Osteoarthritis and Cartilage 23 (2015) 203–209

Osteoarthritis and Cartilage

A family history of knee joint replacement increases the progression of knee radiographic osteoarthritis and medial tibial cartilage volume loss over 10 years

H.I. Khan † *, D. Aitken †, L. Chou †, A. McBride †, C. Ding †, L. Blizzard †, J.-P. Pelletier §, J.M. Pelletier §, F. Cicuttini ‡, G. Jones †

† *Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia*
‡ *Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia*
§ *Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), Notre-Dame Hospital, Montreal, QC, Canada*

ARTICLE INFO

Article history:
Received 11 June 2014
Accepted 14 November 2014

Keywords:
Knee osteoarthritis
Magnetic resonance imaging
Radiographs
Epidemiology
Genetics

SUMMARY

Objectives: Osteoarthritis (OA) has a genetic component but it is uncertain if the offspring of those with knee OA are at a greater risk. The aim of this study was to describe radiographic OA (ROA) progression and cartilage loss over 10 years in a midlife cohort with some having a family history of OA and some community based controls.

Methods: 220 participants [mean-age 45 (26–61); 57% female] were studied at baseline and 10 years. Half were adult offspring of subjects who underwent knee replacement for OA and the remainder were randomly selected controls. Joint space narrowing (JSN) and osteophytes were assessed on radiographs and cartilage volume (tibial, femoral and patellar), cartilage defects, bone marrow lesions (BMLs) and meniscal tears were assessed on Magnetic resonance imaging (MRI).

Results: For ROA, there was a significant difference between offspring and controls in unadjusted analysis for change in total ROA, medial JSN, total medial, total lateral and total osteophyte scores. This difference persisted for medial JSN (difference in ratios = **+1.93 (+1.04, +3.51)**) only, after adjustment for confounders and baseline differences. In unadjusted analysis for cartilage loss, offspring lost more cartilage at the medial tibial (difference in means = −79.13 (−161.92, +3.71)) site only. This difference became of borderline significance after adjustment for baseline differences ($P = 0.055$).

Conclusion: The offspring of subjects having a total knee replacement have a greater worsening of ROA (both JSN and osteophytes) and higher medial tibial cartilage volume loss over 10 years. Most of these changes are mediated by differences in baseline characteristics of offspring and controls except for increase in medial JSN.

Introduction

Osteoarthritis (OA) is a slowly developing chronic disease that has a multifactorial origin with the knee being the most commonly affected joint[1]. The pathogenesis of OA is not fully understood but some of the factors which contribute towards the development of OA include genetics, obesity, joint injury and occupational factors[2]. There is strong evidence that genetic factors play an important role in radiographic OA (ROA) of the hands and the spine[2,3]. A cross-sectional study[4] using the present cohort showed a significant genetic contribution to the severity but not prevalence of knee ROA but the evidence is inconsistent for knee ROA[2–6]. This may reflect the difficulty to target specific genes. A recent meta-analysis of nine genome-wide association studies including 5636 knee OA patients and 16,972 controls, found that only 2 out of 199 published candidate OA genes had any significant association with OA[7]. The inconsistency may be due to different study designs[7], inherent

* Address correspondence and reprint requests to: H.I. Khan, Menzies Research Institute, Medical Science 1 Building, Private Bag 23, 17-Liverpool Street, Hobart, Tasmania, 7000, Australia. Tel: 61-452529766.

E-mail addresses: Hussain.Khan@utas.edu.au (H.I. Khan), Dawn.Aitken@utas.edu.au (D. Aitken), louisa.chou@hotmail.com (L. Chou), amcb25@yahoo.com.au (A. McBride), ChangHai.Ding@utas.edu.au (C. Ding), Leigh.Blizzard@utas.edu.au (L. Blizzard), dr@jppelletier.ca (J.-P. Pelletier), jm@martelpelletier.ca (J.M. Pelletier), Flavia.Cicuttini@monash.edu (F. Cicuttini), Graeme.Jones@utas.edu.au (G. Jones).

http://dx.doi.org/10.1016/j.joca.2014.11.016
1063-4584/

measurement error associated with diagnosis of ROA, short follow-up periods and varying levels of genetic susceptibility of different phenotypic components of knee OA[8,9].

Magnetic resonance imaging (MRI) is being increasingly used to study OA as it allows visualisation of the whole joint[10]. It is possible that different structures comprising the knee joint are under separate genetic influences. Twin studies have already shown high heritability estimates for cartilage volume in all compartments of the knee joint[11]. Previous work using the present cohort has also shown high heritability estimates for tibial and patellar cartilage volume[4] and a significant genetic contribution to medial tibial cartilage loss over 2 years[12]. Along with cartilage volume loss, change in cartilage defects, tibial bone area and quadriceps muscle strength were all shown to be under genetic influence[12]. All these structural changes are thought to contribute towards the progression of the disease, but a limitation in the design of these studies[4,12] was the lack of radiographs at 2 years as it was not expected to see any major changes on radiographs in this time frame in a middle-aged population.

The aim of this population-based longitudinal study was therefore to describe the 10 year change in knee ROA and cartilage volume loss between offspring having at least one parent with a total knee replacement for severe primary knee OA, and age- and sex-matched controls with no family history of knee OA.

Methods

Study subjects

This study was conducted as part of the Offspring study, which is an ongoing population-based study. The Offspring study began in southern Tasmania (primarily in the city of Hobart) in June 2000. Half of the participants were the adult offspring of patients who had a knee replacement performed for idiopathic knee OA at any Hobart hospital from 1996 to 2000[13]. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiographs when possible. The other half were age and sex-matched controls, randomly selected from the population with no history of knee OA in either parent. This study includes data from the baseline visit, 2 year and 10 year follow up.

The Southern Tasmanian Health and Medical Human Research Ethics Committee approved the protocol, and written informed consent was obtained from all participants. Participants were excluded if they had a contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye, or claustrophobia). Participants were also excluded if they had undergone a knee replacement surgery or did so after the commencement of the study. Knee pain and knee injury were not a basis for exclusion.

Anthropometrics

Weight was measured to the nearest 0.1 kg (with the subject's shoes, socks, and bulky clothing removed), with a single pair of electronic scales (Delta Model 707; Seca, Munich, Germany) that were calibrated using a known weight at the beginning of each clinic session. Height was measured to the nearest 0.1 cm (with shoes and socks removed) using a stadiometer. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Knee pain

Knee pain was assessed using an interviewer administered questionnaire as described previously[13]. All the participants were asked the following question:

Have you had knee pain for more than 24 h in the last 12 months or daily pain on greater than 30 days in the last year?

Leg strength

Muscle strength was measured by dynamometry at the lower limb (involving both legs simultaneously). This primarily involves the hip flexors and knee extensors. The participants were instructed in each technique prior to testing, and each measure was performed twice. The repeatability estimate (Cronbach's alpha) was 0.91[4]. The device was calibrated by suspending known weights at regular intervals.

MRI

MRI of the right knee was performed as described previously[14–16]. Knees were imaged in the sagittal plane on a 1.5-T whole-body magnetic resonance unit (Picker International, USA) using a commercial transmit-receive extremity coil at the baseline visit, 2 year and 10 year follow up. The following image sequence was used: (1) a T1-weighted fat-suppressed 3D gradient-recalled acquisition in the steady state, flip angle 55°, repetition time 58 ms, echo time 12 ms, field of view 16 cm, 60 partitions, 512 × 512−pixel matrix, slice thickness of 1.5 mm without an interslice-gap (at all three visits); and (2) a T2-weighted fat saturation 2D fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 256 × 256 matrix, slice thickness of 4 mm with an interslice-gap of 0.5–1.0 mm (at visit 2 and 3).

The same scanner (same model and machine) was used at all the three visits for both T1-weighted fat-suppressed and T2-weighted fat saturation images.

Cartilage volume

Knee cartilage volume was evaluated at baseline and 10 years by a trained observer on T1-weighted gradient echo MR images. Knee cartilage volume was determined by means of image processing on an independent workstation at baseline and follow up. The volumes of individual cartilage plates (medial tibia and femora, and lateral tibia and femora) were isolated from the total volume by manually drawing dis-articulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 × 312 μm by 1.5 mm thickness, continuous sections) for the final three-dimensional rendering to calculate the cartilage volume.

Tibial cartilage volume was assessed using Osiris (University of Geneva, Switzerland) software as previously described[14,17]. The coefficient of variation (CV) ranged from 2.1 to 2.2% for intra-observer repeatability[18]. Femoral cartilage volume was determined using Cartiscope (ArthroLab, Montreal, Canada), as previously described[19–21]. The CV was approximately 2% for intra-observer and inter-scan repeatability[20]. Total cartilage volume was calculated as: tibial + femoral cartilage volume.

Change in cartilage volume was calculated as: follow-up total cartilage volume − baseline total cartilage volume.

Readers were not blinded to the chronological sequence of the scans to reduce measurement error.

Cartilage defects

Cartilage defects were assessed on T1-weighted gradient echo MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites on a 0–4 scale, as previously described[22]: grade 0 = normal cartilage; grade 1 = focal blistering and intra-cartilaginous low-signal intensity area with an intact surface and base; grade 2 = irregularities on the surface or base and loss of

thickness <50%; grade 3 = deep ulceration with loss of thickness >50%; and grade 4 = full-thickness chondral wear with exposure of sub-chondral bone. Intra-observer reliability (expressed as intra-class correlation coefficient (ICC)) ranged from 0.89 to 0.90. Inter-observer reliability was assessed in 50 MR images and yielded an ICC of 0.85–0.90[22].

Bone area

The following measures of bone size were determined: total patella bone volume, and medial and lateral tibial plateau areas as described previously[14]. Contours were drawn around the patella in images 1.5 mm apart on sagittal views. Total volume was calculated for the patella due to its irregular shape, which made it difficult to identify a simpler, representative measure of patella size. Medial and lateral tibial plateau area was determined by creating an isotropic volume from the three input images closest to the joint after reformatting in the axial plane. The areas of the medial and lateral tibial plateaus were then directly measured from these images. The CV was 2.2% for the patella, 2.3% for the medial tibial plateau, and 2.4% for the lateral tibial plateau[14].

Meniscal tears

Meniscal tears were assessed by a trained observer on T1-weighted gradient echo and T2-weighted (side by side) MR images at visit-2 and 3 of the study as previously described[19]. The proportion of the menisci affected by a tear was scored separately (0–2 scale; 0 = absence of a tear, 1 = simple tear of different types: longitudinal, oblique, radial or horizontal, 2 = complex tear signifying loss>50% area of meniscal tissue) at the anterior, middle, and posterior horns. Anterior, middle and posterior scores were summed to create medial and lateral meniscal tear scores. The intra- and inter-observer correlation coefficient ranged from 0.86 to 0.96[20]. Meniscal tears were measured at visits 2 and 3 of the Offspring study, 2 and 10 years after the baseline visit.

Bone marrow lesions (BMLs)

BMLs were assessed on fat suppressed T2-weighted MR images as described previously[23]. BMLs were defined as areas of increased signal intensity in the sub-chondral bone at the medial tibial, medial femoral, lateral tibial, lateral femoral, superior patellar and inferior patellar sites. One trained observer scored the BMLs by measuring the maximum area of the lesion in a specific compartment. The observer manually selected the MRI slice with the greatest BML size. The BML with the highest score was used if more than one lesion was present at the same site. The ICC was 0.97. BMLs were measured at phase 2 of the Offspring study, 2 years after the baseline visit.

Radiology

A standing anteroposterior semiflexed X-ray of the right knee was taken in all subjects at baseline and 10 years. The angle was kept to 10–15° by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90°. Daily quality assurance was performed on the equipment. Radiographs were scored individually for osteophytes and joint space narrowing (JSN), as described previously[18]. Each of the following four features was scored on a scale from 0 to 3 (0 = normal and 3 = severe): medial JSN, lateral JSN, medial osteophytes (femoral and tibial combined) and lateral osteophytes (femoral and tibial combined). Each score was arrived at by consensus with two readers (LC, AM) simultaneously assessing the radiograph with immediate reference to the Osteoarthritis Research Society International (OARSI) atlas[24]. A non-zero score in either JSN or osteophytosis was regarded as evidence of ROA. Reproducibility was assessed in 50 radiographs, 2 weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN.

Change in ROA was calculated as: follow-up ROA score − baseline ROA score.

Readers were not blinded to the chronological sequence of the scans to reduce measurement error.

Statistical analysis

This study was no longer paired as matching is no longer possible due to loss to follow up.

T-tests were used to describe the differences in baseline characteristics and ROA/cartilage volume loss over 10 years between offspring and controls. Negative binomial and linear regression were used to describe radiographic changes (expressed as difference in ratios (dr)) and cartilage loss (expressed as difference in means (dm)) respectively. Multivariable analyses were first adjusted for age, sex and the corresponding baseline measures (i.e., baseline cartilage volume for cartilage loss). We then adjusted for the five baseline measures which were significantly different between offspring and controls in the original whole sample using conditional logistic regression (BMI, knee pain, cartilage defects, bone size and leg strength)[13,25] in order to examine potential mediators. Further analysis was done to explore any sex interaction within offspring and control groups for ROA changes and cartilage volume loss in the multivariable models.

A *P*-value less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed on Intercooled Stata V.12.0 for windows (StataCorp LP).

Results

Of the 371 participants included in the Offspring study, 220 between the ages of 26 and 61 years were followed-up for 10 years. None of the participants who were lost to follow-up underwent a knee replacement surgery. Table I describes the baseline

Table I
Baseline characteristics of the participants who were followed-up and who were lost to follow up. Bold denotes statistically significant results

Characteristic	Follow-up ($n = 220$)	Loss follow-up ($n = 151$)	*P*-value
Age (years)	45.3 ± 6.7	45.1 ± 7.2	0.806
Female (%)	58	59	0.749*
BMI (kg/m^2)	27.2 ± 4.9	26.8 ± 4.3	0.499
Offspring (%)	52	47	0.891*
Radiographic OA (%)	18	15	0.486*
Knee pain present (%)	33	34	0.917*
Medial tibial cartilage volume (mm^3)	2234.1 ± 547.3	2230.8 ± 585.3	0.956
Lateral tibial cartilage volume (mm^3)	2620.9 ± 671.3	2579.3 ± 680.9	0.561
Medial femoral cartilage volume (mm^3)	4594.8 ± 1295.2	4541.4 ± 1145.1	0.734
Lateral femoral cartilage volume (mm^3)	4753.6 ± 1268.3	4719.6 ± 1252.0	0.836
Patellar cartilage volume (mm^3)	3480.2 ± 976.3	3430.3 ± 975.1	0.629
Medial tibial cartilage defects	1.2 ± 0.4	1.2 ± 0.4	0.697
Lateral tibial cartilage defects	1.2 ± 0.4	1.2 ± 0.4	0.948
Medial femoral cartilage defects	0.9 ± 0.5	1.0 ± 0.5	0.443
Lateral femoral cartilage defects	0.9 ± 0.5	0.9 ± 0.5	0.526
Patellar cartilage defects	1.2 ± 0.9	1.2 ± 1.1	0.987
Medial tibial bone area (cm^2)	17.6 ± 2.8	17.1 ± 2.6	0.092
Lateral tibial bone area (cm^2)	**12.2 ± 2.1**	**11.7 ± 1.9**	**0.027**
Patellar bone volume (cm^3)	13.9 ± 3.3	13.5 ± 3.3	0.279

Mean ± standard deviation except for percentages.
* Determined by Chi square test, others by *t*-test.

characteristics of participants who were followed-up (220) compared to participants who were lost to follow up (151). There were no significant differences between the two groups except for a higher lateral tibial bone area in the participants who were followed up.

Table II describes baseline characteristics of the offspring ($n = 115$) and controls ($n = 105$). The mean age of both offspring and controls at baseline was approximately 45 years and both groups had a higher proportion of female participants. Prevalence of ROA at baseline was low in both groups without any significant differences between the two groups. Offspring had a slightly but significantly higher BMI, higher lateral femoral cartilage volume, knee pain prevalence and total cartilage defects score compared to controls.

Comparison between offspring and controls (Table III) for radiographic score changes revealed that offspring had a significantly greater increase in medial JSN, total medial osteophytes, total lateral osteophytes, total osteophytes and total ROA scores. There was no significant difference in lateral and total JSN scores. For cartilage volume loss (Table III), offspring had a significantly greater loss at the medial tibial site only. There was no significant difference in cartilage volume loss at lateral tibial, medial femoral, lateral femoral and patellar sites.

Multivariable comparison (Table IV) between offspring and controls for radiographic score changes revealed that after adjustment for age, sex and the corresponding baseline measures, offspring had a greater increase in medial JSN, total medial osteophytes, total lateral osteophytes, total osteophytes and total ROA scores. However after further adjustment for the baseline factors, which were significantly different between offspring and controls, the difference in ratios remained significantly greater only for medial JSN score. Further adjustment for medial meniscal tears (measured at 2 year) had no effect; however adjustment for medial (tibial + femoral) BMLs (measured at 2 years) changed the effect size by more than 10% [dr = +1.63 (+0.84, +3.03)]. For absolute cartilage volume loss (Table IV), difference in means at the medial tibial site became non-significant ($P = 0.054$) after adjusting for age, sex and corresponding baseline measure and remained so after further adjustment for differences in baseline factors ($P = 0.055$).

There were no significant differences between the two groups for percentage per annum cartilage loss at any site. Medial tibial region showed a higher percentage per annum loss in the offspring group without reaching statistical significance in either the unadjusted [dm = −0.31 (−0.72, +0.03; $P = 0.078$)] or the fully adjusted model [dm = −0.30 (−0.71, +0.01; $P = 0.055$)].

Table II
Baseline characteristics of the study participants. Bold denotes statistically significant results

	Offspring ($N = 115$)	Controls ($N = 105$)	*P*-Value
Age (years)	44.8 ± 6.8	45.8 ± 6.5	0.261
Female (%)	55%	60%	0.436
BMI (kg/m^2)*	**27.9 ± 5.3**	**26.3 ± 4.5**	**0.018**
Any ROA (%)	18%	17%	0.894
Any medial JSN (%)	14%	14%	0.937
Any lateral JSN (%)	3%	4%	0.907
Any tibial osteophytes (%)	15%	8%	0.199
Any femoral osteophytes (%)	14%	4%	0.052
Medial tibial cartilage volume (mm^3)	2271 ± 46	2194 ± 59	0.295
Lateral tibial cartilage volume (mm^3)	2692 ± 670	2544 ± 668	0.104
Medial femoral cartilage volume (mm^3)	4679 ± 1174	4354 ± 1181	0.055
Lateral femoral cartilage volume (mm^3)	**4859 ± 1254**	**4437 ± 1305**	**0.022**
Patellar cartilage volume (mm^3)	3534 ± 949	3421 ± 1006	0.393
Knee pain prevalence (%)*	**45%**	**20%**	**<0.001**
Total tibial bone area (mm^2)*	3017 ± 428	2934 ± 498	0.191
Patellar bone volume (mm^3)	13,970 ± 3196	13,770 ± 3440	0.651
Mean total cartilage defects score*	**4.4 ± 1.3**	**4.0 ± 1.2**	**0.039**
Mean leg strength (kg)*	128 ± 4.5	126 ± 4.4	0.718
Any bone marrow lesion†,§	68%	60%	0.249
Any meniscal tear‡,§	20%	23%	0.367

Where errors are shown, results are means ± SD.
Mean total cartilage defects score (mean of sums of medial tibial, medial femoral, lateral tibial and lateral femoral cartilage defects).
* Significantly different between offspring and controls in the whole baseline study population (using conditional logistic regression).
† Any bone marrow lesion = tibial, femoral and/or patella.
‡ Any meniscal tear = medial and/or lateral.
§ Measured at phase 2 (2 years after the baseline visit).

Table III
Comparison of radiographic changes and cartilage loss (absolute) between offspring and controls. Bold denotes statistically significant results

Outcome factor	Offspring ($N = 115$)	Controls ($N = 105$)	
Radiographic score changes	Mean score ± SD	Mean score ± SD	*P*-Value
Increase in medial JSN	**0.32 ± 0.56**	**0.17 ± 0.39**	**0.019**
Increase in lateral JSN	0.07 ± 0.35	0.09 ± 0.32	0.774
Increase in total JSN	0.39 ± 0.70	0.25 ± 0.52	0.113
Increase in total medial osteophytes	**0.35 ± 0.78**	**0.15 ± 0.41**	**0.025**
Increase in total lateral osteophytes	**0.42 ± 0.92**	**0.18 ± 0.46**	**0.018**
Increase in total osteophytes	**0.77 ± 1.44**	**0.34 ± 0.71**	**0.007**
Increase in total ROA score	**1.15 ± 1.90**	**0.59 ± 0.87**	**0.007**
Cartilage loss (absolute)	Mean loss (mm^3) ± SD	Mean loss (mm^3) ± SD	*P*-Value
Medial tibial	**−610 ± 327**	**−518 ± 347**	**0.047**
Lateral tibial	−300 ± 370	−297 ± 412	0.953
Medial femoral	−698 ± 331	−697 ± 380	0.981
Lateral femoral	−701 ± 337	−689 ± 391	0.821
Patellar	−778 ± 633	−777 ± 643	0.992

Total = tibial + femoral.

Discussion

This is the first study to confirm that offspring of those with a knee replacement for OA have a higher risk of worsening knee OA over 10 years. Despite no difference in ROA (which had a low prevalence) at baseline between the offspring and controls, offspring experienced greater increases in medial JSN and osteophytes at all sites. Offspring also had higher absolute cartilage volume loss. The increases in osteophytes and cartilage volume loss were largely mediated by differences between the offspring and controls at baseline (BMI, knee pain, cartilage defects, bone size and leg strength) as the estimates were reduced by 18–30% for osteophytes and 14% for absolute cartilage volume loss. Increase in medial JSN was independent of these baseline differences and accounted for only 5% reduction in estimates.

Several studies have described the role of genetics in prevalent disease using radiographs[2,26] but very few have examined the influence of genetic factors on disease over time and none have done so in a younger population. Results from this study not only suggest that offspring with a family history of knee OA are at a higher risk of worsening knee OA over 10 years but also highlight the structural

Table IV
Multivariable analyses of differences between offspring and controls in changes in radiographic changes and cartilage loss (absolute). Bold denotes statistically significant results

Outcome factor	Unadjusted	Adjusted*	Adjusted†
Radiographic changes	Difference in ratios and 95% confidence interval		
Increase in medial JSN	**+2.03 (+1.11, +3.51)**	**+2.04 (+1.12, +3.52)**	**+1.93 (+1.04, +3.51)**
Increase in lateral JSN	+0.82 (+0.31, +2.83)	+0.82 (+0.31,+2.83)	+0.53 (+0.21, +1.80)
Increase in total JSN	+1.50 (+0.91, +2.60)	+1.51 (+0.93, +2.53)	+1.44 (+0.82, +2.32)
Increase in total medial osteophytes	**+2.34 (+1.11, +4.53)**	**+2.32 (+1.11, +4.57)**	+1.84 (+0.93, +3.80)
Increase in total lateral osteophytes	**+2.32 (+1.22, +4.63)**	**+2.51 (+1.27, +5.11)**	+1.91 (+0.92, +3.93)
Increase in total osteophytes	**+2.30 (+1.30, +4.03)**	**+2.36 (+1.33, +4.24)**	+1.63 (+0.94, +2.92)
Increase in total ROA score	**+1.90 (+1.31, +3.04)**	**+1.81 (+1.21, +2.79)**	+1.52 (+0.93, +2.23)
Cartilage loss (absolute)	Difference in means (mm^3) and 95% confidence interval		
Medial tibial	**−91.52 (−181.61, +1.31)**	−78.81 (−158.91, +1.23)	−79.13 (−161.92, +3.71)
Lateral tibial	−3.00 (−107.90, +101.78)	+10.62 (−90.59, +112.02)	+35.41 (−69.33, +140.12)
Medial femoral	−1.23 (−101.39, +98.72)	+30.87 (−56.11, +117.91)	+18.59 (−72.24, +109.41)
Lateral femoral	−11.80 (−114.42, +90.80)	+30.72 (−60.42, +121.72)	+45.81 (−45.43, +136.91)
Patellar	−0.90 (−171.57, +169.82)	+15.93 (−132.63, +164.54)	+80.20 (−67.33, +227.69)

Total = tibial + femoral.
* Adjusted for age, sex and corresponding baseline measure.
† Adjusted for* + baseline differences between offspring and controls (BMI, knee pain, cartilage defects score, tibial bone area and leg strength).

and non-structural factors that mediate these changes. The data shows that OA is not very common at age 45 in those with a predisposition to OA but becomes more prevalent over a 10-year time frame compared to a control population. This suggests that the genes responsible may express themselves later in life, possibly through interaction with environmental factors such as BMI and muscle strength, as pointed out by reduction in estimates after adjustment for baseline differences. Another possibility is that the mechanisms counteracting the expression of these genes are more effective at a younger age.

The data from this study also suggests that progression of both JSN and osteophytes are under genetic influence. Previously only Zhai *et al.*[27] have shown high heritability estimates for disease progression in the medial compartment of the knee over 7 years using a twin study design. Our results are consistent with Zhai *et al.* for the progression of JSN only, as they did not find any significant heritability estimates for osteophytes. These results point to some interesting aspects of the role genes play in the progression of OA. Firstly our data suggests that both JSN and osteophytes are under genetic influences as suggested by higher progression of JSN in offspring in the medial compartment and osteophytes at all sites. Previously, Uitterlinden *et al.*[28], have shown that two separate genes control the expression of JSN and osteophytosis in a population-based sample of healthy older adults. Interestingly, progression of osteophytes was mediated by baseline differences between the two groups, whereas progression of medial JSN was independent of these differences. This suggests that the gene responsible for progression of osteophytes possibly interacts with environmental factors such as BMI and muscle strength to express its effect. The twin study design is often criticized due to the assumption of similar shared environment between monozygotic and dizygotic twins. Unlike twins, offspring and controls do not share the same environment, which would explain why consistently higher estimates for progression of osteophytes at all sites were observed.

Offspring also had a significantly higher absolute cartilage volume loss at medial tibial site compared to controls over 10 years. As mentioned previously, the gene coding for COL2A1 has been shown to be associated with JSN[28]. COL2A1 is a structural protein found in articular cartilage, which explains the similar trend shown by medial JSN and medial tibial cartilage loss. Also similar to JSN, we saw the association only in the medial compartment. The fact that we did not see any differences between the two groups for medial femoral cartilage volume loss, raises a few questions: (1) it is possible that cartilage volume loss at medial femoral and medial tibial sites are under separate genetic, structural or environment influences (2) cartilage volume loss at the medial femoral site contributes less to JSN or happens later in life (3) cartilage at these two sites varies in composition (4) other co pathologies such as meniscal tears or BMLs might be associated more strongly with tibial compared to femoral cartilage volume loss (5) we used different methodologies to measure cartilage volume at the two sites, which might have led to measurement error.

Previous work from the offspring study has shown the role of genetics for the development of meniscal tears and BMLs. Ding *et al.*[29] showed that offspring had a significantly higher prevalence for meniscal tears, whereas Zhai *et al.*[30] showed high heritability estimates for both the prevalence and severity of BMLs in offspring group sibling pairs. Interestingly adjusting for medial meniscal tears did not alter the effect size of difference in ratio for change at medial JSN site, but adjusting for BMLs changed the effect size by more than 10%. Moreover, neither explained a majority of the change. It should be noted that both of these structures were scored at the first follow up, 2 years after the baseline visit, as we only had the T1-weighted fat-suppressed MRI sequences at baseline.

Baseline differences mediating the higher risk of ROA progression and cartilage volume loss is biologically plausible. High BMI is a known risk factor for both ROA progression and cartilage volume loss[31]. Tibial bone area, reduced leg strength and cartilage defects are not only risk factors for ROA progression[32,33] but also had high heritability in sib-pair analysis from the present cohort[4]. Interpretation of higher prevalence of knee pain in the offspring is tricky as the assessment of knee pain is subjective and can be influenced by a variety of factors such as recall bias due to family history of OA. Nevertheless there is evidence pointing to genetic contribution to expression of pain in knee OA. We have previously shown high heritability of knee pain in a sib-pair study[4]. Furthermore, polymorphisms in COMT and TRPV1 genes have been identified which could alter the processing of nociceptive pain associated with OA[34]. A high prevalence of knee pain in the offspring suggests that genetic factors may also lead to knee pain. However, adjustment for knee pain did not change the results in the present study. Different baseline characteristics in the offspring (including higher prevalence of MRI assessed structural abnormalities) could also mean that onset of the disease process in the offspring occurs at a younger age.

One of the major strengths of our study is the long follow-up period. This study has the longest follow-up period for any OA study using MRI. Another strength of this study is the exploration of the structural and non-structural factors mediating ROA changes and cartilage volume loss. However, this study has potential limitations as well. Over the 10 years there was a loss to follow-up of around 40%. Such a high number, although not ideal, is expected in a long follow-up period. Although we did not see any major differences in the main study variables between participants who were followed-up and who were lost to follow-up but it can still be a potential source of bias in the results shown in this study. Loss to follow-up also meant that the initial paired design of the study was invalidated. Loss of pairing resulted in a slight gender and age imbalance between offspring and controls. Nonetheless, all our analyses were adjusted for age and sex and adjusting for these had little effect on the results. Moreover, while we could adjust for meniscal tears and BMLs scored at 2 years, we did not have them at baseline possibly leading to greater measurement error. Lastly, tibial and femoral cartilage volume were segmented using different methodology as was outlined in the manuscript. Separate readers performed the measurements, which resulted in differences in how the scans were processed. Although both methods are almost equally sensitive at picking up any change in cartilage volume[35], this difference can still be a source of potential bias.

Conclusion

The offspring of subjects having a total knee replacement have greater worsening of ROA (both JSN and osteophytes) and higher medial tibial cartilage volume loss over 10 years. Most of these changes are mediated by differences in baseline characteristics of offspring and controls except for increase in medial JSN.

Contributions

HIK was responsible for the analysis and interpretation of data, preparation of initial manuscript and revisions of the manuscript.

DA was responsible for data cleaning and management, data interpretation and drafting of the manuscript.

LC was responsible for data collection and drafting of the manuscript.

AM was responsible for data collection and drafting of the manuscript.

LB was responsible for data analysis and drafting of the manuscript.

JPP and JMP were responsible for the measurement of femoral cartilage volume and meniscal tears, and drafting of the manuscript.

CD, FC, and GJ were responsible for protocol development, data acquisition and drafting of the manuscript.

Funding

This work was supported by the National Health and Medical Research Council of Australia and Masonic Centenary Medical Research Foundation. The study sponsor had no role in the design of the study; the collection, analysis, and interpretation of the data; or the writing of the article and the decision to submit it for publication. The researchers work independently of their funder.

Competing interests

Jean-Pierre Pelletier and Johanne Martel Pelletier are shareholders in ArthroLab Inc; the other authors declare no completing interests.

Acknowledgements

We thank the subjects who made this study possible, Catrina Boon and Pip Boon for their role in collecting the data and André Pelletier and Josée Thériault for their expertise in MRI reading.

References

1. Issa SN, Sharma L. Epidemiology of osteoarthritis: an update. Curr Rheumatol Rep 2006;8:7–15.
2. Spector TD, Cicuttini F, Baker J, Loughlin J, Hart D. Genetic influences on osteoarthritis in women: a twin study. BMJ 1996;312:940–3.
3. Bijkerk C, Houwing-Duistermaat JJ, Valkenburg HA, Meulenbelt I, Hofman A, Breedveld FC, *et al*. Heritabilities of radiologic osteoarthritis in peripheral joints and of disc degeneration of the spine. Arthritis Rheum 1999;42:1729–35.
4. Zhai G, Stankovich J, Ding C, Scott F, Cicuttini F, Jones G. The genetic contribution to muscle strength, knee pain, cartilage volume, bone size, and radiographic osteoarthritis: a sibpair study. Arthritis Rheum 2004;50:805–10.
5. Chitnavis J, Sinsheimer JS, Clipsham K, Loughlin J, Sykes B, Burge PD, *et al*. Genetic influences in end-stage osteoarthritis. Sibling risks of hip and knee replacement for idiopathic osteoarthritis. J Bone Joint Surg Br 1997;79:660–4.
6. Hirsch R, Lethbridge-Cejku M, Hanson R, Scott Jr WW, Reichle R, Plato CC, *et al*. Familial aggregation of osteoarthritis: data from the Baltimore Longitudinal Study on Aging. Arthritis Rheum 1998;41:1227–32.
7. Rodriguez-Fontenla C, Calaza M, Evangelou E, Valdes AM, Arden N, Blanco FJ, *et al*. Assessment of osteoarthritis candidate genes in a meta-analysis of 9 genome-wide association studies. Arthritis Rheum 2013;66:940–9.
8. Hunter DJ, Demissie S, Cupples LA, Aliabadi P, Felson DT. A genome scan for joint-specific hand osteoarthritis susceptibility: the Framingham Study. Arthritis Rheum 2004;50:2489–96.
9. MacGregor AJ, Li Q, Spector TD, Williams FM. The genetic influence on radiographic osteoarthritis is site specific at the hand, hip and knee. Rheumatology (Oxford) 2009;48:277–80.
10. Hunter DJ. Advanced imaging in osteoarthritis. Bull NYU Hosp Jt Dis 2008;66:251–60.
11. Hunter DJ, Snieder H, March L, Sambrook PN. Genetic contribution to cartilage volume in women: a classical twin study. Rheumatology (Oxford) 2003;42:1495–500.
12. Zhai G, Ding C, Stankovich J, Cicuttini F, Jones G. The genetic contribution to longitudinal changes in knee structure and muscle strength: a sibpair study. Arthritis Rheum 2005;52:2830–4.
13. Jones G, Ding C, Scott F, Cicuttini F. Genetic mechanisms of knee osteoarthritis: a population based case-control study. Ann Rheum Dis 2004;63:1255–9.
14. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. Arthritis Rheum 2000;43:2543–9.
15. Ding C, Cicuttini F, Scott F, Boon C, Jones G. Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. Arthritis Rheum 2005;52:3918–27.
16. Ding C, Cicuttini F, Scott F, Cooley H, Boon C, Jones G. Natural history of knee cartilage defects and factors affecting change. Arch Intern Med 2006;166:651–8.
17. Ding C, Cicuttini F, Blizzard L, Jones G. Smoking interacts with family history with regard to change in knee cartilage volume

and cartilage defect development. Arthritis Rheum 2007;56:1521–8.
18. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthritis Cartilage 2004;12:169–74.
19. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, Labonté F, Beaudoin G, Bloch DA, *et al*. Meniscal tear and extrusion are strongly associated with progression of symptomatic knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005;64:556–63.
20. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Beaudoin G, Choquette D, Haraoui B, *et al*. Long term evaluation of disease progression through the quantitative magnetic resonance imaging of symptomatic knee osteoarthritis patients: correlation with clinical symptoms and radiographic changes. Arthritis Res Ther 2006;8:R21.
21. Raynauld JP, Kauffmann C, Beaudoin G, Berthiaume MJ, de Guise JA, Bloch DA, *et al*. Reliability of a quantification imaging system using magnetic resonance images to measure cartilage thickness and volume in human normal and osteoarthritic knees. Osteoarthritis Cartilage 2003;11:351–60.
22. Ding C, Garnero P, Cicuttini F, Scott F, Cooley H, Jones G. Knee cartilage defects: association with early radiographic osteoarthritis, decreased cartilage volume, increased joint surface area and type II collagen breakdown. Osteoarthritis Cartilage 2005;13:198–205.
23. Dore D, Quinn S, Ding C, Winzenberg T, Zhai G, Cicuttini F, *et al*. Natural history and clinical significance of MRI-detected bone marrow lesions at the knee: a prospective study in community dwelling older adults. Arthritis Res Ther 2010;12:R223.
24. Altman RD, Hochberg M, Murphy Jr WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;3(Suppl A):3–70.
25. Ding C, Cicuttini F, Scott F, Stankovich J, Cooley H, Jones G. The genetic contribution and relevance of knee cartilage defects: case-control and sib-pair studies. J Rheumatol 2005;32:1937–42.
26. Andrew T, Hart DJ, Snieder H, de Lange M, Spector TD, MacGregor AJ. Are twins and singletons comparable? A study of disease-related and lifestyle characteristics in adult women. Twin Res 2001;4:464–77.
27. Zhai G, Hart DJ, Kato BS, MacGregor A, Spector TD. Genetic influence on the progression of radiographic knee osteoarthritis: a longitudinal twin study. Osteoarthritis Cartilage 2007;15:222–5.
28. Uitterlinden AG, Burger H, van Duijn CM, Huang Q, Hofman A, Birkenhager JC, *et al*. Adjacent genes, for COL2A1 and the vitamin D receptor, are associated with separate features of radiographic osteoarthritis of the knee. Arthritis Rheum 2000;43:1456–64.
29. Ding C, Martel-Pelletier J, Pelletier JP, Abram F, Raynauld JP, Cicuttini F, *et al*. Meniscal tear as an osteoarthritis risk factor in a largely non-osteoarthritic cohort: a cross-sectional study. J Rheumatol 2007;34:776–84.
30. Zhai G, Stankovich J, Cicuttini F, Ding C, Jones G. Familial, structural, and environmental correlates of MRI-defined bone marrow lesions: a sibpair study. Arthritis Res Ther 2006;8:R137.
31. Sandmark H, Hogstedt C, Lewold S, Vingard E. Osteoarthrosis of the knee in men and women in association with overweight, smoking, and hormone therapy. Ann Rheum Dis 1999;58:151–5.
32. Ding C, Cicuttini F, Jones G. Tibial subchondral bone size and knee cartilage defects: relevance to knee osteoarthritis. Osteoarthritis Cartilage 2007;15:479–86.
33. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, *et al*. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum 1998;41:1951–9.
34. Bratus A, Aeschlimann A, Russo G, Sprott H. Candidate gene approach in genetic epidemiological studies of osteoarthritis-related pain. Pain 2014;155:217–21.
35. Aitken D, Ding C, Pelletier JP, Martel-Pelletier J, Cicuttini F, Jones G. Responsiveness of magnetic resonance imaging-derived measures over 2.7 years. J Rheumatol 2014;41:2060–7.