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Is loss in femorotibial cartilage thickness related to severity of contra-lateral radiographic knee osteoarthritis? – Longitudinal data from the Osteoarthritis Initiative

S. Cotofana † ‡ *, O. Benichou §, W. Hitzl ||, W. Wirth † ‡, F. Eckstein † ‡

† *Institute of Anatomy, Paracelsus Medical University, Salzburg, Austria*
‡ *Chondrometrics GmbH, Ainring, Germany*
§ *Eli Lilly & Co, Indianapolis, IN, USA*
|| *Research Office, Biostatistics, Paracelsus Medical University, Salzburg, Austria*

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SUMMARY

Objective: Anti-catabolic disease modifying drugs (DMOADs) aim to reduce cartilage loss in knee osteoarthritis (KOA). Testing such drugs in clinical trials requires sufficient rates of loss in the study participants to occur, preferably at a mild disease stage where cartilage can be preserved. Here we analyze a "progression" model in mild radiographic KOA (RKOA), based on contra-lateral radiographic status.

Methods: We studied 837 participants (62.4 ± 9 yrs; 30 ± 4.9 kg/m^2; 61.8% women) from the Osteoarthritis Initiative (OAI) with mild to moderate RKOA (Kellgren Lawrence grade [KLG] 2–3) and with/without Osteoarthritis Research Society International (OARSI) atlas radiographic joint space narrowing (JSN). These had quantitative measurements of subregional femorotibial cartilage thickness from magnetic resonance imaging (MRI) at baseline and 1-year follow-up. They were stratified by contra-lateral knee status: no (KLG 0/1), definite (KLG2) and moderate RKOA (KLG 3/4).

Results: KLG2 knees with JSN and moderate contra-lateral RKOA had ($P = 0.008$) greater maximum subregional cartilage loss −220 μm [95% confidence interval (CI) −255, −184 μm] than those without contra-lateral RKOA −164 μm [−187, −140 μm]. Their rate of subregional cartilage loss was similar and not significantly different ($P = 0.61$) to that in KLG 3 knees without contra-lateral RKOA (−232 μm; [−266; −198 μm]). The effect of contra-lateral RKOA status was less in KLG2 knees without JSN, and in KLG3 knees.

Conclusion: KLG2 knees with JSN and moderate contra-lateral RKOA, display relatively high rates of subregional femorotibial cartilage loss, despite being at a relatively mild stage of RKOA. They may therefore provide a unique opportunity for recruitment in clinical trials that explore the efficacy of anti-catabolic DMOADs on structural progression.

Introduction

Only symptomatic treatment is currently available for osteoarthritis (OA), and this has been found to have only small to moderate effects[1]. Efforts in developing disease-modifying OA drugs (DMOADs) have yet had little success[2–4]. However, in the interest of delaying surgical replacement of the knee[5], treatment that is effective in reducing or even stopping structural change and progression is highly desirable[6]. Anti-catabolic DMOADs are designed to reduce cartilage loss or other structural alterations in knee OA. Testing such drugs in clinical trials requires sufficient rates of cartilage loss in the study participants (i.e., in the placebo group) in order to demonstrate drug efficacy, preferably at a mild phase of the disease where as much cartilage can be preserved as possible. Further, it has been suspected that mild stages of radiographic knee OA (RKOA), i.e., Kellgren and Lawrence[7] grades (KLG) ≤2 may be more amenable to anti-catabolic DMOADs compared to more advanced stages (KLG ≥ 3), because the vicious circle of tissue degradation and increasing mechanical challenges is still at an mild phase[8–11].

There is recent consensus that knees with moderate RKOA (KLG ≥ 3) display greater cartilage loss than those with relatively

* Address correspondence and reprint requests to: S. Cotofana, Institute of Anatomy, PMU, Strubergasse 21, A-5020 Salzburg, Austria. Tel: 43-662-2420-80410; Fax: 43-662-2024-80409.
E-mail address: sebastian.cotofana@pmu.ac.at (S. Cotofana).

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mild RKOA (KLG ≤ 2)[8,12–15], and at least two studies have shown that the rate of cartilage loss in knees without radiographic joint space narrowing (JSN) was indistinguishable from that in healthy reference participants without RKOA or risk factors of RKOA[16,17]. This provides a certain dilemma, because knees at a mild stage of RKOA, in whom anti-catabolic DMOAD may be potentially most successful, do generally not show sufficient cartilage loss (progression) for a clinical trial to demonstrate structural efficacy of a DMOAD over a 1- or 2-year observational period. Therefore, an indicator of fast progression in knees that still are at a relatively mild stage of disease would be very helpful in the design of DMOAD trials.

Idiopathic knee OA is thought to represent a bilateral disease, and several studies reported higher rates of incident RKOA when the contra-lateral knee displayed definite radiographic change before incidence occurred in the other knee[18–20]. RKOA in one knee, in the absence of the relevant trauma history, may indicate a certain intrinsic susceptibility to develop RKOA in the other knee, potentially comparable to an osteoporotic fracture that indicates an increased risk of skeletal fragility and risk of subsequent fractures at other locations[21,22]. The same relationship may also exist in the context of structural progression of RKOA, i.e., cartilage loss being greater in knees having a contra-lateral knee at a moderate stage when compared to knees having a contra-lateral knee free of disease.

The purpose of this study was therefore to investigate the impact of the contra-lateral RKOA status on the rate of progression (i.e., quantitative cartilage loss) in knees with existing RKOA. We hypothesized that mild RKOA knees with moderate contra-lateral RKOA have higher rates of progression than those without contra-lateral RKOA, and therefore may be useful in DMOAD trials.

Methods

The Osteoarthritis Initiative (OAI)

The data used for this investigation was taken from the OAI (www.oai.ucsf.edu)[13]. The OAI is a multi-center, prospective observational cohort study, with the purpose of improving public health through the prevention or alleviation of pain and disability from knee OA. 4796 individuals were included who were 45–79 years old, had an almost equal distribution between men and women, and included several ethnicities. Participants were evaluated annually by clinical examination on their knee status and knee joint imaging, i.e., X-ray[23,24] and MR imaging techniques[13,25]. General exclusion criteria were the presence of rheumatoid arthritis or other inflammatory arthritis, bi-lateral end-stage knee OA, inability to walk without aids and contradictions to imaging techniques.

Sample selection

The participants included in the current study were selected from the OAI according to the following criteria:

a) Availability of quantitative measurements of subregional femorotibial cartilage thickness at baseline, 1-year (and 2-year) follow-up, obtained from coronal fast low angle shot (FLASH) images[26] or from double echo steady state (DESS) images with water excitation[13]
b) Availability of central radiographic readings for both knees at baseline, 1-year and at the 2-year follow-up survey (release version 0.2.2)
c) Presence of (definite) RKOA at baseline (i.e., KLG ≥ 2), but not end-stage RKOA (i.e., KLG4), in the central readings for the ipsi-lateral (investigated) knee using MRI

According to the above selection criteria, 837 knees from 837 individuals (age 62.4 ±9 yrs; body mass index [BMI] 30 ± 4.9 kg/m^2; 61.8% females) were available with baseline and 1-year follow-up data, and 487 knees from 487 individuals (age 62.3 ± 9 yrs; BMI 29.8 ± 4.8 kg/m^2; 60.8% females) had baseline and 2-year follow-up data (Table I).

Radiographic readings

The X-ray acquisitions relied on posteroanterior weight bearing fixed-flexion radiographs obtained with a Synaflexer frame (Synarc, San Francisco, California, USA)[23,24]. In the present analysis the central radiographic readings (release 0.5) were performed by three expert radiologists or rheumatologists at Boston University (PA, BS, DTF) (https://oai.epi-ucsf.org/datarelease/SASDocs/kXR_SQ_BU_descrip.pdf) assigning KL grades pertinent to the original KL description[7]. The readers were blinded to clinical data and to follow-up time point. Individual radiographic features including JSN were scored 0–3 using the Osteoarthritis Research Society International (OARSI) atlas[27]. Knees with presence of definite osteophytes were graded as KLG2. Those with presence of moderate multiple osteophytes, definite JSN, subchondral sclerosis, and (possible) deformity of the bone were graded as KLG3.

For classification of the ipsi-lateral (investigated) KLG2 knees into those with and into those KLG2 knees without JSN we combined the KL scores (central readings) with the OARSI atlas JSN

Table I
Baseline demographic, clinical and imaging data of the participants with 1-year (n = 837) and 2-year (n = 487) follow-up

	KLG and JSN of investigated knee		
	KLG2 without JSN	KLG2 with JSN	KLG3
	***n* = 158**	***n* = 339**	***n* = 340**
Age (SD)	60.3 (8.6)	61.9 (9.2)	63.9 (8.7)
Females (%)	119 (75.3)	213 (62.8)	185 (54.4)
BMI (SD)	30.1 (4.7)	29.9 (5.1)	30.1 (4.8)
Side of investigated knee			
Right (%)	126 (79.7)	273 (80.5)	258 (75.9)
Previous injury in contra-lateral knee			
Count (%)	37 (23.4)	97 (28.6)	90 (26.5)
Previous injury in investigated knee			
Count (%)	47 (29.7)	123 (36.3)	142 (41.8)
MR sequence of investigated knee			
DESS (%)	60 (38.0)	126 (37.2)	177 (52.1)
FLASH (%)	98 (62.0)	213 (62.8)	163 (47.9)
Presence of JSN in investigated knee			
Medial (%)	0	278 (82.0)	257 (75.6)
Lateral (%)	0	67 (19.8)	95 (27.9)
KLG of contra-lateral knee			
0 (%)	18 (11.4)	42 (12.4)	52 (15.3)
1 (%)	29 (18.4)	58 (17.1)	44 (12.9)
2 (%)	89 (56.3)	148 (43.7)	99 (29.1)
3 (%)	18 (11.4)	70 (20.6)	114 (33.5)
4 (%)	4 (2.5)	21 (6.2)	31 (9.1)
Mean 1-year change in cartilage thickness	***n* = 158**	***n* = 339**	***n* = 340**
OV one/μm (SD)	−153 (133)	−183 (143)	−243 (166)
FTJ/μm (SD)	−35.2 (209)	−54.8 (186)	−123 (230)
Mean 2-year change in cartilage thickness	***n* = 89**	***n* = 196**	***n* = 202**
OV one/μm (SD)	−179 (97)	−213 (150)	−358 (234)
FTJ/μm (SD)	−47.9 (164)	−77.7 (211)	−242 (302)

scores (central readings)[27]. In the following the terminology "KLG2 knees without JSN" refers to knees with KL grade 2 and additional OARSI atlas JSN score = 0 and "KLG2 knees with JSN" refers to knees with KL grade 2 and additional OARSI atlas JSN score ≥ 1.

MR imaging analysis

Details of the OAI MRI protocol acquisition parameters can be found on the OAI webpage www.oai.ucsf.edu and have been previously described in detail. The MR images were shipped from the OAI coordinating center to the cartilage analysis center (Chondrometrics GmbH, Ainring, Germany). After initial quality control, manual segmentation of the tibial and weight-bearing femoral cartilage was performed by 12 readers with thorough experience in quantitative cartilage analysis. The readers were blinded to the aims of the study, to the clinical and radiographic status of the knees studied, and to acquisition order. The test-retest precision of the knee cartilage measurement methodology has been reported previously[28,29]. All segmentations were quality controlled by one expert reader.

The mean cartilage thickness was computed for the medial and lateral tibia (MT/LT) and the weight-bearing aspect of the medial and lateral femur (cMF/cLF)[30]. Further, thickness was computed in 16 subregions, five tibial ones and three femoral ones in each compartment[31–34]. Medial femorotibial (MFTC), lateral femorotibial (LFTC), and total femorotibial joint (FTJ) cartilage thickness was computed as sums of the femorotibial plates. The reproducibility of cartilage thickness measures for cartilage plates has been reported to range from 22 to 37 μm, and those in femorotibial subregions from 19 to 84 μm[31]. An ordered value (OV) approach was used to determine the non-location specific magnitude of cartilage loss in the one (of 16) subregion in each knee in which the greatest loss occurred (in μm), i.e., OV one[16,17,35,36].

The within-subject and within-group consistency of cartilage thickness change over one- and 2-year and longer observation periods in this sample have been reported previously[14]. Whereas rates of change in the second year were reported to be somewhat greater than those in the first year, those in the second 2-year period were of similar magnitude as those in the first 2-year period[37].

Statistical analysis

All statistical analyses were performed using SPSS Statistics 21 (IBM, Armonk, NY, USA). Participants were stratified by ipsi-lateral knee (i.e., the knee in which cartilage loss was studied with MRI) radiographic status based on X-ray readings according to the KL classification (for KL grades) and on the OARSI atlas[27] (for JSN grades) into KLG2 without JSN, KLG2 with JSN, or KLG3. In each of these strata, knees were further stratified by contra-lateral knee radiographic status, to either have "no" (definite) RKOA (KLG0 or 1), "definite" RKOA (KLG2) or "moderate" RKOA (KLG3 or 4) in the other knee (not studied by MRI). Because the purpose of the study was to identify subjects with mild RKOA with an increased chance of progression, and because it was shown previously that KLG2 knees without JSN did not show relevant progression[26,38] but those with JSN did[8,9,39], the primary analytic focus was on comparing rates of progression in KLG2 knees with JSN[39] and with moderate contra-lateral RKOA vs KLG2 knees with JSN without any contra-lateral RKOA. The secondary analytic focus on comparing KLG2 knees with JSN and with moderate contra-lateral RKOA vs KLG3 knees that did not display contra-lateral RKOA.

As the primary measure of cartilage thickness change we selected a non-location dependent measure of subregional cartilage change (i.e., OV one; the subregion with the greatest rate of cartilage loss in each joint[16,35]), and as the secondary measure the integral change in cartilage thickness throughout the entire FTJ. Given the larger sample available, the primary focus was on OV one and FTJ cartilage thickness loss over 1 year ($n = 837$), and it was checked whether results over 2 years were consistent in those that also had 2-years follow-up data ($n = 487$; $n = 350$ were not available for the 2-years follow-up period).

Differences in cartilage thickness change were compared within strata of ipsi-lateral RKOA knee status (KLG2 with/without JSN, KLG3) between groups of contra-lateral RKOA status using Kruskal–Wallis testing and across strata and between different groups of contra-lateral RKOA status using an unpaired Student's *t*-test. Further we used generalized linear models with robust variance estimator (Huber/White/Sandwich estimator) to calculate the odds and the corresponding 95% confidence intervals (CIs) with adjustment for age, sex, BMI and MRI sequence (i.e., FLASH or DESS). Contra-lateral radiographic knee status was used as independent variable, whereas no contra-lateral RKOA was set as reference group. Results were considered significant at a level of $P \leq 0.05$. As supporting evidence, we also computed the number of progressors in each stratum. A progressor was defined as someone in whom the cartilage loss in either MFTC or LFTC (or both) exceeded a threshold of cartilage loss derived from test-retest data on the FLASH (only available in right knees) or DESS MRI sequence, using the smallest detectable change (SDC) method[40]. This data was previously published by our group and the values for being defined as a progressor are 102 μm for FLASH MFTC, 92 μm for FLASH LFTC, 111 μm for DESS MFTC and 121 μm for DESS LFTC[37].

Sensitivity analyses were performed to explore whether the effect of the contra-lateral knee depended on its previous trauma history. This was done to explore whether idiopathic contra-lateral RKOA status was an indicator of intrinsic vulnerability, whereas post-traumatic contra-lateral RKOA status was not. To this end, in a separate analysis, we excluded all cases in which the contra-lateral knee had a history of a self-reported knee trauma, leading to difficulties to walk for at least 1 week. This was the case for 224 (of 837) individuals with 1-year, and for 131 (of 487) individuals with 2-years of follow-up.

Results

Demographics

Of the 837 knees with 1-year follow-up data, 158 were KLG2 without JSN, 339 KLG2 with JSN, and 340 as KLG3 (Table I). Of those that were KLG2 with JSN, 81.7% (medial)/1.8% (lateral) had an OARSI atlas JSN grade 1, and 0.3 (medial)/0% (lateral) had a grade 2 and none had grade 3. Of those that were KLG3, 1.2 (medial)/0.6% (lateral) had an OARSI atlas JSN grade of 1, and 74.4 (medial)/27.4% (lateral) a grade 2 and none had grade 3 JSN. Further demographic data are summarized in Table I.

Primary and secondary comparison

In KLG2 knees with JSN, the rate of maximum subregional cartilage loss for those with moderate contra-lateral RKOA (KLG3 or 4) was −220 μm [95% CI −255, −184 μm] with a smaller Odds ratio (OR) 0.95 [95% CI 0.91–0.98] (crude $P = 0.008$) when compared to those without contra-lateral RKOA (KLG0 or 1) (Table II). The rate of subregional cartilage loss in KLG2 knees with JSN and moderate contra-lateral RKOA (KLG3 or 4) was similar in magnitude, and not significantly different ($P = 0.61$), to that in KLG 3 knees that did not display contra-lateral RKOA (KLG0 or 1). Also, there was no significant difference to the rate of cartilage loss in all KLG3 knees independent of their contra-lateral RKOA (KLG0 to 4) status ($P = 0.23$).

Table II
One-year femorotibial cartilage thickness loss in knees with KLG 2, with and without JSN, and in KLG 3 knees, depending on contra-lateral RKOA status. Results are shown for the subregional with the maximum cartilage thickness loss in each knee (OV one) and for the mean change in the (total) FTJ ($n = 837$)

	Contra-lateral RKOA status	OV one				FTJ			
		Mean change (SD) μm	95% CI	*P* value*	OR** [95% CI]	Mean change (SD) μm	95% CI	*P* value*	OR** [95% CI]
KLG 2 Ø JSN ($n = 158$)	No RKOA ($n = 47$)	−148 (65.1)	−167; −128		1 (Ref.)	−38.6 (137)	−78.9; 1.73		1 (Ref.)
	Definite RKOA ($n = 89$)	−152 (151)	−184; −120	0.56	0.99 [0.95–1.04]	−29.1 (239)	−79.5; 21.3	0.56	1.00 [0.94–1.08]
	Moderate RKOA ($n = 22$)	−165 (168)	−239; −90.1		0.98 [0.91–1.05]	−53.1 (209)	−146; 39.6		0.99 [0.91–1.10]
KLG 2 + JSN ($n = 339$)	No RKOA ($n = 100$)	−164 (119)	−187; −140		1 (Ref.)	−43.9 (157)	−75.1; −12.7		1 (Ref.)
	Definite RKOA ($n = 148$)	−175 (136)	−197; −152	0.01	0.99 [0.96–1.02]	−35.2 (175)	−63.6; −6.81	0.09	1.01 [0.97–1.05]
	Moderate RKOA ($n = 91$)	−220 (170)	−255; −184		0.95 [0.91–0.98]	−98.7 (225)	−146; −51.8		0.95 [0.90–1.00]
KLG 3 ($n = 340$)	No RKOA ($n = 96$)	−232 (168)	−266; −198		1 (Ref.)	−110 (273)	−166; −55		1 (Ref.)
	Definite RKOA ($n = 99$)	−256 (168)	−290; −223	0.35	0.99 [0.95–1.04]	−140 (212)	−183; −98.1	0.44	0.98 [0.91–1.05]
	Moderate RKOA ($n = 145$)	−242 (163)	−269; −215		1.0 [0.96–1.05]	−119 (212)	−154; −84.6		0.99 [0.93–1.07]

No RKOA = KLG0 or 1; definite RKOA = KLG 2; moderate RKOA = KLG3 or 4; *unadjusted testing using Kruskal–Wallis-Test; ** = Generalized linear model with adjustment for age, gender, BMI and MRI sequence.

Looking at FTJ cartilage thickness change in KLG2 knees with JSN and with moderate contra-lateral RKOA (KLG3 or 4), the rate of loss (−98.7 μm [95% CI −145; −51.8]) was greater than in those without contra-lateral RKOA (KLG0 or 1) reporting an odds of OR 0.95 [95% CI 0.90–1.00] (crude $P = 0.051$). Again, their rate of subregional cartilage loss was not significantly different to that in KLG 3 knees without contra-lateral RKOA (KLG0 or 1; $P = 0.75$) or when compared to KLG3 knee independent of their contra-lateral RKOA (KLG0 to 4) status ($P = 0.37$).

The 2-year follow-up data were in general similar with observations made over 1 year follow-up (Table III). Over 1 year, the proportion of "progressors" in KLG2 knees with JSN with moderate contralateral RKOA (KLG3 or 4) was 5.9%, as opposed to 5.5% in those with definite contra-lateral RKOA (KLG2) and only 3.9% in those without contra-lateral RKOA (KLG0 or 1).

Other comparisons on contra-lateral knee effects

In KLG2 knees without JSN, the odds in those with moderate contra-lateral RKOA (KLG3 or 4) was distinct smaller compared to those without RKOA (KLG0 or 1) both at 1-year OR 0.98 [95% CI 0.91–1.05] and at 2-years follow-up OR 0.95 [95% CI 0.86–1.05] (Tables II and III). The proportion of progressors in those with moderate contra-lateral RKOA (KLG3 or 4) was only 1.0% as opposed to 2.8% in those with definite contra-lateral RKOA (KLG2), and 1.7% in those without contra-lateral RKOA (KLG0 or 1). In KLG3 knees, the rates of change in those with moderate contra-lateral RKOA (KLG3 or 4) appeared to be similar to those without contra-lateral RKOA (KLG0 or 1), both over 1- and 2-year observation periods. The proportion of progressors in KLG3 knees with moderate contra-lateral RKOA (KLG3 or 4) was 10.4% as opposed to 7.4% in those with definite contra-lateral RKOA (KLG2), and 7.5% in those without contra-lateral RKOA (KLG0 or 1).

Sensitivity analyses of trauma history

After excluding knees that had a trauma history in the contra-lateral knee ($n = 224$ at 1-year; $n = 131$ at 2-years), observations were generally consistent with those for the total sample, both over one and over 2 years. In KLG2 knees with JSN, the rate of maximum subregional cartilage loss was over the 1 year observational period −203 μm (95% CI −237; −169 μm) for those with moderate contra-lateral RKOA (KLG3 or 4), −172 μm (95% CI −196, −149 μm) for those with definite contra-lateral RKOA (KLG2) and −169 μm (95% CI −197, −142 μm) for those without contra-lateral RKOA (KLG0 or 1) (P [across categories of contra-lateral RKOA] = 0.06). The rate of subregional cartilage loss in KLG2 knees with JSN and with moderate contra-lateral RKOA (KLG3 or 4), was lower, compared to that in KLG3 knees without contra-lateral RKOA (KLG0 or 1) (−249 μm [95% CI −286; −212 μm]; $P = 0.03$).

Excluding additionally those with a trauma history in the ipsilateral (investigated) knee ($n = 312$) observations were consistent with those for the total sample and for the sample without a contra-lateral trauma exclusively, both over the one and over the 2-year observational period (data not shown).

Subregion with the greatest rate of longitudinal cartilage loss (OV one)

The specific subregional location of the OV one within the FTJ was over the 1 year period the central subregion of the lateral tibia (cLT) for KLG2 knees without JSN independent of the contra-lateral

Table III
Two-year femorotibial cartilage thickness loss in knees with KLG 2, with and without JSN, and in KLG 3 knees, depending on contra-lateral RKOA status. Results are shown for the subregional with the maximum cartilage thickness loss in each knee (OV one) and for the mean change in the (total) FTJ ($n = 487$)

	Contra-lateral RKOA status	OV one				FTJ			
		Mean change (SD) μm	95% CI	*P* value*	OR** [95% CI]	Mean change (SD) μm	95% CI	*P* value*	OR** [95% CI]
KLG 2 Ø JSN ($n = 89$)	No RKOA ($n = 30$)	−185 (98.1)	−222; −149		1 (Ref.)	−59.3 (195)	−132; 13.3		1 (Ref.)
	Definite RKOA ($n = 50$)	−166 (79.7)	−189; −143	0.79	1.01 [0.97–1.05]	−26.6 (132)	−64; −10.8	0.29	1.02 [0.95–1.10]
	Moderate RKOA ($n = 9$)	−231 (162)	−356; −107		0.95 [0.86–1.05]	−128 (210)	−289; 33.7		0.96 [0.83–1.10]
KLG 2 + JSN ($n = 196$)	No RKOA ($n = 61$)	−191 (113)	−220; −162		1 (Ref.)	−60.2 (172)	−104; −16.1		1 (Ref.)
	Definite RKOA ($n = 88$)	−213 (163)	−248; −179	0.19	0.99 [0.95–1.04]	−69.5 (226)	−118; −21.6	0.43	0.99 [0.93–1.06]
	Moderate RKOA ($n = 47$)	−241 (163)	−288; −193		0.97 [0.92–1.03]	−116 (227)	−183; −49		0.96 [0.89–1.04]
KLG 3 ($n = 202$)	No RKOA ($n = 53$)	−327 (207)	−385; −271		1 (Ref.)	−199 (283)	−277; −121		1 (Ref.)
	Definite RKOA ($n = 68$)	−373 (246)	−433; −313	0.57	0.96 [0.89–1.04]	−262 (312)	−337; −187	0.57	0.93 [0.84–1.04]
	Moderate RKOA ($n = 81$)	−365 (241)	−418; −312		0.99 [0.91–1.07]	−254 (308)	−323; −186		0.96 [0.87–1.07]

No RKOA = KLG0 or 1; definite RKOA = KLG 2; moderate RKOA = KLG3 or 4; *unadjusted testing using Kruskal–Wallis-Test; ** = Generalized linear model with adjustment for age, gender, BMI and MRI sequence.

RKOA status (KLG0-4). For KLG2 knees and JSN the OV one location was the central subregion of the central (weightbearing) medial femur (ccMF) for those with contra-lateral no and moderate RKAO (KLG0 and KLG3 or 4), but cLT for those with contra-lateral definite RKOA (KLG2). In KLG3 knees the OV one location was independent of the contra-lateral RKOA status (KLG0-4) ccMF. The results for the 2 year observational period were similar to those observed at 1 year (data not shown).

Discussion

To our knowledge, this is the first study to explore a "progression" model of mild radiographic KOA (RKOA) based on contra-lateral radiographic status. Specifically, we asked whether in knees with KLG2 and JSN, the rate of cartilage loss was greater in those with moderate contra-lateral RKOA than in those without contra-lateral RKOA. We found that their rates of maximum subregional cartilage thickness loss were significantly greater, and similar to those of KLG3 knees. In KLG2 knees without JSN, a similar effect was seen, but did not reach statistical significance, whereas in KLG3 knees, contra-lateral knee status was not observed to be a relevant indicator for subsequent cartilage loss. The observed effects were stronger supported by the femoro-tibial subregion with the greatest longitudinal cartilage loss (OV one) than by the total femoro-tibial joint cartilage measure, presumably due to the fact that longitudinally cartilage thinning and thickening are simultaneously detected in knee OA progression[41,42] but the clinical relevance of the OV approach vs a region-specific analysis has not yet been addressed thoroughly and deserves further exploration in upcoming research studies.

To obtain sufficient numbers of participants in each of the nine strata investigated, we pooled longitudinal observations acquired with a sagittal DESS[13,14,43] or coronal FLASH MRI sequences[26]. This may be viewed as a limitation, but previous studies have shown that both protocols produce highly consistent results[44,45]. Further, to account for potential differences in measurements of cartilage thickness change between the protocols, we adjusted the generalized linear models for "MR sequence". Further, we performed a *post hoc* analysis for the sequences used, without statistical significant impact on the output.

Another limitation of the current study is that biomechanical factors such as altered gait patterns, reduced physical activity or modified joint loading of the knee were not considered as confounding criteria for cartilage loss in the contra-lateral (investigated) knee. Biomechanical effects may be linked to the severity of contra-lateral RKOA and any beneficial DMOAD effect might be influenced by biomechanical abnormalities when not considered. Therefore, future studies investigating the contra-lateral knee effect will have to include these biomechanical effects as confounding criteria in their analyses. However, contra-lateral RKOA in this study was not considered as a potential mechanical modifier of cartilage loss in the contra-lateral knee, but as a potential indicator of intrinsic vulnerability.

Idiopathic knee OA is thought to be a bilateral disease and to depend on intrinsic or extrinsic factors that have an impact on both knees. Spector *et al.*[18] were among the first to establish that contra-lateral RKOA was a predictor of incident RKOA. A longitudinal study with 14 years of follow-up showed that when one knee usually is first affected by RKAO, the contra-lateral one follows soon[46]. Davis *et al.*[19] showed that bi-lateral knee OA was more prevalent (5%) than uni-lateral knee OA (2%), and that obesity was a two-fold stronger predictor of bi-lateral OA than was knee injury. In contrast, knee injury was shown to be a 4.7-fold stronger predictor of uni-lateral OA than was obesity. For this reason, we performed a sensitivity analysis, excluding study participants with a previous trauma in the contra-lateral knee. Yet, this analysis was consistent with results obtained in the total sample.

Since change from a normal joint to end-stage RKOA represents a continuum[47], it is reasonable to assume that a relationship between contra-lateral knee status and structural progression (i.e., cartilage loss) in the target knee may also exist at later stages of RKOA. Our results show that this is the case, and that at least KLG2 knees with moderate contra-lateral RKOA generally show greater progression rates that those without contra-lateral RKOA. We have no definite explanation, why this was observed in KLG2, but not in KLG3 knees, and why the effect only was specifically statistically significant in KLG2 knees with JSN. It may be that KLG2 knees with JSN are at a transitional phase where cartilage tissue loss starts, and that this distinct transitional phase is characterized by a higher "vulnerability" towards OA progression. This vulnerability is potentially indicated by moderate RKOA (KLG3 or 4) in the contra-lateral knee and it appears to be more relevant at this stage compared to earlier or later phases of the disease. Although the clinical significance of cartilage tissue loss remains to be explored, recent studies have found that cartilage loss was significantly greater in knees prior to knee replacement (considered a "hard" clinical endpoint) than in knees with the same KLG who did not move on to replacement during this observation period[48,49].

The concrete aim of the study was to test whether sufficient rates of cartilage loss can be observed in knees at a relatively mild radiographic status over short (i.e., one year) observation periods that are acceptable for DMOAD trials. The observed rates of change display a smaller statistical differences in the respective strata after adjustment for co-factors and might be of minor relevance for daily clinical use, but these results highlight a clear trend: the rates of change in KLG2 knees with JSN and with moderate contra-lateral RKOA (KLG3 or 4) are not significantly different to those commonly observed in KLG3 knees, although these (KLG2) knees are still at a "relatively" mild radiographic stage, with only little JSN being present. Mild disease stages are thought to be more amendable to disease modification[8–10,50] and it is plausible to intervene therapeutically at a stage at which cartilage can still be preserved. However, the dilemma is that to demonstrate the effect of a DMOAD to stop cartilage loss in unselected KLG2 knees requires extensive follow-up times, given the small rates of cartilage loss occurring in KLG2 knees, particularly in those without JSN[26,38]. Therefore, KLG2 knees with JSN and with moderate contra-lateral ROA may represent a unique opportunity to test anti-catabolic DMOADs over a more reasonable observation period. This, of course, requires an elaborate recruitment process: To test whether this was feasible, we analyzed the OAI "progression cohort", i.e., subjects that had at least one knee with frequent symptoms and definite RKOA as scored for recruitment purposes by the site investigators. Of these 2780 knees (from 1390 individuals), 13.3% were KLG2 without JSN, 24.3% KLG2 with JSN, 28.1% KLG3, and 8.3% KLG4. Of those that were KLG2 with JSN, only about one third (i.e., 7.9% of the entire cohort) also had moderate contra-lateral RKOA. This indicates that the recruitment effort for a trial studying only KLG2 knees with JSN with moderate contra-lateral RKOA would be relatively high and that almost 1300 patients would have to be screened by radiography, for 100 to be finally enrolled. However, this may be rewarded by an early RKOA model, in which cartilage loss can be observed (and potentially modified) over relatively short (i.e., one year follow-up) periods. Subsequent studies will be required to demonstrate the effect of this selection process and to develop the idea of the contra-lateral knee effect further.

In conclusion, we show that KLG2 knees, and particularly KLG2 knees with JSN, moderate contra-lateral RKOA is associated with greater rates of future cartilage loss compared with KLG2 knees without contra-lateral RKOA. KLG2 knees with JSN and with

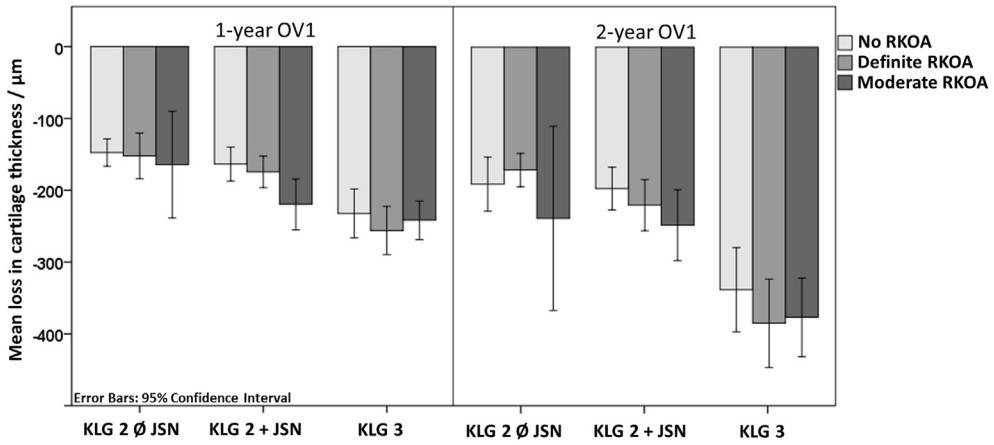

Fig. 1. 1-year and 2-year change in cartilage thickness in the OV one location in knees with KLG 2 and 3 and with and without JSN; (according to the OARSI atlas) having no (KLG0 or 1), definite (KLG2) or moderate (KLG3 or 4) contra-lateral RKOA. Please note that changes are total changes observed in the respective observational period: 1-year and 2-years.

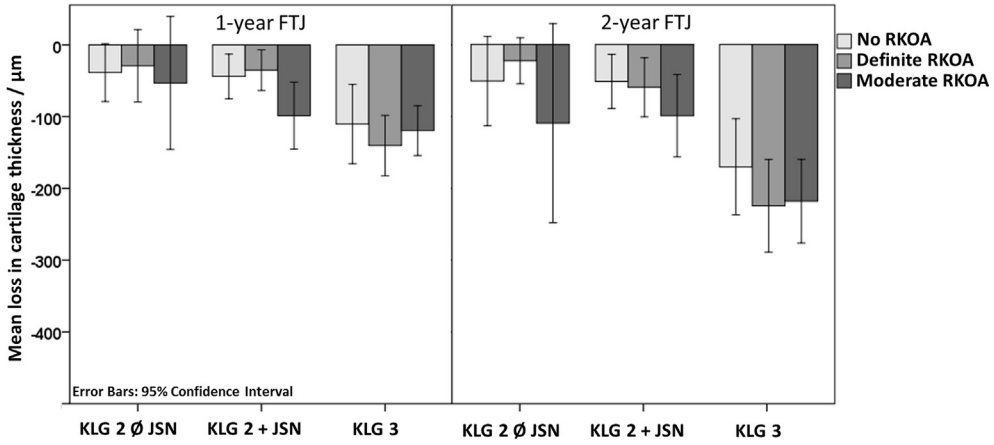

Fig. 2. 1-year and 2-year change in cartilage thickness in the (total) FTJ in knees with KLG 2 and with and without JSN; (according to the OARSI atlas) and KLG3 having no (KLG0 or 1), definite (KLG2) or moderate (KLG3 or 4) contra-lateral RKOA. Please note that changes are total changes observed in the respective observational period: 1-year and 2-years.

moderate contra-lateral RKOA, display rates of femorotibial cartilage loss similar to KLG3 knees, despite being at a mild stage of radiographic disease. They may therefore provide a unique opportunity for recruitment in clinical trials that explore the efficacy of anti-catabolic DMOADs on structural progression but the clinical relevance of the presented findings needs to be explored further. Figs 1 and 2.

Contributions

All authors made substantial contributions to all three sections: (1) the conception and design of the study, data acquisition, analysis and interpretation; (2) drafting the article or revising it critically; (3) final approval of the version to be submitted.

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Conflict of interest

- Sebastian Cotofana has a part time appointment with Chondrometrics GmbH (Ainring, Germany), a company providing quantitative MR image analysis services.
- Wolfgang Wirth has a part time appointment with Chondrometrics GmbH and is co-owner of Chondrometrics GmbH.
- Felix Eckstein is CEO and co-owner of Chondrometrics GmbH. He has provided consulting services to MerckSerono, Novartis and Abbvie. He has received funding support for this study from Pfizer, Eli Lilly, Novartis, MerckSerono, Glaxo Smith Kline, Wyeth, and Centocor. He has received funding support not related to this study from Stryker, Abbvie, Kolon, and Synarc. He has provided educational content for Medtronic.
- Olivier Benichou is employed by Eli Lilly & Co, Indianapolis, IN, USA.
- Wolfgang Hitzl has no competing interests.

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