EXTENDED REPORT

Genetic mechanisms of knee osteoarthritis: a population based case-control study

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Objective: To compare subjects who had at least one parent with a total knee replacement for severe primary knee osteoarthritis with age and sex matched controls who had no family history of knee osteoarthritis

Design: Population based case-control study of 188 matched pairs (mean age 45 years, range 26 to 60).

Methods: Articular cartilage volume and bone size were determined at the patella and at the medial tibial and lateral tibial compartments by processing images acquired using T1 weighted, fat saturated magnetic resonance imaging. Radiographic osteoarthritis (ROA) was assessed from a standing semiflexed radiograph scored for joint space narrowing and osteophytosis. Knee pain was assessed by questionnaire. Height, weight, body mass index (BMI), lower limb muscle strength, and endurance fitness were measured by standard protocols.

Results: Compared with the controls, index offspring had higher BMI ($27.8 \text{ v } 26.0 \text{ kg/m}^2$, $p=0.02$), weaker lower limb muscles ($127 \text{ v } 135 \text{ kg}$, $p=0.006$), more knee pain ($47\% \text{ v } 22\%$, $p<0.001$), and greater medial tibial bone area ($17.6 \text{ v } 17.1 \text{ cm}^2$, $p=0.01$). With the exception of BMI, these differences persisted in multivariate analysis. There was a non-significant trend to higher cartilage volume at tibial sites and increased ROA in the offspring in the total and subgroup analyses, but no difference in height and endurance fitness.

Conclusions: BMI, muscle strength, knee pain, and medial tibial bone area, but not cartilage volume, appear to play a role in the genetic regulation and development of knee osteoarthritis.

Osteoarthritis is the most common form of arthritis and a leading cause of musculoskeletal disability in most developed countries.¹ The knee is one of the most frequently affected joints, with a prevalence of 30% in people older than 65 years² and high resultant disability.³ While its aetiology and pathogenesis remains relatively poorly understood, knee osteoarthritis has been strongly associated with several environmental factors including obesity,^{4–6} previous injury,⁷ and meniscectomy.⁸ In addition, a modest but significant genetic effect of radiographic osteoarthritis (ROA) of the knee has been reported in most studies.^{9–14} However, linkage studies in knee osteoarthritis have been disappointing.¹⁵ Candidate gene studies have also been inconclusive,¹⁵ and no information is available on the genetic mechanisms of knee osteoarthritis.

Recently, we reported ecological data suggesting that variations in knee cartilage volume development in children may explain sex and site differences in the occurrence of knee osteoarthritis in later life.¹⁶ Recent data from both twin and sibling pair studies have also suggested that knee cartilage volume is highly heritable.^{14, 17} This implies that cartilage development may be important in the pathogenesis of knee osteoarthritis in later life, similar to the known relation between peak bone mass and fracture risk.¹⁸ However, non-cartilage factors may also be involved. Recent studies have suggested that bone density is important in the development of knee osteoarthritis¹⁹ and is greater in the offspring of people with this condition,²⁰ while muscle strength may be a risk factor for incident knee osteoarthritis.²¹ Our aim in this population based case-control study was therefore to compare the offspring of subjects who had at least one parent with a total knee replacement for severe primary knee osteoarthritis with age and sex matched controls who had no family history of knee osteoarthritis.

METHODS

The study was carried out in Southern Tasmania (latitude 42° south), primarily in the capital city of Hobart, from June 2000 until December 2001. The study was approved by the Southern Tasmanian health and medical human research ethics committee, and all subjects provided informed written consent.

Index subjects were the adult children of individuals who had had a knee replacement for primary osteoarthritis at any Hobart hospital (both public and private) in the years 1996 to 2000. The diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and to the original radiographs where possible. Of the 188 offspring, the family structure was as follows: one offspring per family, $n=60$; two offspring per family, $n=34$; three offspring per family, $n=10$; four offspring per family, $n=6$; and six offspring per family, $n=1$.

The controls were randomly selected individuals who had no personal or family history of knee osteoarthritis. They were selected by computer generated random numbers from the most recent version of the electoral roll (2000). Controls were individually matched to cases by sex and five year age bands.

Subjects from either group were excluded if they had contraindications to magnetic resonance imaging (MRI), including metal sutures, presence of shrapnel, iron filings in the eye, or claustrophobia. Subjects selected as controls were included as cases if they had a parent who had had a knee replacement for osteoarthritis.

Abbreviations: CV, coefficient of variation; ICC, intraclass correlation coefficient; OARS, Osteoarthritis Research Society International; PWC, physical work capacity; ROA, radiographic osteoarthritis

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). These were calibrated with known weights 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/m²) was calculated. Knee pain was assessed by the questionnaire and was defined as pain for more than 24 hours in the last 12 months, or daily pain on more than 30 days in the last year.

Objective measures of physical activity included measurement of muscle strength by dynamometry at the lower limb (involving both legs simultaneously). The subject was instructed in each technique before testing and each measurement was done twice. A repeatability estimate (Cronbach's α) was 0.91. The devices were calibrated by suspending known weights at regular intervals. Physical work capacity was also assessed by a bicycle ergometer.²² Subjects were asked to cycle at a constant 60 rpm for three minutes at each of three successively increasing but submaximal workloads. Heart rate was recorded at one minute intervals at each workload using an electronic heart rate monitor. Work capacity at 170 beats/min (PWC170) was then assessed by linear regression with extrapolation of the line of best fit to a heart rate of 170 beats/min. The PWC170 was not considered a technically adequate measure unless subjects had spent a minimum of two minutes at each workload and the pulse rate increased by at least 5 beats/min with increasing workloads. Repeatability was not assessed in our subjects but has previously been reported as 0.92.²²

A standing anteroposterior semiflexed x ray of the right knee was taken in all subjects. 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 then assessed using the OARSI atlas.²³ Each of the following was assessed: medial joint space narrowing (0–3), lateral joint space narrowing (0–3), medial osteophytes (femoral and tibial combined) (0–3), and lateral osteophytes (femoral and tibial combined) (0–3). Each score was arrived at by consensus between two readers (GJ, FS) who assessed the radiograph simultaneously with immediate reference to the atlas. Reproducibility was determined in 50 radiographs, taken two weeks apart, and yielded an intraclass correlation coefficient (ICC) of 0.99 for osteophytes and 0.98 for joint space narrowing. This may represent an overestimate of the actual agreement because of the high proportion of normal radiographs. However, in one of our previous studies²⁴ this method also had very high reproducibility for radiographic osteoarthritis of the hands, with ICCs of 0.94 to 0.98.

MRI of the right knee was also undertaken. Knee cartilage volume was determined by image processing on an independent work station using the software program Osiris, as previously described.¹⁶ Knees were imaged in the sagittal plane on a 1.5 T whole body magnetic resonance unit (Picker International, Cleveland, Ohio, USA), using a commercial transmit–receive extremity coil.

The image sequence was as follows: a T1 weighted fat saturation three dimensional gradient recall 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 matrix; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 (512×512 pixels). The image data were transferred to the workstation.

The volume of individual cartilage plates (medial tibial, lateral tibial, and patella) was isolated from the total volume by manually drawing disarticulation 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 and 312 μ m and 1.5 mm thickness, continuous sections) for the final three dimensional rendering. The volume of the particular cartilage plate was determined by summing all the pertinent voxels within the resultant binary volume. Femoral cartilage volume was not assessed, as we have previously established that it correlates strongly with the two tibial sites and the patella site.²⁵ Using this method we had high intraobserver and interobserver reproducibility. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial cartilage, 2.2% for lateral tibial cartilage, and 2.6% for patella.¹⁶

Knee tibial plateau bone area and patellar bone volume were also determined by image processing on an independent work station using the software program Osiris (University of Geneva), as previously described.²⁵ To transform the images to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closest to the knee joint. The bone area of the medial and lateral tibial plateau was then directly measured from the reformatted axial images. The area of patellar bone was determined individually by manually drawing contours around the target patella boundaries on a slice-by-slice basis on sagittal views. The volume of the patella bone was then determined by summing all the pertinent voxels within the resultant binary volume. Total volume was calculated for the patellar bone because its irregular shape made it difficult to identify a simpler representative measure of patellar size. The CVs for these measures in our hands are 2.2–2.6%.²⁶

Statistical methods

A combination of paired t tests and conditional logistic regression was used for the analysis of this matched dataset. Subgroup analyses were also carried out for hypothesis generation with regard to the sex of the parent, the age of the parent at the time of knee replacement, and the age of the offspring. To check whether relatedness of the subjects was biasing the overall results, a stratified analysis restricted to one randomly selected offspring per family and their matched control was also undertaken. To further check the robustness of the standard errors, random effects models were used. A probability (p) value less than 0.05 (two tailed) or a 95% confidence interval (CI) not including the null point were regarded as statistically significant. All statistical analyses were carried out on SPSS version 10.0 for Windows (SPSS Inc, Chicago, Illinois, USA).

RESULTS

There were 376 subjects (214 female, 162 male) comprising 188 offspring and 188 age and sex matched controls. The response rate was 71% for the offspring and 40% for the controls. This was a young sample with an average age of 45 years (range 26 to 61). Characteristics of the group are presented in table 1. Offspring and controls were well matched for age, height, injury history, and fitness. However, offspring weighed more and had a higher BMI and a higher prevalence of knee pain (all $p < 0.05$). ROA was both uncommon and mild in this group, with consistent trends for it to be both more common and more severe in offspring, although this only reached statistical significance in the one offspring per family subgroup.

Table 2 documents the differences in cartilage volume and bone area between offspring and controls. No significant differences were observed in cartilage volume and this persisted in all subgroup analyses (table 3). In contrast, medial tibial plateau bone area was significantly higher in offspring than in controls ($p = 0.01$). This did not apply to the

Table 1 Characteristics of participants (n = 376)

	Whole sample			One offspring per family		
	Offspring (n = 188)	Controls (n = 188)	p Value	Offspring (n = 111)	Controls (n = 111)	p Value
Age (years)	45.2 (6.9)	44.9 (7.1)	0.65	45.5 (6.7)	45.2 (6.8)	0.81
Height (cm)	169 (8)	169 (9)	0.77	170 (9)	169 (9)	0.35
Weight (kg)	80 (16)	76 (17)	0.03	83 (18)	77 (18)	0.006
BMI (kg/m ²)	27.8 (4.9)	26.0 (5.2)	0.02	28.8 (5.7)	26.8 (5.8)	0.007
Knee pain	47%	22%	<0.001	46%	21%	<0.001
Lower limb strength (kg)	127 (49)	135 (50)	0.006	130 (51)	137 (53)	0.06
Physical work capacity	2.94 (1.13)	2.91 (0.99)	0.77	3.10 (1.18)	2.90 (0.87)	0.11
Past knee injury	18%	22%	0.21	19%	22%	0.58
Any ROA	19%	16%	0.53	21%	13%	0.13
Total ROA score (0–2)	0.34 (0.86)	0.24 (0.63)	0.21	0.38 (0.90)	0.17 (0.47)	0.04

Values are mean (SD) or per cent.

BMI, body mass index; ROA, radiographic osteoarthritis.

other bone sites, with the exception of lateral tibial area in the one offspring per family subgroup. In subgroup analysis, there were increases in medial tibial bone area in all offspring subgroups, which reached statistical significance in women, in the older groups (both offspring and parents), in those with a female parent who had a total knee replacement, and in the single offspring per family subgroup.

Table 4 details the multivariate analysis. In the whole sample, after adjustment for ROA and the other significant univariate variables all factors remained statistically significant except BMI, suggesting that they were independently associated with offspring status. Results were generally more marked in the single offspring per family subgroup, where all factors (including BMI) remained significant in multivariate analysis. Results were largely unchanged if random effect models were used (data not shown). If the analysis was restricted to those over 45 years, there was a non-significant trend to increased ROA in the offspring (28% v 20% for prevalence and 0.55 v 0.33 for severity, $p = 0.13$ to 0.17). Past knee injury was not associated with knee pain or structural change in this sample, and adjusting for this factor did not change the results (data not shown).

DISCUSSION

This is the first study to examine differences in knee structural components between offspring of individuals with severe knee osteoarthritis in later life and controls. It does not support the hypothesis that cartilage volume is reduced in the offspring group. However, offspring weighed more and had weaker lower limb muscles, more knee pain, and a greater medial tibial plateau area than controls.

Cartilage loss is the hallmark of established osteoarthritis,²⁷ but it is uncertain whether cartilage or bone is most involved in the pathogenesis of this disorder.²⁸ Recent twin and sibling studies have indicated that the heritability of cartilage

volume is very high.^{14–17} In addition, our original report suggested that cartilage development might be one explanation for the sex and site differences in knee osteoarthritis in later life.¹⁶ As a longitudinal study to answer this question would require many years of follow up, the current study was designed to test this hypothesis indirectly by comparing offspring of individuals with severe knee osteoarthritis with controls.

Our study can confidently reject the hypothesis that cartilage volume is lower in the offspring and does not support a role for cartilage morphology in the pathogenesis of knee osteoarthritis. Indeed, there was a trend to greater cartilage volume in the offspring. This did not reach statistical significance but may indicate that cartilage volume increases in some subjects in the early stages of osteoarthritis because of loss of aggrecan from the matrix and increased water content.²⁸ Our MRI technique accurately and reproducibly assesses cartilage morphology but cannot measure cartilage quality. If cartilage volume is increasing because of swelling then further longitudinal studies may document a higher rate of loss, which will be less likely if cartilage homeostasis is intact. However, in contrast to the lack of difference in cartilage volume between offspring and controls, significant differences were observed in body mass index, knee pain, muscle strength, and tibial plateau area. The latter three were independent factors in multivariate analysis. This suggests that all these factors may play a role in the initiation of knee osteoarthritis, and that the association with BMI is primarily through its association with these factors, BMI being correlated with knee pain and bone size but not with muscle strength in this sample. While BMI is clearly a strong risk factor for knee osteoarthritis, these results imply that the genetic contribution to the relation between BMI and osteoarthritis is small, which is consistent with a recent report suggesting that the heritability of obesity

Table 2 Comparison of cartilage volume, bone area, and bone volume between offspring and controls

	Whole sample			One offspring per family		
	Offspring	Controls	p Value for difference	Offspring	Controls	p Value for difference
<i>Cartilage variables</i>						
Medial tibial volume (ml)	2.32 (0.56)	2.26 (0.60)	0.24	2.36 (0.50)	2.29 (0.60)	0.24
Lateral tibial volume (ml)	2.65 (0.68)	2.57 (0.69)	0.12	2.69 (0.69)	2.57 (0.72)	0.08
Patellar cartilage volume (ml)	3.46 (0.97)	3.47 (0.99)	0.92	3.49 (1.02)	3.50 (0.98)	0.87
<i>Bone variables</i>						
Medial tibial area (cm ²)	17.6 (2.6)	17.1 (2.8)	0.01	17.8 (2.6)	17.0 (2.4)	0.001
Lateral tibial area (cm ²)	12.0 (2.0)	11.9 (2.0)	0.49	12.3 (2.1)	11.8 (2.0)	0.03
Patellar bone volume (ml)	13.6 (3.2)	14.0 (3.5)	0.13	13.8 (3.3)	14.1 (3.6)	0.25

Values are mean (SD).

Table 3 Subgroup analyses of differences in cartilage volume sites (μl) and medial tibial bone area (mm^2): offspring v controls

	Medial tibial difference (95% CI)	Lateral tibial difference (95% CI)	Patella difference (95% CI)	Medial tibial bone area difference (95% CI)
All (188 pairs)	+54 (−36 to +144)	+80 (−21 to +180)	−7 (−151 to +137)	+53 (+13 to +93)
Female (107 pairs)	+39 (−63 to +140)	+44 (−74 to +163)	+55 (−119 to +229)	+75 (+27 to +124)
Male (81 pairs)	+74 (−90 to +238)	+126 (−50 to +301)	−88 (−333 to +156)	+20 (−49 to +91)
Offspring ≤ 45 years (84 pairs)	+36 (−100 to +173)	+87 (−49 to +222)	+33 (−169 to +235)	+52 (−10 to +115)
Offspring >45 years (104 pairs)	+68 (−55 to +191)	+73 (−74 to +221)	−39 (−244 to +165)	+55 (+2 to +107)
Female parent had TKR (117 pairs)	+83 (−36 to +202)	+34 (−90 to +159)	+19 (−169 to +206)	+73 (+20 to +125)
Male parent had TKR (71 pairs)	+6 (−133 to +146)	+154 (−19 to +326)	−49 (−277 to +179)	+22 (−41 to +84)
Parent ≤ 75 years at time of TKR (87 pairs)	+58 (−72 to +188)	+71 (−63 to +206)	−46 (−259 to +166)	+41 (−25 to +106)
Parent >75 years at time of TKR (91 pairs)	+52 (−86 to +190)	+111 (−46 to +268)	−3 (−219 to +213)	+66 (+15 to +118)
One offspring per family (111 pairs)	+69 (−48 to +186)	+124 (−15 to +263)	−16 (−211 to +179)	+81 (+32 to +130)

Significant differences in bold.

CI, confidence interval; TKR, total knee replacement.

is largely independent of the heritability of knee osteoarthritis.²⁹

The underlying mechanism of knee pain remains elusive. Body weight and osteophytosis have been linked to this symptom.^{30–31} However, in our study the difference between cases and controls was independent of these factors and was substantial, with 47% of the offspring having knee pain compared with 22% of the controls. Our definition of knee pain was somewhat more liberal than in previous studies, but the high prevalence was surprising nonetheless, as we expected a much lower prevalence when planning the study, even in the absence of other population based data on knee pain from Australia. Knee pain had high heritability in a smaller sibling pair study in this sample,¹⁴ confirming a significant genetic contribution. This suggests that genetic factors leading to knee pain may mediate the genetic risk of knee osteoarthritis, and that knee pain could be considered to represent a pre-osteoarthritis state. However, further longitudinal studies are required to determine the relation between unexplained knee pain and subsequent osteoarthritis, as knee pain may be subject to recall bias if there is a positive family history. Similar comments apply to muscle strength. This was 8 kg lower in the offspring, again suggesting a direct role in pathogenesis and consistent with prospective studies in older populations.²¹ While this was also under strong genetic control in the sibling pairs within this study,¹⁴ it is clear that strength can also be influenced by the environment; thus exercise programs in younger life may be protective of knee osteoarthritis.

In this study, medial tibial plateau area was modestly but significantly higher in offspring. This association was consistent in subgroup analysis, being positive in all groups but especially in the older groups (both offspring and

parents) and in women (both offspring and those with a female parent). This implies a role for local bone size in the pathogenesis of knee osteoarthritis. A previous study has suggested a role for bone density as predictor of knee osteoarthritis¹⁹ and as a mediator of the genetic effect in a study of similar design to the current one.²⁰ Subchondral bone also may have role to play. It is unclear whether it has role in initiation, but it is suggested that it influences progression, based on the Bristol OA500 study.^{32–33} Tibial bone area is highly heritable¹⁴ but most of the heritability is mediated through body size. Tibial bone area is markedly increased in individuals with early osteophytosis.²⁶ In this sample, bone area increased with age, BMI, and pain (C Ding *et al*, unpublished data) and was predictive of knee replacement (A Wluka *et al*, unpublished data). The difference in bone size persisted after adjustment for these other factors and ROA, suggesting that the bone change is independent of these factors and ROA, and possibly precedes detectable radiographic change. These observations are consistent with bone size having an initiating role in knee osteoarthritis in adult life.

Our bone area measure has potential limitations. It was originally derived to adjust for bone size and has not been validated against cadaveric specimens. However, its measurement is highly reproducible, has face validity, and the current study provides support for content validity. However, it remains to be seen whether bone area is associated with environmental factors and would thus be modifiable.

Our study has other possible limitations. First, there was no significant increase in ROA (either prevalence or severity) in the offspring, apart from in the one offspring per family subgroup. This is most likely to reflect the young age of the cohort and the relative rarity of ROA at this age. However, the

Table 4 Multivariate conditional logistic regression analysis of factors discriminating subjects with a parent with total knee replacement for osteoarthritis from controls

	Univariate OR (95% CI)	Multivariate* OR (95% CI)
<i>All subjects (188 pairs)</i>		
Knee pain (yes v no)	3.10 (1.92 to 5.01)	2.85 (1.70 to 4.78)
BMI (kg/m^2)	1.03 (0.99 to 1.07)	1.01 (0.97 to 1.05)
Lower limb muscle strength	0.59 (0.41 to 0.86)	0.61 (0.40 to 0.93)
Medial tibial bone area	1.44 (1.06 to 1.96)	1.53 (1.02 to 2.29)
<i>One offspring per family (111 pairs)</i>		
Knee pain (yes v no)	2.86 (1.56 to 5.25)	2.94 (1.36 to 6.40)
BMI (kg/m^2)	1.13 (1.05 to 1.23)	1.11 (1.01 to 1.22)
Lower limb muscle strength	0.59 (0.35 to 0.99)	0.43 (0.22 to 0.85)
Medial tibial bone area	2.09 (1.25 to 3.51)	2.59 (1.36 to 4.96)

*Adjusted for factors in the table as well as for radiographic osteoarthritis (which was not a significant variable in either model). The coefficients are per unit for BMI and per SD for muscle strength and bone area. Significant values in bold.

BMI, body mass index; OR, odds ratio.

link between total knee replacement and family risk is relatively weak, at 1.5 times.¹³ This has only been documented for siblings and not offspring; thus it is possible that the offspring risk is weaker than this. However, one would then have expected no differences in any factors between offspring and controls.

Second, while the response rate was acceptable at 71% in the offspring, it was 40% in the controls. We have limited data to assess the reasons for non-response, but selection bias may still be present and would tend to operate in two ways. The first is that subjects with a direct interest in the results may be more likely to take part (for example, those with knee pain and past injury). The second is that those who are more interested in their health may be more likely to take part. These biases imply a lower rate of knee pain, a tendency to higher body weight, and lower muscle strength in the general population than observed in our control population. This bias is unlikely to have an effect on knee bone size, as subjects will be unaware of this factor. Similarly, the high response rate in the offspring suggests that knee pain will be higher than the controls even if no non-responders had knee pain. Overall, this indicates that some caution is necessary in interpreting the results. While the pain and bone size associations appear robust, the muscle strength and body weight observations require confirmation in other populations, preferably in longitudinal studies.

Finally, some of the offspring were related (128 from 51 families).¹⁴ This violates the assumption of independence in hypothesis testing. However, the results did not change if random effects models were used to allow for this. Furthermore, if the analysis is restricted to one offspring per family, the strength of the associations increases, implying that this potential bias is not of major concern.

Conclusions

Our study suggests that body mass index, muscle strength, knee pain, and medial tibial bone area, but not cartilage volume, all play a role in the genetic regulation and development of knee osteoarthritis. Further confirmation of these results in longitudinal studies is required.

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