Osteoarthritis and Cartilage 22 (2014) 2059–2066

Osteoarthritis and Cartilage

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

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ARTICLE INFO

Article history:
Received 30 January 2014
Accepted 11 September 2014

Keywords:
Longitudinal change
Magnetic resonance imaging
Knee osteoarthritis
Cartilage thickness
Contra-lateral radiographic knee status

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

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http://dx.doi.org/10.1016/j.joca.2014.09.020
1063-4584/

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)