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

F. Pan † *, H. Khan †, C. Ding †, T. Winzenberg †, J. Martel-Pelletier ‡, J.-P. Pelletier ‡, F. Cicuttini §, G. Jones † **

† *Menzies Research Institute Tasmania, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia*
‡ *Osteoarthritis Research Unit, University of Montreal Hospital Research Centre (CRCHUM), 900 St. Denis Street, Pavillon R, Montreal, Quebec H2X 0A9, Canada*
§ *Department of Epidemiology and Preventive Medicine, Monash University Medical School, Commercial Road, Melbourne 3181, Australia*

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SUMMARY

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[1]. The knee joint is the major site of OA with a prevalence of 30% in those aged 65 and above[2].

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[3]. Genetic factors have been extensively investigated in sibling studies, familial aggregation and twin pair studies, with heritability estimates of approximately 39–65%[4–6]. Genome-wide association studies (GWAS) have identified multiple loci involved in the risk of knee OA, but there has been little independent replication[7,8]; moreover, little is known about the contribution of genetic factors to progression of knee OA over time[9].

Previous studies have shown genetic contributions to knee structures and their changes, including bone size, cartilage volume, cartilage defects and muscle strength[10–13]. There are limited

* Address correspondence and reprint requests to: F. Pan, Menzies Research Institute Tasmania, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia.
** Address correspondence and reprint requests to: G. Jones, Menzies Research Institute Tasmania, University of Tasmania, 17 Liverpool Street, Hobart, Tasmania 7000, Australia. Tel: 61-3 6226-7705; Fax: 61-3 6226-7704.
E-mail addresses: Feng.Pan@utas.edu.au (F. Pan), H.I.Khan@utas.edu.au (H. Khan), ChangHai.Ding@utas.edu.au (C. Ding), Tania.Winzenberg@utas.edu.au (T. Winzenberg), jm@martelpelletier.ca (J. Martel-Pelletier), dr@jppelletier.ca (J.-P. Pelletier), Flavia.Cicuttini@monash.edu (F. Cicuttini), Graeme.Jones@utas.edu.au (G. Jones).

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studies on bone marrow lesions (BMLs)[14], meniscal extrusion[15] and meniscal tears[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 two sources, as described previously[2,17]. Half of the participants were the adult children (offspring) of participants who had a TKR performed for primary knee OA at any Hobart hospital from 1996 to 2000. This diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiograph where possible. The other half were controls selected at random 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 removed) using a stadiometer. Body mass index (BMI) (kg/m^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[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 × 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 × 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[19] 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[15,20]. 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[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[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.*[23] 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

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