A Longitudinal Study of the Association Between Knee Alignment and Change in Cartilage Volume and Chondral Defects in a Largely Non-Osteoarthritic Population

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ABSTRACT. ***Objective.*** It remains unclear whether malalignment of the knee is a cause of knee OA or a marker of disease progression. We investigated whether baseline malalignment of the knee predicts subsequent change in knee cartilage volume and chondral defects in subjects with and without radiographic knee osteoarthritis (OA).

Methods. A convenience sample of 315 male and female subjects (mean age 45 yrs, range 26–61) was followed up for a mean period of 2.4 years. Anatomic knee alignment was assessed on a standing anterior-posterior semiflexed view of the right knee and defined as the angle subtended by a line drawn through the midshaft of the femur with respect to one drawn through the midshaft of the tibia. T1-weighted fat saturation magnetic resonance imaging scans were performed on the same knee at baseline and followup for cartilage volume and chondral defects.

Results. Knee alignment was normally distributed in this sample with a mean of 178.2° (SD 1.9°). Fifty-five percent of subjects were < 178.5°, while 14% were > 180°. After adjustment for age, sex, body mass index, previous knee injury, and OA family history, neither category of alignment at baseline was associated with subsequent loss of lateral and medial tibial cartilage volume. Similarly, there was no association between malalignment and progression of chondral defects. The results remained the same when stratified by radiographic OA status.

Conclusion. Our adequately powered study shows that baseline knee alignment is not associated with subsequent loss of cartilage volume or progression of chondral defects over 2 years. Further studies with a longterm followup are needed, but these results suggest malalignment is primarily a marker of disease progression. (J Rheumatol 2007;34:181–6)

Key Indexing Terms:
KNEE ALIGNMENT OSTEOARTHRITIS CARTILAGE VOLUME CHONDRAL DEFECTS

Osteoarthritis (OA) is the most common form of arthritis in developed countries. The knee is one of the most frequently affected joints, with a prevalence of 30% in people older than 65 years, and results in substantial morbidity and disability in the elderly[1,2] and imposes considerable economic burden on our society[3]. However, poor understanding of its etiology and pathogenesis contributes to the slow development of interventions that modify the course of the disease, particularly in the early stages. While genetic factors[4,5] and several environmental factors including obesity[6-11], previous injury[12,13], vitamin D[14], and meniscectomy[15-17] have been reported to be associated with knee OA, alignment, which refers to the colinearity of the hip, knee, and ankle, is thought to play a role in the development of knee OA[18]. The knee is most vulnerable to changes in the normal coronal plane relationship of the joints of the lower extremity[19]. In the normal state, 60–80% of the compressive load transmitted across the knee is on the medial compartment[20]. Alteration in the alignment may redistribute the medial and/or lateral loads at the joint, and this mechanical effect makes it biologically plausible that varus and/or valgus alignment may contribute to the development of site-specific OA.

Previous studies have reported that varus alignment was associated with a 4-fold increase in the odds of progression of medial tibiofemoral OA, while valgus alignment was associated with a 2 to 5-fold increase in the odds of lateral progression[18,21]. A recent article reported that, for every one degree increase in baseline varus angulation, there was an average

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Supported by National Health and Medical Research Council of Australia, Masonic Centenary Medical Research Foundation.

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Accepted for publication August 11, 2006.

annual loss of medial femoral cartilage of 17.7 μl, suggesting that malalignment is linked to subsequent cartilage loss[22]. However, all these observations have been from populations with well established radiographic osteoarthritis (ROA); thus, malalignment is a marker of progression or possibly disease severity but has not been proven to be a risk factor for development of the disease. Indeed, there was no significant association between malalignment and medial progression in subjects without knee OA at baseline[21]. However, the study sample was relatively small.

We set out to examine whether knee malalignment at baseline predicts subsequent loss of knee cartilage or chondral defect development in subjects with and without ROA.

MATERIALS AND METHODS

Subjects. The study was carried out in Southern Tasmania, primarily in the capital city of Hobart, as described[23]. It was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects provided informed written consent.

A convenience sample was utilized for this study. The sample was originally designed to look at genetic mechanisms of knee OA and a matched design was used[24]. Subjects were selected from 2 sources. Half of the subjects were the adult children of subjects who had a knee replacement performed for primary knee OA at any Hobart hospital in the years 1996–2000. The diagnosis was confirmed by reference to the medical records of the orthopedic surgeon and the original radiograph where possible. The other half were randomly selected individuals who had no personal or family history of knee OA. These 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 5-year age bands. Subjects 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. No women were on hormone replacement therapy at the time of the study. All subjects were then followed up for a mean of 2.4 years.

Radiography. A standing anteroposterior semiflexed view of the right knee was performed in all subjects at baseline. Knee alignment was measured on the knee radiography. Full-limb radiography is ideal for the alignment assessment, but, with its pelvic radiation, cost, and equipment needs, is problematic particularly in larger studies. We therefore chose to measure the knee alignment on the knee radiography by using a method validated previously[25,26]. The femoral anatomic axis was found by drawing a line from the middle point of the tibial spine tips to a point 10 cm above the tibial spines, midway between the medial and lateral femoral cortical bone surfaces. For the tibial anatomic axis, a line is drawn from the middle point of the tibial spine tips to a point 10 cm below the tibial spines, midway between the medial and lateral tibial cortical bone surfaces. In the event of short radiographs, the furthest point was used. The medial angle of intersection of the axes was then measured by protractor (ORNA Design, Stirflex) to 0.1° manually. This anatomic angle was then converted to mechanical-axis angle based on the predicting equation provided by Kraus, *et al*[26]: mechanical angle = 0.69*anatomic angle + 53.69. An angle less than 178.5° was then defined as varus while greater than 180° was defined as valgus based on the normal values provided by Moreland, *et al*[25]. The measurement was done by a single observer (GZ). The intraobserver reproducibility was assessed in 30 subjects with 2 measurements at least one month apart with an intraclass correlation coefficient (ICC) of 0.97.

Radiographic features of OA were also assessed on the same radiograph utilizing the Altman atlas[27]. Each of the following was assessed: medial joint space narrowing (JSN; 0–3), lateral JSN (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 with 2 readers (GJ, FS) simultaneously assessing the radiograph with immediate reference to the atlas. Reproducibility was assessed in 50 radiographs 2 weeks apart and yielded an ICC of 0.99 for osteophytes and 0.98 for JSN[28]. The presence of radiographic OA was defined as a total score = 1.

MRI. An MRI scan of the right knee was obtained at baseline and followup, using the same machine and the same protocol as described previously[28,29]. Knee tibial cartilage volume, and tibial and femoral cartilage defects (0–4 scale) were assessed in a manner identical to that used in our previous studies, with excellent reproducibility[28,29]. A prevalent cartilage defect was defined as a cartilage defect score of ≥ 2 at any site within the medial or lateral tibiofemoral compartment. The percent loss in cartilage volume per year was calculated as: [100*([cartilage volume at baseline – cartilage volume at followup]/cartilage volume at baseline)/ time between scans in yrs]. Changes in tibiofemoral cartilage defects were calculated by subtracting tibiofemoral cartilage defect scores (0–8 scale) at baseline from tibiofemoral cartilage defect scores (0–8 scale) at followup. A change in cartilage defects ≥ 1 was defined as progression in cartilage defects.

Other variables. At baseline, 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) that were 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. Overweight was defined as a BMI more than 25 kg/m^2 while obesity was defined as a BMI more than 30 kg/m^2.

Demographic variables such as age and sex were collected by standard questionnaire. Subjects were also asked the following questions in the assessment of previous knee injury and their occupation involving significant knee bending: Have you had a previous knee injury requiring non-weight bearing treatment for more than 24 hours or surgery? And if employed, does your occupation involve significant knee bending and carrying heavy objects?

Statistics. Descriptive statistics of characteristics of the sample were tabulated. The annual cartilage loss at lateral and medial compartments was normally distributed. Associations between varus/valgus knee alignment and loss of cartilage volume/change in tibial plateau area were assessed by linear regression modeling, while associations between varus/valgus knee alignment and progression of chondral defects were assessed by logistic regression modeling before and after adjustment for age, sex, previous knee injury, and case-control status. Dose response associations were also assessed by linear or logistic regression modeling. A p value less than 0.05 (2-tailed) or a 95% confidence interval (CI) not including the null point was considered statistically significant. Given the sample size, the study had 80% power to detect a standardized regression coefficient of at least 0.16 between varus/valgus knee and loss of cartilage volume at alpha level of 0.05. For the chondral defects, the minimum odds ratio (OR) to be detected was 1.7. All statistical analyses were performed on Stata/SE version 9 for Windows (StatCorp LP, College Station, TX, USA).

RESULTS

A total of 315 subjects (183 women and 132 men) with a mean age of 45 took part. The average followup time was 2.4 years with a range of 1.7 to 3.3 years. The characteristics and comparison between subjects with normal knee alignment and those with varus/valgus are presented in Table 1. Of the subjects, 55% had varus alignment while 14% had valgus, but all were mild, with a mean alignment of 178.2° ± 1.9°. The prevalence of valgus was higher in subjects with ROA (19%) than those without ROA (13%) although it was not statistically significant. Baseline lateral tibial cartilage volume was statistically different between subjects with normal knee alignment and those with varus alignment, while baseline lateral tibial bone area and longitudinal change of medial tibial bone area were significantly different between subjects with normal knee alignment and those with valgus alignment.

Table 1. Characteristics and comparison between subjects with knee alignment of < 178.5°, 178.5°–180°, and > 180°*.

Characteristic	< 178.5° n = 174	178.5°–180° n = 96	> 180° n = 45
Sex (% female)	(62)	(57)	(51)
Age, yrs	45.5 ± 6.3	44.8 ± 6.7	45.7 ± 6.5
BMI, kg/m^2	27.1 ± 4.9	27.3 ± 4.9	27.4 ± 7.3
Previous knee injury, %	16.1	19.8	28.9
Radiographic OA, %	16.1	17.7	24.4
Lateral tibial cartilage volume at baseline, ml	2.5 ± 0.6†	2.7 ± 0.7	2.7 ± 0.8
Medial tibial cartilage volume at baseline, ml	2.2 ± 0.6	2.3 ± 0.6	2.3 ± 0.6
Lateral bone area at baseline, cm^2	11.8 ± 2.0	12.0 ± 1.8	12.7 ± 2.4†
Medial bone area at baseline, cm^2	17.3 ± 2.8	17.3 ± 2.6	17.8 ± 2.3
Medial chondral defects score (possible range 0–8)	2.2 ± 0.9	2.1 ± 0.6	2.1 ± 0.5
Lateral chondral defects score (possible range 0–8)	2.0 ± 0.7	2.0 ± 0.8	2.3 ± 1.2
Annual change in cartilage volume, %			
Lateral tibial	–1.2 ± 3.4	–1.9 ± 3.4	–1.8 ± 3.9
Medial tibial	–2.3 ± 4.2	–2.9 ± 4.0	–2.9 ± 4.1
Annual change in bone size, %			
Lateral tibial	0.2 ± 2.9	–0.1 ± 2.9	–0.5 ± 2.7
Medial tibial	0.6 ± 1.8	0.6 ± 1.8	–0.2 ± 1.7‡
Medial chondral defects progression/regression, %	23/28	24/23	11/25
Lateral chondral defects progression/regression, %	21/23	22/23	16/39

* Values are expressed in mean ± SD for continuous variables and percentage for dichotomous variables. Unpaired t test, chi-square test, or Mann-Whitney U test were used in the comparison where appropriate. † $p \leq 0.05$. ‡ $p = 0.01$. OA: osteoarthritis.

Tables 2 and 3 present the results of univariate and multivariate analysis of association between varus/valgus alignment and loss of cartilage volume/change in tibial plateau area in the whole sample and in subjects with and without ROA separately. Overall, there was no statistically significant association between varus/valgus alignment and loss of knee cartilage volume/change in the tibial plateau area. This persisted when analysis was stratified by ROA. Similarly, there was no significant association between varus/valgus alignment and progression of chondral defects (Table 4).

Table 5 presents the results of dose response analysis of association between knee alignment and loss of cartilage volume and change in the tibial plateau area. Only medial tibial bone size was significantly associated with increased degree of knee alignment (i.e., more varus) and this remained in subjects with ROA but not subjects without ROA.

When considering subjects with more varus alignment (≤ 176°, n = 38), there was no significant cartilage loss ($p = 0.94$).

DISCUSSION

In this longitudinal study of a relative large sample with the majority having no ROA, we found no evidence that malalignment of the knee at baseline predicted subsequent loss of knee cartilage volume or progression of chondral defects.

It is well known that patients with knee OA are commonly bowlegged or have knock-knee deformity, meaning that they have a varus or valgus alignment of their lower limb[30]. However, it is unclear whether varus/valgus alignment is a cause of knee OA or merely a part of the pathogenesis of the disease. Sharma, *et al*[18] reported that varus alignment at baseline increased risk of medial knee OA progression over the 18 months of followup, and valgus alignment increased risk of

Table 2. Association between varus (y/n) and annual percentage change in medial tibial cartilage volume and bone size.

	Overall Sample (n = 315)			Subjects without ROA (n = 259)			Subjects with ROA (n = 56)		
	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p
Medial tibial cartilage	0.57	0.61	0.18	0.55	0.58	0.26	0.68	0.84	0.46
Medial tibial bone size	0.27	0.30	0.15	0.29	0.31	0.20	0.19	0.15	0.73

* Varus was defined as knee angle < 178.5°. Multivariate analysis with age, sex, body mass index, previous knee injury, and family history of OA in the equation. ROA: radiographic osteoarthritis.

Table 3. Association between valgus (y/n) and annual percentage change in lateral tibial cartilage volume and bone size.

	Overall Sample (n = 315)			Subjects without ROA (n = 259)			Subjects with ROA (n = 56)		
	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p
Lateral tibial cartilage	–0.37	–0.39	0.49	–0.06	–0.05	0.94	–1.23	–1.53	0.26
Lateral tibial bone size	–0.62	–0.66	0.16	–0.76	–0.62	0.09	–0.16	–0.29	0.77

* Valgus was defined as knee angle > 180°. Multivariate analysis with age, sex, body mass index, previous knee injury, and family history of OA in the equation. ROA: radiographic osteoarthritis.

Table 4. Association between varus (y/n)/valgus (y/n) and progression in medial/lateral chondral defects.

	Overall Sample (n = 315)			Subjects without ROA (n = 259)			Subjects with ROA (n = 56)		
	Univariate Analysis OR	Multivariate Analysis OR	95% CI	Univariate Analysis OR	Multivariate Analysis OR	95% CI	Univariate Analysis OR	Multivariate Analysis OR	95% CI
Progression of medial chondral defects	1.15	1.18	0.68, 2.07	0.96	0.98	0.52, 1.82	2.44	2.27	0.46, 11.26
Progression of lateral chondral defects	0.69	0.64	0.27, 1.54	0.71	0.70	0.25, 1.96	0.55	0.51	0.08, 3.27

* Varus was defined as knee angle < 178.5°; valgus was defined as knee angle > 180°. Multivariate analysis with age, sex, body mass index, previous knee injury, and family history of OA in the equation. The analysis was done site specifically, e.g., medial chondral defects progression vs varus, while lateral chondral defects progression vs valgus. ROA: radiographic osteoarthritis; OR: odds ratio; CI: confidence interval.

Table 5. Association between degree of knee alignment and annual percentage change in knee cartilage volume and bone size.

	Overall Sample (n = 315)			Subjects without ROA (n = 259)			Subjects with ROA (n = 56)		
	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p	Univariate Analysis Regression Coefficient	Multivariate Analysis Regression Coefficient	p
Lateral tibial cartilage	–0.16	–0.15	0.22	–0.17	–0.17	0.22	–0.08	–0.07	0.82
Medial tibial cartilage	–0.17	–0.17	0.10	–0.14	–0.14	0.21	–0.28	–0.34	0.20
Lateral tibial bone size	–0.04	–0.04	0.66	–0.04	–0.05	0.62	–0.04	–0.02	0.94
Medial tibial bone size	–0.14	–0.14	0.01	–0.14	–0.11	0.04	–0.14	–0.11	0.32

* Multivariate analysis with age, sex, body mass index, previous knee injury, and family history of OA in the equation. Regression coefficient is expressed as percentage change in cartilage volume/bone size per 1° increase in knee angle. ROA: radiographic osteoarthritis.

subsequent lateral knee OA progression on plain radiographs. Cicuttini, *et al*[22] reported in a 1.9-year followup study that subjects with a more varus knee angle at baseline had a significantly increased loss of medial femoral articular cartilage, while subjects with valgus alignment at baseline had an increased loss of lateral tibial cartilage. Although both longitudinal studies showed that malalignment is associated with knee OA progression, they could not answer the above question, as subjects in both studies were from an OA-affected population and their malalignment at baseline might be a consequence of the disease, particularly if the malalignment is larger[22]. Indeed, in our study, prevalence of valgus was higher in subjects with ROA than those without.

In this longitudinal study, we found no evidence that baseline malalignment predicted subsequent loss of knee cartilage volume or progression of chondral defects. The advantage of our study is that, in contrast to the previous reports[18,22], the majority of study participants had no ROA, allowing us to test a causal relationship between malalignment and OA development. In addition, we utilized MRI, which allowed direct visualization of articular cartilage, thus more accurately measuring cartilage loss than JSN on a plain radiograph. The average loss of knee cartilage was 1.5–2.5% per annum, which is lower than the 5% loss reported previously in the OA population[31]. In contrast to the previous report[22], the malalignment in this sample was also much milder and less variable than in OA cohorts, suggesting that the disease itself may result in a higher variance. Recent reports suggest cartilage loss is the major determinant of knee alignment[30,32]; our results support that malalignment is a marker of OA rather than a cause of the

disease. However, normal aging may cause increased varus alignment that then predisposes people to OA[30]. This effect may only cause cartilage loss in later life and, thus, there is a need to study an older population with a longer followup period to confirm these results.

There are potential limitations in our study. First, we measured alignment on knee radiograph rather than full-limb radiograph, which may lead to misclassification in the assessment of malalignment. However, the method we used is validated[25,26] and our reproducibility was high, suggesting this was not a major issue. Second, the study was originally designed to look at genetic mechanisms of knee OA and utilized a matched design[24]. The matching was broken for the current study and the adjustment for family history of knee OA was through the analysis, but the results did not differ if examined in offspring and controls separately. While the sample is a convenience sample, which may limit our generalizability, Miettinen[33] states that for these associations to be generalizable to other populations, 3 key criteria need to be met regarding selection, sample size, and adequate distribution of study factors, all of which are met by this study, suggesting that this is not a major concern. Third, the followup period may be too short given that OA is a slowly developing disease. However, a previous study with a similar time frame but a substantially smaller sample with established OA reported significant associations using MRI based outcomes[22], suggesting short-term followup may be valid for MRI as compared to radiographs. Finally, we had more than 80% power to detect the effects reported[18,22]. However, we may not have had enough power to detect a small effect. The average difference of cartilage loss in the current study was 0.6%, which corresponds to a standardized regression coefficient of 0.05, and the OR observed in the current study for chondral defect progression was 1.1; to detect such a small effect would require 10 times the current sample size or even more, but such a small effect is unlikely to be clinically significant, and powering a study to detect such a small effect seems pointless.

Our adequately powered study shows that baseline knee alignment is not associated with subsequent loss of cartilage volume or progression of chondral defects over 2 years. Further studies with a longterm followup are needed, but these results suggest malalignment is primarily a marker of disease progression.

ACKNOWLEDGMENT

We extend special thanks to the subjects and orthopedic surgeons who made this study possible. The role of C. Boon in coordinating the study is gratefully acknowledged. We thank Martin Rush for performing the MRI scans and Kevin Morris for technical support.

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