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Brief Report

Cartilage loss in radiographically normal knees depends on radiographic status of the contralateral knee – data from the Osteoarthritis Initiative

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SUMMARY

Objective: To test whether radiographically normal knees with contralateral radiographic knee osteoarthritis (OA), but without contralateral trauma history, display greater cartilage thickness loss than knees from subjects with bilaterally radiographically normal knees.
Methods: 828 radiographically normal knees (Kellgren Lawrence grade [KLG] 0) from the Osteoarthritis Initiative [OAI] were studied; 150 case knees displayed definite radiographic knee OA (KLG $\geq$ 2) contralaterally, and had MRI double echo steady state (DESS) images available at 12 and 48 month follow-up. 678 reference knees displayed KLG0 at the contralateral side. Cartilage thickness change was determined in femorotibial subregions and location-independent cartilage thinning scores were computed. Case and reference knees were compared using ANCOVA.
Results: Of the 150 KLG0 case knees, 108 had a contralateral KLG2 knee (50 without, and 58 with joint space narrowing [JSN]), 31 a KLG3 and 11 a KLG4 knee. The cartilage thinning score tended to be greater in case than reference knees; the cartilage thinning score in KLG0 case knees with contralateral radiographic JSN (−858 μm; [95% confidence interval −1016, −701 μm]) was significantly greater ($P = 0.0012$) than that in bilaterally KLG0 reference knees (−634 μm; [−673, −596 μm]), whereas KLG0 knees with contralateral KLG2 without JSN only showed relatively small thinning scores (−530 μm, [−631, −428 μm]). Region-specific analysis suggested greater rates of cartilage loss in case than in reference knees in the lateral, rather than medial, femorotibial compartment.
Conclusions: Radiographically normal knees with contralateral JSN may serve as a human model of early OA, for testing disease modifying drugs in clinical trials designed to prevent cartilage loss before the onset of radiographic change.
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Introduction

Testing of disease modifying osteoarthritis drugs (DMOADs) to prevent structural progression at an early disease stage requires human models of early knee osteoarthritis (OA), with a reasonable likelihood of progression in the foreseeable future. Ideally, prevention of structural pathology should commence prior to the onset of radiographic change, and should aim to maintain structurally normal knees. As preventive treatment is unlikely to be without side effects and risks, it is further important to identify patients who should undergo preventive treatment of a radiographically normal knee in view of a positive benefit/risk ratio of the intervention.

Previous studies suggested that (idiopathic) knee osteoarthritis is a bilateral disease that generally affects both limbs[1–3]. Further,

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we observed that knees with radiographic OA display greater cartilage thickness loss if the contralateral knee exhibited advanced radiographic knee OA (Kellgren Lawrence grade [KLG] 3 or 4) and OARSI atlas[4] joint space narrowing (JSN), compared to knees in which the contralateral knee was radiographically normal[5]. Also, radiographically normal (KLG0) knees were observed to incur greater likelihood of incident radiographic OA if the contralateral knee had definite radiographic knee OA than if the contralateral knee was radiographically normal[3].

The purpose of the current study was to test the hypothesis whether radiographically normal knees (KLG0) with definite contralateral radiographic knee OA (KLG2-4), and particularly those with advanced contralateral radiographic knee OA (JSN grade 1–3[4]), display greater cartilage thickness loss compared with KLG0 knees from subjects who are bilateral KLG0. Since previous knee trauma may explain a unilateral knee OA status due to secondary OA, whereas participants with primary unilateral radiographic knee OA may be intrinsically susceptible to knee OA and suffer from a greater likelihood of encountering cartilage loss in the knee that is currently still radiographically normal[1–3,6], we selected all KLG0 knees from the OAI with definite radiographic knee OA but without known trauma history (KLG2-4) in the contralateral knee. Confirmation of the above hypothesis may provide some clues to the clinical management of patients with primary unilateral knee OA, and more importantly, a human model of early knee OA for testing DMOADs in clinical trials designed to prevent cartilage loss before the onset of radiographic change.

Methods

Study design

The current study was based on data from the OAI, a prospective, observational cohort study (http://www.oai.ucsf.edu/, clinicaltrials.gov identifier: NCT00080171). The OAI enrolled 4,796 participants aged 45–79 years and collected clinical data, 3 T magnetic resonance images (MRIs) and fixed-flexion radiographs at four clinical centers[7]. The OAI was approved by the Committee on Human Research, the Institutional Review Board (IRB) for the University of California, San Francisco (UCSF) and the IRBs at each clinical site.

In the current study, we analyzed 828 radiographically normal knees (KLG0 by the central radiographic readings performed at Boston University, version 0.7/1.7) of 828 OAI participants. 150 of these were KLG0 at OAI 12-month evaluation (baseline for this study), displayed definite radiographic knee OA (KLG $\geq$ 2) in the contralateral knee, did not report a trauma history in that contralateral knee (OAI variable INJR/INJL), and had MRI available at the 12 and 48 month time point. 678 represented a random selection of total of 849 OAI KLG0 knees that displayed a radiographically normal status (KLG0) at the contralateral side, with MRI available at 12 and 48 months[8]. 12 and 48 month follow-up data were used, because 12 months represented the baseline assessment for the ancillary study for which MRI assessment in participants with bilateral KLG0 status was performed[8]. In 4 knees the radiographic scores were missing at 12 month follow-up, and in these the scores were obtained from the OAI baseline and 24 month readings. Knee pain classification was based on the OAI public release variables RKSX and LKSX "Right/Left knee symptom status"[7], with knees categorized: a) pain, aching or stiffness no most days of at least 1 month in the past 12 months (frequent pain); b) pain, aching or stiffness in the past 12 months, but not on most days of a month (infrequent pain); c) no pain, aching or stiffness in the past 12 months.

Cartilage thickness measurement by MRI

Femorotibial cartilage thickness measurement was based on manual segmentation and computation using Chondrometrics software (Chondrometrics GmbH, Ainring, Germany), for which test-retest precision has been reported[7,9]. The analysis was performed using the double echo steady state (DESS) MRI sequence with water excitation[7], with 12 and 48 month images being processed as pairs by the same reader with blinding to image acquisition order and contralateral radiographic status. The mean cartilage thickness (ThCtAB.Me) was determined for the medial (MFTC) and lateral femorotibial compartment (LFTC), the medial and lateral tibia (MT/LT), the medial and lateral weight-bearing femur (cMF/cLF), 5 tibial (central, external, internal, anterior, posterior), and 3 femoral subregions[9] in each compartment ($n = 16$), and in combined central compartment subregions (cMFTC/cLFTC).

Location-independent cartilage thinning/thickening scores were computed by summing all negative/positive changes across the 16 subregions within each knee[10]. Ordered values (OVs) were computed by ordering the subregional changes in each knee in ascending order[11], with OV1 representing the subregion with the largest thickness loss and OV16 that with the largest thickness gain in each knee.

Statistical analysis

The primary analytic focus of this exploratory study was a comparison of the "thinning score" between the 150 KLG0 "case" knees with definite contralateral radiographic knee OA (KLG$\geq$2) vs the 678 radiographically normal knees from subjects who were bilaterally KLG0 (reference). The secondary analytic focus was a comparison of the "thinning score" between the subset of the 100 KLG0 case knees with advanced contralateral radiographic knee OA (defined as presence of any OARSI JSN[4] in the medial or lateral compartment) vs the 678 reference knees. Statistical comparisons were performed using ANCOVA, with adjustment for age, sex, and the body mass index (BMI). Cohen's D [C D] was used as a measure of effect size, to permit comparisons across different analyses independent of group sizes. Comparisons for all other measures (compartments, plates, subregions, OVs and thickening scores) were considered exploratory. A sensitivity analysis was performed amongst case knees based on contralateral JSN status (0–3); differences between these strata were not tested statistically.

Results

Demographics and radiographic status

Of the 150 case knees, 61 were right and 89 left knees; 108 were KLG2 in the contralateral knee (50 JSN grade0 and 58 JSN grade1), 31 KLG3 (all JSN grade2) and 11 KLG4 (all JSN grade3); 21%/36%/43% exhibited frequent pain/infrequent pain/no pain over most days of the month, in at least one of the past 12 months. The 150 participants (age 65.1 $\pm$ 8.6 years, BMI 27.8 $\pm$ 4.3 kg/m^2) were 89 women and 61 men (85.3% white/Caucasian, 13.3% black/African American, 1.3% other). In comparison, the other OAI participants (with at least one KLG2-4 knee) were 63.6 $\pm$ 9.0 years with a BMI of 29.6 $\pm$ 4.8 kg/m^2) were 1387 women and 1013 men (76.5% white/Caucasian, 21.0% black/African American, 2.6% other). Of the 678 reference knees studied, 677 were right knees and one was a left knee 21%/45%/34% exhibited frequent pain/infrequent pain/no pain as defined above. The 678 participants (age 59.6 $\pm$ 8.8 years, BMI of 26.7 $\pm$ 4.2 kg/m^2) were 384 women and 294 men (90.1% white/Caucasian, 8.0% black/African American, 1.9% other). Cases were slightly older, had a slightly higher BMI and were slightly more

black/African American than reference knees, but the difference was not deemed clinically relevant in context of the question studied. Baseline cartilage thickness did not differ statistically significantly between case and reference knees in the medial (3.4 ± 0.5 mm vs 3.4 ± 0.5 mm, $P = 0.99$) femorotibial compartment, but case knees had a slightly lower lateral compartment cartilage thickness (3.8 ± 0.6) than control knees (3.9 ± 0.6, $P = 0.03$). Further descriptive information on baseline demographics and cartilage thickness values is provided in Supplementary Table 1.

Cartilage thickness change in case and reference knees

The cartilage thinning score tended to be greater (Cohen's D = 0.21) in KLG0 case knees with definite (KLG≥2) contralateral radiographic knee OA (−749 ± 696 μm; [95% confidence interval −861, −637 μm]) than in KLG0 reference knees with a radiologically normal contralateral knee (−634 ± 516 μm [−673 μm, −596 μm]); however, the difference failed to reach statistical significance ($P = 0.07$; Table I). Yet, Ordered Value (OV) 1–3 differed significantly between case and reference knees ($P \leq 0.01$ without adjustment for multiple comparisons, and Cohen's D ≤ 0.32; Table I), with OV1 displaying a longitudinal change of −209 ± 184 μm [−239 μm, −179 μm] vs −166 ± 121 μm [−175 μm, −157 μm]. Neither the thickening scores, nor the cartilage plate measures, nor the other OVs displayed statistically significant differences (Table I), nor did cartilage thickness changes in any subregions (data not shown).

The cartilage thinning score was significantly greater (−858 ± 794 μm [−1016 μm, −701 μm]; $P = 0.0012$; Cohen's D = 0.40) in KLG0 case knees with advanced contralateral knee OA (JSN>0) than in KLG0 reference knees (Table I), and significant differences were also noted for OV 1–5 ($P \leq 0.01$ without adjustment for multiple comparisons; Cohen's D ≤ 0.50; Table I). Interestingly, the region-specific analysis suggested greater rates of cartilage loss in case knees in the lateral compartment (LFTC, cLFTC, and LT, Cohen's D ≤ 0.37) than in the medial one (Table I). In subregions, differences of $P < 0.05$ were noted in the central, internal and posterior LT (Cohen's D ≤ 0.42; data not shown). Neither the thickening scores, nor the medial cartilage plate or subregion measures displayed statistically significant differences between the groups (Table I). Further descriptive information on the longitudinal change in cartilage thickness cartilage thickness values, specifically the median and range, is provided in Supplementary Table 2.

Sensitivity analyses showed that cartilage thinning scores in case knees increased with contralateral JSN status (−530 μm, −745 μm, −982 μm, and −1109 μm in those with contralateral JSN 0,1, 2 and 3), and this was also reflected by the OVs and lateral compartment measures (Table II). Interestingly, the cartilage thinning score in KLG0 knees with contralateral KLG2 without JSN (−530±μm) appeared to be less than that in KLG0 knees that had a contralaterally normal KLG0 knee (−634 μm). Amongst case knees, cartilage thickening scores appeared to be smallest in those with contralateral JSN2 (389 ± 329 μm [269 μm, 510 μm]), and greatest in those with contralateral JSN0 (600 ± 341 μm [503 μm, 697 μm]). Change in the latter appeared to be greater in comparison with reference knees (529 ± 366 μm [501 μm, 556 μm]).

Discussion

This study aimed to test the hypothesis that radiographically normal knees with contralateral radiographic knee OA, but without contralateral trauma history (cases), display greater rates of cartilage thickness loss than knees from subjects with bilaterally radiographically normal knees (reference). We found that cartilage thinning scores in case knees with contralateral radiographic JSN were significantly greater than in reference knees, whereas KLG0

Table I
Longitudinal change (mean, standard deviation and 95% confidence interval) in cartilage thickness in KLG 0 knees a) with a contralateral (CL) KLG 0 knee; b) with a CL KLG ≥2 knee, and c) with a CL OARSI JSN>0 knee

	KLG0 with CL KLG 0 ($n = 678$)	KLG 0 with CL KLG≥2 ($n = 150$)			KLG 0 with CL JSN>0 ($n = 100$)		
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	*P*	C D	Mean ± SD (95% CI)	*P*	C D
Thinning	−634 ± 516 (−673, −596)	−749 ± 696 (−861, −637)	0.07	0.21	−858 ± 794 (−1016, −701)	**<0.01**	0.40
Thickening	529 ± 366 (501, 556)	528 ± 343 (472, 583)	0.57	0.00	492 ± 340 (424, 559)	0.77	0.10
MFTC	2 ± 112 (−6, 11)	−9 ± 131 (−31, 12)	0.62	0.10	−21 ± 144 (−50, 7)	0.23	0.20
LFTC	−17 ± 117 (−26, −8)	−32 ± 150 (−56, −8)	0.34	0.12	−55 ± 168 (−88, −21)	**0.02**	0.30
cMFTC	−9 ± 182 (−23, 5)	−33 ± 227 (−70, 4)	0.56	0.13	−60 ± 244 (−109, −12)	0.09	0.27
cLFTC	−27 ± 200 (−43, −12)	−71 ± 278 (−115, −26)	0.09	0.20	−103 ± 318 (−166, −39)	**0.01**	0.34
MT	−8 ± 58 (−13, −4)	−10 ± 57 (−19, −1)	0.95	0.03	−17 ± 61 (−29, −5)	0.33	0.15
cMF	11 ± 74 (5, 16)	1 ± 95 (−15, 16)	0.50	0.13	−4 ± 105 (−25, 16)	0.30	0.19
LT	−26 ± 70 (−31, −20)	−38 ± 88 (−52, −24)	0.13	0.17	−53 ± 97 (−73, −34)	**<0.01**	0.37
cLF	9 ± 68 (3, 14)	6 ± 87 (−8, 20)	0.94	0.04	−1 ± 97 (−20, 18)	0.39	0.13
OV 1	−166 ± 121 (−175, −157)	−209 ± 184 (−239, −179)	**<0.01**	0.32	−234 ± 213 (−276, −192)	**<0.01**	0.50
OV 2	−116 ± 85 (−122, −109)	−142 ± 127 (−162, −121)	**0.01**	0.28	−160 ± 145 (−189, −131)	**<0.01**	0.46
OV 3	−88 ± 69 (−94, −83)	−107 ± 97 (−122, −91)	**0.01**	0.25	−122 ± 109 (−144, −101)	**<0.01**	0.45
OV 4	−68 ± 63 (−72, −63)	−79 ± 72 (−90, −67)	0.16	0.17	−89 ± 79 (−104, −73)	**0.01**	0.32
OV 5	−51 ± 55 (−55, −47)	−59 ± 65 (−70, −49)	0.24	0.15	−69 ± 73 (−84, −55)	**0.01**	0.32
OV 6	−36 ± 52 (−40, −32)	−43 ± 58 (−52, −34)	0.32	0.13	−53 ± 64 (−65, −40)	**0.02**	0.31
OV 7	−23 ± 46 (−27, −20)	−28 ± 52 (−36, −20)	0.56	0.10	−37 ± 56 (−48, −25)	**0.03**	0.28
OV 8	−11 ± 44 (−14, −7)	−14 ± 49 (−22, −6)	0.72	0.08	−23 ± 53 (−33, −12)	0.05	0.27
OV 9	2 ± 44 (−1, 5)	0 ± 45 (−8, 7)	0.98	0.05	−8 ± 46 (−17, 1)	0.13	0.22
OV 10	14 ± 43 (11, 17)	12 ± 45 (4, 19)	0.92	0.05	5 ± 46 (−5, 14)	0.12	0.21
OV 11	27 ± 44 (24, 30)	26 ± 44 (19, 33)	0.69	0.02	19 ± 45 (11, 28)	0.33	0.17
OV 12	40 ± 46 (37, 44)	41 ± 46 (34, 49)	0.28	−0.03	36 ± 47 (26, 45)	0.92	0.10
OV 13	55 ± 47 (52, 59)	56 ± 50 (48, 64)	0.35	−0.02	51 ± 50 (41, 61)	0.93	0.09
OV 14	73 ± 51 (69, 77)	75 ± 51 (66, 83)	0.30	−0.04	69 ± 52 (59, 80)	0.95	0.07
OV 15	98 ± 61 (94, 103)	100 ± 58 (91, 109)	0.32	−0.03	97 ± 62 (85, 109)	0.60	0.03
OV 16	143 ± 80 (137, 149)	150 ± 71 (138, 161)	0.16	−0.08	150 ± 76 (135, 165)	0.15	−0.08

CL = contralateral; KLG = Kellgren Lawrence grade; SD = standard deviation; CI = confidence interval; CD = Cohens D; MFTC = medial femorotibial compartment; LFTC = lateral femorotibial compartment; cMFTC = central MFTC; cLFTC = central LFTC; MT = medial tibia, cMF = weightbearing medial femur, LT = lateral tibia, cLF = weightbearing lateral femur, OV = Ordered Value.
P values < 0.05 were marked bold.

Table II
Longitudinal change in cartilage thickness (mean, standard deviation and 95% confidence interval) in KLG 0 knees a) with a contralateral (CL) OARSI JSN = 0 knee; b) with a CL OARSI JSN = 1 knee, c) with a CL OARSI JSN = 2 knee; d) with a CL OARSI JSN = 3 knee

	KLG0 with CL JSN 0 ($n = 50$)	KLG0 with CL JSN 1 ($n = 58$)	KLG0 with CL JSN 2 ($n = 31$)	KLG0 with CL JSN 3 ($n = 11$)
	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)	Mean ± SD (95% CI)
Thinning	−530 ± 357 (−631, −428)	−745 ± 590 (−900, −590)	−982 ± 705 (−1240, −723)	−1109 ± 1602 (−2186, −33)
Thickening	600 ± 341 (503, 697)	540 ± 341 (450, 630)	389 ± 329 (269, 510)	526 ± 328 (306, 747)
MFTC	14 ± 99 (−14, 43)	6 ± 116 (−24, 37)	−80 ± 174 (−144, −17)	0 ± 146 (−98, 99)
LFTC	12 ± 90 (−13, 38)	−41 ± 130 (−75, −6)	−51 ± 115 (−93, −9)	−139 ± 367 (−385, 108)
cMFTC	22 ± 178 (−29, 72)	−17 ± 184 (−65, 32)	−154 ± 325 (−273, −34)	−27 ± 203 (−164, 109)
cLFTC	−6 ± 154 (−50, 37)	−87 ± 272 (−159, −16)	−77 ± 193 (−147, −6)	−257 ± 662 (−702, 189)
MT	4 ± 47 (−10, 17)	−6 ± 59 (−21, 10)	−41 ± 63 (−64, −18)	−8 ± 51 (−42, 26)
cMF	11 ± 69 (−9, 30)	12 ± 90 (−12, 35)	−40 ± 124 (−85, 6)	8 ± 110 (−66, 82)
LT	−7 ± 54 (−22, 9)	−48 ± 92 (−72, −23)	−52 ± 57 (−73, −31)	−89 ± 183 (−212, 33)
cLF	19 ± 60 (2, 36)	7 ± 61 (−9, 23)	1 ± 84 (−30, 31)	−49 ± 219 (−196, 98)
OV 1	−159 ± 87 (−184, −135)	−215 ± 195 (−267, −164)	−241 ± 158 (−299, −183)	−313 ± 385 (−571, −54)
OV 2	−105 ± 66 (−124, −87)	−140 ± 120 (−172, −109)	−177 ± 123 (−223, −132)	−212 ± 276 (−397, −26)
OV 3	−76 ± 56 (−92, −60)	−105 ± 66 (−122, −87)	−139 ± 96 (−174, −104)	−167 ± 245 (−331, −2)
OV 4	−58 ± 49 (−72, −44)	−80 ± 63 (−96, −63)	−101 ± 65 (−124, −77)	−102 ± 160 (−209, 5)
OV 5	−40 ± 39 (−51, −29)	−58 ± 53 (−71, −44)	−85 ± 66 (−110, −61)	−85 ± 146 (−183, 13)
OV 6	−24 ± 36 (−35, −14)	−43 ± 48 (−55, −30)	−67 ± 59 (−89, −46)	−63 ± 126 (−148, 21)
OV 7	−11 ± 37 (−21, 0)	−30 ± 47 (−42, −17)	−50 ± 58 (−71, −29)	−36 ± 88 (−95, 23)
OV 8	3 ± 36 (−8, 13)	−15 ± 45 (−27, −4)	−36 ± 56 (−56, −16)	−24 ± 79 (−77, 28)
OV 9	15 ± 39 (3, 26)	−2 ± 42 (−13, 9)	−19 ± 45 (−36, −3)	−9 ± 62 (−51, 33)
OV 10	26 ± 38 (15, 36)	11 ± 43 (0, 23)	−8 ± 45 (−25, 8)	4 ± 62 (−37, 46)
OV 11	40 ± 38 (29, 51)	27 ± 43 (15, 38)	6 ± 39 (−8, 21)	19 ± 61 (−22, 60)
OV 12	53 ± 43 (41, 65)	43 ± 48 (31, 56)	21 ± 39 (7, 35)	37 ± 56 (−1, 74)
OV 13	67 ± 47 (54, 80)	58 ± 48 (45, 71)	39 ± 51 (21, 58)	48 ± 60 (8, 88)
OV 14	85 ± 49 (71, 99)	75 ± 49 (62, 87)	55 ± 53 (36, 75)	81 ± 59 (42, 121)
OV 15	107 ± 51 (92, 121)	105 ± 53 (91, 119)	83 ± 76 (55, 111)	94 ± 58 (54, 133)
OV 16	150 ± 63 (132, 168)	163 ± 70 (145, 182)	127 ± 83 (96, 157)	144 ± 69 (98, 191)

CL = contralateral; KLG = Kellgren Lawrence grade; SD = standard deviation; CI = confidence interval; CD = Cohens D; MFTC = medial femorotibial compartment; LFTC = lateral femorotibial compartment; cMFTC = central MFTC; cLFTC = central LFTC; MT = medial tibia, cMF = weightbearing medial femur, LT = lateral tibia, cLF = weightbearing lateral femur, OV = Ordered Value.

case knees with contralateral KLG2 without JSN only showed relatively small thinning scores. Region-specific analysis suggested greater rates of cartilage loss in case knees in the lateral rather than the medial femorotibial compartment.

A limitation of this study is that only a subset of 678 of the 849 potential reference knees from the OAI were studied; however, this group still exceeded the case group by a factor of >4 so that inclusion of all knees would have only slightly increased the statistical power. A further limitation is that the structural status of the knees studied was only available from radiography, but not from semiquantitative multi-tissue MRI assessment of structural pathology. The primary analysis failed to reach statistical significance, but KLG0 case knees with contralateral radiographic JSN displayed greater cartilage thinning than reference knees; of note is that this combination (KLG0 in one knee and JSN in the other) is relatively rare and certainly represents a recruitment challenge.

A strength of the study was the use of location-independent analysis of cartilage thickness change, which has been shown to be more sensitive to differences in rates of change between different risk strata than region-specific analysis and also was shown to be superior in other aspects in clinical studies[10]. The use of location-independent analysis proved particularly useful in this study, as it was not anticipated that differences between case and reference knees originated from the lateral rather than the medial femorotibial compartment, with the latter being far more often affected in OA knees[12] Yet, a cross sectional analysis suggested that knees with early knee OA displayed thinner cartilage only in the lateral tibia[13], and a longitudinal study in patients with anterior cruciate ligament injury[14] identified cartilage thinning to predominate in the posterior lateral tibia. Lateral femorotibial cartilage thinning may thus be a characteristic typical of early (preradiographic) knee OA. A distinct advantage of location-independent analyses is that no *a priori* knowledge is required on where in the joint increased rates of cartilage loss may occur, and that it takes into account cartilage loss wherever it occurs in an individual joint.

The current study suggests that cartilage thinning increases in radiographically normal knees as a function of the contralateral JSN grade. This extends previous findings in OA knees with definite radiographic change[5] and also concurs with previous observations that radiographically normal knees incur a greater likelihood of incident radiographic knee OA if the contralateral knee displays radiographic knee OA rather than being radiographically normal[3]. A potential clinical implication of these findings may be, that in patients with unilateral knee OA, the radiographically normal knee may be susceptible to increased rates of cartilage loss and requires clinical attention, potentially even treatment. Such clinical attention should not focus on one compartment only but include specifically also the lateral compartment, where greater rates of cartilage loss appear to occur during a potential “early stage” of knee OA in radiographically normal knees. Increased rates of cartilage loss were not observed if the contralateral knee only displayed KLG2 without JSN. These findings clearly suggest that the risk of structural progression is greater in radiographically normal knees when the contralateral knee displays radiographic JSN>0, whereas in the absence of contralateral JSN contralateral osteophytes do not appear to be associated with greater rate of cartilage loss in KLG0 knees.

In conclusion, this study shows that radiographically normal knees with contralateral JSN may be a model for testing DMOADs in clinical trials designed to prevent cartilage loss before the onset of radiographic change.

Author contributions

- Study conception and design: FE, FR, WW
- Acquisition of data: SM, LS, WW

- Analysis & interpretation of data: All authors
- Writing of first manuscript draft: FE and WW
- Critical manuscript revision and approval of final manuscript: All authors

WW had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

Dr Maschek and Dr Wirth are part time employees and co-owners of Chondrometrics GmbH. Dr Roemer is a part time employee of Chondrometrics, and is shareholder, CMO and Director of Research of Boston Imaging Core Lab (BICL), LLC. Dr Duda and Dr Sharma have no conflicts to declare. Dr Eckstein is CEO/CMO and co-owner of Chondrometrics GmbH, and he has provided consulting services to Merck KGaA, Samumed, Tissuegene, Servier, Galapagos and Roche. He also has received speaker honoraria from Medtronic.

Role of the study sponsor

The statistical analysis and writing of this article was independent from and not contingent upon approval from the study sponsors.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.joca.2018.10.006.

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