SIMULATION OF DRUG EFFECTS ON OA DISEASE PROGRESSION MEASURED WITH MRI - ORDERED VALUES ARE MORE SENSITIVE THAN ANALYSIS OF CARTILAGE PLATES AND SUBREGIONS

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Purpose: To overcome challenges of the spatial heterogeneity of MRI-based subregional cartilage loss in OA, an ordered value (OV) approach was proposed. This approach ranks subregional cartilage thickness changes in each knee according to magnitude, assigning the region with the greatest cartilage loss to OV1, the one with the 2nd greatest loss to OV2, and the one with the smallest loss or largest increase in thickness to OV16. The approach includes 8 medial and 8 lateral femorotibial subregions and was shown to be effective in differentiating rates of cartilage loss in OA knees with and without JSN. Here we explore, by simulation, to what extent the OV approach is superior in identifying potential effects of a DMOAD on structural progression in OA.

Methods: 610 knees with radiographic OA (300 with JSN; 310 without) from the Osteoarthritis Initiative were analyzed at baseline and 12 month follow-up (public use data sets 0.E.1, 1.E.1, 0.2.2). The knees were randomized into two equally sized groups. The following simulations were performed: A) all negative subregional changes (thickness loss) were reduced in the treatment group, B) all positive changes (thickening; swelling or hypertrophy) were reduced, C) both types of changes were reduced, assuming a 25% reduction by a DMOAD. For each of the three simulation types, the following models were run: 1) homogenous reduction of 25% in each subregion in the treatment group; 2) random reductions between 0% and 50% (mean=25%, SD=12.5%) across knees, but the same value in all subregions of each knee; 3) random reductions between 0% and 50% (mean=25%, SD=12.5%) across different subregions and knees. Effects were reported when consistent results were obtained for simulating the DMOAD effect in each of the randomized subcohorts versus the other (as a placebo [Mann-Whitney-U test; p<0.01]).

Results: Running simulations A-C and models 1-3, significant treatment effects were occasionally observed in cartilage compartments, plates and subregions, but in no case these were consistent when simulating treatment effects in the other randomized subcohort. In contrast, OV1 revealed consistent significant differences in the treated vs. placebo group (p for OV1 between 4.4×10⁻⁷ and 1.1×10⁻¹¹), and OV1-5 displayed significant results in all models, independent of whether the treatment was simulated for one or the other randomized subcohort. This also applied when simulating a DMOAD reducing cartilage thickening, with OV16 displaying treatment-related p-values of 1.5×10⁻⁷ to 7.7×10⁻¹³, and with OV13-16 displaying consistent significance across all models. Simulation of a DMOAD stabilizing cartilage generated p-values for treatment effects between 1.2×10⁻⁹ and 9.2×10⁻¹¹ in OV1, and values of 3.3×10⁻⁰⁶ to 4.0×10⁻¹¹ in OV16, independent of which randomized subcohort was used.

Conclusion: Limitations of the study are that subregional changes are partly due to precision error, and that it is unknown to what extent DMOADs can reduce (subregional) cartilage thinning or thickening. Therefore, a conservative DMOAD effect of only 25% was applied. A strength of the approach was that the simulation accounted for potential variability of treatment effects between knees and regions, and that the simulation was based on actual measurements of (subregional) cartilage change in OAI participants. Therefore, the principal observations should hold, even if the actual magnitude of the effect of a DMOAD was larger or smaller. The results suggest that a) the OV approach is more effective in detecting DMOAD effects than the conventional approach, b) that, unlike conventional approaches, it is capable of capturing effects of a drug stabilizing cartilage (i.e. reducing both loss and thickening), and c) that the OV approach is less sensitive to randomization effects than region based analysis of cartilage loss. These results will have to be confirmed empirically; the current simulation, however, suggests that ordered values (OVs) of subregional cartilage change in MRI are a potentially very powerful tool for detecting drug effects on structural progression in OA.

DIRECT COMPARISON OF ONE- AND TWO-YEAR SENSITIVITY TO CHANGE OF FIXED FLEXION RADIOGRAPHY VERSUS SUBREGIONAL MRI CARTILAGE MORPHOLOGY: DATA FROM THE OSTEOPOROSIS INITIATIVE

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Purpose: Longitudinal studies investigating risk factors for structural progression of osteoarthritis (OA) or disease modifying interventions have mainly relied on measurement of minimum joint space width (mJSW) as primary outcome. Direct cartilage morphometry by magnetic resonance imaging (MRI) may be beneficial, because of a potentially greater sensitivity to change and because, contrary to radiography, it is not confounded by meniscal extrusion. Here we directly compare the sensitivity to change of fixed flexion radiography versus MRI-based (subregional) knee cartilage thickness in OA Initiative knees over 12 and 24 months.

Methods: Radiographic and MRI data from the OAI (public use data sets 0.E.1, 1.E.1, 2.E.1 [imaging] and 0.2.2 [clinical]) were studied in two subsamples: 1) Baseline and 12 month follow-up (12M) in 275 knees with radiographic but not necessarily symptomatic knee OA, using a coronal FLASH MRI sequence; 2) Baseline, 12M, and 24 month follow-up (24M) in 100 knees with radiographic and symptomatic OA, using a sagittal DESS MRI sequence. The radiographs were measured semi-automatically and independently of each other and MRI data were read in pairs (or triplets), with blinded to time point, by seven readers. The standardized response mean (SRM) for mJSW and fixed JSW locations (distance between the external borders of the medial [0%] and the lateral compartment [100%]) were compared with that in (subregional) MRI cartilage thickness of the medial femorotibial compartment (MFTC). Pearson correlation coefficients were computed between both methods.

Results: In the FLASH subsample (n=275), the 12M SRM was -0.22 for radiographic mJSW, and -0.34 for MRI-based cartilage thickness in MFTC. In the DESS subsample, 12M SRMs were -0.24 (radiographic mJSW) and -0.30 (MFTC), and 24M SRMs -0.20 and -0.38, respectively. The smallest SRM (i.e. the most sensitive) for radiography was observed in the FLASH sample (12M) at the 20% fixed distance position (p<0.01), the most sensitive MRI parameter in this subsample being the combined central femoral and tibial subregion (SRM:-0.37). The smallest SRM for MRI was observed in the DESS sample (24M) in cMFTC (SRM: -0.53) the most sensitive radiographic parameter in this subsample being the fixed distance position at 20% (SRM:-0.27). The greatest Pearson correlation coefficients in the FLASH sample over 12M were found between mJSW and the combined external tibial and femoral subregion (eMFTC) (r=0.31, p<0.01). In the DESS sample, the correlation was greatest between the 22.5% fixed distance position and the central subregion of the medial tibia (cMT) over 12M (r=0.33, p<0.01) and between the 27.5% fixed distance location and cMT over 24M (r=0.53, p<0.01). The correlations between fixed distance positions and MRI parameters tended to exceed the correlations observed between mJSW and MRI in the DESS cohort over 24M but not in the FLASH cohort over 12M.

Conclusions: The sensitivity to change in fixed flexion radiography was higher for fixed locations than for mJSW. However, radiography provided a somewhat lower sensitivity to change than MRI. Correlations (Pearson) between mJSW and MRI were statistically significant, but only moderate (r<0.53). Site-matched correlations (external, central, internal) between fixed locations in radiographs and subregions in MRI were not consistently higher than the coefficients between mJSW and MFTC.

THREE DIMENSIONAL DISTRIBUTION OF ACETABULAR CARTILAGE THICKNESS IN PATIENTS WITH HIP DYSPLASIA BY SEMI-AUTOMATIC COMPUTER ANALYSIS OF HIGH-RESOLUTIONAL COMPUTER TOMOGRAPHY - ARTHROGRAPHY

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Purpose: Previous reports showed usefulness of three dimensional (3D)