Familial effects on structural changes relevant to knee osteoarthritis: a prospective cohort study

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S U M M A R Y
Objective: Genetic factors play an important role in the pathogenesis of knee osteoarthritis (OA), but which knee structural changes mediate this is unclear. This study aimed to describe the differences in knee structural changes over 8–10 years between offspring having at least one parent with total knee replacement (TKR) for severe primary knee OA and controls with no family history of knee OA.

Design: 115 offspring (mean age 45 years) with a family history of TKR for severe knee OA were compared with 104 (mean age 46 years) controls. T1 or T2-weighted fat saturated magnetic resonance imaging (MRI) was performed respectively to evaluate knee cartilage defects, bone marrow lesions (BMLs), meniscal extrusion and tears at baseline and 10 years. Multivariate logistic regression model was used to adjust for potential confounders.

Results: Offspring had a greater increase in cartilage defect score (1.03 vs 0.52, \(P = 0.007\)) and meniscal extrusion score (0.28 vs 0.10, \(P = 0.027\)) over 10 years, and a greater increase in meniscal tear score (0.40 vs 0.10, \(P = 0.012\)) over 8 years in the medial but not the lateral tibiofemoral compartment. Changes in BMLs over 8-years were not different between the two groups. These associations were independent of potential confounders, and strengthened after further adjustment for each other.

Conclusion: With the exception of BMLs, offspring with a family history of knee OA have a greater risk of increases in multiple knee structural abnormalities in the medial tibiofemoral compartment suggesting pleiotropic familial effects.

Introduction

Osteoarthritis (OA) is the most common form of skeletal disorder worldwide and one of the leading causes of pain and disability, resulting in a large social and economic burden. The knee joint is the major site of OA with a prevalence of 30% in those aged 65 and above.

It is well-established that knee OA is a multifactorial and highly heterogeneous disease as a result of a complex interaction between local biomechanical factors, such as obesity, mechanical stress and muscle weakness, and systemic factors, such as age, sex and genetics. Genetic factors have been extensively investigated in sibling studies, familial aggregation and twin pair studies, with heritability estimates of approximately 39–65% in OA. Genomic-wide association studies (GWAS) have identified multiple loci involved in the risk of knee OA, but there has been little independent replication; moreover, little is known about the contribution of genetic factors to progression of knee OA over time.

Previous studies have shown genetic contributions to knee structures and their changes, including bone size, cartilage volume, cartilage defects and muscle strength. There are limited
studies on bone marrow lesions (BMLs)\textsuperscript{14}, meniscal extrusion\textsuperscript{15} and meniscal tears\textsuperscript{16}. These studies have mainly been cross-sectional or short-term with no long-term studies. Therefore, the aim of this study was to describe whether offspring of people having at least one parent with total knee replacement (TKR) for severe knee OA had a higher rate of change in knee structures of relevance to OA in comparison with controls with no knee OA family history over 8–10 years.

Materials and methods

Participants

This study was carried out in southern Tasmania in the capital city of Hobart. The initial measurements were taken from June 2000 to December 2001, and follow-up evaluations were conducted 2 years and 10 years later. Participants were selected from the state Electoral Roll (2000), without a history of knee OA in either parent which was confirmed by history and medical records. Participants from either group were excluded on the basis of contraindication to Magnetic resonance imaging (MRI) (including metal sutures, presence of shrapnel, iron filing in eye, and claustrophobia). This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all participants provided informed written consent.

Anthropometrics

Weight was measured to the nearest 0.1 kg (with shoes, socks and bulky clothing removed) using a single pair of electronic scales (Seca Delta Model 707) calibrated using a known weight at the beginning of each clinic. Height was measured to the nearest 0.1 cm (with shoes and socks) using a stadiometer. Body mass index (BMI) (kg/m\textsuperscript{2}) was calculated.

Knee injury

Knee injury was assessed at baseline by asking ‘Have you had a previous knee injury requiring non-weight-bearing treatment for more than 24 h or surgery?’.

Radiographs

A standing anteroposterior semiflexed view of the right knee was performed in all participants and scored individually using the Altman atlas for osteophytes and joint space narrowing (JSN) on a scale of 0–3 as previously described\textsuperscript{18}. The presence of radiographic OA (ROA) was defined as any score $\geq$1 for JSN or osteophytes.

Knee MRI

An MRI scan of the right knee was performed with a 1.5 T whole-body magnetic resonance unit (Picker, Cleveland, OH, USA) using a commercial transmit-receive extremity coil. The following image sequences were used: (1) a T1-weighted fat suppression three-dimension 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 $\times$ 512–pixel matrix, slice thickness of 1.5 mm without an interslice gap; (2) a T2-weighted fat saturation two-dimensional fast spin echo, flip angle 90°, repetition time 3067 ms, echo time 112 ms, field of view 16 cm, 15 partitions, 228 $\times$ 256–pixel matrix, slice thickness of 4 mm with an inter-slice gap of 0.5–1.0 mm.

Cartilage defects

Cartilage defects at baseline and 10 years were assessed as previously described\textsuperscript{15} on T1-weighted MR images at the medial tibial, medial femoral, lateral tibial, and lateral femoral sites, as follows: grade 0 = normal cartilage; grade 1 = focal blistering and intracartilaginous 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 subchondral bone. The presence of any cartilage defect was defined as a score of $\geq$2 at any site. The average scores of cartilage defects at the medial tibiofemoral (0–8) and lateral tibiofemoral (0–8) compartments were used in the study. A cartilage defect score increase was defined as an increase of one or greater at any site.

Meniscal extrusion

The extent of meniscal extrusion on the medial or lateral edges of the tibial femoral joint space, not including the osteophytes, was evaluated at baseline and at 10 years for the anterior, body, and posterior horns of the menisci, as previously described\textsuperscript{15,22}. A score from 0 to 2 was used (0 = no extrusion, 1 = partial meniscal extrusion, and 2 = complete meniscal extrusion with no contact with the joint space). The presence of any meniscal extrusion was defined as any score $\geq$1. The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal extrusion score for each of the medial and lateral tibiofemoral compartments which had a possible range from 0 to 6. A meniscal extrusion score increase was defined as an increase of one or greater at any site.

Meniscal tears

At baseline there were only T1-weighted MRI scans which were not suitable for comparison of meniscal tears and BMLs over time. Meniscal tears were assessed at 2 years and 10 years for the anterior, body, and posterior horns of each of the medial and lateral menisci on 0–2 score (0 = no tear, 1 = simple tears of different types: longitudinal, oblique, radial or horizontal signifying loss $<$50% area of meniscal tissue, and 2 = macerated tear signifying loss $>$50% area of meniscal tissue), as previously described\textsuperscript{20,21}. The presence of any meniscal tear was defined as any score $\geq$1. The scores of anterior, body and posterior horns of medial or lateral menisci were summed to create a total meniscal tear score at the medial/lateral tibiofemoral compartment which had a possible range from 0 to 6. A meniscal tear score increase was defined as an increase of one or greater at any site.

BMLs

BMLs were assessed at 2 years and 10 years on T2-weighted MRI and defined as areas of increased signal adjacent to the subcortical bone at the medial tibial, medial femoral, lateral tibial and lateral femoral sites, as previously described\textsuperscript{22}. The readers for BMLs were trained by a radiologist including the differentiation of OA-related BML from similar signal such as contusion/necrosis/edema etc.\textsuperscript{22} and consulted the radiologist if there were any doubts. The maximum area (cm$^2$) of the lesion of different sites was measured, and the BML with the largest size was recorded if more than one lesion was present at the same site. The presence of any BML was defined as any score $>0$. The scores of BML at the medial tibiofemoral and lateral tibiofemoral compartments were the sum of the
corresponding sites. To adjust for measurement error, a least significant criterion (LSC) was used to define a significant change in BML size (based on previous studies). An increase in BML size was defined as any change greater than the LSC at any site.

**Data analysis**

T-tests and Chi-square tests were used to compare differences in means and percentage where appropriate. Logistic regression modelling was used to assess the potential relationships between the status of participants (offspring or controls) and four outcomes of knee structural change (increase in cartilage defect score, increase in meniscal extrusion score, increase in meniscal tear score, and increase in BML score), before and after adjustment for common confounders (Step 1: age, sex, BMI, ROA, baseline variable of the outcome of interest, history of knee injury and smoking). To exclude a potential effect of other knee structural changes, further adjustment for knee structural changes of relevance to each other (Step 2) in this cohort was also conducted. P values less than 0.05 (2-tailed) or 95% confidence intervals (CIs) not including the “1” point were regarded as statistically significant difference. All statistical analyses were performed using SPSS Statistics (version 20, Chicago IL). The Hochberg method was used to adjust for multiple testing on regression results.

**Results**

**Participants**

A total of 372 participants (186 offspring and 186 controls) aged from 26 to 61 years (mean age of 45 years) were enrolled at baseline. After 2 years (range 1.8–2.6 years), 326 participants (162 offspring and 164 controls) took part and 219 participants (115 offspring and 104 controls) were studied at 10 years (range 9.1–11.4 years). Comparison of the participants lost to follow-up with those included in the present study showed that the proportion of smokers in those lost to follow-up was higher (59% vs 42%) but no significant differences in other study factors including structural abnormalities was observed (data not shown).

Table I presents the characteristics of participants who completed 10 years of follow-up. There were no significant differences in terms of age, sex, height, history of knee injury and ROA at baseline between offspring and controls; however, offspring were heavier and had a higher proportion of smokers at baseline.

**Offspring-control status and knee structural changes**

**Cartilage defects**

In this sample, no significant differences were found between offspring and controls in the prevalence of knee cartilage defect as well as the mean tibiofemoral cartilage defect score at baseline (Table I). However, there was a significant difference in the change in cartilage defect score in the medial but not the lateral tibiofemoral compartment (Table II). In multivariable analysis after adjustment for common confounders, the odds ratio (OR) for medial tibiofemoral cartilage defect increase in the offspring group was 2.5-fold higher than in controls (Table III). This association persisted after further adjustment for other structural factors.

**Meniscal extrusion**

There were no differences in the meniscal extrusion score between the two groups at baseline (Table I), but offspring had a greater increase in average score in the medial but not lateral tibiofemoral compartment (Table II). In multivariable analysis, offspring had a 3.1-fold higher risk of meniscal extrusion score increase in the medial tibiofemoral compartment and this increase after adjustment for other structures (Table III). This analysis cannot be performed for lateral meniscal extrusion score increase due to the small numbers of cases.

**Meniscal tear**

At 2 years, meniscal tears did not differ between offspring and controls (Table I). Offspring had a greater increase in the score in the medial tibiofemoral compartment over 8 years (Table II). In multivariable analysis OR for offspring having a meniscal tear score increase as controls was 3.8-fold higher for the medial tibiofemoral compartment. Consistent results were observed after further adjustment for changes in other structures (Table III). Meaningful ORs cannot be obtained for the lateral tibiofemoral compartment as only two participants had increased scores.

**BML**

There were no differences between offspring and controls in terms of the prevalence of BML, BML score at the 2-year visit, and change in BML size in any compartment over 8 years.

### Table I

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Offspring</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>44.8 (6.8)</td>
<td>45.8 (6.5)</td>
<td>0.261</td>
</tr>
<tr>
<td>Female (%)</td>
<td>60</td>
<td>55</td>
<td>0.435</td>
</tr>
<tr>
<td>Height, cm</td>
<td>170.0 (8.5)</td>
<td>168.7 (8.9)</td>
<td>0.270</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>80.9 (17.2)</td>
<td>75.1 (14.6)</td>
<td>0.008</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>27.9 (5.3)</td>
<td>26.3 (4.5)</td>
<td>0.018</td>
</tr>
<tr>
<td>Previous knee injury (%)</td>
<td>15</td>
<td>23</td>
<td>0.116</td>
</tr>
<tr>
<td>Ever smoking (%)</td>
<td>50</td>
<td>33</td>
<td>0.008</td>
</tr>
<tr>
<td>ROA (%)</td>
<td>17</td>
<td>18</td>
<td>0.865</td>
</tr>
<tr>
<td>Total cartilage defect score</td>
<td>4.2 (1.2)</td>
<td>3.9 (1.3)</td>
<td>0.095</td>
</tr>
<tr>
<td>Any cartilage defect (%)</td>
<td>41</td>
<td>32</td>
<td>0.197</td>
</tr>
<tr>
<td>Any meniscal tear (%)</td>
<td>1.7</td>
<td>0.7</td>
<td>0.423</td>
</tr>
<tr>
<td>Change in meniscal tear score</td>
<td>0.0 (0.1)</td>
<td>0.0 (0.2)</td>
<td>0.313</td>
</tr>
<tr>
<td>Any meniscal tear (%)</td>
<td>0.5</td>
<td>0.3</td>
<td>0.119</td>
</tr>
<tr>
<td>Change in the knee structure over 8 years</td>
<td>0.0 (0.7)</td>
<td>0.2 (0.5)</td>
<td>0.529</td>
</tr>
</tbody>
</table>

Bold denotes statistically significant result.

1 Defined as score ≥ 1 in any compartment.
2 Defined as score ≥ 2 in any compartment.
3 Defined as score > 0 in any compartment.
4 Mean (SD) except for percentages; P values determined by t test or Pearson Chi-square test (where appropriate).

### Table II

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Offspring</th>
<th>Controls</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in cartilage defects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial compartment</td>
<td>1.0 (1.5)</td>
<td>0.5 (1.2)</td>
<td>0.007</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td>0.5 (1.1)</td>
<td>0.5 (1.0)</td>
<td>0.848</td>
</tr>
<tr>
<td>Change in meniscal extrusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial compartment</td>
<td>0.3 (0.8)</td>
<td>0.1 (0.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td>0.0 (0.0)</td>
<td>0.1 (0.4)</td>
<td>0.181</td>
</tr>
<tr>
<td>Change in meniscal tear</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial compartment</td>
<td>0.4 (1.0)</td>
<td>0.1 (0.5)</td>
<td>0.012</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td>0.1 (0.7)</td>
<td>0.1 (0.4)</td>
<td>0.778</td>
</tr>
<tr>
<td>Change in BML, cm²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial compartment</td>
<td>0.2 (0.7)</td>
<td>0.1 (0.5)</td>
<td>0.298</td>
</tr>
<tr>
<td>Lateral compartment</td>
<td>0.3 (0.7)</td>
<td>0.1 (0.4)</td>
<td>0.113</td>
</tr>
</tbody>
</table>

Bold denotes statistically significant result.

1 Change in mean score (SD).
2 Change in the knee structure over 10 years.
3 Change in the knee structure over 8 years.
After adjustment for multiple testing using the Hochberg method (Table III), the significant associations remained apart from the meniscal extrusion before adjustment for all other structural changes suggesting these results are not due to chance.

Discussion

To the best of our knowledge, this is the first longitudinal study with a long-term follow-up to examine the relationship between family history of knee OA and knee structural change. We found offspring who had at least one parent with TKR for severe knee OA had an increased risk of worsening of knee structural abnormalities including cartilage defects, meniscal extrusion and tears but not BMLs, suggesting familial factors may be involved in specific knee structural damage. These associations were specific for the medial but not the lateral tibiofemoral compartment, most likely reflecting a predisposition to medial knee OA in their parents. Furthermore, these findings may suggest a greater environmental effect on change in BMLs and change in lateral cartilage defect, and thus they could be modifiable.

Based on familial aggregation and twin studies, there is substantial evidence that genetic factors have an important role in the etiology of knee OA13,37. Most studies are cross-sectional or case—control studies. There are few studies describing the role of genetic factors in structural knee OA progression. Botha-Scheepers et al.14 reported siblings of proband having progression had 4.3-fold greater risk of radiologic progression of JSN in the knee over 2-year follow-up. Zhai et al.15 also found a strong genetic influence on the progression of ROA in a longitudinal twin study. To date, limited data are available on the roles of genetic factors in the pathogenesis of progression in knee structures prior to end-stage disease13,38. It is known that cartilage defects, BMLs and meniscal pathology play an important role in knee OA, being associated with the adverse structural outcomes2,25,32 and knee pain32. Previously, in a larger sample from this cohort, we reported that offspring with family history of knee OA had a higher prevalence of cartilage defects 14 as compared to controls but no differences in the prevalence of meniscal extrusion2,25 and tears15. However, in the subsample of participants with available longitudinal data, there was no statistical difference in cartilage defects at baseline most likely due to the smaller sample size. Nonetheless, despite the smaller sample size available for long-term follow-up, we showed that offspring had a greater increase in multiple structural abnormalities, independent of baseline structures. The only exception was no effect for BMLs but the ORs were around one, suggesting that this is not a power issue.

Offspring had an elevated risk for an increase in cartilage defects, meniscal extrusion and tears over 8–10 years in the medial tibiofemoral compartment after adjustment for age, sex, BMI, ROA, knee injury, smoking and other knee structural factors of relevance to each other, suggesting familial effects on progression in these structures and the influence of familial factors is compartment-specific. These results are comparable with an earlier familial study that reported a 3.2-fold increased risk of prevalence of ROA in siblings33, but appear to be greater than those reported by Neame et al.34. The difference in results may be explained by the difference in study population of the study by Neame et al. where siblings were compared with the subjects from knee pain studies. This could overestimate the prevalence of knee OA among this group, and therefore resulting in a lower risk of prevalence of knee OA in siblings than ours. Additionally, a previous study with 2-years follow-up in this population found that offspring had a greater increase in the medial tibial cartilage defects compared to controls, which underlie the progression of cartilage defects.

Although meniscal pathology may be the result of knee injury, knee malalignment and high BMI31, there are data supporting a genetic contribution to meniscal pathology16,35,36. Sun et al.35 reported significantly higher levels of gene expression responsible for biological processes in OA meniscal cells as compared to normal meniscal cells, which suggests that aberrant expression of genes may be involved in meniscal pathology. Furthermore, in a longitudinal study by Englund et al., people with bony enlargement of finger joints had an increased risk of the development of meniscal pathology, implying that meniscal pathology may be affected by genetic factors, given a strong genetic component of bony enlargement of finger joints35. A previous cross-sectional study from our group found that offspring with a family history of knee OA had a two-fold higher risk for the presence of lateral anterior and posterior meniscal tear as compared to controls, indicated genetic factors may be a risk factor for meniscal tears16. The present study supports independent familial effects on each knee structural change as the higher risk of progression in cartilage defects, meniscal extrusion and tears in offspring was observed after adjustment for known confounders and for each other. All of these factors have been considered part of the MRI diagnosis of knee OA32 and thus could be identified early in ‘at risk’ people.

The present study failed to detect any differences in the progression of BMLs in any compartment between offspring and controls, which contrasts with a previous sib pair study in this sample that showed a heritability estimate of 50% for prevalent BMLs34. Thus, it may be that familial factors are only responsible for the initial development of BMLs but not for progression.

Despite some strengths of this study, including its longitudinal design, long-term follow-up, and the use of MRI to evaluate knee structural changes, there are several potential limitations. Firstly, although some potential confounders have been adjusted in the current study, we cannot rule out the possibility that unidentified confounders or unmeasured factors influence the risk for change in knee structures independently of family history of knee OA. Furthermore, although knee alignment was not assessed in the current study, a previous study from this cohort demonstrated that this factor is not related to knee structural change, suggesting the absence of alignment assessment is not a limitation for this study. Secondly, because of the rarity of lateral meniscal tears and extrusion, we were unable to determine if familial factors have
effects on progression in lateral compartment. Thirdly, genetic factors may play different roles across different ethnic groups. The present study only recruited Caucasians, thus it is inappropriate to extrapolate to other ethnic groups. Lastly, the loss to follow-up may lead to bias; however, there were no significant differences between the participants included in this study and the rest of the cohort in many studied factors apart from only a slightly higher percentage of smokers in those lost to follow-up and adjusting for this factor did not influence results.

In conclusion, offspring with family history of knee OA have an increased risk of progression of multiple knee structures in the medial tibiofemoral compartment compared to controls suggesting pleiotropic familial effects.

Author contributions

FP participated in the design of the study, analysis and interpretation of the data and manuscript preparation. HK participated in acquisition of data and revising manuscript. CHD participated in acquisition of data and revising manuscript. FC participated in acquisition of data and revising manuscript. JPP participated in interpretation of the data and manuscript preparation. All authors read and approved the final manuscript.

Competing interest statement

The authors declare no conflict of interest.

References


