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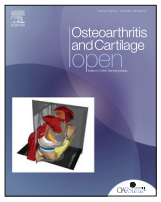

Approaches to optimize analyses of multidimensional ordinal MRI data in osteoarthritis research: A perspective

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ABSTRACT

Objective: Knee osteoarthritis (OA) is a disease of the whole joint involving multiple tissue types. MRI-based semi-quantitative (SQ) scoring of knee OA is a method to perform multi-tissue joint assessment and has been shown to be a valid and reliable way to measure structural multi-tissue involvement and progression of the disease. While recent work has described how SQ scoring may be used for clinical trial enrichment and disease phenotyping in OA, less guidance is available for how these parameters may be used to assess study outcomes.
Design: Here we present recommendations for summarizing disease progression within specific tissue types. We illustrate how various methods may be used to quantify longitudinal change using SQ scoring and review examples from the literature.
Results: Approaches to quantify longitudinal change across subregions include the count of number of subregions, delta-subregion, delta-sum, and maximum grade changes. Careful attention should be paid to features that may fluctuate, such as bone marrow lesions, or with certain interventions, for example pharmacologic interventions with anticipated cartilage anabolic effects. The statistical approach must align with the nature of the outcome.
Conclusions: SQ scoring presents a way to understand disease progression across the whole joint. As OA is increasingly recognized as a heterogeneous disease with different phenotypes a better understanding of longitudinal progression across tissue types may present an opportunity to match study outcome to patient phenotype or to treatment mechanism of action.

1. Introduction

Osteoarthritis (OA) affects 300 million adults worldwide; with an aging population and the growing obesity epidemic, the prevalence is increasing [1,2]. OA was recently ranked as the 11th highest contributor to global disability of 291 conditions studied [3]. While traditionally considered a disease of aging, recent data suggest that over half of knee OA patients in the US are under the age of 65 [2]. Despite the clinical and economic burden of OA, no disease-modifying OA drugs (DMOADs) are currently available and current treatments are only modestly efficacious for symptoms and usually with side effects, serious in some cases [4,5].

One of the reasons for the failure of DMOAD trials is the primary use of radiography to determine study eligibility and to measure structural endpoints [6,7]. Many exclusionary conditions are X-ray-occult, tissue damage varies widely in supposedly eligible joints defined as Kellgren-Lawrence grades 2 and 3, and joint space loss as an outcome measure is a surrogate of damage in multiple tissues including cartilage and meniscus [8,9]. Moreover, posteroanterior radiography does not show synovitis, joint effusion and bone marrow lesions, features that are associated with pain and structural progression. Longitudinal reproducibility of X-ray positioning is challenging and often problematic [10]. Knee OA is a disease involving all tissues of the affected joint, including cartilage, bone, ligaments, menisci, muscles and synovium. The progression of OA is a complex process involving inflammatory, mechanical, genetic and metabolic factors and prediction of the disease course is challenging [11]. MRI-based semi-quantitative (SQ) scoring of knee OA is a method to perform multi-tissue joint assessment and has been shown to be a valid and reliable way to measure structural multi-tissue

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involvement and progression of knee osteoarthritis [12,13]. Both cross-sectional presence and changes in features assessed by SQ imaging have been shown to be associated with subsequent progression [14–16].

The two most widely used SQ scoring systems for knee OA, MOAKS (MRI Osteoarthritis Knee Score) and WORMS (Whole-Organ Magnetic Resonance Imaging Score), rely on ordinal ratings of knee features by expert readers [14,17]. While guidance is available to describe how SQ scoring may be applied and can be used for clinical trial enrichment, less information is available on how these parameters should be used to assess outcomes [12,13,18–21].

Definitions of longitudinal change using MOAKS sores have been suggested previously, but suggestions for analytic strategies how to best leverage these rich multi-dimensional datasets are largely missing [21]. Without a robust analytic approach to best synthesize these ratings we may be under-utilizing the richness of the SQ MRI-based data. Here we describe how MOAKS can be used to quantify longitudinal change in knee OA and highlight its potential as an outcome measure in addition to other commonly used metrics such as quantitative approaches based on image segmentation.

2. Scoring methodology

The MOAKS system describes key pathoanatomic features of the joint, including cartilage damage (both in surface area extent and in full-thickness loss), meniscus damage, osteophytes, bone marrow lesions (BMLs), Hoffa-synovitis, effusion-synovitis and others [14]. The knee joint is divided into subregions (e.g., 14 for cartilage and bone marrow lesions) and locations (e.g., 10 locations for osteophyte assessment), and each is scored for a given feature on an ordinal scale ranging from 0 to 3. The MOAKS system and its application has been described previously and a brief overview is provided in the appendix [12,14].

2.1. Quantifying longitudinal change

Different approaches have been suggested to quantify longitudinal change in cartilage, osteophytes, and BMLs:

Count of number of subregions: Worsening across subregions is quantified by the number of subregions with a worse (higher) score at follow-up as compared to baseline, by the change in the number of subregions affected (score = 0 at baseline and >0 at follow-up), and by the number of subregions with true worsening of damage (i.e., score of >0 at baseline that shows worsening at follow-up). Improvement across subregions is quantified as the number of subregions with improvement from baseline to follow-up (i.e., lower score at follow-up as compared to baseline).

Delta-subregion (Delta-SR): building on the approach of change in number of subregions affected, the delta-SR approach considers worsening and improvement simultaneously. This is particularly relevant for bone marrow lesions that may show fluctuation in both directions over time in multiple subregions (Fig. 1). Both the number of subregions with worsening and the number of subregions with improvement are calculated, and the delta-SR change is calculated as the number of subregions with worsening minus the number of subregions with improvement.

Delta-sum: Add the absolute score across all subregions separately for each timepoint. Longitudinal change (delta-sum) can be quantified by taking the difference between follow-up and baseline. This approach has the drawback that the same delta-sum score may reflect minor changes in multiple subregions or large change in only few subregions.

Maximum grade: Calculate the change in each subregion. Longitudinal change is quantified as the maximum change across all subregions.

2.2. Additional considerations

- *Within-grade changes:* within-grade changes are changes that do not fulfill the definition of a full-grade change but do represent definite SQ visual change (e.g., within a subregion, the extent of cartilage area affected increasing from 25% to 60% would not meet the definition of full grade change; both timepoints would be coded as a grade of 2: 10–75% of subregion affected. Such a change would meet the definition of within-grade change). These changes have been shown to be clinically meaningful, and including such changes in SQ assessment of longitudinal change increases sensitivity to change [22]. Validity has been confirmed for longitudinal cartilage assessment showing strong associations with quantitative cartilage loss based on 3D segmentation approaches [23]. An example of calculating change metrics with and without including within-grade changes is provided in Table 1. An illustrative example of within-grade BML change is shown in Fig. 2.
- *Compartment specific vs. whole knee:* Cartilage morphology, BMLs, and osteophytes may be summarized over the whole joint, or separately for the medial femorotibial joint (MFTJ), lateral femorotibial joint (LFTJ), and patella-femoral joint (PFJ) [24]. For example, by counting the number of subregions with BML for the whole knee (range: 0 to 14) or in each compartment separately (range: 0 to 5 in the LFTJ and MFTJ, 0 to 4 in the PFJ) or by calculating the delta-sum across all SR in the whole knee or in each compartment separately, as shown in Roemer et al. [25]. Analyzing the data separately by compartment or for the whole joint may have implications for the statistical approach (see statistical considerations below).
- *Additional consideration for features that may fluctuate:* Some joint features, including BMLs, Hoffa-synovitis, and effusion-synovitis, may show both worsening and improvement. For example, a participant

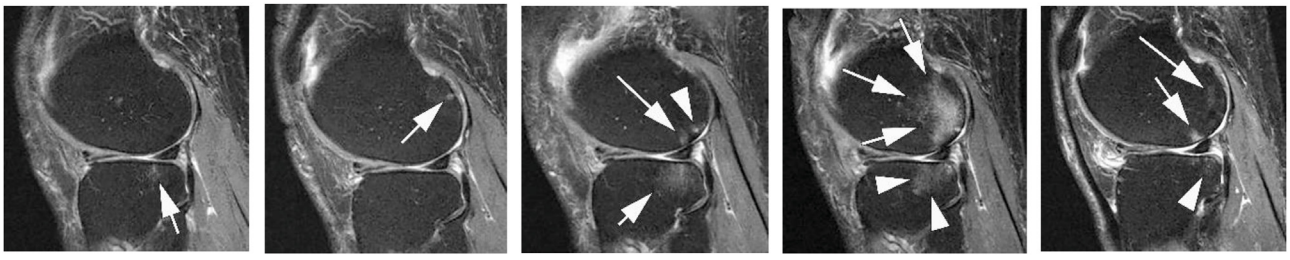

Fig. 1. Example longitudinal assessment of bone marrow lesions (BML) in the lateral tibio-femoral compartment. BMLs are fluctuating features of OA that may show decrease in some subregions and increase in others over time. A. Baseline sagittal intermediate-weighted fat-suppressed MRI shows a grade 1 MOAKS BML in the posterior lateral tibia displaying high-signal intensity, comprised of an ill-defined (edema-like) component only (arrow). B. Follow-up MRI one year later shows complete resolution of tibial BML but a dot-like small new BML at the posterior lateral femur (arrow). C. Further follow-up 1-year later shows incidence of a large grade 3 BML at the posterior lateral tibia (short arrow), complete resolution of posterior femoral BML, but new small BMLs at the posterior lateral femur (arrowhead) and central lateral femur (long arrow). D. Three years after baseline, there is a single large grade 3 BML at the posterior lateral femur that reaches into the central subregion of the lateral femur. Tibial BML show a similar size compared to previous visit (arrowheads). E. After four years, the large femoral BML has largely regressed with two remaining small grade 1 BMLs at the posterior (short arrow) and central lateral femur (long arrow). Also, the tibial BML shows decrease in size - now to ta small grade 1 lesion (arrowhead).

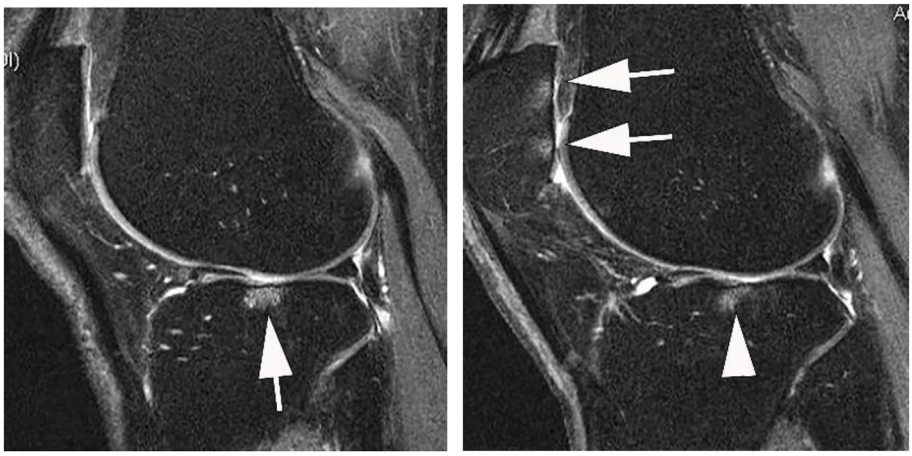

Fig. 2. Scoring of within-grade changes of structural features of OA (applied particularly to cartilage and BMLs) has shown validity and may be clinically relevant. A. Baseline sagittal intermediate weighted fat-suppressed MRI shows a grade 1 BML at the central subregion of the lateral tibia (arrow). B. At 1 year follow-up the BML is still present but has visually decreased in size (arrowhead). This will be scored as a within-grade change over time (i.e. definite visual change not fulfilling a full grade change on the MOAKS scale). In addition, there are two new BMLs at the lateral patella (arrows).

with two SRs with worsening BML score and two SRs with improving BML score would have a delta-SR score of zero. A participant with no change in BML score in any SR would also have a delta-SR score of zero. This approach should be used with caution for features that may fluctuate. It is recommended that in addition, the number of SRs with worsening and SRs with improvement are presented separately [13,16,26]. Improving scores may be expected with certain interventions, for example pharmacologic interventions with anticipated cartilage anabolic effects, and studies investigating such interventions should also consider separate assessment of worsening and improvement.

Hoffa-synovitis, Effusion-synovitis: Longitudinal changes are quantified by subtracting the follow-up score from the baseline score and can be further categorized as improvement, no change, and worsening.

Meniscus: The maximum meniscal morphology score is considered separately for the medial and lateral meniscus. The original MOAKS description does not specify how to sort the different meniscal pathologies in regard to ordinal fashion based on severity but only considers presence vs. absence of a specific tear or pathology. Past analyses have defined the following order: normal, meniscal signal, any tear type, any maceration [16,24]. Complete and progressive partial maceration is considered worse than partial maceration [14]. Furthermore and based on the available literature e.g. a complex tear will be considered "worse" (in regard to clinical impact and risk of overall structural progression) than a horizontal degenerative tear [27,28]. Modifications of MOAKS now include presence of posterior meniscal root tears that are considered exclusionary at baseline due to a markedly increased risk of rapid progressive OA [13,18]. Longitudinal change is quantified by the change in the maximum score. The number of subregions with worsening is computed by taking the number of subregions with a higher score at follow-up as compared to baseline in the anterior, body and posterior horn, separately for medial and lateral menisci. This can also be done for

Table 1
Example of Quantifying Longitudinal Change in cartilage area extent over three time points.

	LFTJ					MFTJ					PFJ			
	cLF	pLF	aLT	cLT	pLT	cMF	pMF	aMT	cMT	pMT	aLF	aMF	LP	MP
Timepoint 1	0	0	0	0	1	1	2	1	0	0	1	0	2	0
Timepoint 2	0	1	2	0	1+	1	3	1	0	0	2	0	2+	1
Timepoint 3	0	1	3	1	1+	1+	3	1	1	0	2	0	2	2

	+ denotes within-grade change (WGC) worsening		
	Maximum Score:		Number of SRs affected:
	T1: 2 T2: 3 T3: 3	Change: T1 to T2: +2 T2 to T3: +1	T1: 6 T2: 9 T3: 11	Change: T1 to T2: +3 T2 to T3: +2
	Absolute score:		Number of SRs with worsening:	
	T1: 8 T2: 14 T3: 18	Delta-Sum: T1 to T2: 6 T2 to T3: 4	exclude WGC: T1 to T2: 5 T2 to T3: 4	include WGC: T1 to T2: 7 T2 to T3: 6
	Delta-SR (exclude WGC) T1 to T2 Number of SRs with worsening: 5 Number of SRs with improvement: 0 Number of SRs with no change: 9 Delta-SR: +5 T2 to T3 Number of SRs with worsening: 4 Number of SRs with improvement: 0 Number of SRs with no change: 10 Delta-SR: +4		Delta-SR (include WGC) T1 to T2 Number of SRs with worsening: 7 Number of SRs with improvement: 0 Number of SRs with no change: 7 Delta-SR: +7 T2 to T3 Number of SRs with worsening: 6 Number of SRs with improvement: 0 Number of SRs with no change: 8 Delta-SR: +6	

Example shows results on a whole knee level. Compartmental definitions may be applied in addition.
MFTJ: medial tibiofemoral joint; LFTJ: lateral tibiofemoral joint; PFJ: patellofemoral joint; c = Central; p = Posterior; a = Anterior; LF = lateral femur; LT = lateral tibia; MF = medial femur; MT = Medial tibia; LP = lateral patella; MP = medial patella.

changes in meniscal morphology category (i.e., from normal to tear, normal to maceration or tear to maceration). Changes in meniscal extrusion are quantified as the follow-up score minus the baseline score and categorized into worsening vs. no worsening. Incident meniscal root tears are commonly considered separately due to their potential marked clinical relevance.

Examples of how various change parameters are calculated are provided in Tables 1 and 2.

3. Statistical approaches

The various approaches to quantifying longitudinal change may result in variables that are counts, ordered categories, binary categories, or continuous parameters. Each has its own set of considerations for statistical analysis. Analyzing at the SR, compartment, or whole knee level also has statistical implications. Here we describe various methods to model changes in MOAKS features as study outcomes.

Count data, such as the number of subregions with worsening MOAKS score, are often skewed and cannot be normalized with a simple transformation (e.g., natural log, square root) and thus should be modeled with a model appropriate for count outcomes [29]. Poisson regression is a generalized linear model where the outcome is modeled with a Poisson distribution, a natural log link function, and an identify function for variance (that is, mean = variance). Negative binomial regression may be needed in the case of overdispersion (excess variance). Fig. 3 shows the distribution of 24 month change in MOAKS cartilage area extent in the FNIH OA Biomarkers Consortium cohort [16]. Approximately 40% of participants experienced no change in cartilage area extent, and the count of number of subregions with worsening ranges from 0 to 8. Such data are not appropriate for linear regression.

In the case of outliers or where a dose-response relationship between predictor and outcome is not assumed, it may be advisable to categorize count data based on distribution. In the example above (Fig. 3), the number of SRs with worsening in cartilage area extent was categorized as worsening in 0, 1, 2, or 3+ SRs for analysis [16]. Categorical outcomes can be analyzed with logistic regression. Binary logistic regression is appropriate for a dichotomous outcome, e.g., any worsening vs. no worsening, and estimates the odds of outcome for those with vs. without the predictor of interest (e.g., the increased odds of worsening for participants on treatment vs. placebo). Ordinal logistic regression is appropriate for an ordered categorical outcome, e.g., worsening in 0, 1, 2, or 3+ SRs. There are various ways to model the ordering, including cumulative logits, adjacent-categories logits, and continuation ratio logits

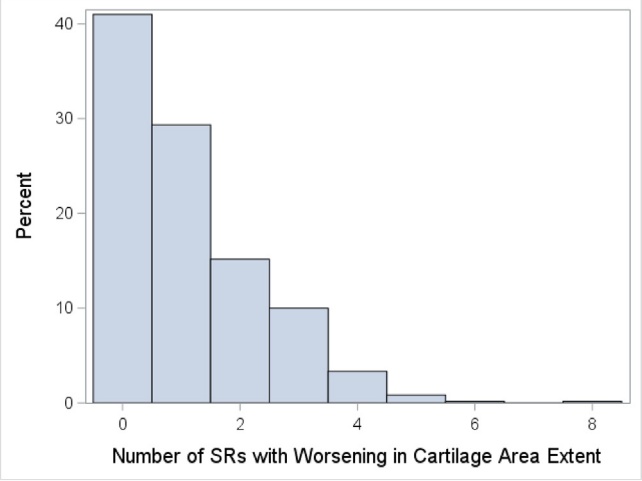

Fig. 3. The distribution of twenty-four-month change in MOAKS cartilage area extent in the FNIH OA Biomarkers Consortium cohort shows right skewness. The number of subregions with worsening in MOAKS cartilage area extent is shown on the x-axis and the percent of participants is shown along the y-axis. Over 40% of participants had zero subregions with worsening in MOAKS cartilage area extent.

Table 2
Quantifying Longitudinal Change in BMLs over three time points.

	LFTJ					MFTJ					PFJ			
	cLF	pLF	aLT	cLT	pLT	cMF	pMF	aMT	cMT	pMT	aLF	aMF	LP	MP
Timepoint 1	1	1	0	0	1	1	2	0	0	0	0	0	0	1
Timepoint 2	1-	0	0	2	1	1+	2+	0	0	0	0	2	0	0
Timepoint 3	1-	0	0	3	1+	1	2-	0	0	0	0	2	0	0

+ denotes within-grade change (WGC) worsening
- denotes within-grade change (WGC) improvement

Maximum Score:		Number of SRs affected:	
T1: 2	Change:	T1: 6	Change:
T2: 2	T1 to T2: +2	T2: 6	T1 to T2: 0
T3: 3	T2 to T3: +1	T3: 6	T2 to T3: 0
Absolute score:		Number of SRs with worsening:	
T1: 7	Delta-Sum:	exclude WGC:	include WGC:
T2: 9	T1 to T2: 2	T1 to T2: 2	T1 to T2: 4
T3: 10	T2 to T3: 1	T2 to T3: 1	T2 to T3: 2

Delta-SR (exclude WGC)	Delta-SR (include WGC)
T1 to T2	T1 to T2
Number of SRs with worsening: 2	Number of SRs with worsening: 4
Number of SRs with improvement: 2	Number of SRs with improvement: 3
Number of SRs with no change: 10	Number of SRs with no change: 7
Delta-SR: 0	Delta-SR: 1
T2 to T3	T2 to T3
Number of SRs with worsening: 1	Number of SRs with worsening: 2
Number of SRs with improvement: 0	Number of SRs with improvement: 2
Number of SRs with no change: 13	Number of SRs with no change: 10
Delta-SR: 1	Delta-SR: 0

MFTJ: medial tibiofemoral joint; LFTJ: lateral tibiofemoral joint; PFJ: patellofemoral joint; c = Central; p = Posterior; a = Anterior; LF = lateral femur; LT = lateral tibia; MF = medial femur; MT = Medial tibia; LP = lateral patella; MP = medial patella.

[30]. A detailed discussion of these models is beyond the scope of this article; each makes an assumption about the ordinal nature of the outcome. Multinomial logistic regression (generalized logits) does not assume an ordering of the outcome classes. While ignoring the ordered nature of the outcome may intuitively seem inappropriate, it allows the analyst to assess whether or which assumptions about the ordered outcome are appropriate to make about the relationship between outcome and predictor.

Continuous data, such as the delta-sum score, may have an approximate Gaussian distribution and therefore can be analyzed with methods such as linear regression. If scores are available across multiple time points, then absolute scores can be analyzed with repeated measures models, such as linear mixed effects models, and the delta-sum score can be estimated from the model. Verifying distributional assumptions (e.g., by plotting the distribution of the residuals) is essential, as delta-sum may be right skewed in some populations (e.g., early OA).

Many statistical methods, such as t-tests, Chi-square tests, and linear regression, assume that observations are independent. Special attention must be paid when analyzing repeated measures or clustered data, for example, when conducing analyses at the compartment level vs. whole knee level, or when including two vs. one knees per participant [31]. As an example, an outcome that classifies each participant as having any vs. no worsening on osteophyte score can be analyzed with a simple Chi-square test or logistic regression model. If instead each participant contributes two knees, and each knee is categorized as having any vs. no worsening in osteophyte score (two observations per participant), or if any vs. no osteophyte worsening is computed at the compartment level (LFTJ, MFTJ, PFJ: three observations per knee) then models that account for the correlated nature of the data (knees nested within participants, compartments nested within knees) are required. There are many methods available for clustered data, such as random-effect, mixed-effect, and marginal models; a thorough review of such methods is presented elsewhere [32,33].

MOAKS includes scores across multiple joint features, compartments, and SRs, allowing for the computation of potentially many outcomes. With nested data it may or may not be of interest to test for differences in level; e.g., in a model with two knees per person it may not be of interest to test whether outcomes are different in left vs. right knee, but may be of interest to test for differences in injured vs. uninjured knee. In the case of nested models with compartments or SRs, pairwise comparisons should be approached cautiously. Investigators using MOAKS must be aware of the problem of multiple testing: testing multiple hypotheses without correction to the alpha level can result in inflated Type I error rates. Many methods exist to correct alpha for multiple comparisons [34].

4. Examples

Roemer and colleagues used the delta-sum and delta-SR approach in a post-hoc analysis of the effects of sprifermin on cartilage and non-cartilaginous joint tissues [35]. Mann–Whitney − Wilcoxon tests assessed differences between treatment groups. The authors found significant differences between the treatment groups in cartilage area extent in the PFJ (delta-sum approach; treatment 0.05, 95 % CI (−0.06, 0.17) vs. placebo 0.44, 95 % CI (−0.18, 1.06), $p = 0.048$; delta-SR approach; treatment (0.02 95 % CI (−0.04, 0.08) vs. placebo 0.22, 95 % CI (−0.05, 0.49), $p = 0.046$). While no significant differences were found between treatment groups for BMLs, this paper illustrates how the two approaches quantify longitudinal change for parameters that may improve over time: the delta-sum and delta-SR values for the treatment group were both negative, indicating overall improvement in BML score.

Collins and colleagues used the delta-sum approach to quantify 5-year structural changes in the MeTeOR (Meniscal Tear in Osteoarthritis Research) trial, a multicenter RCT of arthroscopic partial meniscectomy vs. physical therapy in patients with degenerative meniscal tear and mild-to-moderate knee OA [36]. The authors calculated the absolute score separately for cartilage area extent, full-thickness loss, osteophytes, and BMLs at baseline, 18-months, and 5-years follow-up and then used linear mixed-effects models to assess the association between treatment group and score and to estimate changes in score, i.e., delta-sum. The authors found significant differences in delta-sum osteophyte score between treatment groups over both the baseline to 18 month and 18–60-month time periods, with the APM group demonstrating higher delta-sum scores (i.e., more worsening).

The RESTORE RCT evaluated the effects of intra-articular platelet rich plasma (PRP) injections on symptoms and joint structure in patients with knee OA [37]. Secondary MRI outcomes included the number of subregions with worsening in full-thickness cartilage damage (categorized as 0, 1, 2, or $\geq$3), change in whole knee effusion-synovitis (categorized as worsened, no change, or improved), any worsening in Hoffa-synovitis (referred to as intercondylar in this study), and any worsening in BML size across all subregions. Changes in full-thickness cartilage damage and whole knee effusion-synovitis were analyzed with multinomial logistic regression and worsening in Hoffa-synovitis and BML size were analyzed with log-binomial regression models. Seventeen percent of the PRP group demonstrated worsening in full-thickness cartilage damage in 3 or more subregions compared to 7% of the placebo group for an increased odds of worsening of 2.7 (95% CI: 1.16–6.34).

Roemer et al. and Collins et al. demonstrate how change in maximum grade and change in number of SRs can be used to quantify longitudinal change in the FNIH OA Biomarkers study, and how within-grade changes can be included or excluded from these calculations [16,26]. The FNIH OA Biomarkers study was a nested case-control study that aimed to evaluate the longitudinal validity of imaging and biochemical markers as efficacy of intervention biomarkers in knee OA. Case knees were those with joint space narrowing and pain worsening over 48 months. 24-month changes in cartilage area extent were associated with case status in analyses both including and excluding within-grade change; 68% of the control group and 54% of the case group had no worsening in cartilage area extent when within-grade changes were excluded; when within-grade changes were excluded the percent with no change dropped to 48% and 27% respectively. Additional details of the cartilage results of the FNIH study are presented in Fig. 3.

5. Discussion

In this perspective we described how whole-organ SQ scoring of MRI i.e., MOAKS can be used to quantify longitudinal change in knee OA. The details captured in MOAKS or comparable systems like WORMS provide a nuanced picture of disease progression across multiple tissues. While SQ scoring has been proposed for disease phenotyping and eligibility assessment in clinical trials of knee OA [13,18], the outcomes described here may also be used as trial outcomes to assess structural disease progression and evaluate treatment efficacy.

Here we present recommendations for summarizing disease progression within specific tissue types. There has been interest in whether and how a composite outcome reflecting disease progression across the entire joint might be defined. The OMERACT Technical Advisory Group defines a multi-outcome domain (MOD) as “a within-patient combination of component outcomes, and an individual patient's evaluation depends on the observation of all of the components in that patient with a single overall rating determined according to a specified rule” and a composite outcome domain (COD) as “a number of component outcomes and is defined as the occurrence in a patient of one, some or all of these specified components” [38]. A composite outcome in a DMOAD trial might be reaching either a pre-specified pain threshold or undergoing total knee replacement [39]. Driban and colleagues attempted to define a multi-outcome domain using quantitative measures of cartilage damage, BMLs, and effusion-synovitis volume to reflect damage across multiple tissues [40]. The authors report two composite scores: a ‘cumulative cartilage damage’ score reflecting structural progression and a ‘BML plus effusion-synovitis’ score reflecting symptomatic progression. SQ scoring systems such as MOAKS, which provide rich detail across multiple tissues, may provide an opportunity to further investigate multi-outcome

domains for DMOAD trials. While it is unclear whether and how features should be combined across domains, unsupervised machine learning methods could help inform how and when to combine features [41].

Patterns of both patient-reported symptoms and of structural damage vary substantially between knee OA patients, suggesting that different phenotypes (subpopulations) of OA exist [42,43]. As such, a "one-size fits all" approach is unlikely to work in developing therapies for knee OA – interventions must be tailored to and tested in the appropriate population [44]. The Rapid OsteoArthritis MRI Eligibility Score (ROAMES) provides a framework for how SQ scoring can be used to perform phenotypic stratification of DMOAD clinical trial participants [18]. The multi-tissue assessment provided by SQ scoring systems such as MOAKS provides an opportunity to not only stratify at trial enrollment but also to match phenotype to outcome. A challenge to be resolved in future work is based on the fact that structural phenotype may overlap and one joint may exhibit more than one phenotype.

A DMOAD trial outcome must be sensitive to change [45]. There are few studies directly comparing the sensitivity to change of quantitative vs. SQ MRI assessments. Some work has suggested that quantitative measures of cartilage thickness may be more sensitive to change than SQ measures, while others have found sensitivity to change to be similar [45,46]. Including within-grade changes in SQ MRI scores has been shown to improve sensitivity to change for both cartilage and BML assessment [22]. Recent studies have shown that both full-grade and within-grade changes in MOAKS cartilage scores correspond with longitudinal quantitative cartilage thickness loss [23,47]. While standardized response means (SRMs) are often used to assess responsiveness, the interpretation of this measure (mean change divided by standard deviation of change) is less intuitive for non-Gaussian outcomes, making direct comparison between SQ and quantitative measures difficult. Recent findings from RCTs may shed light on sensitivity to change. For example, the RESTORE RCT, assessing the effect of intra-articular platelet-rich plasma vs placebo injection, found no significant difference in structural endpoints between treatment groups and. The study finds that approximately 50% of participants experienced areas with cartilage thinning and 15% had worsening of full-thickness cartilage damage over 18 months [37]. The SRM for the primary outcome of quantitative percentage change in medial tibial cartilage volume was approximately 0.2. Over 18 months in the MeTeOR trial approximately 60% of non-operatively treated participants experienced worsening in cartilage surface area extent score and 50% in full-thickness cartilage loss score [48].

To-date, no MRI-based measures of disease progression are approved by FDA as surrogate endpoints for DMOAD trials. FDA guidance does not refer to the type of surrogate endpoint (e.g., SQ vs. quantitative measure, imaging vs. biochemical biomarker), but does require that there be "substantial confidence, either based on empirical evidence from randomized, controlled comparisons from clinical trials and/or based on a comprehensive understanding of the disease process and product mechanism of action, that an effect on the candidate structural endpoint will reliably predict an effect on the clinical outcomes of interest." [49] There is precedent for the use of SQ scoring of imaging as trial outcomes, such as the Sharp or modified-Sharp score for erosion and joint space narrowing in rheumatoid arthritis [50]. Future work should investigate establishing a minimal clinically important difference (MCID) for OA structural endpoints.

Another major hurdle in assessing treatment efficacy in DMOAD trials is the lack of validated structural endpoints and the uncertainty around the magnitude of change in these endpoints that would translate to a clinically meaningful benefit to patients [6,49]. The rich data provided by SQ assessment provides an opportunity to investigate which combination of features best measure how a patient feels or functions, or how the joint survives. However, determining when and how to summarize these data does not come without challenges. For example, while summarizing scores across all subregions results in a single continuous outcome measure and facilitates the use of traditional analytic approaches, it leads to a loss of information, as sums are the result of a spectrum of affected subregions and severity grades. A high total score (i.e., summing across subregions) could reflect small amounts of damage in many subregions, or large amounts of damage in few subregions – a fact that is also relevant for defining longitudinal change. It may also obscure changes for features with fluctuating damage (e.g., BMLs) and thus lead to challenges in correlating changes in structural features with symptoms. Prior work by Runhaar and colleagues attempted to define subregional osteoarthritis progression using MOAKS [21]. The authors define thresholds for both improvement and progression in BMLs, cartilage defects, osteophytes, and meniscal pathologies. While this is an important step in conceptualizing SQ-based progression, the guidance we present here represents a more general approach to defining change that could be tailored to a specific trial or intervention.

To date no disease-modifying therapies are approved for knee OA. SQ imaging assessment of longitudinal change provides an opportunity to better understand disease progression across multiple tissue types, which may allow future trials to match outcome to patient phenotype or to treatment mechanism of action. The detailed data provided by these assessments will allow researchers to determine whether and how to best combine scores such that changes are reflective of clinically relevant outcomes and to determine what magnitude of change represents clinical benefit.

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Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

Conflicts of interest

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Appendix A. Supplementary data

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