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How Do Short-Term Rates of Femorotibial Cartilage Change Compare to Long-term Changes? Four Year Follow-up Data From the Osteoarthritis Initiative

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Abstract

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Conflict of interest: Felix Eckstein is CEO of Chondrometrics GmbH, a company providing MR image analysis services. He provides consulting services to MerckSerono, Novartis, and Sanofi Aventis. Susanne Maschek, Wolfgang Wirth, and Martin Hudelmaier have part time appointments with Chondrometrics GmbH; Susanne Maschek und Wolfgang Wirth are also share-holders of Chondrometrics GmbH. Charles E. Mc Culloch, Kent Kwoh, John Lynch, Michael Nevitt and Leena Sharma have no competing interests.

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Specific contributions are:

1. the conception and design of the study: FE, CE McC, MN, WW
2. acquisition of data: JL, MN, KK, SM, MH, WW
3. analysis and interpretation of data: FE, CE McC, JL, MN, KK, SM, MH, LS, WW
4. Drafting the article: FE, CE McC, MN, WW
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7. Statistical expertise: CE McC, MN
8. Obtaining of funding: FE, MN, KK, LS
9. Collection and assembly of data: JL, MN, SM, MH, WW

Objective—To compare unbiased estimates of short- vs. long-term cartilage loss in osteoarthritic knees.

Method—441 knees (216 Kellgren Lawrence [KL] grade 2, 225 KL grade 3) from participants of the Osteoarthritis Initiative were studied over a four year period. Femorotibial cartilage thickness was determined using 3Tesla double echo steady state magnetic resonance imaging, the readers being blinded to time points. Because common measurement time points bias correlations, short-term change (year-one to year-two: Y1→Y2) was compared with long-term change (baseline to year-four: BL→Y4), and initial (BL→Y1) with subsequent (Y2→Y4) observation periods.

Results—The mean femorotibial cartilage thickness change [standardized response mean] was −1.2%/−0.8% [−0.42/−0.28] over one (BL→Y1/Y1→Y2), −2.1%/−2.5% [−0.56/−0.55] over two (BL→Y2/Y2→Y4), −3.3% [−0.63] over three (Y1→Y4), and −4.5% [−0.78] over four years. Spearman correlations were 0.33 for Y1→Y2 vs. BL→Y4, and 0.17 for BL→Y1 vs. Y2→Y4 change. Percent agreement between knees showing progression during Y1→Y2 vs. BL→Y4 was 59%, and 64% for BL→Y1 vs. Y2→Y4. The area under the receiver operating characteristic curve was 0.66 for using Y1→Y2 to predict BL→Y4, and 0.59 for using BL→Y1 to predict Y2→Y4 change.

Conclusion—Weak to moderate correlations and agreement were observed between individual short- vs. long-term cartilage loss, and between initial and subsequent observation periods. Hence, longer observation periods are recommended to achieve robust results on cartilage loss in individual knees. At cohort and subcohort level (e.g. KLG3 vs. KLG2 knees), the mean cartilage loss increased almost linearly with the length of the observation period and was constant throughout the study.

Keywords

Short term; Long term; knee; cartilage thickness; magnetic resonance imaging; osteoarthritis

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INTRODUCTION

Epidemiological studies and clinical trials make increasing use of magnetic resonance imaging (MRI)-based measures of cartilage morphology as a structural endpoint of osteoarthritis (OA) progression [1–4]. Such measures are used to identify risk factors of OA progression and to evaluate the effect of disease modifying interventions. Studies have suggested that high rates of longitudinal cartilage loss, measured quantitatively with MRI, were associated with an increased risk of having TKA in the future [5,6]. Moreover, quantitative MRI measures have been shown to be sensitive to change over 1-year follow-up periods [1–4,7–11].

Although short-term follow-up studies (e.g. 1 year) of cartilage change are attractive for providing rapid results, the ratio of the true mean change to the measurement's precision error and to the variability of true change among subjects is low. The latter is particularly relevant if rates of change vary substantially over consecutive short-term intervals within individuals due to intermittent OA progression [12]. Measurement over longer study periods may overcome these limitations, because the ratio between the "mean measure change" and the "variability of the measured change" becomes larger; this increases the power with which the effect of an exposure on the outcome can be detected. However, long-term follow-up studies are more costly, have greater participant drop-out, exceed conventional funding periods, and consume a greater amount of the patent-life of a drug. They are therefore less attractive from an industry and funding agency perspective.

Clarifying whether short-term change (1 year) is an adequate proxy of longer-term change is thus an important step in qualifying a biomarker for use in short-term clinical studies.

Evaluating the consistency of rates of progression in consecutive time periods may provide insights into the trajectory of OA progression, e.g. linear or intermittent. Previous studies comparing rates of change for cartilage morphology measures over different time intervals have relied on common measurement points for these intervals, e.g. the same baseline measurement for short- vs. long-term change [7–11], or the same intermediate measurement for initial vs. subsequent change [12]. This involves a bias in estimates of the true correlation of changes in different intervals: When the same baseline measurement is used for calculation of short-term vs. long-term changes, the effect of baseline precision errors is in the same direction and the true correlation between short- and long-term changes is overestimated. When changes in initial and subsequent intervals are calculated using the same intermediate measurement, the precision error of the intermediate time point affects observed changes in both observation periods in opposite directions, and the true correlation may be underestimated or appear negative [12].

Therefore, the current study was designed to address the following questions:

1. What is the magnitude of (subregional) femorotibial cartilage thickness change in OA knees, and how large is the variability of and sensitivity to change for one-, two-, three-, and four-year observation periods?
2. How do results over these periods differ for Kellgren Lawrence grade (KLG) 2 and KLG3 knees, and what are the numbers of progressors vs. non-progressors over different observation periods?
3. What is the correlation between short- vs. long-term changes, and what the level of agreement in classifying knees as progressors or non-progressors?
4. What is the correlation between initial vs. subsequent observation periods, and what is the level of agreement in classifying knees as progressors or non-progressors?

METHODS

OAI cohort and sample selection

The data used for the study originate from the Osteoarthritis Initiative (OAI), which is an ongoing multi-center study (http://www.oai.ucsf.edu/) targeted at identifying sensitive (imaging) biomarkers of onset and progression of knee OA. 4796 participants are studied using fixed flexion radiography [13,14] and magnetic resonance imaging (MRI) of both knees [15]. OAI participants were 45–79 years old, with or "at risk of" symptomatic knee OA in at least one knee. General exclusion criteria were presence of rheumatoid or other inflammatory arthritis, bilateral end-stage knee OA, inability to walk without aids, and MRI contraindications.

Subjects selected for the current study were from the progression subcohort (n=1390), based on having at least one knee with both definite osteophytes [16,17] and frequent symptoms at baseline. The knee selected had to have MRI acquisitions available at baseline (BL) and year 1,2 and 4 follow-up (Y1, Y2, Y4), frequent pain at baseline, and a baseline KL grade of 2 or 3 [18] based on central reading of serial fixed-flexion knee radiographs [13] at the Boston University Clinical Epidemiology Research and Training Unit (for details please see http://www.oai.ucsf.edu/datarelease/ImageAssessments.asp).

MRI analysis

In the OAI, 3Tesla MRIs are generally available from BL to Y4 at 12 month intervals [15,19]. Amongst the different MRI sequences acquired [15,19] the double oblique sagittal double echo steady state (DESS) water excitation sequence was used for cartilage segmentation in the current study, as it has previously been validated in context of quantitative cartilage analysis [15,20,21]. For blinding purposes, the OAI Coordinating Center removed all links to acquisition dates and participant ID in the image DICOM headers and shipped the images to the analysis center (Chondrometrics GmbH, Ainring, Germany). After initial quality control (M.H.), segmentation of the images was performed by 12 readers who all had received formal training in cartilage segmentation. A random time point was processed first; the other time points were then processed using the first data set as a reference, without knowledge of the order of acquisition. The total area of subchondral bone (tAB) and the cartilage surface area (AC) were segmented manually in the medial (MT) and lateral tibiae (LT), and in the weight-bearing (central) part of the medial (cMF) and lateral femoral condyles (cLF). The weight-bearing aspect was separated from the posterior aspects of the condyles using a 75% distance measure between the intercondylar notch and their most posterior aspects, as described previously [21,22]. To minimize segmentation errors and deviations between readers, all segmentations were quality controlled by one expert (S.M.), also with full blinding to time point of the MRI acquisition.tAB or AC segmentations were corrected by the readers, if found necessary by the expert. The mean cartilage thickness over the tAB (ThCtAB), including denuded areas but excluding osteophytes was determined in each cartilage plate. Medial femorotibial compartment (MFTC) cartilage thickness was computed as the sum of MT and cMF, lateral compartment (LFTC) cartilage thickness as the sum of LT and cLF, and total femorotibial joint (FTJ) cartilage thickness as the sum of MFTC and LFTC. Changes in central subregions of MFTC (cMT and ccMF) and LFTC (cLT and ccLF) [23] were summarized as cMFTC and cLFTC [24]. Finally, the data were delivered to the OAI coordinating center, and unblinding for the order of the image acquisition times was done after the final delivery had been made and the data base had been locked.

The test-retest precision of the MRI measurement methodology of articular cartilage morphology has been reviewed previously [1,2], with six to seven of the current team of 12 readers being involved in recently published reproducibility studies [20,25].

Statistical considerations and analysis

As part of the current study, 455 knees had cartilage morphology data measured at all time-points (BL, Y1, Y2 and Y4). Of these, five were excluded due to BL→Y1 interval being shorter than 10 months, and nine because both knees from the same person had cartilage measurements, which cannot be viewed as independent observations. In these latter cases, the right knees were used, leaving 441 knees for analysis.

To allow for a comparison with data from prior studies, we compared “observed” changes between BL and Y1 with “observed” changes between BL and Y4 (BL→Y1 vs. BL→Y4), although, as argued above, this approach may introduce a degree of positive covariation, because it uses the same baseline measurement for both intervals. This effect is similar to the magnitude of the measurement error; it biases the changes observed between the short (BL → Y1) and long term intervals (BL→ Y4) in the *same* direction and causes the correlations of “observed” changes to systematically overestimate the correlation of the “true” changes. To obtain *unbiased* estimates of correlation between short- and long-term changes, the changes from Y1→Y2 were compared to the changes from BL→Y4, as these do not share common measurement points.

To explore the relationship between changes in initial vs. subsequent time periods, we first compared “observed” changes during BL→Y1 with Y1→ Y4, and BL→Y2 with Y2→Y4. Because the shared intermediate measurement (Y1 or Y2) introduces a degree of negative covariation that distorts “observed” changes between the first and the subsequent time interval in *opposite* directions [12], we compared BL→Y1 versus Y2→Y4 to obtain unbiased estimates. BL→Y2 versus Y1→Y4 was also studied for comparison.

The mean change in ThCtAB (μm) was determined as a measure of the "magnitude of change". Percent changes were derived by relating the mean change in a group to the mean ThCtAB at baseline for the same group, and 95% confidence (CI) intervals for estimates of change were determined for key results, using large sample binomial confidence intervals. The standardized response mean (SRM, defined as the mean change divided by the standard deviation of change) was used as a measure of the "sensitivity to change" for the total cohort, and for KLG2 and KLG3 knees separately.

The correlation of the observed changes between different time intervals was determined using non-parametric (Spearman's rho) coefficients. The "smallest detectable change" (SDC) method [26] was used to identify knees with progression (i.e. with significant loss of ThCtAB) in the total femorotibial joint (FTJ), in either compartment (MFTC and LFTC), and in femorotibial cartilage plates (MT, cMF, LT, cLF). Cutpoints (change in μm) for the dichotomous separation of progressors vs. non-progressors were derived from precision errors for repeated measurements of DESS images in the OAI pilot study [27] (test-retest acquisitions at both BL and Y1 = four measurements) as defined by Bruynestein et al. [26]. In Table 2 these cutpoints of change in ThCtAB are listed for all regions of interest studied. The agreement of "progression" in different time intervals was assessed by calculating the "overall percent agreement" (percentage of knees with either progression [or non-progression] in both intervals, in relation to the total number of knees), the "positive predictive value" (PPV = percentage of knees with progression in the shorter [or initial] observation interval that also showed progression in the longer [or subsequent] observation interval), the sensitivity, and the specificity. Because all these agreement measures depend on a specific threshold chosen (by the SDC method [26]), and because low thresholds may inflate the calculated PPV, but impact sensitivity, we additionally determined the receiver operating characteristics (ROC) curves using a fixed long-term and a variable short-term threshold. Based on values for sensitivity and specificity, the area under the curve (AUC) was calculated, to assess the predictive value of short-term loss for long-term changes.

RESULTS

Of the 441 knees (230 right, 211 left) from 441 OAI participants (191 men, 250 women; age [mean±SD] 60.9±8.8years; BMI 29.8±4.7) 216 were KLG2 (80men, 136 women; age 59.4±8.4 years, BMI 29.7±4.7) and 225 KLG3 (111 men, 114 women; age 62.3±9.0years, BMI 29.9±4.6). The BL→Y1 observation period was 381±34 days, the Y1→Y2 period 359±40 days, the BL→Y2 period 740±33 days, the Y2→Y4 period 728±40 days, the Y1→Y4 period 1087±48 days, and the BL→Y4 period 1469±36 days.

Magnitude of change, sensitivity to change, percentage of progressor knees

The mean change of ThCtAB in the FTJ (total cohort) was −1.2% (95% CI= −1.5%/−0.9%) and −0.8% (95% CI = −1.1%/−0.6%) over both one year periods (BL→Y1, Y1→Y2), −2.1% (95% CI = −2.4%/−1.7%) and −2.5% (95% CI = −2.9%/−2.1%) over both two year periods (BL→Y2, Y2→Y4), −3.3% (95% CI = −3.8%/−2.8%) over three years (Y1→Y4) and −4.5% (95% CI = −5.0%/−3.9%) over four years (BL→Y4) (Table 1). The SRMs were −0.42/−0.28 for the one year, −0.56/−0.55 for the two year, −0.63 for the three year, and −0.78 for the four year observation periods (Table 1). The magnitude of change increased proportional to the observation period (Figure 1), whereas the SRM approximately doubled for a four vs. one year observation period (Table 1).

Changes were greater in MFTC than in LFTC, greater centrally (cMFTC/cLFTC) than in total compartments, and greater in KLG3 than in KLG2 knees; these differences were consistent across all observation periods (Table 1; Fig. 1). Amongst femorotibial plates, the greatest changes were in cMF, and the smallest in cLF over all observation periods. cMFTC was the (sub)region with the greatest change; in KLG3 knees the mean change was −4.4% (95% CI=−5.4%/−3.5%) and −2.6% (95% CI=−3.6%/−1.6%) over both one year periods (BL→Y1, Y1→Y2), −7.0% (95% CI=−8.3%/−5.6%) and −7.1% (95% CI=−8.5%/−5.6%) over both two year periods (BL→Y2, Y2→Y4), −9.5% (95% CI=−11.2%/−7.8%) over three years (Y1→Y4), and −13.5% (95% CI = −15.6%/−11.5%) over four years (BL→Y4). SRMs for cMFTC change in KLG3 knees were −0.61/−0.35 for the one year, −0.68/−0.65 for the two year, −0.75 for the three year, and −0.87 for the four year observation periods.

The percentage of knees showing progression above the SDC threshold for FTJ were 25% and 19% for both one-year periods (BL→Y1, Y1→Y2), 34% and 35% for both two-year periods (BL→Y2, Y2→Y4), 41% over three years (Y1→Y4), and 51% over four years (BL→Y4; Table 2). The greatest percentage of progressors was observed in MFTC, and the lowest in cLF (Table 2). KLG3 knees showed greater number of progressors than KLG2 knees (12–40% vs. 6–20% for BL→Y1; 26–63% vs. 14–40% for BL→Y4; Table 2).

Relationship of changes between short- vs. long-term observation periods

Spearman correlation coefficients for observation periods that shared a common baseline measurement (e.g. BL→Y1 vs. BL→Y4) ranged from 0.42 (cLF) to 0.61 (cMFTC; Table 3). The coefficients were lower for short vs. long-term periods that did not share the same baseline measurement (e.g. Y1→Y2 vs. BL→Y4: 0.21 [MT] to 0.34 [LFTC]; Table 3; Figure 2). The correlations for Y1→Y2 vs. BL→Y4 tended to be greater in KLG3 (0.28 to 0.41) than in KLG2 knees (0.15 to 0.26; Table 3).

The overall percent agreement in progression/non-progression in FTJ between Y1→Y2 and BL→Y4 was 59%, the sensitivity 28%, the specificity 91%, the PPV 77%, and the area under the receiver operating characteristic curve 0.66 for using Y1→Y2 to predict BL→Y4. Percent agreement ranged from 60% (MFTC) to 79% (cLF) between regions, and was greater for KLG2 than for KLG3 knees (Table 4).

Relationship of (individual) changes between consecutive observation periods

The mean changes and number of progressors for Y1→Y2 tended to be lower than those for BL→Y1, but were very similar for Y2→Y4 compared with BL→Y2 (Tables 1,2). Spearman correlation coefficients between BL→Y1 vs. Y2→Y4 ranged from 0.03 (cLF) to 0.24 (cMFTC and cMF), whereas lower (and generally negative) correlations were observed for time periods that shared a common intermediate time point (BL→Y1/Y1→Y4 or BL→Y2/Y2→Y4; Table 3). The correlations for BL→Y1 vs. Y2→Y4 were somewhat greater in KLG3 (0.13 to 0.30) than in KLG2 knees (−0.08 to 0.24; Table 3). The correlations for BL→Y2 versus Y1→Y4 were substantially greater compared to those for BL→Y1 vs. Y2→Y4 (Table 3).

The overall percent agreement (FTJ) between BL→Y1 and Y2→Y4 was 64%, the sensitivity 34%, the specificity 80%, the PPV 48%, and the area under the receiver operating curve 0.59 for using BL→Y1 to predict Y2→Y4 change. Percent agreement ranged from 63% (MFTC) to 80% (cLF) between regions, and again was greater for KLG2 than for KLG3 knees (Table 4).

DISCUSSION

This is the first study to report the correlation and agreement of cartilage thickness loss over short-term (one year) vs. long-term (four year), and between initial and subsequent follow-up periods, with measurements not sharing a common (baseline or intermediate) measurement point. At an empirical level, the study confirms that the use of common baseline measurement overestimates the true correlation of short- vs. long-term change [7], and that the use of a common intermediate measurement underestimates the true correlation of initial- vs. subsequent change [12]. Although the measurement error can still increase the variation and attenuate the correlation for these comparisons, this occurs to a much lesser degree than if a common baseline or intermediate value is used.

441 knees from 441 participants of the OAI progression subcohort with KLG 2 or 3 and frequent knee pain at baseline were studied. In the other 534 participants of the OAI progression subcohort, in whom at least one knee fulfilled the same criteria (KLG 2 or 3, and frequent knee pain), the age was 61.6±9.0 y and the BMI 31.1±5.2 (61% women). In the entire progression subcohort (57% women) the age was 61.4±9.1 y and the BMI 30.2±4.9. The age and sex distribution of the current subsample was similar (60.9±8.8y; 57% women), whereas the BMI was slightly lower (29.8±4.7) compared with the OAI progression subcohort participants not studied. Nevertheless, given the large variation of BMI in both subsamples, we feel the 441 subjects studied can be considered representative of all KLG2 and 3 knees of the OAI progression subcohort.”

The mean cartilage loss across the cohort increased almost linearly with the length of the observation period, albeit the images were read with full blinding of the image analysis center to the acquisition order. Further, differences in cartilage thickness change between femorotibial regions and between KLG2 and KLG3 knees were consistent across all observation periods. The sensitivity to change (SRM) also increased with longer observation periods, but not proportionally to the increase in the magnitude of the thickness change, because the standard deviation of the change also increased. Comparisons between observation periods that did not share common measurements showed that, at an individual knee level, weak to moderate correlations and agreement of progression are observed between short- vs. long-term change, and between initial vs. subsequent observation periods.

MRI-based measures of cartilage thickness have previously been shown to be sensitive to change over one year observation periods. Annualized rates of change are, however, generally lower than the precision errors of the measurements [1,24,25,28]. This provides a plausible explanation as to why, at an individual knee level, only weak to moderate correlations and agreement are observed between short- and long-term cartilage loss, if no common baseline measurement time point is used. Hence, contrary to previous suggestions [7], there appear to exist certain challenges in the use of short-term individual (knee level) data to predict long term individual (knee level) cartilage loss. However, future improvements in MR acquisition or image analysis technology might reduce test-retest (reproducibility) errors of quantitative cartilage measurements and may hence yield a greater association between short and long-term measurements of cartilage thickness change.

Only weak to moderate (positive) correlations and agreement were observed between initial and subsequent observation periods, when not using common intermediate time points. This may partially result from OA progressing at a different (non-linear) pace during subsequent follow-up period in individual knees. For the reasons mentioned above, however, it is difficult to accurately estimate individual rates of progression in OA knees. This limits the ability to reliably study the trajectory of OA progression (i.e. linear vs. intermittent) in individual knees. The correlations for BL→Y2 vs. Y1→Y4 were substantially greater than those observed for BL→Y1 vs. Y2→Y4, likely because the observation periods are partly overlapping, but also likely because comparison of the longer (two vs. three year) observation periods are more robust and less sensitive to precision errors than the shorter ones (one vs. two years). This nicely demonstrates that longer observation periods are preferable to obtain robust information on individual cartilage change longitudinally.

As reported previously for one-year observation periods [29,30], changes in cartilage thickness were consistently greater in KLG3 than in KLG2 knees also for two-, three-, and four-year observation periods. Further, the relative difference in progression between the two subcohorts was consistent across the various observation intervals. This demonstrates that, once observed rates of change are averaged across a number of individuals, prediction of subsequent rates of change becomes more reliable. It further demonstrates that risk factors of cartilage loss, such as joint space narrowing at baseline (KLG3 vs. KLG2), can be effectively detected using short term (i.e. one year) observational cartilage thickness data. As precision errors have been reported to be similar for KLG2 and 3 [25], higher rates of change in KLG3 knees are likely responsible for the greater correlations between short- and long-term change compared with KLG2 knees, given a more favourable relationship between the magnitude of change and precision error.

The magnitude of change observed in the cohort during the first year was somewhat greater than that during for the second year; however, the first year observation period was also longer than the second year period. During both two-year observation periods, which were similar in length, rates of change were remarkably similar. This finding of consistent rates of change over several observation periods resolves discrepancies from earlier studies in smaller cohorts, some of which reported greater (annualized) rates of change for short (6 months) vs. longer term observation periods (24 months) [8–10] while other found the opposite[11]. Hence, there is no indication that the rate of cartilage loss in OA knees varied throughout this four year study. These observations confirm that the mean rate of cartilage loss in knee OA observed over the short term accurately reflect those to be expected over long-term periods. Further, there is no evidence that rates of change increase or decreases over time, or with shorter or longer observation periods.

The SRM did not increase linearly, but roughly by a factor of 1.5 when the observation period was doubled. Because the mean changes were similar for subsequent observation intervals of equal length and because image-analysis-related precision errors can be assumed to be similar for short- and long-term observation periods, this finding suggests that the standard deviation of change between individual knees increases over time in clinical studies. Therefore, the ability to discriminate drug effects or risk factors of OA does not increase linearly with the length of the observation period, and therefore the increased cost of a longer study needs to be carefully balanced against the actual gains in statistical power.

In conclusion, this study provides unbiased estimates of observed change in cartilage thickness for short- vs. long-term and for initial vs. subsequent observation periods in OA knees, without sharing common baseline or intermediate time points. Weak to moderate correlations were observed between short- and long-term cartilage thickness change, and between initial vs. subsequent observation periods in individual knees. These findings suggest that, at an individual knee level, one-year measurements of cartilage thickness change cannot be viewed as a reliable proxy of long-term change. Longer observation periods hence appear to be required to achieve robust results in individual knees. At a cohort and subcohort level (e.g. KLG3 vs. KLG2 knees), however, femorotibial cartilage loss increased almost linearly with the length of the observation period and was constant throughout the four year study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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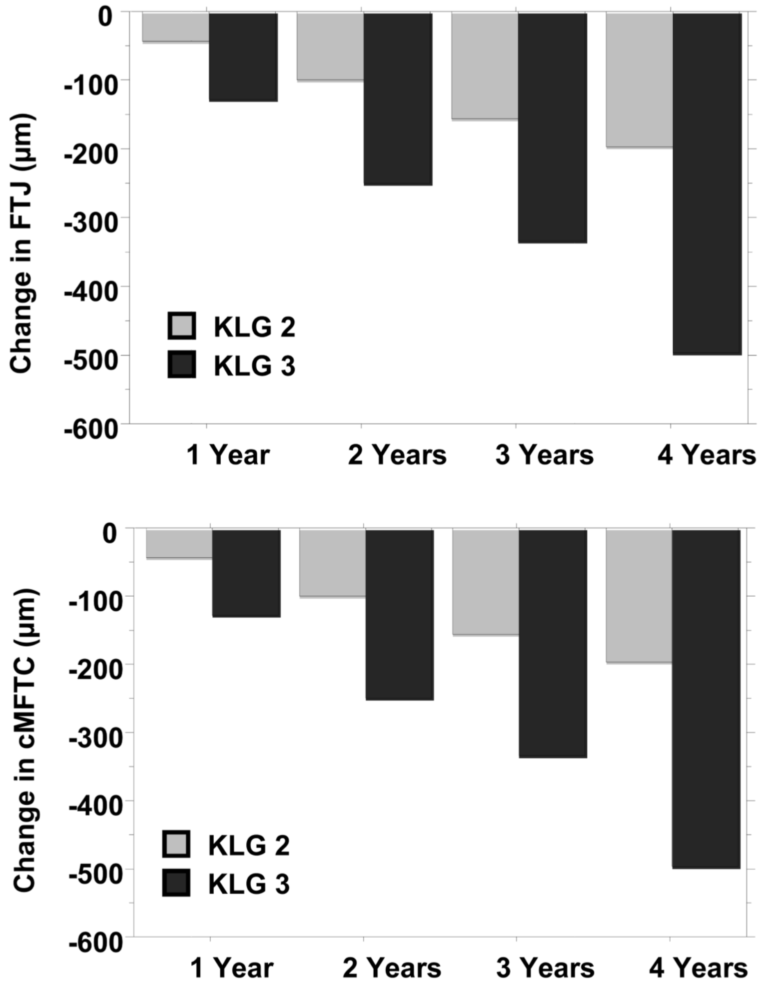

Figure 1.

Bar graphs showing

top) the magnitude of longitudinal change in cartilage thickness in total femorotibial joint (FTJ)

bottom) the magnitude of longitudinal change in in cartilage thickness the central medial femorotibial (cMFTC)

Change in cartilage thickness (Δ ThCtAB in μm) over 1 year, 2 years, 3 years, and 4 years in knees with Kellgren Lawrence grade (KLG) 2 and 3, respectively. Changes between BL and Y1 follow-up and between Y1 and Y2 were averaged to compute the 1 year change, and changes between BL and Y2 and between Y2 and Y4 were averaged to compute the 2 year change. Changes between Y1 and Y4 were used to compute the 3 year (3Y) and those between BL and Y4 to compute the 4 year change (4Y).

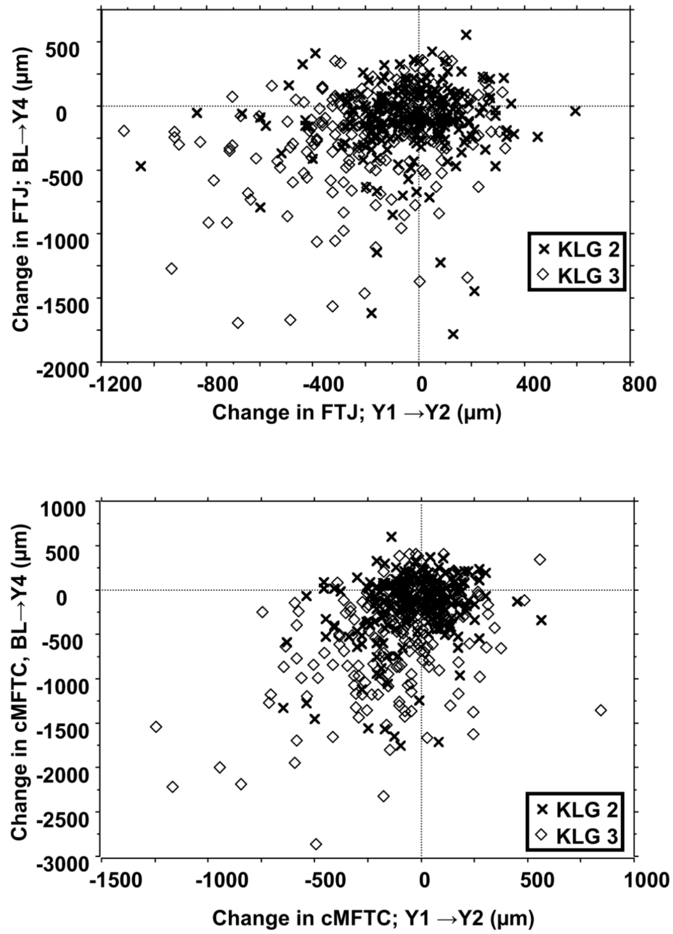

Figure 2.

Scatter plot showing

top) the relationship between short-term (Y1→ Y2) and long-term (BL→ Y4) change in central medial femorotibial (ThCtAB in µm) for KLG 2 and KLG3 knees, respectively. **bottom)** the relationship between initial (BL→ Y1) and subsequent (Y2→Y4) change in total femorotibial cartilage thickness (ThCtAB in µm) for KLG 2 and KLG3 knees, respectively.

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Table 1

Mean change in cartilage thickness (MC in μm and %) and standardized response mean (SRM) over different intervals in different regions of the knee

		BL → Y1			Y1 → Y2			BL → Y2			Y2 → Y4			Y1 → Y4			BL → Y4		
	Joint Region	**MC**	**MC%**	**SRM**	**MC**	**MC%**	**SRM**	**MC**	**MC%**	**SRM**	**MC**	**MC%**	**SRM**	**MC**	**MC%**	**SRM**	**MC**	**MC%**	**SRM**
All knees (n=441)	FTJ	−88	−1.2	−0.42	−61	−0.8	−0.28	−149	−2.1	−0.56	−175	−2.5	−0.55	−236	−3.3	−0.63	−324	−4.5	−0.78
	MFTC	−52	−1.5	−0.33	−38	−1.1	−0.26	−91	−2.7	−0.45	−107	−3.2	−0.48	−145	−4.3	−0.55	−198	−5.8	−0.62
	LFTC	−36	−0.9	−0.30	−22	−0.6	−0.17	−58	−1.5	−0.36	−68	−1.8	−0.35	−91	−2.4	−0.39	−126	−3.3	−0.48
	cMFTC	−105	−2.5	−0.42	−69	−1.7	−0.30	−173	−4.2	−0.53	−178	−4.5	−0.51	−246	−6.1	−0.61	−351	−8.5	−0.69
	cLFTC	−61	−1.2	−0.34	−43	−0.9	−0.22	−104	−2.0	−0.41	−95	−1.9	−0.32	−138	−2.8	−0.39	−199	−3.9	−0.50
	MT	−16	−0.9	−0.22	−14	−0.9	−0.19	−30	−1.8	−0.36	−42	−2.5	−0.43	−56	−3.4	−0.49	−72	−4.3	−0.58
	cMF	−37	−2.1	−0.31	−24	−1.4	−0.24	−61	−3.5	−0.42	−65	−3.8	−0.43	−89	−5.2	−0.50	−126	−7.2	−0.56
	LT	−22	−1.2	−0.34	−19	−1.0	−0.26	−41	−2.2	−0.48	−40	−2.2	−0.44	−58	−3.2	−0.53	−81	−4.4	−0.63
	cLF	−13	−0.7	−0.16	−3	−0.2	−0.04	−16	−0.8	−0.16	−29	−1.5	−0.22	−32	−1.7	−0.22	−45	−2.3	−0.27
KLG 2 (n=216)	FTJ	−43	−0.6	−0.23	−42	−0.6	−0.21	−86	−1.1	−0.38	−128	−1.7	−0.36	−171	−2.2	−0.43	−214	−2.8	−0.52
	MFTC	−17	−0.5	−0.12	−24	−0.6	−0.20	−41	−1.1	−0.26	−63	−1.7	−0.32	−86	−2.4	−0.40	−103	−2.8	−0.42
	LFTC	−27	−0.7	−0.26	−18	−0.5	−0.15	−45	−1.1	−0.32	−66	−1.7	−0.29	−84	−2.1	−0.33	−111	−2.8	−0.41
	cMFTC	−43	−0.9	−0.21	−44	−1.0	−0.23	−87	−1.9	−0.35	−111	−2.5	−0.36	−155	−3.4	−0.46	−198	−4.3	−0.51
	cLFTC	−47	−0.9	−0.27	−36	−0.7	−0.18	−84	−1.6	−0.33	−97	−1.8	−0.29	−133	−2.5	−0.35	−181	−3.4	−0.43
	MT	−1	−0.1	−0.02	−9	−0.5	−0.16	−11	−0.6	−0.18	−26	−1.5	−0.29	−36	−2.0	−0.36	−37	−2.1	−0.39
	cMF	−16	−0.8	−0.15	−14	−0.8	−0.16	−30	−1.6	−0.25	−36	−1.9	−0.28	−51	−2.7	−0.34	−66	−3.5	−0.37
	LT	−18	−0.9	−0.28	−19	−1.0	−0.27	−37	−1.9	−0.45	−39	−2.0	−0.39	−58	−3.0	−0.49	−76	−3.9	−0.56
	cLF	−9	−0.4	−0.12	1	0.0	0.01	−8	−0.4	−0.09	−27	−1.3	−0.19	−26	−1.3	−0.16	−35	−1.7	−0.22
KLG 3 (n=225)	FTJ	−131	−1.9	−0.59	−78	−1.2	−0.34	−209	−3.1	−0.72	−220	−3.3	−0.81	−299	−4.5	−0.89	−429	−6.3	−1.08
	MFTC	−86	−2.7	−0.51	−53	−1.7	−0.31	−139	−4.4	−0.61	−149	−4.9	−0.63	−202	−6.5	−0.69	−288	−9.1	−0.82
	LFTC	−44	−1.2	−0.34	−26	−0.7	−0.20	−70	−1.9	−0.39	−71	−2.0	−0.43	−97	−2.7	−0.47	−141	−3.9	−0.55
	cMFTC	−163	−4.4	−0.61	−93	−2.6	−0.35	−256	−7.0	−0.68	−242	−7.1	−0.65	−334	−9.5	−0.75	−498	−13.5	−0.87
	cLFTC	−74	−1.5	−0.40	−49	−1.0	−0.25	−123	−2.6	−0.50	−94	−2.0	−0.37	−143	−3.0	−0.45	−217	−4.5	−0.57
	MT	−30	−1.9	−0.36	−19	−1.2	−0.22	−49	−3.1	−0.50	−57	−3.7	−0.57	−76	−4.9	−0.60	−106	−6.6	−0.75
	cMF	−57	−3.6	−0.47	−34	−2.2	−0.30	−90	−5.7	−0.56	−92	−6.2	−0.57	−126	−8.3	−0.64	−183	−11.5	−0.75
	LT	−27	−1.5	−0.40	−18	−1.1	−0.25	−46	−2.6	−0.50	−40	−2.3	−0.50	−58	−3.4	−0.58	−86	−4.9	−0.70
	cLF	−17	−0.9	−0.19	−7	−0.4	−0.09	−24	−1.3	−0.21	−31	−1.6	−0.26	−38	−2.0	−0.27	−55	−2.9	−0.32

FTJ = total femorotibial joint, MFTC/LFTC = medial/lateral femorotibial compartment, cMFTC/cLFTC = central aspect of the MFTC/LFTC, MT/LT = medial/lateral tibia, cMF/cLF = central, weight-bearing part of the medial/lateral femoral condyle, BL = baseline, Y1/Y2/Y4 = Year 1/2/4 follow-up

Table 2

Number and percentage (%) of knees identified as progressors according to the smallest detectable changes (SDC) method [26] in different anatomical joint regions

	Joint Region	Threshold µm	BL → Y1 N	BL → Y1 %	Y1 → Y2 N	Y1 → Y2 %	BL → Y2 N	BL → Y2 %	Y2 → Y4 N	Y2 → Y4 %	Y1 → Y4 N	Y1 → Y4 %	BL → Y4 N	BL → Y4 %
All knees (n=441)	FTJ	226	109	25	83	19	149	34	155	35	181	41	225	51
	MFTC	111	132	30	108	24	161	37	160	36	194	44	218	49
	LFTC	121	97	22	88	20	111	25	128	29	136	31	160	36
	MT	67	89	20	85	19	115	26	133	30	162	37	183	41
	cMF	92	108	24	87	20	143	32	141	32	163	37	195	44
	LT	74	80	18	81	18	122	28	115	26	149	34	188	43
	cLF	116	41	9	42	10	57	13	67	15	87	20	88	20
KLG 2 (n=216)	FTJ	226	31	14	34	16	49	23	55	25	63	29	86	40
	MFTC	111	43	20	45	21	55	25	58	27	70	32	76	35
	LFTC	121	39	18	38	18	43	20	53	25	58	27	71	33
	MT	67	27	13	32	15	33	15	47	22	56	26	64	30
	cMF	92	36	17	35	16	46	21	47	22	54	25	63	29
	LT	74	35	16	39	18	53	25	50	23	67	31	86	40
	cLF	116	14	6	16	7	19	9	26	12	34	16	30	14
KLG 3 (n=225)	FTJ	226	78	35	49	22	100	44	100	44	118	52	139	62
	MFTC	111	89	40	63	28	106	47	102	45	124	55	142	63
	LFTC	121	58	26	50	22	68	30	75	33	78	35	89	40
	MT	67	62	28	53	24	82	36	86	38	106	47	119	53
	cMF	92	72	32	52	23	97	43	94	42	109	48	132	59
	LT	74	45	20	42	19	69	31	65	29	82	36	102	45
	cLF	116	27	12	26	12	38	17	41	18	53	24	58	26

FTJ = total femorotibial joint, MFTC/LFTC = medial/lateral femorotibial compartment, MT/LT = medial/lateral tibia, cMF/cLF = central, weight-bearing part of the medial/lateral femoral condyle; BL = baseline, Y1/Y2/Y4 = Year 1/2/4 follow-up; the threshold used for the identification of progressors was computed using results from the OAI pilot study

Table 3

Spearman correlation coefficients (ρ) of changes in cartilage thickness in different anatomical joint regions between study intervals

		Short-term vs. Long-term change		**Initial vs. Subsequent change**			
		BL → Y1 BL → Y4	**Y1 → Y2 BL → Y4**	**BL → Y1 Y1 → Y4**	**BL → Y2 Y2 → Y4**	**BL → Y1 Y2 → Y4**	**BL → Y2 Y1 → Y4**
All knees (n=441)	FTJ	0.50	**0.33**	−0.05	0.01	**0.17**	**0.43**
	MFTC	**0.56**	**0.29**	−0.01	0.05	**0.23**	**0.40**
	LFTC	**0.46**	**0.34**	−0.08	−0.05	**0.13**	**0.40**
	cMFTC	**0.61**	**0.31**	0.09	*0.09*	**0.24**	**0.44**
	cLFTC	**0.47**	**0.33**	−0.09	−0.02	*0.11*	**0.37**
	MT	**0.46**	**0.21**	**−0.21**	**−0.13**	*0.11*	**0.27**
	cMF	**0.60**	**0.29**	0.03	0.08	**0.24**	**0.42**
	LT	**0.48**	**0.33**	−0.09	0.00	**0.19**	**0.46**
	cLF	**0.42**	**0.28**	**−0.21**	**−0.14**	0.03	**0.27**
KLG 2 (n=216)	FTJ	**0.41**	**0.23**	**−0.21**	−0.11	0.07	**0.31**
	MFTC	**0.50**	**0.18**	**−0.22**	*−0.16*	0.08	**0.24**
	LFTC	**0.39**	**0.26**	**−0.22**	−0.12	0.09	**0.33**
	cMFTC	**0.53**	**0.18**	*−0.15*	*−0.15*	0.10	**0.23**
	cLFTC	**0.46**	**0.26**	*−0.17*	−0.12	0.06	**0.29**
	MT	**0.38**	*0.15*	**−0.38**	**−0.31**	0.00	0.13
	cMF	**0.54**	*0.17*	*−0.17*	−0.11	*0.14*	**0.30**
	LT	**0.51**	**0.26**	−0.09	0.03	**0.24**	**0.46**
	cLF	**0.27**	**0.24**	**−0.42**	**−0.27**	−0.08	*0.15*
KLG 3 (n=225)	FTJ	**0.54**	**0.37**	−0.01	0.02	**0.18**	**0.47**
	MFTC	**0.57**	**0.37**	0.07	*0.14*	**0.27**	**0.48**
	LFTC	**0.52**	**0.41**	0.03	0.01	*0.15*	**0.46**
	cMFTC	**0.64**	**0.39**	**0.19**	**0.19**	**0.30**	**0.54**
	cLFTC	**0.48**	**0.39**	−0.03	0.06	*0.14*	**0.45**
	MT	**0.49**	**0.28**	*−0.14*	−0.05	*0.15*	**0.35**
	cMF	**0.62**	**0.35**	0.11	*0.16*	**0.25**	**0.47**
	LT	**0.45**	**0.39**	−0.09	−0.04	0.13	**0.45**
	cLF	**0.54**	**0.31**	−0.03	−0.03	0.13	**0.37**

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FTJ = total femorotibial joint, MFTC/LFTC = medial/lateral femorotibial compartment, MT/LT = medial/lateral tibia, cMF/cLF = central, weight-bearing part of the medial/lateral femoral condyle, BL = baseline, Y1/Y2/Y4 = Year 1/2/4 follow-up. Bold and italic values indicate statistically significant correlations (bold: $p<0.01$; italic: $p<0.05$)

Table 4

Agreement, sensitivity, specificity, positive predictive value (PPV), and area under the receiver operating characteristics curve (AUC) of progression throughout various time intervals determined using the smallest detectable change method (SDC) [26]

		Short-term vs. long-term change (Y1 → Y2 vs. BL → Y4):					Initial vs. subsequent change (BL → Y1 vs. Y2 → Y4):				
		Agreement %	**Sensitivity %**	**Specificity %**	**PPV %**	**AUC**	**Agreement %**	**Sensitivity %**	**Specificity %**	**PPV %**	**AUC**
All knees (n=441)	FTJ	59.2	28.4	91.2	77.1	0.66	63.7	33.5	80.1	47.7	0.59
	MFTC	59.6	33.9	84.8	68.5	0.63	63.3	40.6	76.2	49.2	0.63
	LFTC	67.8	33.1	87.5	60.2	0.65	65.3	28.1	80.5	37.1	0.57
	MT	61.5	26.8	86.0	57.6	0.58	67.3	29.3	83.8	43.8	0.58
	cMF	61.0	28.2	87.0	63.2	0.65	67.6	37.6	81.7	49.1	0.63
	LT	64.9	30.3	90.5	70.4	0.67	73.5	33.9	87.4	48.8	0.61
	cLF	79.1	21.6	93.5	45.2	0.68	79.6	13.4	91.4	22.0	0.55
KLG 2 (n=216)	FTJ	65.7	26.7	91.5	67.6	0.62	68.5	16.4	86.3	29.0	0.53
	MFTC	65.3	30.3	84.3	51.1	0.59	67.1	25.9	82.3	34.9	0.60
	LFTC	68.1	28.2	87.6	52.6	0.61	68.5	22.6	83.4	30.8	0.54
	MT	67.6	20.3	87.5	40.6	0.53	72.2	14.9	88.2	25.9	0.53
	cMF	66.7	20.6	85.6	37.1	0.62	72.7	25.5	85.8	33.3	0.59
	LT	66.2	30.2	90.0	66.7	0.66	76.4	34.0	89.2	48.6	0.64
	cLF	82.4	13.3	93.5	25.0	0.67	83.3	7.7	93.7	14.3	0.47
KLG 3 (n=225)	FTJ	52.9	29.5	90.7	83.7	0.68	59.1	43.0	72.0	55.1	0.60
	MFTC	54.2	35.9	85.5	81.0	0.64	59.6	49.0	68.3	56.2	0.61
	LFTC	67.6	37.1	87.5	66.0	0.68	62.2	32.0	77.3	41.4	0.58
	MT	55.6	30.3	84.0	67.9	0.61	62.7	37.2	78.4	51.6	0.58
	cMF	55.6	31.8	89.2	80.8	0.66	62.7	43.6	76.3	56.9	0.63
	LT	63.6	30.4	91.1	73.8	0.68	70.7	33.8	85.6	48.9	0.58
	cLF	76.0	25.9	93.4	57.7	0.68	76.0	17.1	89.1	25.9	0.60

FTJ = total femorotibial joint, MFTC/LFTC = medial/lateral femorotibial compartment, MT/LT = medial/lateral tibia, cMF/cLF = central, weight-bearing part of the medial/lateral femoral condyle; BL = baseline, Y1/Y2/Y4 = Year 1/2/4 follow-up. The agreement, sensitivity, specificity, and PPV were calculated using the number of knees classified as progressors or non-progressors by the SDC method (see Table 2).