

The Determinants of Change in Patella Cartilage Volume in Osteoarthritic Knees

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ABSTRACT. Objective. The rate of change in patella articular cartilage and factors influencing it, in subjects with osteoarthritis (OA), is unknown. We performed a cohort study to determine this.

Methods. One hundred ten subjects with OA had baseline skyline and lateral radiographs and magnetic resonance imaging (MRI) on their knee. They were followed 2 years later with a repeat MRI of the same knee. Patella and tibial cartilage volume was measured at baseline and followup. Risk factors assessed at baseline were tested for their association with change in patella cartilage volume over time.

Results. The annual percentage loss of patella cartilage was $4.5 \pm 4.3\%$. Sex, body mass index (BMI), and pain score at baseline were associated with an increase in cartilage loss. The rate of patella cartilage loss was greater in women than men, 5.3% versus 3.5% ($p < 0.03$), independent of age, BMI, and pain score. No association was seen between change in patellar cartilage volume and change in either medial or lateral tibial cartilage volume ($r = 0.02$, $p = 0.86$ and $r = 0.08$, $p = 0.43$, respectively).

Conclusion. In OA, patella cartilage volume is lost at $4.5 \pm 4.3\%$ per year. The main factors affecting this are sex, BMI, and baseline pain score. The poor correlation between patella cartilage loss and cartilage loss in the tibial compartment suggests that the pathogenetic mechanisms for OA in the patellofemoral and tibiofemoral joint may differ. Further work will be required to determine whether the rate of patella cartilage loss in OA is steady or phasic, and to determine which factors can be modified to reduce cartilage loss. (J Rheumatol 2002;29:2615–9)

Key Indexing Terms:

CARTILAGE

PATELLA

OSTEOARTHRITIS

Osteoarthritis (OA) is a common cause of disability in people aged over 65 years¹. Symptomatic knee OA has been shown to be commonly related to patellofemoral disease^{2,3}. However, very little is known about the rate of progression of patellofemoral joint OA or the optimum method for determining this. One study compared skyline and lateral radiographs and suggested that skyline radiographs were more sensitive for detecting progression⁴. In that study the joint

spaces in the lateral and medial facets were reduced by an average of 0.4 and 0.5 mm, respectively, over a 31 month period.

There has been increasing interest in the use of magnetic resonance imaging (MRI) in the measurement of knee cartilage volume as a possible outcome measure in arthritis^{5–7}. Measurement of patella cartilage has been shown to be a valid measure of cartilage volume when MRI cartilage volume is compared to anatomical dissection, and to be reproducible, with coefficient of variations of less than 5%^{5–7}. MRI assessment of the joint has potential advantages compared to radiographs in that joint cartilage is directly visualized and the whole 3-dimensional structure can be examined. The 3-dimensional measurement is less likely to be influenced by repositioning, which is important in longitudinal studies. Measurement of patella cartilage volume may be a useful measure of progression of OA in the patellofemoral joint.

We examined a cohort of subjects with predominantly mild to moderate symptomatic knee OA over 2 years, to determine the change in patella cartilage volume over that time and to determine which factors may influence this.

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MATERIALS AND METHODS

Patients were recruited using a combined strategy including advertising through local newspapers and the Victoria branch of the Arthritis Foundation of Australia as well as collaboration with general practitioners, specialist rheumatologists, and orthopedic surgeons. The study was approved by the ethics committee of the Alfred and Caulfield hospitals in Melbourne, Australia. All patients gave informed consent. Subjects aged 40 years or more who fulfilled American Rheumatism Association clinical diagnostic criteria for OA knee⁸ and had radiographic evidence of osteophytes or joint space narrowing were examined. Subjects were excluded if any other form of arthritis was present, if there was contraindication to MRI, or if a total knee replacement was planned. 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) ($\text{weight}/\text{height}^2$) was calculated. Pain, stiffness, and function dimensions derived from the Western Ontario and McMaster University Osteoarthritis Index (WOMAC) were measured⁹. Patients were asked to rate the change in these dimensions since their last visit using a 5 cm visual analog scale (VAS).

Each subject had an MRI performed on their symptomatic knee at baseline and about 2 years later. Where both knees had OA and were symptomatic, the knee with least severe OA was used. Patella and tibial cartilage volumes were determined by means of image processing on an independent work station using the software program Osiris^{10,11}. Knees were imaged in the sagittal plane on the same 1.5 T whole-body MRI unit (Signa Advantage HiSpeed, GE Medical Systems, Milwaukee, WI, USA) using a commercial receive-only extremity coil. The following sequence and variables were used: a T1 weighted fat suppressed 3-D gradient recall acquisition in 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 11 min 56 s. 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 readers measured all the MRI, and were blinded regarding the time sequence of the MRI. The average time to measure the MRI was 20 min. The coefficients of variation (CV) were 2.1% for patella cartilage volume and 3.4% and 2.0% for medial and lateral tibial cartilage, respectively¹¹.

The following radiographic views of the patellofemoral joint were obtained at baseline: (1) a standing lateral (mediolateral) view in 30° flexion, and (2) a skyline (inferosuperior) view in 45° flexion using a perspex positioning wedge with the subject supine. All radiographs were independently assessed by 2 trained observers using an atlas to classify disease in the tibiofemoral (TFJ) and patellofemoral joint (PFJ)¹². The observers were blind to the clinical findings. Radiological features of OA in the TFJ and PFJ were graded on a 4 point scale (0–3) for both individual features of osteophytes and joint space. In case of disagreement between observers, the radiographs were reviewed with a third independent observer. Intraobserver reproducibility for osteophytes in the different compartments varied from 0.90 to 0.93 and for joint space narrowing from 0.88 to 0.92. Interobserver reproducibility varied from 0.82 to 0.86 for osteophytes and 0.81 to 0.85 for joint space narrowing (kappa statistic).

Descriptive statistics for characteristics of the subjects were tabulated. Independent t tests were used for comparison of means. Chi-square tests or Fisher's exact test (where appropriate) were used to compare characteristics between the groups. Change in patella and medial and lateral tibial cartilage volume over the period of time was divided by time between MRI scans to obtain an annual rate of change. Principal outcome measures in analyses were annual percentage patella cartilage loss from baseline and the volume of cartilage lost annually. Multiple linear regression techniques were used to explore the factors affecting the rate of change in cartilage volume. All analyses were performed using the SPSS statistical package (version 10.0.5; SPSS, Cary, NC, USA).

RESULTS

One hundred ten subjects took part in this study (Table 1).

Most had mild or moderate patellofemoral OA (Table 1), with only 21 (19%) having grade 3 patellofemoral osteophytes and/or joint space narrowing on skyline radiographs and 8 (7.3%) on lateral patellofemoral views. The non-normalized patella cartilage volume was significantly greater in men than in the women (Table 1).

The average amount of patella cartilage lost per year $[(\text{patella cartilage at commencement of study} - \text{patella cartilage at the end of study})/\text{time between scans}]$ was $145 \pm 154 \mu\text{m}^3/\text{yr}$ (Table 2). When this was calculated as a percentage of the initial baseline cartilage $[(\text{initial patella cartilage volume} - \text{followup patella cartilage volume})/\text{initial patella cartilage volume per year}]$, this represented an annual rate of loss of patella cartilage of $4.5 \pm 4.3\%$. The absolute amount of patella cartilage lost was somewhat greater in women than men, although this was not statistically significant (Table 2). The percentage of patella cartilage loss, which takes into account the baseline patella cartilage volume, was significantly greater in women than men (Table 2).

Univariate analysis showed sex and baseline pain score were significant predictors of annual percentage loss ($p = 0.06$ and $p = 0.02$, respectively). These increased in significance as predictors of the percentage of patella cartilage lost after adjustment for age, BMI, and baseline pain score, with BMI also becoming a significant predictor of percentage patella cartilage loss (Table 3). After adjustment for these confounders the rate of patella cartilage loss was (mean \pm SE) $5.3 \pm 0.5\%$ for women and $3.4 \pm 0.6\%$ for men (Table 2). Change in weight over the study period, grade of osteophyte, and grade of joint space narrowing had no significant effect on change in patella cartilage volume. There was no significant change in rate of patella cartilage loss when we adjusted for use of simple analgesics (paracetamol) ($4.6 \pm 0.7\%$). Thirty-four (31%) subjects reported using a non-steroidal antiinflammatory drug at least weekly during this study. There was no significant change in the rate of patella cartilage loss when subgroup analysis was performed excluding these subjects ($5.0 \pm 4.1\%$).

We examined the tibial cartilage loss in this population. The annual rate of lateral tibial cartilage loss was $5.1 \pm 7.3\%$, the medial tibial cartilage loss was $4.6 \pm 6.6\%$. There was no significant correlation between the annual rate of patella and lateral tibial cartilage loss ($r = 0.08$, $p = 0.43$) or between patella and medial cartilage loss ($r = 0.02$, $p = 0.86$). In contrast, there was a significant relationship between loss of cartilage in the medial and lateral tibiofemoral joints ($r = 0.25$, $p = 0.007$).

DISCUSSION

In this cohort of 110 symptomatic subjects with mild to moderate OA, followed over 2 years, we found that the rate of patella cartilage loss was $4.5 \pm 4.3\%$ per year. The rate of patella cartilage loss was greater in women than in men.

Table 1. Characteristics of study population. Data are mean \pm SD unless otherwise indicated.

	Total Population, (n = 110)	Men, (n = 44)	Women, (n = 66)	p
Age, yrs	63.2 (10.2)	63.2 (10.0)	63.1 (10.3)	0.99
Height, cm	167.0 (9.1)	175.3 (5.8)	161.5 (6.2)	< 0.001
Weight, kg	80.9 (15.3)	85.4 (13.6)	77.9 (15.6)	0.01
BMI, weight (kg)/height ² (m ²)	29.0 (5.1)	27.7 (3.4)	29.9 (5.9)	0.03
Time between scans, yrs	1.9 (0.2)	1.9 (0.2)	1.9 (0.3)	0.68
No. (%) with moderate patellofemoral OA*	46 (42)	21 (49)	25 (38)	0.15
No. (%) with moderate tibiofemoral OA**	63 (57)	25 (57)	33 (50)	0.10
Patella cartilage volume at baseline, μm^3	3201 (1034)	3734 (1145)	2845 (776)	< 0.001
Patella cartilage volume at followup, μm^3	2926 (979)	3474 (1080)	2561 (703)	< 0.001

* Moderate patellofemoral OA defined as \geq grade 2 patellofemoral osteophyte or joint space narrowing. ** Moderate tibiofemoral OA defined as \geq grade 2 osteophytes or joint space narrowing in either the medial or lateral tibiofemoral compartment. Comparisons made using Student's t test, or Fisher's exact test*.

Table 2. Annual change in patella cartilage.

	Total	Men	Women	p
Average amount of patella cartilage lost per year (μm^3), mean (SD)*	145 (154)	140 (175)	149 (140)	0.79
Percentage change, mean (SD)	-4.5 (4.3)	-3.6 (4.0)	-5.2 (4.5)	0.05
Adjusted percentage change**, mean (SE)	-4.6 (0.6)	-3.4 (0.6)	-5.3 (0.5)	0.03

* Calculated as (patella cartilage at start of study minus patella cartilage at end of study)/time between scans.

** Multivariate analysis with age, BMI, and baseline pain score in regression equation.

Table 3. Factors affecting annual percentage patella cartilage loss.

	Univariate Analysis, Regression Coefficient (95% CI)	Multivariate Analysis*, Regression Coefficient (95% CI)	p
Age ¹	4.4×10^{-4} (0, 0.001)	1.3×10^{-4} (-0.001, 0.002)	0.75
Sex ²	0.016 (-0.001, 0.032)	0.019 (0.003, 0.033)	0.02
BMI ³	-6.45×10^{-3} (-0.002, 0.001)	-1.9×10^{-3} (-0.004, 0.000)	0.04
Pain score at baseline ⁴	2.1×10^{-4} (-1.1×10^{-4} , 2.8×10^{-4})	2.8×10^{-4} , (1×10^{-4} , 3×10^{-4})	0.004

* Multivariate analysis with age, sex, BMI, and initial patella cartilage volume in regression equation. ¹ Change per 1 year increase in age. ² Females compared to males. ³ Change per unit increase in BMI. ⁴ Change per unit increase in pain score.

High BMI and baseline pain score were associated with increased annual percentage patella cartilage loss. Following adjustment for these confounders the rate of patella cartilage loss was $5.3 \pm 0.5\%$ for women and $3.4 \pm 0.6\%$ for men. The rate of loss of patellar cartilage was not related to loss of tibial cartilage.

No data are available on longitudinal change in patella cartilage volume. The radiographic approximation of articular cartilage (joint space width) has been the measurement used to follow progression of OA, particularly at the tibiofemoral joint. However, there is little information available on the rate of progression of patellofemoral OA, even as measured radiologically. Indeed, whether the lateral view or skyline view of the knee is a better measure of change is

unknown. One study compared them to examine radiological progression of patellofemoral OA in 54 hospital referred patients (108 knees) with knee OA followed over an average of 31 months⁴. Minimum joint space was measured by metered caliper. On the lateral view measured joint space decreased in 51% of knees but increased in 43%, with overall no significant mean group change with time (-0.2 mm; 95% confidence interval 0.1 to -0.5). By contrast, on the skyline view joint space decreased in at least one facet in 71% of knees, with significant decrease in mean joint space for both lateral facets (-0.4 mm; 95% CI -0.2 to -0.6) and medial facets (-0.5 mm; 95% CI -0.1 to -0.8). How this relates to change in a 3-dimensional structure such as cartilage volume, as measured in our study, is unknown. Use of

the lateral view is complicated by possible patellar subluxation with progressive disease. Patellar subluxation changes the measured joint space⁴. This reduces the validity of this measure as a measure of disease progression. Similarly, in the skyline view differences in knee flexion alter joint space narrowing, adding another source of error⁴. Positioning may be less important when measuring a 3-dimensional structure such as knee cartilage volume, making this measure comparatively more reliable.

We have presented the average change in cartilage volume of the cohort. However, it is important to be able to determine the minimum detectable difference in percentage change for an individual. At a 5% level of significance, this can be estimated by multiplying the coefficient of variation for a single volume measurement by 2.8¹³. As the coefficient of variation in our study was 2.1% for measurement of patella cartilage volume, this would be $\pm 5.9\%$ per year.

Recently, there has been increasing interest in the use of MRI in the measurement of knee cartilage volume⁵⁻⁷. There are few available data regarding change in tibiofemoral cartilage. One study has suggested the rate of cartilage loss in the lateral and medial tibial cartilages in OA is about 5%¹⁴. Two small studies of 16 and 11 subjects published in abstract form only suggested that tibiofemoral articular cartilage is lost at a rate of roughly 6% per year^{15,16}. There are no data available on patella cartilage. However, the rate of cartilage loss in the tibial cartilage is of similar magnitude to what we observed at the patella, suggesting that this is biologically plausible¹⁴⁻¹⁶.

Some studies^{17,18}, although not all¹⁹, suggest that the pathogenetic mechanisms involved in patellofemoral and tibiofemoral OA may differ. A population based study of 325 unrelated, middle aged women showed that obesity was associated with both tibiofemoral and patellofemoral OA, but that distal interphalangeal OA was associated with tibiofemoral but not patellofemoral OA¹⁸. In the same study there was an inverse association between premenopausal status and patellofemoral OA but not tibiofemoral OA. Another study compared 109 men and women with symptomatic, radiographic OA in the tibiofemoral and/or patellofemoral compartments of the knee joint with 218 community controls matched for age and sex¹⁷. This study showed that obesity and meniscectomy were strong risk factors for medial tibiofemoral OA, while Heberden's nodes and family history were more closely associated with patellofemoral OA. Our data lend some support to the notion that the TFJ and PFJ may have different pathogenetic mechanisms, since we observed no correlation with joint cartilage loss at the patella and either the medial or tibiofemoral joints. In contrast, there was a significant correlation between cartilage loss in an individual subject in the medial and lateral tibiofemoral joints.

We found that the rate of patella cartilage loss is higher in women than men. It has been shown that women tend to

have more severe patellofemoral disease². However, there are no data available on whether patellofemoral disease progresses more rapidly in women than men. We also observed an effect of BMI on loss of patellar cartilage. BMI has been shown to be associated with patellofemoral OA in cross-sectional studies^{17,20}. However, no data are available on whether it is associated with progression of patellofemoral OA. In this study pain at baseline was a risk factor for patella cartilage loss. The mechanism for this is unclear. It may be that knee pain acts indirectly and affects the knee biomechanics, which in turn increases patella cartilage loss. For example, it is well described that knee pain is associated with quadriceps muscle weakness²¹.

Measurement of cartilage volume is limited by the contrast between articular cartilage and the adjacent tissues. Our method has been validated against cadavers and has excellent reproducibility, with coefficients of variation of 2-3%^{10,11}. To improve in-plane resolution, we use a matrix of 512×192 pixels, resulting in an in-plane resolution of 0.31×0.83 mm. This is the only longitudinal study of MRI measured patella knee cartilage volume that we are aware of. Nevertheless, it is likely that, given the number of subjects we have, longer duration of followup will be needed to determine the role of other potential risk factors such as current activity level, grade of patellofemoral OA, and change in body weight.

In subjects with knee OA, patella cartilage volume is lost at a rate of about 4.5% per annum. Our data suggest the rate of patella cartilage loss may be greater in women compared to men and is associated with increased BMI and baseline pain score. The poor correlation between patella cartilage loss and cartilage loss in the tibial compartment suggests that the pathogenetic mechanisms for OA in the patellofemoral and tibiofemoral joint may differ. These data may be useful to calculate sample size estimations for studies investigating either preventive strategies or chondroprotective agents in patellofemoral joint OA. Further work will be required to determine whether the rate of patella cartilage loss in OA is steady or phasic, and to determine which factors can be modified to reduce cartilage loss.

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REFERENCES

1. Felson D, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly: The Framingham Osteoarthritis Study. *Arthritis Rheum* 1987;30:914-8.
2. McAlindon TE, Snow S, Cooper C, Dieppe PA. Radiographic patterns of osteoarthritis of the knee joint in the community: the importance of the patellofemoral joint. *Ann Rheum Dis* 1992;51:844-9.
3. Ledingham J, Regan M, Jones A, Doherty M. Radiographic patterns

- of osteoarthritis of the knee in patients referred to hospital. *Ann Rheum Dis* 1993;52:520-6.
4. Lanyon P, Jones A, Doherty M. Assessing progression of patellofemoral osteoarthritis: a comparison between two radiographic methods. *Ann Rheum Dis* 1996;55:875-9.
 5. Peterfy CG, van Dijke CF, Janzen DL, 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.
 6. Eckstein F, Schnier M, Haubner M, et al. Accuracy of cartilage volume and thickness measurements with magnetic resonance imaging. *Clin Orthop* 1998;352:137-48.
 7. Cicuttini F, Forbes A, Morris K, et al. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis Cartilage* 1999;7:265-71.
 8. Altman R, Asch E, Bloch D, 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.
 9. Bellamy N. Outcome measures in osteoarthritis clinical trials. *J Rheumatol* 1995;22 Suppl 43:49-51.
 10. Cicuttini F, Forbes A, Morris K, et al. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis Cartilage* 1999;7:265-71.
 11. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site differences in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. *Arthritis Rheum* 2000;43:2543-9.
 12. Burnett S, Hart DJ, Cooper C, Spector TD. A radiographic atlas of osteoarthritis. London: Springer-Verlag; 1994.
 13. Cummings SR, Black D. Should perimenopausal women be screened for osteoporosis? *Ann Intern Med* 1986;104:817-23.
 14. Wluka A, Stuckey S, Snaddon J, Cicuttini F. The determinants of change in tibial cartilage volume in osteoarthritic knees. *Arthritis Rheum* 2002: (In press).
 15. Peterfy C, White DL, Zhao J, Van Dijke CF, Genant HK. Longitudinal measurement of knee articular cartilage volume in OA [abstract]. *Arthritis Rheum* 1998;41 Suppl:S361.
 16. Raynauld JP, Kauffman C, Godbout B, et al. Knee osteoarthritis progression evaluated by magnetic resonance imaging and a novel quantification software tool [abstract]. *Arthritis Rheum* 2000;43 Suppl:S399.
 17. Cooper C, McAlindon T, Snow S, et al. Mechanical and constitutional risk factors for symptomatic knee osteoarthritis: differences between medial tibiofemoral and patellofemoral disease. *J Rheumatol* 1994;21:307-13.
 18. Cicuttini FM, Spector T, Baker J. Risk factors for osteoarthritis in the tibiofemoral and patellofemoral joints of the knee. *J Rheumatol* 1997;24:1164-7.
 19. McAlindon T, Zhang Y, Hannan M, et al. Are risk factors for patellofemoral and tibiofemoral knee osteoarthritis different? *J Rheumatol* 1996;23:332-7.
 20. Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. *J Rheumatol* 1996;23:1221-6.
 21. March L. Osteoarthritis. *Med J Australia* 1997;166:98-103.