 1), cartilage thickness measurements in central, external and internal subregions of the medial tibia and central, external and internal (internal = adjacent to the

intercondylar notch) subregions of the central, weight-bearing part of the medial femoral condyle were added to combined central (cMFTC), external (eMFTC), and internal (iMFTC) femorotibial subregions. Based on previous findings that reported similar responsiveness [39], the current analysis relied on the segmentation of every second slice of the DESS (1.4mm intervals).

Statistical analysis

The mean change (MC), standard deviation (SD) of change, and 95% confidence intervals of change were determined for JSW (FFR) and cartilage thickness measures (MRI). Percent changes were computed as $100 * MC [\mu m]/(Mean baseline value [\mu m])$ for each sample. The standardized response mean (SRM=MC/SD of change) was used to describe the responsiveness (=sensitivity to change), because it has been widely used in quantitative OA studies and can therefore be easily compared between studies. The correlation of changes between the two imaging methodologies was calculated using parametric (Pearson r) correlation coefficients. For the analysis of location-specific correlations, the seven fixed-distance measures between JSW(x=0.150) and JSW(x=0.300) were partitioned into two external (JSW(x=0.150) and JSW(x=0.175)), three central (JSW(x=0.200), JSW(x=0.225), and JSW(x=0.250)), and two internal (JSW(x=0.275) and JSW(x=0.300)) measures. The maximum correlation observed between matched locations (external JSW vs. eMFTC, central JSW vs. cMFTC, internal JSW vs. iMFTC) was compared to the maximum correlation observed for non-matched locations.

To assess whether the SRM differed significantly between FFR-based JSW and MRI-based cartilage thickness, the observed changes in each knee were scaled by the standard deviation of the changes among all knees in each of the DESS and FLASH subsamples. A two-sided sign-test was then applied to the difference between these standardized changes (MRI cartilage thickness – radiographic JSW), to determine whether the number of positive or negative differences was significantly greater than expected by chance. Because this result depends on the estimated SD, bootstrapped (n=100,000) samples of both cohorts were generated and randomization tests (randomly inverting the sign of the scaled differences) were carried out to account for the uncertainty in the estimate of the SD of change in testing for differences between SRM of change in JSW and cartilage thickness. P-values were estimated as the proportion of p-values from bootstrapped sign tests as small as the one computed from the observed results. These tests were applied to compare the responsiveness between FFR-based mJSW and MRI-based cartilage thickness in MFTC, and between the most sensitive fixed location measure (FFR) and the most sensitive subregion (MRI) within each sample. The required significance level (p<0.05) was adjusted (p<0.025) to account for these two parallel comparisons within each sample (mJSW vs MFTC and most sensitive fixed location (JSW) vs. most sensitive subregion (MRI)). Because the objective of the study was not to test for significant differences in either one of the two samples, but to see whether the results were consistent in both samples, we did not correct for the analysis for two samples. Further, no correction was made for analyzing two observation periods, because these were considered complimentary and results were not interpreted independently or in isolation.

RESULTS

The FLASH sample comprised 445 knees from 281 women and 164 men (age [mean±SD]: 63.2±9.4 years, BMI: 30.1±4.7kg/m^2). Of these knees, 255 were KLG 2, 135 KLG 3, and 55 KLG 4 (Table 1). The DESS two year sample comprised 522 knees from 300 women and 222 men (age: 61.2±8.8 years, BMI: 30.3±5.0 kg/m^2). Of these knees, 256 were KLG 2, 261 KLG 3, and 5 KLG 4 (Table 1). The participants in the DESS sample for whom one-year follow-up data were available, contained 375 knees from 209 women and 166 men (age:

61.0±8.9 years, BMI: 30.2±5.1 kg/m^2, Table 1). When compared to the entire OAI progression cohort (Table 1), the FLASH sample contained a larger proportion of female participants (63% vs. 57%) and the participants in the FLASH sample were on average 1.8 years older, 1.4 cm shorter and of lower weight (−1.6 kg). There were only marginal differences between the DESS sample and the entire OAI progression cohort with regard to gender, age, BMI, height, or weight (Table 1).

Mean change (in %), the SD of change (in %), and the SRMs for FFR-based JSW and MRI-based cartilage thickness are shown in Tables 2 and 3. Mean change (in μm), SD of change (in μm), and 95% confidence intervals of change (in μm) are shown in Online Tables 1 and 2 (in μm). The fixed location measure JSW(X=0.25) was the most responsive FFR measure in the FLASH sample, whereas JSW(X=0.225) was the most responsive measure for FFR in the DESS sample; cMFTC was consistently the most responsive MRI subregion.

In the FLASH sample, the SRM observed for MFTC (−0.28) was greater than that for mJSW (−0.15), but the difference did not reach statistical significance (p=0.08). This also applied to the difference between the most sensitive MRI and FFR measures in the FLASH sample (cMFTC: −0.32 vs. JSW(X=0.250): −0.22; p=0.36). In the DESS sample, the SRMs observed over one year were greater for MFTC than for mJSW (−0.34 vs −0.22), and for the most sensitive MRI subregion than for the most sensitive FFR measure (cMFTC: −0.44 vs. JSW(x=0.225): −0.28), but again the differences did not reach statistical significance after correcting for multiple comparisons (p=0.034 and p=0.213, respectively), whereas over two years, the SRM in the DESS sample was significantly greater for MFTC than for mJSW (−0.43 vs −0.31; p=0.017) and significantly greater for the most sensitive MRI measure than for the most sensitive FFR measure (cMFTC: −0.51 vs. JSW(0.225): −0.44; p=0.0006).

Rates of change and SRMs for strata with different KL grades are shown in Tables 2 and 3, and in Online Tables 1 and 2. With MRI, the absolute longitudinal changes (in μm) and SRMs were greatest in KLG3 and smallest in KLG2 knees, and were in between for KLG4 knees (FLASH sample). With FFR, JSW measures showed a smaller rate of change and responsiveness in KLG 4 knees than in KLG 3 and KLG2 knees, except for the more internally located fixed location measures (FLASH sample, Online Table 1). Because only 5 knees were graded as KLG 4 in the DESS sample, no separate results were reported for these knees.

There was a significant (positive) correlation between mJSW and MFTC (ThCtAB) changes in both the FLASH (r=0.42) and the DESS sample (12/24 months: r=0.24/0.42, Online Table 3). The correlations in the FLASH sample were higher between mJSW and MRI-based measures than between fixed location measures and MRI, while the correlation between mJSW and MRI did not exceed the correlations observed between fixed location measures and MRI in the DESS sample. Changes in the weight-bearing femur (cMF) tended to have larger Pearson's correlation coefficients with JSW changes (FLASH r   0.42, DESS 12M/24M: r   0.26/0.47) than changes in the tibia (FLASH r   0.28, DESS 12M/24M: r   0.23/0.34, Online Table 3).

Amongst combined femorotibial subregions and FFR fixed location measures, changes showed larger correlation values for external and central than for internal measures (Online Table 3). However, correlation coefficients between fixed locations in radiographs and anatomically matched subregions in MRI were not consistently higher than non-location-matched correlation coefficients (Online Table 3).

DISCUSSION

Given the availability of newer and potentially more responsive imaging measures of cartilage, we directly compared the responsiveness of location-specific JSW measures from standardized fixed-flexion radiographs with subregional cartilage thickness measures from MRI in two large samples of the OAI progression subcohort. Key findings are that location-specific measures of JSW display greater responsiveness than minimum JSW, that the central femorotibial compartment is the most sensitive MRI subregion, and that MRI measures display a greater responsiveness than both location-specific and minimum JSW measures. Whereas moderate correlations were observed between JSW and MRI-based cartilage thickness changes, location-matched JSW and MRI measures did not exhibit consistently stronger correlations than non-location-matched comparisons, indicating that radiography is incapable of determining the regional distribution pattern (internal to external) of femorotibial cartilage loss in the medial compartment.

Previous studies that have directly compared radiography and MRI generally encompassed much smaller samples [18,20,40–42] and only one recent study compared fixed-location measures of JSW with 3T MRI measurements (based on 150 knees from the OAI)[19]. Whereas some of these studies observed a greater responsiveness for MRI than FFR[18,40,41], the more recent study [19] found greater SRMs for the new FFR-based fixed location measures than for mJSW and concluded the responsiveness of the fixed location measures to be comparable to global cartilage plate measures in 3T MRI. Using subregional measures of cartilage loss in MRI and a much larger sample, the current study more clearly demonstrated the superiority of MRI in terms of sensitivity to structural change. Further, end stage (KLG4) knees displayed substantial rates and sensitivity to change with MRI, but not with FFR, and MRI does not apply ionizing radiation. However, given the particular context and goal of a study, JSW still is a useful measure, because radiographic image acquisition and image analysis is less expensive and provides less burden on patient time. However, fixed-flexion radiography requires larger samples and/or longer observation times due to the somewhat lower sensitivity.

A greater sensitivity to change of JSW was reported by Hellio Le Graverand et al. for fluoroscopically acquired Lyon Schuss radiography than for FFR [18,43]. In the same study, Lyon Schuss also was more sensitive to change than MRI-based cartilage thickness change in MFTC [18,43]. A reason for this observation is likely related to optimal alignment of the tibia plateau when using fluoroscopic control [44] or the modified Lyon Schuss technique [45].

The SRMs reported here for MRI are smaller than those from the FDA OARSI meta-analysis of published evidence between 2002 and 2009 [16]. However, they are in the same range of other reports from the OAI [46,47] and other recent longitudinal studies [18,42,48]. In the FDA OARSI initiative meta-analysis, a trend was noted for earlier MRI studies having reported greater SRMs, potentially due to insufficient technology for effectively blinding readers to time points of image acquisitions. Further, SRMs in the OAI may be lower due to the relatively broad inclusion criteria, whereas smaller studies may have had more selective inclusion criteria in terms of risk factors for progression, and greater percentages of participants with advanced radiographic knee OA. As observed in previous studies [28,49], we found that knees with advanced radiographic OA (KLG3) showed substantially greater rates of change and SRMs than those with KLG2, both with MRI and with FFR, and KLG3 knees may therefore be of particular interest for inclusion in clinical trials.

A limitation of the current study is that the knees analyzed using the sagittal DESS and the coronal FLASH protocol were not identical and that the results from these two protocols cannot be compared directly. However, a previous study directly compared longitudinal

changes in 80 knees from the progression subcohort between these two protocols and has reported a similar rate and sensitivity to change for coronal FLASH and sagittal DESS MRI[39]. Moreover, the knees analyzed in the FLASH and DESS sample were not selected specifically for the purpose of this study, which is reflected in the somewhat heterogeneous selection criteria. In contrast to a previous publication on the FLASH cohort [28], however, the current study used a KL classification provided by a central group of readers, who also provided the central KL readings in the DESS sample [29]. Knees without definite radiographic OA (KLG 2) were excluded, to obtain samples that should be representative of clinical trial populations, to which the direct comparison between SRMs from JSW and MRI is particularly relevant.

Another limitation of the current study is that alignment readings are not yet available for the OAI cohort and we were hence unable to exclude knees with valgus malalignment, who are known to loose less cartilage medially than laterally [19,48,50]. Still, the lack of exclusion of valgus knees does not limit the comparability between medial compartment measures from radiography and MRI.

Finally, given its generality, the non-parametric sign-test was employed to test whether the sensitivity to change of MRI- and FFR-based measures differed. Further work is needed to explore whether this test can be replaced by other, more sensitive, parametric or non-parametric statistical approaches.

Most of the previous studies reported weak to moderate correlations between MRI-based cartilage loss and JSW changes in radiography [20,23,41,42] but did not attempt to correlate spatially matched measures. The correlations between changes in anatomically matched FFR and MRI locations explored here were not generally greater than those between non-matched locations. A likely reason is that the medial JSW in radiographs does not correspond with the summed cartilage thickness of MT and cMF at each location and only provides an indirect measure, particularly for the internal regions adjacent to the intercondylar area. Whereas focal loss of cartilage thickness will affect (subregional) MRI measures of cartilage thickness, it may not impact the JSW assessed by FFR in situations where the adjacent cartilage or the meniscus maintains the JSW in the compartment and the area of focal cartilage loss is not in direct contact with the opposite joint surface during imaging. Moreover, several studies found meniscus position and integrity to be strongly associated with JSN and JSW: In a study including 233 subjects with symptomatic OA and 58 asymptomatic controls, Gale at al. found a significant association between meniscal subluxation scored on MR and the severity of JSN in knees with symptomatic OA[8]. Hunter at al. reported that the meniscus position and its degeneration not only account for a substantial proportion of the variance JSW, but also found that changes in meniscal position cause a substantial proportion of change in JSW [6]. Further, radiographic JSW in the medial compartment may also be influenced by cartilage and meniscus status in the lateral compartment (and vice versa), because pseudo-widening of the medial JSW may occur in knees with lateral JSN when load is shifted to the lateral compartment. Therefore, whereas radiography provides a 2D depiction of the joint space width and a composite measure of cartilage thickness, meniscus integrity and extrusion [6], MRI directly depicts the articular cartilage (and other structures) in 3D. Studies interested in measuring subregional changes of cartilage thickness with great sensitivity to change hence profit from selecting high-resolution MRI as an imaging modality.

In conclusion, location-specific measures of JSW display superior responsiveness to measurement of minimum JSW from fixed-flexion radiographs, the central femorotibial compartment is the most responsive subregion of MRI-based cartilage thickness change, and MRI-based measures display superior responsiveness to (location-specific and minimum)

JSW. Location-matched radiographic and MRI subregions did not exhibit stronger correlations than non-location-matched comparison, suggesting that radiographic measures of JSW are not sensitive to regional differences in the pattern of medial femorotibial cartilage loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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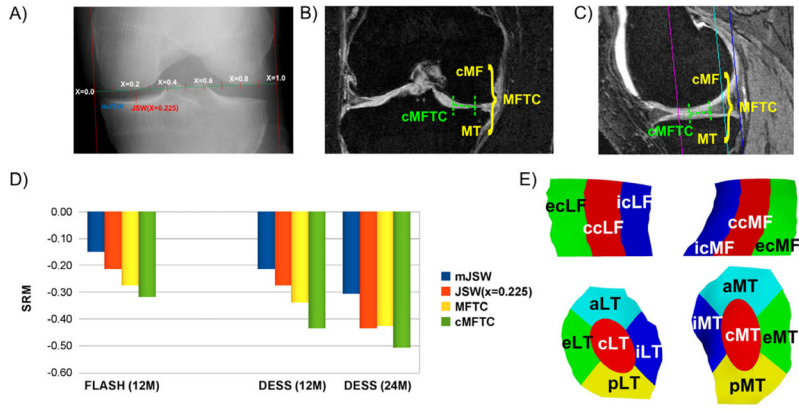
Figure 1.
A) Illustration showing the radiography-based measurement of the minimal joint space width (mJSW) and of the joint space width at the central fixed location JSW(x=0.225). B) Illustration showing the coronal FLASH MRI-based measurement in the medial femorotibial compartment (MFTC) and in the most sensitive subregion of the MFTC (cMFTC = central subregion of MFTC). C) Illustration showing the sagittal DESS MRI-based measurement in the MFTC and in the most sensitive subregion of the MFTC (cMFTC). D) Bar graph showing the sensitivity to change (standardized response mean = SRM = mean change/ standard deviation of the change) for mJSW, MFTC, and the most sensitive fixed location JSW(x) in the FLASH sample over 12 months (12M, JSW(x)=JSW(x=0.25)), in the DESS sample over 12M (JSW(x)=JSW(x=0.225)), and in the DESS sample over 24 months (24M, JSW(x)=JSW(x=0.225)). The DESS sample over 12 months is a sub-sample of the 24 months cohort, for which a complete set of 12 months measurements was available. E) Illustration showing the central (c), external (e), internal (i), anterior (a), and posterior subregions (p) computed in the medial (MT) and lateral tibia (LT) and in the central, weight-bearing part if the medial (cMF) and lateral (cLF) femoral condyle (only central, external, and internal subregions).

Table 1

Baseline (BL) demographics, observation period, Kellgren and Lawrence grades (KLG), and joint-space narrowing scores (JSN) in the medial femorotibial compartment (MFTC) for the coronal FLASH sample, the sagittal DESS sample, and the entire OAI progression cohort as reference.

		FLASH sample	DESS sample (12M)	DESS sample (24M)	OAI Progression Cohort
N		445	375	522	1390
Gender	Women (%)	281 (63.1%)	209 (55.7%)	300 (57.5%)	793 (57.1%)
	Men (%)	164 (36.9%)	166 (44.3%)	222 (42.5%)	597 (42.9%)
Side	Left (%)	2 (0.4%)	186 (49.6%)	261 (50.0%)	
	Right (%)	443 (99.6%)	189 (50.4%)	261 (50.0%)	
Age (years)	Average	63.2	61.0	61.2	61.4
	SD	9.4	8.9	8.8	9.1
BMI (kg/m^2)	Average	30.1	30.2	30.3	30.2
	SD	4.7	5.1	5.0	4.9
Height (cm)	Average	167.3	168.6	168.7	168.7
	SD	8.8	9.0	9.2	9.3
Weight (kg)	Average	84.6	86.1	86.3	86.2
	SD	16.0	16.1	16.0	16.3
KLG	0	0 (0.0%)	0 (0.0%)	0 (0.0%)	275.0 (21.5%)
	1	0 (0.0%)	0 (0.0%)	0 (0.0%)	173.0 (13.5%)
	2	255 (57.3%)	182 (48.5%)	256 (49.0%)	479.0 (37.5%)
	3	135 (30.3%)	188 (50.1%)	261 (50.0%)	357.0 (27.9%)
	4	55 (12.4%)	5 (1.3%)	5 (1.0%)	106.0 (8.3%)
medial JSN	0	150 (33.7%)	130 (34.7%)	181 (34.7%)	707.0 (55.3%)
	1	154 (34.6%)	101 (26.9%)	140 (26.8%)	346.0 (27.1%)
	2	102 (22.9%)	141 (37.6%)	198 (37.9%)	266.0 (20.8%)
	3	39 (8.8%)	3 (0.8%)	3 (0.6%)	71 (5.6%)
BL mJSW (mm)	Average	3.7	3.9	3.9	4.0
	SD	1.6	1.5	1.5	1.5
BL ThC (mm)	Average	3.3	3.4	3.4	N/A
	SD	0.8	0.7	0.7	N/A

All knees in the FLASH and the DESS sample had definite radiographic OA at baseline (BL), defined as Kellgren and Lawrence grade (KLG) >= 2 (obtained from central readings). SD = standard deviation. BMI = Body Mass Index. mJSW = minimum joint space width, ThC = Thickness of cartilage. 12M = 12 months follow-up, 24M = 24 months follow-up.

*
Height measurements were missing for ten participants from the FLASH sample and for ten participants from the DESS sample. Weight and BMI measurements were missing for one participant from the FLASH sample and for one participant from the DESS sample. FFR = fixed-flexion radiography

Table 2

Mean change (MC in %), standard deviation (SD in %) of the change and responsiveness (sensitivity to change; SRM = standardized response mean) in cartilage thickness (ThCtAB) and medial joint space width (JSW) in the coronal FLASH sample (n=445 knees) over 12 months.

	All knees			KLG 2			KLG 3			KLG 4		
	MC %	SD %	SRM	MC %	SD %	SRM	MC %	SD %	SRM	MC %	SD %	SRM
MFTC	−1.1	3.9	−0.28	−0.6	3.2	−0.18	−1.9	4.7	−0.41	−1.9	5.6	−0.34
eMFTC	−1.4	6.5	−0.22	−0.8	4.6	−0.17	−2.7	9.1	−0.30	−2.5	11.2	−0.22
cMFTC	−1.6	5.0	−0.32	−0.9	4.3	−0.22	−2.7	5.6	−0.49	−2.8	8.2	−0.34
iMFTC	−0.7	3.4	−0.22	−0.3	2.9	−0.11	−1.3	3.7	−0.35	−1.5	5.0	−0.30
MT	−0.7	3.4	−0.21	−0.2	2.9	−0.07	−1.5	4.0	−0.37	−1.5	4.4	−0.35
cMF	−1.5	5.7	−0.26	−0.9	4.8	−0.20	−2.5	6.9	−0.36	−2.3	8.8	−0.26
eMT	−1.6	7.2	−0.23	−0.9	4.7	−0.19	−3.1	10.6	−0.30	−2.8	14.8	−0.19
cMT	−1.2	4.9	−0.23	−0.3	4.1	−0.09	−2.4	5.2	−0.46	−2.4	8.1	−0.29
iMT	−0.5	4.0	−0.12	−0.2	3.7	−0.05	−0.7	4.1	−0.18	−1.3	4.9	−0.27
aMT	−0.1	5.0	−0.02	0.5	4.5	0.11	−0.9	5.3	−0.17	−0.9	6.2	−0.15
pMT	−0.6	4.4	−0.13	−0.4	4.1	−0.10	−0.7	4.5	−0.17	−1.0	5.7	−0.17
ecMF	−1.3	8.1	−0.16	−0.7	6.4	−0.11	−2.3	10.4	−0.22	−2.1	13.0	−0.16
ccMF	−2.1	7.6	−0.28	−1.6	6.7	−0.23	−3.2	8.5	−0.38	−3.5	12.3	−0.28
icMF	−1.0	5.0	−0.20	−0.5	3.9	−0.12	−1.9	5.9	−0.32	−1.7	7.8	−0.22
mJSW	−2.3	15.2	−0.15	−1.9	14.1	−0.13	−4.2	16.0	−0.26	0.3	21.2	0.02
JSW(x=0.150)	−2.0	14.2	−0.14	−1.7	12.8	−0.13	−3.1	15.3	−0.20	−1.0	22.5	−0.04
JSW(x=0.175)	−2.1	13.2	−0.16	−1.7	11.7	−0.14	−3.5	14.5	−0.24	−0.6	22.2	−0.03
JSW(x=0.200)	−2.3	12.9	−0.18	−1.8	11.4	−0.16	−3.9	14.7	−0.27	−0.7	21.0	−0.03
JSW(x=0.225)	−2.3	11.7	−0.20	−1.9	10.4	−0.18	−3.5	12.6	−0.28	−1.9	21.0	−0.09
JSW(x=0.250)	−2.2	10.3	−0.22	−1.9	9.1	−0.21	−2.8	11.4	−0.24	−2.7	16.4	−0.17
JSW(x=0.275)	−1.8	9.8	−0.19	−1.5	8.6	−0.17	−1.8	11.1	−0.17	−4.6	14.9	−0.31
JSW(x=0.300)	−1.0	9.9	−0.10	−0.8	8.9	−0.09	−0.6	10.7	−0.05	−3.4	14.6	−0.23

All knees had definite radiographic OA, defined as Kellgren and Lawrence grade (KLG) >= 2 (obtained from central readings; KLG 2: n=255, KLG 3: n=135, KLG 4: n=55). e/c/iMFTC = external/central/internal subregion of the medial femorotibial compartment; MT = medial tibia; a/pMT anterior/posterior subregion of the medial tibia; cMF = central, weight-bearing part of the medial femoral condyle; mJSW = minimal joint space width, JSW(X) = joint space width at fixed location measures in the medial femorotibial compartment (0.15 − 0.3).

Table 3

Mean change (MC in %), standard deviation (SD in %) of the change and responsiveness (sensitivity to change; SRM = standardized response mean) in cartilage thickness (ThCtAB) and medial joint space width (JSW) in the sagittal DESS sample over 12 (n=375) and 24 months (n=522).

		All knees			KLG 2			KLG 3		
		MC %	SD %	SRM	MC %	SD %	SRM	MC %	SD %	SRM
12 months:	MFTC	−1.6	4.6	−0.34	−0.5	3.6	−0.14	−2.7	5.5	−0.49
	eMFTC	−2.3	8.2	−0.28	−0.8	6.5	−0.13	−4.1	10.0	−0.41
	cMFTC	−2.7	6.2	−0.44	−0.8	4.4	−0.18	−4.9	7.5	−0.65
	iMFTC	−0.6	4.8	−0.12	−0.2	4.4	−0.04	−0.8	5.0	−0.15
	MT	−1.1	4.5	−0.25	−0.4	3.4	−0.12	−1.8	5.4	−0.33
	cMF	−2.0	6.6	−0.31	−0.6	5.2	−0.11	−3.6	7.8	−0.46
	eMT	−3.2	10.6	−0.30	−1.4	7.4	−0.19	−5.6	14.4	−0.39
	cMT	−2.4	6.6	−0.36	−0.8	5.1	−0.15	−4.1	7.8	−0.53
	iMT	0.4	6.4	0.05	0.3	6.2	0.04	0.7	6.5	0.10
	aMT	−0.4	5.8	−0.07	0.1	5.0	0.02	−0.8	6.5	−0.12
	pMT	−0.3	5.3	−0.06	−0.3	4.9	−0.06	−0.2	5.6	−0.04
	ecMF	−1.3	9.1	−0.15	−0.3	7.9	−0.03	−2.6	10.5	−0.25
	ccMF	−3.1	8.8	−0.35	−0.8	5.9	−0.13	−5.9	11.4	−0.51
	icMF	−1.6	6.4	−0.24	−0.7	5.7	−0.12	−2.3	7.0	−0.33
	mJSW	−3.3	15.3	−0.22	−1.1	12.3	−0.09	−6.2	18.3	−0.34
	JSW(x=0.150)	−3.3	13.6	−0.24	−1.2	9.7	−0.12	−5.8	17.0	−0.34
	JSW(x=0.175)	−3.3	12.5	−0.26	−1.2	8.8	−0.13	−5.7	15.8	−0.36
	JSW(x=0.200)	−3.2	11.6	−0.28	−1.0	8.4	−0.12	−5.6	14.4	−0.39
	JSW(x=0.225)	−3.1	11.0	−0.28	−0.7	7.9	−0.09	−5.5	13.4	−0.41
	JSW(x=0.250)	−2.6	10.0	−0.26	−0.7	7.4	−0.09	−4.5	11.9	−0.38
	JSW(x=0.275)	−2.5	9.4	−0.26	−0.7	7.2	−0.09	−4.3	11.0	−0.39
	JSW(x=0.300)	−1.9	9.8	−0.20	−0.7	8.1	−0.09	−3.0	10.6	−0.28
24 months	MFTC	−2.6	6.1	−0.43	−0.9	4.4	−0.20	−4.5	7.3	−0.62
	eMFTC	−3.9	11.4	−0.34	−1.1	8.4	−0.14	−7.5	14.3	−0.52
	cMFTC	−4.2	8.2	−0.51	−1.6	5.5	−0.29	−7.1	10.0	−0.71
	iMFTC	−1.1	5.1	−0.22	−0.5	4.5	−0.11	−1.6	5.6	−0.28
	MT	−1.9	5.4	−0.35	−0.6	3.9	−0.16	−3.1	6.5	−0.48

	All knees			KLG 2			KLG 3		
	MC %	SD %	SRM	MC %	SD %	SRM	MC %	SD %	SRM
cMF	-3.3	8.4	-0.40	-1.1	6.2	-0.18	-5.8	10.1	-0.58
eMT	-5.2	14.3	-0.37	-2.0	9.7	-0.21	-9.5	19.1	-0.49
cMT	-3.5	8.0	-0.43	-1.3	5.4	-0.24	-5.8	9.7	-0.59
iMT	-0.1	6.8	-0.01	0.0	6.9	-0.01	0.1	6.7	0.01
aMT	-0.8	6.2	-0.13	0.0	5.3	-0.01	-1.4	6.8	-0.21
pMT	-0.7	7.1	-0.10	0.1	6.0	0.01	-1.3	7.9	-0.16
ecMF	-2.7	12.2	-0.22	-0.3	10.0	-0.03	-5.6	14.2	-0.40
ccMF	-4.9	11.4	-0.43	-1.9	8.0	-0.24	-8.7	14.5	-0.60
icMF	-2.2	6.9	-0.32	-1.0	5.8	-0.17	-3.4	7.6	-0.45
mJSW	-5.4	17.5	-0.31	-3.0	14.8	-0.20	-9.1	20.7	-0.44
JSW(x=0.150)	-5.2	15.3	-0.34	-3.5	13.2	-0.27	-7.8	17.6	-0.44
JSW(x=0.175)	-5.4	14.1	-0.38	-3.5	11.8	-0.29	-8.2	16.4	-0.50
JSW(x=0.200)	-5.2	13.2	-0.39	-3.1	11.1	-0.28	-8.1	15.2	-0.53
JSW(x=0.225)	-5.3	12.1	-0.44	-3.3	10.2	-0.32	-7.9	13.8	-0.57
JSW(x=0.250)	-4.9	11.4	-0.43	-3.5	9.6	-0.36	-6.8	13.2	-0.51
JSW(x=0.275)	-4.6	10.8	-0.43	-3.3	8.9	-0.36	-6.4	12.6	-0.51
JSW(x=0.300)	-3.7	10.5	-0.35	-2.6	9.2	-0.28	-5.0	12.0	-0.42

All knees had definite radiographic OA, defined as Kellgren and Lawrence grade (KLG) >= 2 (obtained from central readings; 12 months: KLG 2: n=182, KLG 3: n=188, KLG 4: n=5 [data not shown separately]; 24 months: KLG 2: n=256, KLG 3: n=261, KLG 4: n=5 [data not shown separately]). e/c/iMFTC = external/central/internal subregion of the medial femorotibial compartment; MT = medial tibia; a/pMT anterior/posterior subregion of the medial tibia; cMF = central, weight-bearing part of the medial femoral condyle; mJSW = minimal joint space width, JSW(X) = joint space width at fixed location measures in the medial femorotibial compartment (0.15 – 0.3). The DESS sample analyzed over 12 months is a sub-sample of the 24 months cohort, for which a complete set of 12 months measurements was available.