EXTENDED REPORT

Rate of cartilage loss at two years predicts subsequent total knee arthroplasty: a prospective study

F M Cicuttini, G Jones, A Forbes, A E Wluka

Ann Rheum Dis 2004;**63**:1124–1127. doi: 10.1136/ard.2004.021253

See end of article for authors' affiliations

Correspondence to: Associated Professor Flavia Cicuttini, Department of Epidemiology and Preventive Medicine, Monash University Medical School, Alfred Hospital, Melbourne 3004, Australia; flavia.cicuttini@med.monash.edu.au

Accepted 26 March 2004
Published online first 28 April 2004

Objective: To determine whether cartilage volume loss is an independent predictor of knee replacement.
Design: Prospective community based, four year prospective cohort study.
Methods: 123 subjects with mild to moderate symptomatic radiographic knee osteoarthritis were recruited by either advertising, the Victorian branch of the Arthritis Foundation of Australia, treating general practitioners, orthopaedic surgeons, or rheumatologists; 113 completed the study. Magnetic resonance imaging was carried out at baseline and at 2 years on the symptomatic knee. Rate of change in tibial cartilage volume was calculated. Subjects were then followed up at year 4 to determine whether they had undergone a knee replacement.
Results: The rate of tibial cartilage loss over two years was an independent predictor of knee replacement at four years. For every 1% increase in the rate of tibial cartilage loss there was a 20% increase risk of undergoing a knee replacement at four years (95% confidence interval, 10% to 30%). Those in the highest tertile of tibial cartilage loss had 7.1 (1.4 to 36.5) higher odds of undergoing a knee replacement than those in the lowest tertile. WOMAC score at baseline, female sex, and tibial bone size (but not age and radiographic score) were also predictors of knee replacement.
Conclusions: The data suggest that treatment targeted at reducing the rate of knee cartilage loss in subjects with symptomatic osteoarthritis may delay knee replacement. This has important implications in terms of prevention and therapeutic interventions in osteoarthritis.

Osteoarthritis is a major cause of work related and long term disability in people over the age of 50.[1] Therapeutic options that affect progression of disease are limited.[2] Recently glucosamine was shown to influence progression of knee osteoarthritis in women. This was a landmark observation as it was the first therapeutic agent to have an effect on progression of osteoarthritis.[2] However, there is still much debate about the outcome measure used in that study and the interpretation of the results.[3] Many patients with severe osteoarthritis eventually proceed to joint replacement in order to manage their symptoms of pain and limitation of function.[4] However, joint replacement is an expensive procedure with potential complications, particularly when the procedure needs to be repeated.[5]

The factors that influence whether a subject proceeds to a joint replacement are social and cultural as well as disease related.[4 6–8] A recent study investigating the predictors of listing for total hip replacement among attenders in primary care with a new episode of hip pain showed that pain duration, pain severity, and restriction of internal rotation were the major clinical predictors at presentation for being put on a waiting list for the procedure.[8] Radiographic predictors of osteoarthritis have similar performance to the clinical measures, although the relation between symptoms and structural change is inconsistent. Factors such as sex,[6] socioeconomic status,[7] and physician preference[9] have also been shown to affect the likelihood of having an arthroplasty. Little work has been done on measurement of structural change in joints and progression to arthroplasty.

Only recently has the quantification of articular cartilage been studied. Indeed, there has been increasing interest in its use as an outcome measure in osteoarthritis. We and others have validated this as a method for measuring articular cartilage volume accurately, and showed that it is reproducible[10–12] and correlates with the radiographic grade of osteoarthritis.[13] Cartilage volume has also been shown to be sensitive to change, subjects with osteoarthritis losing about 5% of their knee cartilage per annum.[14] Change in symptoms has also been shown to relate to change in cartilage volume.[15]

In this study we examined a cohort of subjects with predominantly mild to moderate symptomatic osteoarthritis, to determine whether the change in articular knee cartilage volume over two years is an independent predictor of progression to knee replacement.

METHODS

Subjects with early knee osteoarthritis were recruited by advertising through local newspapers and the Victorian branch of the Arthritis Foundation of Australia and in collaboration with general practitioners, rheumatologists, and orthopaedic surgeons. The study was approved by the ethics committee of the Alfred and Caulfield Hospitals in Melbourne, Australia. All subjects gave their informed written consent.

In all, 123 subjects entered the study and had magnetic resonance imaging (MRI) at baseline and two years later. They were contacted at year 4 to determine whether they had had a knee replacement. Inclusion criteria were age over 40, knee symptoms (at least one pain dimension of the WOMAC score above 20% and osteophytes present), and radiographic knee osteoarthritis (ACR radiographic criteria[16]). Subjects were excluded if any other form of arthritis was present, if they had contraindications to MRI (for example, a pacemaker, cerebral aneurysm clip, cochlear implant, presence of

Abbreviations: ACR, American College of Rheumatology; WOMAC, Western Ontario and McMaster Universities osteoarthritis index; VAS, visual analogue scale

Table 1 Characteristics of the study population

	Joint replacement (n = 18)	No joint replacement (n = 95)	p Value
Age (years)	64.1 (9.3)	63.1 (10.3)	0.83
Sex (per cent female)	67%	56%	0.44
BMI (kg/m^2)	29.9 (5.8)	28.6 (4.9)	0.28
Tibial bone area (mm^2)	3624 (517)	3413 (591)	0.16
WOMAC (pain, stiffness, function)	517.4 (172.9)	397.2 (222.5)	0.02
Pain	102.8 (35.3)	77.1 (41.2)	0.02
Stiffness	51.5 (16.7)	37.4 (22.5)	0.01
Function	374.4 (138)	290.0 (170.1)	0.05
Kellgren–Lawrence radiographic grade			
I	0	9	0.21
II	7	44	
III	11	42	
Baseline tibial cartilage volume (mm^3)	3526 (685)	3705 (932)	0.34
Annual loss of tibial cartilage (mm^3)	274 (208)	194 (191)	0.10
Per cent tibial cartilage loss	7.6 (5.8)	5.0 (5.0)	0.05

Values are mean (SD).
p Values are for the comparison between subjects who underwent knee replacement and those who did not.
Comparisons were made using Student's *t* test or the χ^2 test, as appropriate.
BMI, body mass index; WOMAC, Western Ontario and McMaster Universities osteoarthritis index.

shrapnel in strategic locations, metal in the eye, and claustrophobia), were unable to walk 50 feet without the use of assistive devices, had hemiparesis of either lower limb, and if total knee replacement was already planned. At year 4, all subjects were contacted and asked whether they had undergone a replacement of the same knee in which they had baseline and year 2 MRI. This was confirmed by contacting the treating physician in all cases.

Weight was measured to the nearest 0.1 kg (shoes and bulky clothing removed), using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes removed) using a stadiometer. Body mass index (BMI) (weight (kg)/height^2 (m)) was calculated. Function and pain were assessed by WOMAC (VAS, 10 cm).[17]

Each subject had a weight bearing anteroposterior tibio-femoral radiograph of the symptomatic knee at baseline, taken in full extension. Where both knees had osteoarthritis and were symptomatic, the knee with the least severe radiographic osteoarthritis was used. These were independently scored by two trained observers who employed a published atlas to classify disease in the tibio-femoral joint according to the Kellgren and Lawrence scale. The radiological features of tibio-femoral osteoarthritis were graded in each compartment, on a four point scale (0–3) for individual features of osteophytes and joint space narrowing.[18] In cases of disagreement between observers, the films were reviewed with a third independent observer. Intraobserver reproducibility (κ statistic) for agreement on features of osteoarthritis was 0.93 for osteophytes (grade 0,1 *v* 2,3) and 0.93 for joint space narrowing (grade 0,1 *v* 2,3). Interobserver reproducibility was 0.86 for osteophytes and 0.85 for joint space narrowing.[13]

Each subject had MRI on the symptomatic knee at baseline and approximately two years later. Knee cartilage volume was determined by means of image processing on an independent work station using the software program Osiris, as previously described.[13 14] Knees were imaged in the sagittal plane on the same 1.5 T whole body magnetic resonance unit (Signa Advantage HiSpeed GE Medical Systems, Milwaukee, Wisconsin, USA) using a commercial receive-only extremity coil. The following sequence and parameters were used: a T1 weighted fat suppressed 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; 512×192 matrix; one acquisition time of 11 minutes 56 seconds. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.83 mm (512×192 pixels).

Two trained observers read each MRI. The scans were measured by two observers independently. Each subject's baseline and follow up MRI was scored unpaired and blinded to subject identification and timing. The same two observers measured cartilage volume on each scan once. Their results were compared. If the results were within ±20%, an average

Table 2 Factors affecting risk of knee replacement

	Univariate analysis	Multivariate analysis*	95% CI	p Value
Age†	0.005	0.9	0.7 to 1.3	0.55
Sex (F *v* M)	2.3	9.9	1.5 to 65.4	0.02
BMI	0.05	0.9	0.8 to 1.1	0.38
Tibial bone area‡	0.001	1.2	1.0 to 1.4	0.02
Per cent tibial cartilage loss§	0.10	1.2	1.1 to 1.3	0.008
WOMAC¶	0.002	1.5	1.1 to 2.0	0.01
Radiological grade of OA**	0.77	1.8	0.6 to 6.1	0.32

*Multivariate analysis with age, sex, BMI, % tibial cartilage loss, WOMAC score, and bone size in regression equation.
†Change per five year increase in age.
‡Change per 100 mm^2 increase in tibial bone area.
§Change per 1% increase in tibial cartilage loss.
¶Change per 100 unit increase in WOMAC score.
**Based on Kellgren–Lawrence grade: change per unit increase in grade.
BMI, body mass index; CI, confidence interval; F, female; M, male; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Universities osteoarthritis index

Table 3 Relation between tertiles of tibial cartilage loss between time 0 and 2 years and incidence of knee replacement at year 4

	Number knee replacements (%)	OR	Adjusted OR (95% CI)*†
Rate of tibial cartilage loss <3% per annum (n = 37)	3 (8.1)	1	1
Rate of tibial cartilage loss 3–8% per annum (n = 40)	7 (17.5)	2.4	2.3 (0.4 to 12.2)
Rate of tibial cartilage loss >8% per annum (n = 36)	8 (22.2)	3.2	7.1 (1.4 to 36.5)

*Multivariable logistic regression adjusting for age, gender, BMI, % tibial cartilage loss, WOMAC score and bone size.
†p = 0.02 for trend.
CI, confidence interval; OR, odds ratio.

of the results was used. If they were outside this range, the measurements were repeated until the independent measures were within ±20%, and the averages used. Repeat measurements were made blind to the results of the comparison of the previous results. The coefficient of variation (CV) for the tibial cartilage volume measures was 2.6%.[13 14] Tibial plateau area was determined by creating an isotropic volume from the three input images closest to the knee joint, which were reformatted in the axial plane. The area was directly measured from these images. The CV for the tibial plateau area was 2.3%.[13 14] The results of the MRI were not given to the patients or their treating medical practitioners.

Statistics

Descriptive statistics for characteristics of the subjects were tabulated. Unpaired *t* tests were used for comparison of means. The χ^2 test was used to compare nominal characteristics between the groups. Change in cartilage volume (follow up cartilage volume subtracted from initial cartilage volume) and percentage change (1 − [follow up cartilage volume divided by initial cartilage volume], expressed as a percentage) over the period of time was divided by time between MRI scans to obtain an annual rate of change. The principal outcome measure in the analyses was the presence or absence of joint replacement. Logistic regression was used to explore the possible factors affecting the risk of joint replacement, including age, sex, height, weight, BMI, WOMAC scores (pain, stiffness, function), bone size, and radiographic grade of osteoarthritis. All analyses were done using the SPSS statistical package (version 10.0.5, SPSS, Cary, North Carolina, USA). A probability (p) value less than 0.05 was considered statistically significant.

RESULTS

One hundred and thirteen subjects (92%) completed follow up (table 1). Five subjects had died, three were lost to follow up, and two moved overseas or interstate. Subjects who had undergone a knee replacement had a higher baseline WOMAC score than subjects who did not undergo knee replacement (table 1). This was observed for the total score, with similar results in all domains (pain, function, and stiffness). Although the baseline tibial cartilage volume was similar in the two groups, there was a higher relative loss in those who subsequently underwent a knee replacement. No other significant differences were observed in univariate analysis.

Age and BMI were not risk factors for knee replacement in this cohort (table 2), but women were at increased risk of progressing to knee replacement ($p<0.01$). Baseline knee WOMAC score (a measure of pain, stiffness, and function) was a significant risk factor for progressing to a knee replacement, independent of age, sex, rate of cartilage loss, or baseline radiological grade of osteoarthritis. Tibial bone size at baseline also predicted knee replacement, with greater bone size increasing the risk. There was no significant effect of baseline radiological osteoarthritis or baseline cartilage volume. Annual per cent tibial cartilage loss between 0 and 2 years was a significant risk factor for progressing to a knee replacement, independent of age, sex, baseline radiological grade of osteoarthritis, and bone size ($p = 0.008$). For every 1% increase in rate of tibial cartilage loss there was a 20% increase in the risk of undergoing a knee replacement at 4 years (95% confidence interval, 10% to 30%).

The study subjects were categorised into tertiles of rate of tibial cartilage loss: <3% per annum, 3–8% per annum, and >8% per annum (table 3). The odds ratios for undergoing a joint replacement relative to the baseline category of <3% per annum were 2.3 for 3–8% annual loss and 7.1 for >8% annual loss, after adjustment for age, sex, BMI, WOMAC score, bone size, and baseline radiological severity of the osteoarthritis ($p = 0.02$ for trend).

DISCUSSION

In this cohort of 113 symptomatic subjects with mild to moderate osteoarthritis who were followed for four years, the rate of tibial cartilage loss between years 0 and 2 was an independent predictor of knee replacement at year 4. The correlation was linear, with evidence of a dose–response relation. WOMAC score at baseline, female sex, and tibial bone size were also predictors of a knee replacement.

We are not aware of any previous study that has examined the relation between loss of knee cartilage and progression to a knee replacement. The current gold standard for assessing structural change in osteoarthritis is joint space narrowing.[19] Although it is well recognised that joint replacement is usually undertaken when there is little articular cartilage remaining, we are not aware of any studies that have examined change in joint space width and progression to joint replacement, nor are there data on baseline grade of osteoarthritis and subsequent progression to joint replacement after this time. In our study, severity of osteoarthritis at baseline was not an independent risk factor for progression to arthroplasty at year 4.

There has been much debate as to whether there are ''fast'' and ''slow'' losers of articular cartilage among subjects with osteoarthritis. Raynauld *et al* suggested this in a small MRI study of 32 subjects published in abstract form.[20] To our knowledge no other study has confirmed this. In our previous study where we examined cartilage loss over two years we were not able to identify these subgroups clearly, and the rate of cartilage loss was normally distributed.[14] In the current study, we report a positive dose–response relation between rate of tibial cartilage loss and progression to joint replacement, which does not support the concept of fast and slow losers

Other factors that predicted progression to knee replacement in our cohort were being female, WOMAC score (pain, function and stiffness), and bone size. Previous studies have suggested that knee osteoarthritis tends to be more severe in women than in men.[6] However, it has recently been found that despite more severe disease, women may be less likely to proceed to a joint replacement.[6] This was not the case in our cohort. The finding that baseline pain and function level are predictors of a knee replacement are consistent with the current indication for joint replacement, which is both *x* ray and symptom driven.[8] In this study we found that the model examining factors affecting joint replacement was strengthened by the addition of bone size in the regression equation. The available data suggest that bone size is an important determinant of normal cartilage volume, independently of BMI,[13] and thus it may simply be a confounder. However, there is emerging evidence that bone size plays a role in the initiation of this disease, while cartilage volume is the final pathway[21]—an alternative explanation for these findings.

This is the largest published longitudinal study of MRI measured knee cartilage volume of which we are aware. We recruited subjects with symptomatic osteoarthritis from a broad base and did not select for any particular subgroup of patients with osteoarthritis. Thus it is unlikely that we selected for a group which was more likely to lose cartilage. Nevertheless, this will need to be confirmed using larger numbers of subjects followed over longer periods, particularly to determine the role of other potential risk factors such as change in body weight and physical activity. A major strength of our study was that our main outcome (joint replacement) is clinically important and objective.

Conclusions

We have shown for the first time that the rate of structural change at the knee—articular cartilage loss—is an independent risk factor for subsequent replacement of that knee. This was independent of age, sex, baseline level of pain, and the radiological severity of osteoarthritis. This suggests that treatments targeted at reducing the rate of knee cartilage loss, even in more advanced disease, may delay knee replacement. This has important implications for prevention and therapeutic interventions in knee osteoarthritis.

ACKNOWLEDGEMENTS

This study was supported by the National Health and Medical Research Council through Project Grant and Clinical Center for Research Excellence in Therapeutics. We would like to acknowledge Judy Hankin for recruitment of study subjects and doing duplicate volume measurements, the MRI Unit at the Alfred Hospital for their cooperation, and Kevin Morris for technical support. We would especially like to thank the study participants who made this study possible.

Authors' affiliations

F M Cicuttini, A Forbes, A E Wluka, Department of Epidemiology and Preventive Medicine, Monash University Medical School, Alfred Hospital, Melbourne, Australia
G Jones, Menzies Centre for Population Health Research, Hobart, Tasmania, Australia

REFERENCES

1 **Cooper C**. Epidemiology. In: Klippel J, Dieppe P, eds. *Rheumatology*, 2nd ed, vol 2. London: CV Mosby, 1998:8.2.1.
2 **Reginster JY**, Deroisy R, Rovati LC, Lee RL, Lejeune E, Bruyere O, *et al*. Long-term effects of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. *Lancet* 2001;**357**:251–6.
3 **McAlindon T**. Glucosamine for osteoarthritis: dawn of a new era? *Lancet* 2001;**357**:247–8.
4 **Hawker GA**, Wright JG, Coyte PC, Williams JI, Harvey B, Glazier R, *et al*. Determining the need for hip and knee arthroplasty: the role of clinical severity and patients' preferences. *Med Care* 2001;**39**:206–16.
5 **Drake C**, Ace M, Maale G. Revision total hip arthroplasty. *AORN J* 2002;**76**:414–17.
6 **Hawker G**, Wright J, Coyte P, Williams JI, Harvey B, Glazier R, *et al*. Differences between men and women in the rate of use of hip and knee arthroplasty. *N Engl J Med* 2000;**342**:1016–22.
7 **Hawker G**, Wright J, Glazier R, Coyte PC, Harvey B, Williams JI, *et al*. The effect of education and income on need and willingness to undergo total joint arthroplasty. *Arthritis Rheum* 2002;**46**:3331–9.
8 **Birrell F**, Afzal C, Nahit E, Macfarlane GJ, Cooper C, Croft PR, *et al*. Predictors of hip joint replacement in new attenders in primary care with hip pain. *Br J Gen Pract* 2003;**53**:26–30.
9 **Coyte P**, Hawker G, Croxford R, Attard C, Wright J. Variation in rheumatologists' and family physicians' perceptions of the indications for and outcomes of knee replacement surgery. *J Rheumatol* 1996;**23**:586–9.
10 **Peterfy CG**, van Dijke CF, Janzen DL, Gluer CC, Namba R, Majumdar S, *et al*. Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: optimization and validation. *Radiology* 1994;**192**:485–91.
11 **Eckstein F**, Schnier M, Haubner M, Priebsch J, Glaser C, Englmeier KH, *et al*. Accuracy of cartilage volume and thickness measurements with magnetic resonance imaging. *Clin Orthop* 1998;(352):137–48.
12 **Cicuttini F**, Forbes A, Morris K, Darling S, Bailey M, Stuckey S. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis Cart* 1999;**7**:265–71.
13 **Cicuttini FM**, Wluka A, Wolfe R, Forbes A. Comparison of cartilage volume and radiological assessment of the tibiofemoral joint. *Arthritis Rheum* 2003;**48**:682–8.
14 **Wluka AE**, Stuckey S, Snaddon J, Cicuttini FM. The determinants of change in tibial cartilage volume in osteoarthritic knees. *Arthritis Rheum* 2002;**46**:2065–72.
15 **Wluka AE**, Wolfe R, Davis SR, Stuckey S, Cicuttini FM. Tibial cartilage volume change in healthy postmenopausal women: a longitudinal study. *Ann Rheum Dis* 2004;**64**:444–9.
16 **Altman R**, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis Rheum* 1986;**29**:1039–49.
17 **Bellamy N**. Outcome measures in osteoarthritis clinical trials. *J Rheumatol* 1995;**22**(suppl 43):49–51.
18 **Altman RD**, Hochberg M, Murphy WA, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. *Osteoarthritis Cart* 1995;**3**(suppl A):3–70.
19 **Altman R**, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, *et al*. Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. *Osteoarthritis Cart* 1996;**4**:217–43.
20 **Raynauld JP**, Pelletier JP, Beaudoin G, *et al*. A two-year study in osteoarthritis patients following the progression of the disease by magnetic resonance imaging using a novel quantification imaging system [abstract 311]. *Arthritis Rheum* 2002;**46**(suppl):S150.
21 **Jones G**, Ding C, Scot T F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area. *Osteoarthritis Cart* 2004;**12**:169–74.