Responsiveness of Magnetic Resonance Imaging-derived Measures Over 2.7 Years

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ABSTRACT. ***Objective.*** To compare the responsiveness of magnetic resonance imaging (MRI)-derived measures of knee osteoarthritis over 2.7 years.

Methods. There were 430 community-based participants (mean age 63.0 yrs, range 51–79 yrs; 51% female) measured at baseline and 2.7 years later. MRI of the right knee at both timepoints was performed to assess cartilage volume, cartilage defects, bone marrow lesions (BML), meniscal pathology, and tibial bone area. Global measurements were calculated as the sum of tibial and femoral measures. Standardized response mean (SRM) was calculated as the mean of change divided by the SD of change.

Results. Global tibiofemoral cartilage volume and cartilage defects had the best SRM of –0.80 and 0.62, respectively. Site-specific measurements were lower (SRM range for cartilage volume –0.48 to –0.54 and cartilage defects 0.33 to 0.49). The SRM for BML was 0.12, meniscal pathology 0.39, and tibial bone area –0.09. Cartilage volume and/or defects tended to be more responsive in those with knee pain, those who were obese, those who were older, and those with radiographic osteoarthritis.

Conclusion. Global cartilage volume demonstrated the best sensitivity to change, suggesting that if we relied solely on SRM to optimize clinical trial design, then cartilage volume would be the best outcome measure. However, clinical trials have shown that cartilage volume may be less responsive to treatment compared to other measures that have lower SRM (such as BML). Therefore, although one can optimize trial efficiency by finding more responsive endpoints, both sensitivity to change and magnitude of benefit should be considered. (J Rheumatol First Release Aug 15 2014; doi:10.3899/jrheum.130953)

Key Indexing Terms:
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Radiography remains the only approved method to assess structural change in clinical knee osteoarthritis (OA) trials of disease-modifying OA drugs (DMOAD). The focus is to measure joint space width (JSW) as a surrogate for hyaline cartilage; however, this method has limitations. A number of structures contribute to JSW including cartilage defects, cartilage volume, and meniscal tear/extrusion[1,2]. Trials using JSW as an outcome showed limited change over time in the placebo arm, and relatively small or no differences between placebo and active treatment in the case of strontium ranelate[3], risedronate[4], chondroitin[5], and glucosamine[6,7]. Further, there is now growing awareness that knee OA is a disease of the whole synovial joint, not just the cartilage. Magnetic resonance imaging (MRI) can directly visualize joint structures including bone, cartilage, menisci, synovium, and ligaments. It is now generally agreed in the scientific community that MRI is superior to radiography in monitoring the progression of knee OA[8]. To have MRI accepted as a measurement tool in clinical trials, responsive outcome measures for assessing structural changes using MRI are needed.

Responsiveness is the sensitivity to change or the ability to detect change using a particular instrument[9]. The standardized response mean (SRM) is 1 of several available effect size indices used to gauge the responsiveness of scales

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to clinical change. It is calculated as the mean of change divided by the SD of change. There is general consensus that an SRM of 0.2 or less is small, 0.5 or greater is moderate, and 0.8 or greater is large[10].

Studies examining the responsiveness of MRI measures have mainly focused on cartilage and found that in general, SRM vary across different subregions in the knee[11,12]. Eckstein, *et al*[12] reported that the greatest rate of cartilage loss was observed in the weight-bearing medial femoral condyle (SRM –0.30). Similarly, Hunter, *et al*[11] reported the greatest consistent change was seen in the central medial femur (SRM –0.394). In contrast, Wildi, *et al*[13] reported that global cartilage volume demonstrated the best sensitivity to change (SRM –1.72). A recent systematic review by Hunter, *et al*[8] examined the responsiveness and reliability of MRI-based measures in assessing structural change in knee OA. The responsiveness analysis included data from 42 publications and calculated SRM for many quantitative and semiquantitative structures, including cartilage volume, cartilage lesions, bone marrow lesions (BML), meniscus, and bone size. The pooled SRM for global cartilage volume was –0.89. Few studies have directly compared the responsiveness of different MRI measures in the same cohort. Thus, the aim of our current study was to compare the responsiveness of different MRI-derived measures over 2.7 years in a sample of community-dwelling older adults.

MATERIALS AND METHODS

Subjects. Our study was conducted as part of the Tasmanian Older Adult Cohort study. Subjects between the ages of 50 and 80 years were randomly selected from the electoral roll in Southern Tasmania (population 229,000), with an equal number of men and women (response rate 57%, 1099/1904). Exclusion criteria included contraindication for MRI and institutionalization. Followup data was collected for 875 participants about 2.7 years later. The MRI machine was decommissioned halfway through the followup period; therefore, followup MRI scans were only available for about half of the participants. This research was conducted in compliance with the Declaration of Helsinki, and was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. All subjects gave informed written consent.

Anthropometrics. Weight was measured to the nearest 0.1 kg (Seca Delta Model 707). Height was measured to the nearest 0.1 cm using a stadiometer. Body mass index (BMI) was calculated (kg/m^2).

MRI. Images of the right knee at baseline and followup were acquired with a 1.5T whole-body magnetic resonance unit (Picker). Sagittal image sequences included (1) a T1-weighted fat saturation 3D gradient-recalled acquisition in the steady state, flip angle 30º, repetition time 31 ms, echo time 6.71 ms, field of view 16 cm, 60 partitions, 512 × 512 pixel matrix, and slice thickness of 1.5 mm without an interslice gap; and (2) a T2-weighted fat saturation 2-D fast spin echo, flip angle 90º, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 × 256 pixel matrix, and slice thickness of 4 mm with an interslice gap of 1.0 mm.

The MRI readers in our study have all undergone extensive training, and demonstrate significant expertise and experience in scoring MRI features.

Tibial cartilage volume was assessed by 1 trained reader on T1-weighted MR images by means of image processing on an independent workstation using Osiris (University of Geneva) software as previously described[14,15,16]. The volumes of individual cartilage plates (medial tibia and lateral tibia) were isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section-by-section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 mm and 1.5 mm thickness, continuous sections) for the final 3-D rendering. Baseline and followup images were read unpaired. The coefficient of variation (CV) ranged from 2.1%–2.2% for intraobserver repeatability[14].

Femoral cartilage volume was determined by trained readers by means of image processing on an independent workstation using Cartiscope (ArthroLab), as previously described[17,18,19]. The segmentation of the cartilage-synovial interfaces was carried out with the semiautomatic method under reader supervision and with corrections when needed. Cartilage volume was evaluated directly from a standardized view of 3-D cartilage geometry as the sum of elementary volumes[17,18,19]. Baseline and followup images were read paired with the chronological order known to the reader. The CV was about 2% for intraobserver and interscan repeatability[17]. The cartilage volume assessment was done for the medial and lateral condyles delineated by the Blumensaat's line[18].

Absolute change in cartilage volume was calculated as:

followup cartilage volume – baseline cartilage volume

This was calculated at each of the 4 sites (medial tibial, lateral tibial, medial femoral, and lateral femoral), as well as for a global measure (sum of tibial and femoral measures, tibiofemoral).

Cartilage defects were assessed by 1 trained reader on T1-weighted MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, as previously described[16,20] as follows: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous low-signal intensity area with an intact surface and base; grade 2 = irregularities on the surface or base and loss of thickness < 50%; grade 3 = deep ulceration with loss of thickness > 50%; and grade 4 = full-thickness chondral wear with exposure of subchondral bone. Baseline and followup images were read unpaired. The ICC ranged from 0.80–0.95 for intraobserver repeatability. Change in cartilage defect score was calculated as:

followup cartilage defect score – baseline cartilage defect score

BML were assessed on T2-weighted MR images and defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites. One trained reader scored BML by measuring the maximum area of the lesion (mm^2) at baseline and followup using software cursors, as previously described[21]. The observer manually selected the MRI slice with the greatest BML size. The BML with the highest score was used if more than 1 lesion was present at the same site. Baseline and followup images were read paired with the chronological order known to the observer. The ICC was 0.97 for intraobserver repeatability. Change in BML size was calculated as:

followup BML area – baseline BML area

BML were also scored using a semiquantitative scoring system at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites. A scale from 0 to 3 was used, where 0 = normal/absent; 1 = mild, < 25% of the region; 2 = moderate, 25% to 50% of the region; and 3 = severe, > 50% of the region. Baseline and followup images were read paired with the chronological order known to the observer.

Meniscal damage was assessed by trained readers on T1-weighted MR images as previously described[19,22]. The proportion of the menisci affected by a tear, partial extrusion, or full extrusion was scored separately (yes/no) at the anterior, middle, and posterior horns (medially/laterally). Baseline and followup images were read unpaired. The intrareader and interreader correlation coefficient ranged from 0.86 to 0.96 for the meniscal tear and 0.85 to 0.92 for the meniscal extrusion[23]. These scores were summed to create a total meniscal pathology score that had a possible range from 0–18

(0–6 for tears, 0–6 for partial extrusions, and 0–6 for full extrusion). A meniscal pathology score increase was defined as an increase in tear, partial extrusion, or full extrusion score.

Tibial plateau bone area was assessed by 1 trained reader on T1-weighted MR images and defined as the cross-sectional surface area of the tibial plateau, as previously described[16,24,25,26]. Baseline and followup images were read unpaired. The CV was 2.2%–2.6% for intraobserver repeatability[25]. Change in tibial bone area was calculated as:

followup bone area – baseline bone area

Radiograph. A baseline standing anteroposterior semiflexed view of the right knee with 15° of fixed knee flexion was performed and scored individually for osteophytes and joint space narrowing (JSN) on a scale of 0–3[27]. The presence of radiographic OA (ROA) was defined as any score ≥ 1 for JSN or osteophytes.

Knee pain. Baseline knee pain was assessed using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) index pain score[28]. WOMAC uses a 10-point scale from 0 (no pain) to 9 (most severe pain) on 5 subscales including knee pain while walking on a flat surface, going up and down stairs, at night while in bed, sitting or lying, and standing upright. Participants were classified as having "any knee pain" if they answered 1 to 9 on any of the 5 subscales.

Data analysis. The SRM was used to assess responsiveness. It was calculated as the mean of change divided by the SD of change for each MRI measure — i.e., for the site-specific measurements as well as the global measurements (tibiofemoral). A negative SRM expresses cartilage volume loss whereas a positive SRM indicates cartilage volume gain. As a result of a large amount of bi-directional change in the areal BML measure (i.e., BML increasing and decreasing), we also calculated an SRM based on the absolute value of change as the numerator divided by the SD of change.

Stratified analyses were also performed to examine responsiveness in different subgroups [ROA presence/absence, knee pain presence/absence, non-obese (BMI < 30) vs obese (BMI ≥ 30), men vs women, and age less than or equal to the median (≤ 62) vs greater than the median (> 62)].

All statistical analyses were performed on Intercooled Stata V.12.0.

RESULTS

Subjects. There were 430 participants included who had an MRI scan at baseline and followup (Table 1). The average time to followup was 2.7 years (SD 0.4, range 2.0–4.7).

Responsiveness of MRI measures. The mean change and SRM for each MRI measure are presented in Table 2. The SRM for the cartilage volume measures at the 4 sites within the knee were in the moderate range. The SRM for tibiofemoral cartilage volume (global measure) was substantially higher. Cartilage defects demonstrated moderate responsiveness at the 4 sites within the knee, and similarly the SRM was substantially higher for the global measure. A subgroup analysis in those with a baseline cartilage defect showed similar responsiveness. Meniscal tears demonstrated a higher SRM compared to meniscal extrusion measures. Total meniscal pathology score demonstrated a small to moderate SRM. The SRM for tibial bone area were small. The SRM for both the areal and ordinal BML measures at the 4 sites were small and did not improve using a global measure (tibiofemoral BML size/grade). This was consistent in a subgroup analysis restricted to those with a baseline BML. However, Table 3 presents the SRM for the areal BML measure using an absolute value of change as the numerator of the SRM equation. Using this method, the responsiveness is substantially higher.

Stratified analysis. Table 4 presents the SRM for each MRI measure stratified by ROA, knee pain, obesity, sex, and age.

The SRM for cartilage defects were consistently higher in those with ROA compared to those without ROA. Tibial bone area responsiveness was also higher in those with ROA compared to those without.

The SRM for both cartilage volume and cartilage defects were higher in those with knee pain compared to those without knee pain. The BML ordinal measure was also somewhat more responsive in those with knee pain versus those without.

The SRM for both cartilage volume and cartilage defects were consistently higher in those who were obese versus non-obese.

Table 1. Characteristics of participants at baseline, n = 430.

Characteristics	Mean (SD, range), or %
Age, yrs	63.0 (7.2, 51–79)
Male sex, %	49
BMI, kg/m^2	27.6 (4.4, 19–46)
ROA present, %	57
Knee pain present, %	49
MRI measures	
Tibiofemoral cartilage volume, mm^3	13,417 (3267, 7167–25,401)
Cartilage defects present†, %	32
BML present, %	43
Mean BML size, tibiofemoral, mm^2	101 (115, 5–727)
Mean ordinal score, tibiofemoralϕ	2.3 (1.6, 1–10)
Total meniscal pathology score‡	5.6 (1.3, 0–10)
Total tibial bone area, mm^2	3384 (472, 2405–4696)

†Defined as grade 2 or higher. ϕPossible range 0–12. ‡Possible range 0–18. BMI: body mass index; ROA: radiographic osteoarthritis; MRI: magnetic resonance imaging; BML: bone marrow lesion.

Table 2. SRM for structural change in TASOAC over 2.7 years.

	Mean Change (SD of change)	SRM
Cartilage volume		
Medial tibial, mm^3	–185 (342)	–0.54
Lateral tibial, mm^3	–151 (298)	–0.51
Medial femoral, mm^3	–126 (234)	–0.54
Lateral femoral, mm^3	–110 (231)	–0.48
Tibiofemoral, global, mm^3	–538 (669)	–0.80
Cartilage defects		
Medial tibial, 0–4	0.2 (0.5)	0.35
Lateral tibial, 0–4	0.2 (0.5)	0.33
Medial femoral, 0–4	0.3 (0.5)	0.49
Lateral tibial, 0–4	0.2 (0.5)	0.35
Tibiofemoral, global, 0–16	0.7 (1.2)	0.62
Cartilage defects (restricted to those with a baseline cartilage defect)†, n = 133		
Medial tibial, 0–4	0.3 (0.6)	0.48
Lateral tibial, 0–4	0.2 (0.6)	0.30
Medial femoral, 0–4	0.3 (0.6)	0.43
Lateral tibial, 0–4	0.2 (0.6)	0.36
Tibiofemoral, global, 0–16	0.9 (1.4)	0.68
Bone marrow lesion (areal)		
Medial tibial, mm^2	3 (49)	0.06
Lateral tibial, mm^2	5 (45)	0.11
Medial femoral, mm^2	0.2 (33)	0.01
Lateral femoral, mm^2	6 (63)	0.09
Tibiofemoral, global, mm^2	14 (112)	0.12
Bone marrow lesion (areal; restricted to those with a baseline bone marrow lesion), n = 168		
Medial tibial, mm^2	1 (54)	0.03
Lateral tibial, mm^2	6 (44)	0.14
Medial femoral, mm^2	–1 (49)	–0.02
Lateral femoral, mm^2	11 (97)	0.11
Tibiofemoral, global, mm^2	18 (135)	0.13
Bone marrow lesion (ordinal)		
Medial tibial, 0–3	0.10 (0.5)	0.11
Lateral tibial, 0–3	0.05 (0.5)	0.09
Medial femoral, 0–3	0.02 (0.5)	0.03
Lateral tibial, 0–3	0.06 (0.5)	0.13
Tibiofemoral, global, 0–12	0.18 (1.1)	0.17
Bone marrow lesion (ordinal; restricted to those with a baseline bone marrow lesion), n = 168		
Medial tibial, 0–3	0.09 (0.7)	0.12
Lateral tibial, 0–3	0.07 (0.7)	0.10
Medial femoral, 0–3	–0.02 (0.7)	–0.03
Lateral tibial, 0–3	0.07 (0.7)	0.11
Tibiofemoral, global, 0–12	0.21 (1.5)	0.14
Meniscal pathology		
Tear, 0–6	0.4 (1.0)	0.39
Partial extrusion, 0–6	0.003 (0.35)	0.01
Full extrusion, 0–6	0.02 (0.16)	0.12
Total meniscal pathology score, 0–18	0.43 (1.1)	0.39
Tibial bone area		
Medial tibial, mm^2	–24 (112)	–0.22
Lateral tibial, mm^2	12 (85)	0.14
Tibial, global, mm^2	–12 (141)	–0.09

†Defined as grade 2 or higher. SRM: standardized response mean; TASOAC: Tasmanian Older Adult Cohort.

There were no clear or consistent differences in the SRM for each MRI measure split by sex.

The SRM for cartilage volume were consistently higher in those who were older than the median age compared to those equal or less than the median age. Cartilage defect measures also demonstrated somewhat better SRM in those who were older than the median age compared to those equal to or younger than the median age.

Table 3. SRM for areal bone marrow lesion change, using an absolute value of change as the numerator of the SRM equation.

	Absolute Value of Mean Change (SD of change)	SRM
Bone marrow lesion (areal)		
Medial tibial, mm^2	11 (48)	0.23
Lateral tibial, mm^2	9 (45)	0.21
Medial femoral, mm^2	8 (31)	0.27
Lateral femoral, mm^2	15 (62)	0.24
Tibiofemoral, global, mm^2	36 (107)	0.34
Bone marrow lesion (areal; restricted to those with a baseline bone marrow lesion), n = 168		
Medial tibial, mm^2	21 (50)	0.41
Lateral tibial, mm^2	17 (42)	0.40
Medial femoral, mm^2	19 (46)	0.40
Lateral femoral, mm^2	32 (92)	0.35
Tibiofemoral, global, mm^2	71 (116)	0.61

SRM: standardized response mean.

DISCUSSION

Our longitudinal study has compared the responsiveness of different MRI measures over about 2.7 years. Global cartilage measurements — tibiofemoral cartilage volume and cartilage defects — had the best SRM of –0.80 and 0.62, respectively. Meniscal pathology showed small to moderate responsiveness, and both BML and tibial bone area showed small responsiveness.

MRI has not been formally accepted by regulatory authorities for assessing structural change in OA clinical trials of DMOAD. To support the inclusion of MRI structure in regulatory guidance statements, it is necessary to identify which structures are most responsive to change. In our study, the most responsive MRI measure was tibiofemoral (global) cartilage volume (SRM –0.80). A semiquantitative measure of cartilage damage (tibiofemoral cartilage defects) demonstrated moderate responsiveness (SRM 0.62). Plain radiography generally has SRM in the 0.3–0.4 range[29,30],

Table 4. SRM for structural change in TASOAC over 2.7 years – stratified by baseline ROA, knee pain, obesity, sex, and age.

	ROA		Knee Pain		Obesity*		Sex		Age**	
	No	Yes	No	Yes	No	Yes	M	F	Age ≤ Median	Age > Median
Cartilage volume										
Medial tibial, mm^3	–0.41	–0.63	–0.54	–0.55	–0.50	–0.66	–0.60	–0.49	–0.36	–0.79
Lateral tibial, mm^3	–0.47	–0.51	–0.46	–0.56	–0.49	–0.55	–0.41	–0.62	–0.49	–0.52
Medial femoral, mm^3	–0.46	–0.59	–0.52	–0.55	–0.52	–0.60	–0.59	–0.49	–0.47	–0.62
Lateral femoral, mm^3	–0.49	–0.45	–0.43	–0.53	–0.45	–0.55	–0.54	–0.41	–0.41	–0.56
Tibiofemoral, global, mm^3	–0.84	–0.77	–0.72	–0.90	–0.74	–1.06	–0.90	–0.71	–0.69	–0.97
Cartilage defects										
Medial tibial, 0–4	0.25	0.43	0.29	0.42	0.34	0.39	0.35	0.36	0.31	0.41
Lateral tibial, 0–4	0.26	0.40	0.24	0.40	0.29	0.46	0.28	0.37	0.39	0.26
Medial femoral, 0–4	0.39	0.56	0.55	0.44	0.48	0.51	0.48	0.49	0.44	0.53
Lateral tibial, 0–4	0.25	0.44	0.24	0.47	0.32	0.41	0.29	0.41	0.34	0.35
Tibiofemoral, global, 0–16	0.48	0.75	0.56	0.69	0.59	0.74	0.58	0.67	0.60	0.65
Bone marrow lesion (areal)										
Medial tibial, mm^2	0.09	0.07	0.08	0.03	0.06	0.06	–0.01	0.10	0.00	0.09
Lateral tibial, mm^2	0.06	0.15	0.09	0.14	0.11	0.08	0.14	0.09	0.07	0.14
Medial femoral, mm^2	–0.09	0.06	0.03	–0.01	0.00	0.05	0.05	–0.06	–0.01	0.02
Lateral femoral, mm^2	0.11	0.05	0.12	0.10	0.08	0.16	0.13	0.04	0.12	0.04
Tibiofemoral, global, mm^2	0.11	0.13	0.12	0.13	0.11	0.18	0.16	0.09	0.11	0.13
Bone marrow lesion (ordinal)										
Medial tibial, 0–3	0.11	0.13	0.08	0.14	0.13	0.05	0.11	0.11	0.11	0.12
Lateral tibial, 0–3	0.06	0.09	0.05	0.13	0.09	0.10	0.11	0.08	0.09	0.09
Medial femoral, 0–3	–0.01	0.07	0.08	–0.03	0.06	–0.04	0.04	0.02	–0.03	0.10
Lateral tibial, 0–3	0.12	0.11	0.09	0.16	0.12	0.17	0.18	0.08	0.17	0.08
Tibiofemoral, global, 0–12	0.13	0.18	0.14	0.20	0.18	0.14	0.21	0.13	0.16	0.18
Meniscal pathology										
Tear, 0–6	0.42	0.37	0.40	0.40	0.42	0.30	0.35	0.43	0.45	0.30
Partial extrusion, 0–6	0.00	0.02	0.09	–0.07	0.02	–0.04	0.06	–0.04	0.10	–0.10
Full extrusion, 0–6	0.09	0.19	0.11	0.13	0.09	0.21	0.08	0.16	0.10	0.15
Total meniscal pathology score, 0–18	0.43	0.38	0.43	0.36	0.42	0.30	0.37	0.41	0.49	0.26
Tibial bone area										
Medial tibial, mm^2	–0.08	–0.39	–0.17	–0.26	–0.29	–0.05	–0.01	–0.45	–0.39	–0.04
Lateral tibial, mm^2	0.10	0.15	–0.05	0.35	0.22	–0.01	0.43	–0.17	0.06	0.21
Tibial, global, mm^2	–0.01	–0.16	–0.19	–0.01	–0.10	–0.05	0.23	–0.55	–0.25	0.13

*Non–obese (BMI < 30) versus obese (BMI ≥ 30). **Age less than or equal to the median (≤ 62) versus greater than the median (> 62). SRM: standardized response mean; TASOAC: Tasmanian Older Adult Cohort; ROA: radiographic osteoarthritis; BMI: body mass index.

demonstrating the potential benefit of both quantitative and semiquantitative MRI measurements over radiograph.

Better sensitivity to change was seen using a global measure compared to site-specific measures for both cartilage volume and cartilage defects. For cartilage volume, the SRM at the 4 sites ranged between –0.48 to –0.54 (moderate); however, the global measure of cartilage volume (tibiofemoral cartilage volume) was substantially higher (–0.80). Similarly for cartilage defects, the SRM did not vary much per site and the global measure was considerably higher. This is consistent with previous studies[8,13] that have reported that global measurements of both cartilage defects [assessed using the Whole-Organ MRI Score (WORMS)] and cartilage volume showed increased sensitivity to change. However, this contrasts with other studies that have shown that the individual region with the largest magnitude of change appears to be the central medial femur[11,12,31]. Higher SRM are meant to provide advantages for adequately powering studies because the minimum sample size required for a clinical trial is related to the SRM[32]. The results from our study suggest that using a global measure for cartilage will enhance the power with which the effect of a therapeutic intervention can be seen in OA clinical trials.

The SRM values in our study were consistent with the systematic review performed by Hunter, *et al*[8], in which global cartilage volume and semiquantitative measures of cartilage demonstrated good responsiveness. Hunter, *et al*[8] reported low responsiveness for a quantitative BML measure (SRM 0.11) — derived from only 1 study[33] — and this is consistent with our areal BML measure (SRM 0.12). However, additional analysis revealed that the responsiveness for quantitative BML change substantially increased when the SRM was calculated using an absolute value of change as the numerator. This suggests that the low SRM for BML is likely attributable to bi-directional change in BML size over time. Bone area demonstrated low responsiveness both in Hunter, *et al's*[8] review (SRM 0.12) and in our current study (–0.09). Further, the results from our study are also similar to what has been reported using WORMS. Hunter, *et al*[34] found the SRM for both cartilage and BML varied largely by compartment; however, on average, cartilage demonstrated moderate responsiveness and BML low responsiveness. Also, our semiquantitative SRM for meniscal change (0.39) is comparable to the SRM that Hunter, *et al*[8] reported (0.27), which was derived using WORMS.

Our findings suggest that some subgroups demonstrate better sensitivity to change, supporting previous studies[12,35,36]. Cartilage — both volume and defect — measurements were more responsive in those with knee pain, in those who were obese, and in those who were older. Cartilage defects (but not volume) were consistently more responsive in those with ROA. These findings are qualitative observations, because we did not statistically test the differences between each subgroup. Doing so would have required 135 comparisons. Identifying subgroups of participants who demonstrate increased sensitivity to change is appealing for the development of clinical OA trials. However, when designing a study to test an intervention, sensitivity to change is but 1 important factor. The population being selected must be clinically relevant and reflect the population in whom an intervention would be used. There is no evidence that subgroups who demonstrate the greatest change over time have equal ability to respond to treatment[31]. This has been well recognized in most disease-modifying OA clinical trials, which tend to exclude severe radiological OA. In our recent clinical trial[37], zoledronic acid treatment appeared to have more of an effect on BML in those without ROA. Therefore, if treatments are focused on those with more advanced disease, the pathological changes may be less amenable to therapy and one may miss important effects.

Cartilage volume demonstrated the best sensitivity to change, a finding that suggests that if we relied solely on SRM to optimize clinical trial design, then cartilage volume would be the best outcome measure. However, in clinical trials, much larger effects have been seen for BML versus cartilage volume. Laslett, *et al*[37] saw significant improvements in BML size (measured quantitatively) with zoledronic acid treatment, despite the low SRM values seen for this measure. The treatment group experienced a 36% reduction in BML size compared to the control group. In comparison, Wildi, *et al*[38] found that chondroitin sulphate reduced cartilage volume loss over 12 months, albeit the effect was small. The treatment group experienced a 1.8% reduction in global cartilage volume loss compared to the control group. Raynauld, *et al*[39] showed that licofelone treatment resulted in a 1.4% reduction in global cartilage volume loss over 24 months compared to naproxen treatment. Therefore, although one can optimize trial efficiency by finding more responsive endpoints, magnitude of effect appears at least equally important in selecting outcome measures. As discussed above, bi-directional change is common for BML over time and could explain why BML change appears to be an outcome sensitive to change in a clinical trial, but not in observational studies.

Our study has potential limitations. First, responsiveness is a measure of a particular instrument applied to a particular situation and population, and cannot be viewed in any absolute sense[9]. Second, we did not have data on knee alignment and could not test whether responsiveness varied by alignment, as has been shown previously[35]. Third, cartilage defects were assessed on T1-weighted gradient-recalled echo (GRE) MR images and it has been proposed that GRE type sequences are less suited to detect cartilage defects[40]. However, there is evidence to demonstrate that GRE-type sequences are accurate and reliable for detecting cartilage defects with high sensitivity and speci-

ficity compared to arthroscopic results[41,42,43,44]. While our measure of cartilage defects may contain some measurement error and misclassification, it is unlikely to affect the responsiveness. Wildi, *et al*[13] recently demonstrated that despite cartilage defect assessment providing consistently higher scores on intermediate-weighted fast spin-echo sequences compared to GRE-type sequences, neither sequence demonstrated a superior sensitivity to detect cartilage defect change over 2 years because the SRM values were similar between the 2 sequences. Lastly, tibial and femoral cartilage volume were segmented using different methodology. Separate readers performed the measurements, which resulted in differences in how the scans were processed. For tibial cartilage volume assessment, the images were read unpaired, whereas for femoral cartilage volume assessment, the images were read paired, with the chronological order known to the reader. Despite these differences, the SRM were nearly identical; however, femoral cartilage volume showed less change and less variability of change over time. Such differences may be attributable to the different processes used for reading tibial and femoral cartilage volume.

For cartilage, the best sensitivity to change is seen with a global, quantitative measure. Therefore, using global cartilage volume assessments in clinical trials will enhance the likelihood of a therapeutic intervention being detected. However, although one can optimize clinical trial efficiency by finding more responsive endpoints, magnitude of effect appears at least equally important in selecting outcome measures. MRI measures with low SRM could still be appropriate outcome measures in clinical trials.

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REFERENCES

1. 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.
2. 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.
3. Reginster JY, Badurski J, Bellamy N, Bensen W, Chapurlat R, Chevalier X, et al. Efficacy and safety of strontium ranelate in the treatment of knee osteoarthritis: results of a double-blind, randomised placebo-controlled trial. Ann Rheum Dis 2013; 72:179-86.
4. Bingham CO 3rd, Buckland-Wright JC, Garnero P, Cohen SB, Dougados M, Adami S, et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum 2006;54:3494-507.
5. Hochberg MC, Zhan M, Langenberg P. The rate of decline of joint space width in patients with osteoarthritis of the knee: a systematic review and meta-analysis of randomized placebo-controlled trials of chondroitin sulfate. Curr Med Res Opin 2008;24:3029-35.
6. Pavelka K, Gatterova J, Olejarova M, Machacek S, Giacovelli G, Rovati LC. Glucosamine sulfate use and delay of progression of knee osteoarthritis: a 3-year, randomized, placebo-controlled, double-blind study. Arch Intern Med 2002;162:2113-23.
7. Reginster JY, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O. Long-term effects of glucosamine sulfate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251-6.
8. Hunter DJ, Zhang W, Conaghan PG, Hirko K, Menashe L, Reichmann WM, et al. Responsiveness and reliability of MRI in knee osteoarthritis: a meta-analysis of published evidence. Osteoarthritis Cartilage 2011;19:589-605.
9. Norman GR, Wyrwich KW, Patrick DL. The mathematical relationship among different forms of responsiveness coefficients. Qual Life Res 2007;16:815-22.
10. Husted JA, Cook RJ, Farewell VT, Gladman DD. Methods for assessing responsiveness: a critical review and recommendations. J Clin Epidemiol 2000;53:459-68.
11. Hunter DJ, Niu J, Zhang Y, Totterman S, Tamez J, Dabrowski C, et al. Change in cartilage morphometry: a sample of the progression cohort of the Osteoarthritis Initiative. Ann Rheum Dis 2009; 68:349-56.
12. Eckstein F, Maschek S, Wirth W, Hudelmaier M, Hitzl W, Wyman B, et al. One year change of knee cartilage morphology in the first release of participants from the Osteoarthritis Initiative progression subcohort: association with sex, body mass index, symptoms and radiographic osteoarthritis status. Ann Rheum Dis 2009;68:674-9.
13. Wildi LM, Martel-Pelletier J, Abram F, Moser T, Raynauld JP, Pelletier JP. Assessment of cartilage changes over time in knee osteoarthritis disease-modifying osteoarthritis drug trials using semiquantitative and quantitative methods: pros and cons. Arthritis Care Res 2013;65:686-94.
14. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum 2000;43:2543-9.
15. Ding C, Cicuttini F, Blizzard L, Jones G. Smoking interacts with family history with regard to change in knee cartilage volume and cartilage defect development. Arthritis Rheum 2007;56:1521-8.
16. Doré D, Quinn S, Ding C, Winzenberg T, Cicuttini F, Jones G. Subchondral bone and cartilage damage: A prospective study in older adults. Arthritis Rheum 2010;62:1967-73.
17. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50:476-87.
18. Raynauld JP, Kauffmann C, Beaudoin G, Berthiaume MJ, de Guise JA, Bloch DA, et al. Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. Osteoarthritis Cartilage 2003;11:351-60.
19. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, Labonte F, Beaudoin G, Bloch DA, et al. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005;64:556-63.
20. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthritis Cartilage 2005;13:198-205.
21. Doré D, Quinn S, Ding C, Winzenberg T, Zhai G, Cicuttini F, et al.

Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. Arthritis Res Ther 2010;12:R223.
22. Dore DA, Winzenberg TM, Ding C, Otahal P, Pelletier JP, Martel-Pelletier J, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis 2013;72:1170-5.
23. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Beaudoin G, Choquette D, Haraoui B, et al. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. Arthritis Res Ther 2006;8:R21.
24. Ding C, Cicuttini F, Scott F, Cooley H, Boon C, Jones G. Natural history of knee cartilage defects and factors affecting change. Arch Intern Med 2006;166:651-8.
25. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthritis Cartilage 2004;12:169-74.
26. Cicuttini FM, Wluka AE, Stuckey SL. Tibial and femoral cartilage changes in knee osteoarthritis. Ann Rheum Dis 2001;60:977-80.
27. 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.
28. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988;15:1833-40.
29. Emrani PS, Katz JN, Kessler CL, Reichmann WM, Wright EA, McAlindon TE, et al. Joint space narrowing and Kellgren-Lawrence progression in knee osteoarthritis: an analytic literature synthesis. Osteoarthritis Cartilage 2008;16:873-82.
30. Reichmann WM, Maillefert JF, Hunter DJ, Katz JN, Conaghan PG, Losina E. Responsiveness to change and reliability of measurement of radiographic joint space width in osteoarthritis of the knee: a systematic review. Osteoarthritis Cartilage 2011;19:550-6.
31. Hunter DJ, Li L, Zhang YQ, Totterman S, Tamez J, Kwoh CK, et al. Region of interest analysis: by selecting regions with denuded areas can we detect greater amounts of change? Osteoarthritis Cartilage 2010;18:175-83.
32. Snedecor GW, Cochran WG. Statistical methods. 8th ed. Iowa City: Iowa State University Press; 1989.
33. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Abram F, Choquette D, Haraoui B, et al. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. Ann Rheum Dis 2008;67:683-8.
34. Hunter DJ, Conaghan PG, Peterfy CG, Bloch D, Guermazi A, Woodworth T, et al. Responsiveness, effect size, and smallest detectable difference of Magnetic Resonance Imaging in knee osteoarthritis. Osteoarthritis Cartilage 2006;14 Suppl A:A112-5.
35. Duryea J, Neumann G, Niu J, Totterman S, Tamez J, Dabrowski C, et al. Comparison of radiographic joint space width with magnetic resonance imaging cartilage morphometry: analysis of longitudinal data from the Osteoarthritis Initiative. Arthritis Care Res 2010;62:932-7.
36. Eckstein F, Cotofana S, Wirth W, Nevitt M, John MR, Dreher D, et al. Greater rates of cartilage loss in painful knees than in pain-free knees after adjustment for radiographic disease stage: data from the osteoarthritis initiative. Arthritis Rheum 2011;63:2257-67.
37. Laslett LL, Doré DA, Quinn SJ, Boon P, Ryan E, Winzenberg TM, et al. Zoledronic acid reduces knee pain and bone marrow lesions over 1 year: a randomised controlled trial. Ann Rheum Dis 2012;71:1322-8.
38. Wildi LM, Raynauld JP, Martel-Pelletier J, Beaulieu A, Bessette L, Morin F, et al. Chondroitin sulphate reduces both cartilage volume loss and bone marrow lesions in knee osteoarthritis patients starting as early as 6 months after initiation of therapy: a randomised, double-blind, placebo-controlled pilot study using MRI. Ann Rheum Dis 2011;70:982-9.
39. Raynauld JP, Martel-Pelletier J, Bias P, Laufer S, Haraoui B, Choquette D, et al. Protective effects of licofelone, a 5-lipoxygenase and cyclo-oxygenase inhibitor, versus naproxen on cartilage loss in knee osteoarthritis: a first multicentre clinical trial using quantitative MRI. Ann Rheum Dis 2009;68:938-47.
40. Link TM. MR imaging in osteoarthritis: hardware, coils, and sequences. Radiol Clin North Am 2009;47:617-32.
41. Doré D, Winzenberg T, Ding C, Cicuttini F, Jones G. Reply. Arthritis Rheum 2010;62:3831-2.
42. Disler DG, McCauley TR, Wirth CR, Fuchs MD. Detection of knee hyaline cartilage defects using fat-suppressed three-dimensional spoiled gradient-echo MR imaging: comparison with standard MR imaging and correlation with arthroscopy. AJR Am J Roentgenol 1995;165:377-82.
43. Recht MP, Piraino DW, Paletta GA, Schils JP, Belhobek GH. Accuracy of fat-suppressed three-dimensional spoiled gradient-echo FLASH MR imaging in the detection of patellofemoral articular cartilage abnormalities. Radiology 1996;198:209-12.
44. Disler DG, McCauley TR, Kelman CG, Fuchs MD, Ratner LM, Wirth CR, et al. Fat-suppressed three-dimensional spoiled gradient-echo MR imaging of hyaline cartilage defects in the knee: comparison with standard MR imaging and arthroscopy. AJR Am J Roentgenol 1996;167:127-32.