EXTENDED REPORT

How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis?

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Background: No consistent relationship between the severity of symptoms of knee osteoarthritis (OA) and radiographic change has been demonstrated.

Objectives: To determine the relationship between symptoms of knee OA and tibial cartilage volume, whether pain predicts loss of cartilage in knee OA, and whether change in cartilage volume over time relates to change in symptoms over the same period.

Method: 132 subjects with symptomatic, early (mild to moderate) knee OA were studied. At baseline and 2 years later, participants had MRI scans of their knee and completed questionnaires quantifying symptoms of knee OA (knee-specific WOMAC: pain, stiffness, function) and general physical and mental health (SF-36). Tibial cartilage volume was determined from the MRI images.

Results: Complete data were available for 117 (89%) subjects. A weak association was found between tibial cartilage volume and symptoms at baseline. The severity of the symptoms of knee OA at baseline did not predict subsequent tibial cartilage loss. However, weak associations were seen between worsening of symptoms of OA and increased cartilage loss: pain ($r_s = 0.28$, $p = 0.002$), stiffness ($r_s = 0.17$, $p = 0.07$), and deterioration in function ($r_s = 0.21$, $p = 0.02$).

Conclusion: Tibial cartilage volume is weakly associated with symptoms in knee OA. There is a weak association between loss of tibial cartilage and worsening of symptoms. This suggests that although cartilage is not a major determinant of symptoms in knee OA, it does relate to symptoms.

Osteoarthritis (OA), the most common form of arthritis, is a major burden to the community.[1] Indeed, the estimated direct and indirect costs of arthritis in the United States exceed $65 billion dollars a year.[2] OA has a significant impact on function, activities of daily living, work, and function within society. Its prevalence rises with age.[3] With an aging society, its impact will continue to grow.

The relationship between the clinical symptoms of knee OA, such as pain and function, and the structural changes of OA measured radiographically is unclear.[3–5] It is well established that with increasing radiographic severity of knee OA the prevalence of knee pain increases.[3 5 6] However, the severity of pain does not relate to the degree of radiographic OA, nor has radiographic change been linked consistently with symptoms of disease.[4 7] This is contrary to intuition, which would suggest that as structural damage occurs, the severity of symptoms would increase. Whether knee pain predicts progression of knee OA is controversial, with different studies disagreeing on the presence of an effect.[8–13] Similarly, longitudinal studies have shown no consistent correlation between change in symptoms of knee OA and radiographic changes over 1–12 years.[11 14 15] To account for these inconsistencies, expert committees have suggested that in clinical research of OA we need to focus separately on both subjective symptomatic relief and on objective markers of change in joint morphology, such as joint space width, as a surrogate marker for articular cartilage, to define response.[16]

Until recently, radiographic change has been the accepted way in which to assess structural change in OA, using joint space narrowing as a proxy for articular cartilage. However, recently, magnetic resonance imaging (MRI) has been used to measure articular cartilage non-invasively.[17–19] This method has been shown to be a valid and reproducible measure of cartilage that is sensitive to change.[17–20] It is

emerging as a possible measure of disease severity in knee OA.[21]

We sought to examine the relationship between pain and other symptoms of knee OA and articular tibial cartilage volume in an existing cohort with mild to moderate symptomatic OA.[22] We sought to determine (*a*) whether the severity of pain and symptoms in knee OA relates to tibial cartilage volume; (*b*) whether the degree of pain is predictive of cartilage loss; and (*c*) whether change in cartilage volume is associated with changes in the severity of knee pain, stiffness, and functional impairment.

METHODS

Patient selection

The subjects included in this study all had symptomatic knee OA, with *x* ray examinations and MRI scans at baseline, and had been recruited by advertising in local newspapers, the Victorian branch of the Arthritis Foundation of Australia, and by contacting treating doctors (general practitioners, rheumatologists, and orthopaedic surgeons), as previously described.[22] The study was approved by the ethics committee of the Alfred Hospital and Caulfield Medical Centre, Melbourne, Australia. All patients gave informed consent.

Inclusion and exclusion criteria

Men and women aged 40 years or more were included who fulfilled American College of Rheumatology clinical and radiographic criteria for knee OA (all had osteophytes present).[23] For inclusion patients were required to have pain on more than half the days of a month and at least

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Abbreviations: BMI, body mass index; MRI, magnetic resonance imaging; OA, osteoarthritis; SF-36, Short Form-36; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index

one pain dimension of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score above 20%.[24]

The following were exclusion criteria for entry into the study: any contraindication to MRI (for example, pacemaker, cerebral aneurysm clip, cochlear implant, presence of metal/shrapnel in strategic locations, such as in the eye, and claustrophobia), inability to cooperate with study requirements and give informed consent, dementia, other forms of arthritis, an inability to walk 50 feet (15 m) without the use of assistive devices, hemiparesis of either leg, and those awaiting knee replacement or with grade IV knee OA.[25]

Measures

At baseline and at 2 year follow up subjects completed a questionnaire regarding demographic details and incorporating validated instruments to measure the level of current physical activity[26] and quality of life (physical and mental health components of the Standard Form-36 (SF-36), standardised to the 1995 Australian population, where higher scores indicate better status).[27 28] Symptoms related to knee OA were assessed with the knee-specific WOMAC index, which assesses pain (5 items), stiffness (2 items), and function (17 items) using visual analogue scores, where higher scores indicate worse status.[29] Weight was measured to the nearest 0.1 kg (shoes, socks, and bulky clothing removed) using a single pair of electronic scales. Height was measured to the nearest 0.1 cm (shoes and socks removed) using a stadiometer. Body mass index (BMI) (weight/height^2 in kg/m^2) was calculated.

For inclusion and classification, each subject had a weightbearing anteroposterior tibiofemoral radiograph of the symptomatic knee or knees taken in full extension at baseline. Where both knees had OA and were symptomatic, the knee with least severe radiographic OA was used. This was to reduce loss to follow up related to joint replacement surgery. The radiographs were independently scored by two trained observers, who used a published atlas to grade them according to Kellgren and Lawrence.[25] In the case of disagreement between observers, the films were reviewed by a third independent observer.

At baseline and 2 years later, each subject's assigned study knee was imaged by MRI. The knee was examined in the sagittal plane at baseline and about 2 years later with the same 1.5 T whole body magnetic resonance unit (Signa Advantage HiSpeed GE Medical Systems Milwaukee, WIS) using a commercial receive-only extremity coil. The following sequence and parameters were used: a T_1 weighted fat suppressed 3D gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512 (frequency direction, superior-inferior)×192 (phase encoding direction, anterior-posterior) matrix; one acquisition time 11 min 56 s. Sagittal images were obtained at a partition thickness of 1.5 mm. Knee cartilage volume was determined by image processing on an independent work station using the software program Osiris.[19 30]

As previously described, two trained observers, who were unaware of the time sequence, read each MRI independently, in an unpaired fashion.[22] The coefficient of variation of measurement of total tibial cartilage volume was 2.6%, based on a previous study.[30] The change in knee cartilage volume was obtained by subtracting the follow up knee cartilage volume from the initial volume. The annual percentage change was calculated by: ((change in knee cartilage volume)/(initial knee cartilage volume × time between scans)) × 100%.

Statistical analysis

We studied one knee of each participant. To describe baseline characteristics we used mean and range. To assess whether relationships existed at baseline between symptoms and knee cartilage volume, or between the change in symptoms related to OA (WOMAC pain, stiffness, and function subscales, SF-36 physical and mental components) and change in knee cartilage volume, Spearman correlation coefficients were used. A p value <0.05 (two tailed) was regarded as significant. All analyses were performed using the SPSS statistical package (version 10.0.5, SPSS, Chicago, IL). With 120 subjects included in the final analysis, we were able to detect correlations of absolute value 0.25 and greater, with an α of 0.05 and power of 0.8.

RESULTS

One hundred and thirty two subjects entered the study. Information was complete for 117 (89%) subjects. All had pain at baseline and had radiographic OA (at least one osteophyte present). Table 1 shows the baseline characteristics of participants. Nine did not complete the study as they did not have a second MRI because of geographic inaccessibility (two), loss of interest (three), knee surgery (two), and severe unrelated illness or death (two). Information about symptoms was incomplete or missing for six subjects. There were no significant differences in age, sex, BMI, or distribution of radiographic OA between subjects who were lost to follow up and those who completed the study. Table 2 shows the mean change in symptoms and cartilage volume. Symptoms relating to knee OA, including knee pain, stiffness, and functional impairment, improved on average over the period of observation (table 2). During the same period, general physical and mental health deteriorated (table 2).

At baseline, more severe symptoms relating to knee OA (pain, stiffness, and function) were significantly but weakly inversely related to tibial cartilage volume (table 3). Patients with lower cartilage volume had more severe symptoms of knee OA than those with higher cartilage volume.

The relationship between the baseline severity of symptoms of OA, including pain, stiffness, and function, and of general level of functioning at baseline and subsequent annual change in cartilage volume was similar to the relationship between baseline symptoms and cartilage volume, but was weak at best (table 4).

When viewed over time, worsening of symptoms was associated with increasing cartilage loss (table 5). However, the strength of the correlation with pain ($r_s = 0.28$, p = 0.002), function ($r_s = 0.21$, p = 0.02), and stiffness

Table 1 Baseline characteristics of the 132 study participants

Characteristic	
Age years, mean (range)	63.1 (41–86)
Sex, number of women (%)	71 (54)
Body mass index (kg/m^2), mean (range)	28.8 (20.0–43.6)
Pain, mean (range)*	82 (13–205)
Stiffness, mean (range)*	40 (0–96)
Function, mean (range)*	313 (42–711)
Physical function, mean (range)†	38 (16–58)
Mental function, mean (range)†	52 (16–58)
Kellgren and Lawrence grade, No (%)‡	
I	12 (9)
II	58 (45)
III	56 (43)
Tibial plateau area (µm^2), mean (range)	3450 (2280–5040)

*WOMAC pain, stiffness, and function subscales; †SF-36 components, standardised to Australian normal values; ‡two x ray results lost by subject after study entry, but before classification.

Table 2 Changes in symptoms and knee cartilage volume between baseline and 2 years later

	Baseline (n = 117)	Follow up (n = 117)	Mean change from baseline (95% CI)
Pain, mean (range)*	81 (13–205)	66 (0–210)	−17 (−26 to −8)
Stiffness, mean (range)*	40 (0–96)	31 (0–82)	−10 (−14 to −6)
Function, mean (range)*	307 (42–711)	247 (0–681)	−64 (−96 to −32)
Physical function, mean (range)†	39 (16–58)	38 (13–58)	−0.24 (−1.7 to 1.2)
Mental function, mean (range)†	53 (25–67)	52 (26–68)	0.39 (−2.2 to 1.4)
Mean tibial cartilage volume (μm^3), mean (range)	3660 (1980–6610)	3270 (1840–5610)	−390 (−460 to −330)

*WOMAC pain, stiffness, and function subscales (higher score indicates worse symptoms); †SF-36 components, standardised to Australian normal values (lower score indicates worse function).

(r_s = 0.17, p = 0.07) was weak. Nevertheless, these relationships were consistent for both medial and lateral tibial cartilage when considered individually (data not shown), and whether difference in cartilage was measured by change in volume or percentage change in volume. Similar but lesser correlations were found with physical function but not mental function (tables 3 and 5).

DISCUSSION

We have shown that increased symptoms of knee OA have a weak, but statistically significant, association with decreased articular cartilage volume. At baseline, we found that the relationship between the severity of symptoms of knee OA (pain, function, and total knee symptoms as measured by the knee-specific WOMAC) is weak, at best. Over 2 years of follow up, those who lost the greatest amount of joint cartilage had the greatest deterioration (increase in severity) of their joint symptoms, and conversely, those who showed an apparent increase in cartilage were more likely to show symptomatic improvement. The relationship between severity of symptoms of knee OA at baseline and subsequent progression of OA, measured by annual cartilage loss, was similar to the other relationships, but weak at best.

It is well established that the prevalence of pain and symptoms of knee OA increases with increasing radiographic severity of the disease.[3–5] However, no similar, consistent, relationship has been demonstrated between the severity of symptoms of knee OA and increasing radiographic severity.[4 7 31–33] In contrast, our results, using cartilage volume as a measure of disease severity, show a consistent but weak relationship between symptoms of knee OA (all dimensions of symptoms measured by the WOMAC: pain, stiffness, and functional impairment) and disease severity. This may be because cartilage volume, as a measure of disease severity, is possibly a more sensitive measure than the radiological grade of disease.

Similarly, longitudinal studies attempting to correlate changes in radiographic OA with changes in symptoms related to knee OA have been unable to show any significant consistent relationship in all measures used.[12 14 15] This has resulted in some authors questioning the focus of OA research on joint cartilage.[15] Nevertheless, the current recommendations suggest that clinical studies of knee OA should include a measure of articular cartilage, whether it be radiological, or MRI based.[16] Using cartilage volume as a measure of disease severity, we were able to demonstrate a consistent relationship between change in symptoms of knee OA and change in knee cartilage. This relationship is modest at best, but is consistent for all dimensions of symptoms measured by the WOMAC, and consistent in both medial and lateral tibiofemoral compartments.

Our results for the severity of symptoms of OA and structural change differ from those of previous studies, which did not consistently demonstrate a relationship such as we have found, although some have reported similar positive results relating individual aspects of symptoms and structural change.[9 12 14 15] This may be partly related to differences in the sensitivity of the tools used to measure either radiographic progression, as a marker of structural change, or change in symptoms. Unlike other investigators, we measured cartilage directly and measured symptoms with tools that provide a numerical scale of severity and are sensitive to change.[22 29] Previous studies have used radiographic joint space width or grade of joint space narrowing as a surrogate, indirect marker of articular cartilage. The radiographic grade of joint space narrowing, osteophyte, and subchondral sclerosis, are limited as measures of disease progression.[9 12 14] These are discrete ordinal scales, insensitive to change; most people with OA are unlikely to change grade over a 2 year period.[34] Other studies have used joint space narrowing, measured in millimetres.[15] However, this measurement has limitations, in addition to being an indirect measure of articular cartilage, having recently been shown to be highly susceptible to significant measurement error, requiring the positioning of the knee, the radiographic source, and the film to be strictly standardised.[35] In addition, changes in joint space narrowing may also be affected by changes in structures other than articular

Table 3 Correlation between symptoms of knee OA and tibial cartilage volume at baseline

	Correlation coefficient*	p Value
Pain†	−0.17	0.05
Stiffness†	−0.16	0.08
Function†	−0.20	0.03
Physical function‡	0.07	0.42
Mental function‡	−0.12	0.18

*Spearman's correlation coefficient; †WOMAC pain, stiffness, and function subscales (higher score indicates worse symptoms); ‡results of SF-36 standardised to Australian normal values (lower score indicates worse function).

Table 4 Correlation between symptoms of knee OA at baseline and annual loss of tibial cartilage volume

	Correlation coefficient*	p Value
Increased pain score†	0.13	0.14
Increased stiffness score†	0.09	0.32
Increased function score†	0.15	0.10
Decreased physical function score‡	−0.07	0.42
Decreased mental function score‡	0.18	0.05

*Spearman's correlation coefficient; †WOMAC pain, stiffness, and function subscales (higher score indicates worse symptoms); ‡results of SF-36 standardised to Australian normal values (lower score indicates worse function).

Table 5 Correlation between the change in symptoms of knee OA with the loss of cartilage volume

	Correlation coefficient*	p Value
Increased pain score†	−0.28	0.002
Increased stiffness score†	−0.17	0.07
Increased function score†	−0.21	0.02
Decreased physical function score‡	0.11	0.26
Decreased mental function score‡	−0.08	0.39

*Spearman's correlation coefficient; †WOMAC pain, stiffness, and function subscales (higher score indicates worse symptoms); ‡results of SF-36 standardised to Australian normal values (lower score indicates worse function).

cartilage, such as the menisci.[36] Furthermore, this study categorised radiographic progression (deterioration *v* stable and/or improved) and so did not examine progression using a continuous variable.[15] Various measures of joint pain and function have previously been used, including grade of pain, visual analogue score for pain, Lequesne index, subjective improvement, and the Steinbrocker functional index, to measure disability.[9 12 14 15] Although some of these are sensitive to change, those studies using these tools to assess symptoms had an ordinal or dichotomous measure of progression.

Cartilage volume, measured from MRI images, provides a continuous measure of the severity of OA which is sensitive to change, although it may be affected by measurement error.[22] It is dependent on contrast between articular cartilage and the adjacent tissues. However, our method has been validated with cadavers and has excellent reproducibility, with coefficients of variation of 2–3%, in health and OA, in adults and in children.[19 30 37–39] Especially in longitudinal studies such as this one, partial volume averaging, or differences related to differences in positioning, may add to the error. To reduce this and improve in-plane resolution, we used a matrix of 512×192 pixels, resulting in an in-plane resolution of 0.31×0.83 mm. The method has been shown to be highly reproducible using 2 mm slices.[18] We used fine slices (1.5 mm thick) across the knee to further reduce any effect of differences in positioning.

The main limitation of our study is that it includes only subjects with symptomatic disease: all subjects had pain for study inclusion. Whether our findings can be generalised to subjects with asymptomatic disease requires further study. However, in our self referred, community based cohort, the observed change in symptoms and knee cartilage over the course of our study is similar to that reported in other studies of knee OA.[14 15 40–42] It is unlikely that we selected a group of subjects in whom the structural change at the knee was more likely to be associated with deterioration in knee symptoms. Indeed, it is more likely that we underestimated the relationship between cartilage volume and symptoms because where both knees were symptomatic we used the knee with the least severe radiographic OA. However, we used a knee-specific WOMAC to measure symptoms of OA to overcome this.

We are unable to comment reliably on change in individual patients or on the effect of baseline differences between subjects. We can only reliably comment on change within the group. The minimum detectable difference (at a 5% level of significance) for change in an individual subject, is 2.8 multiplied by the coefficient of variation for a single volume measurement.[43] In our study this is ±7.28% a year.[22] Hence only seven subjects had a change in cartilage volume that could be confidently claimed to be a true change and not within the bounds of measurement error. Also, we used non-parametric statistics for robustness against any departures

from normal distribution assumptions, but this precluded adjustments for body size, or other variables, including non-steroidal anti-inflammatory drug use. However, less than one third of subjects were regular users of these drugs at baseline. By the end of the study, this had decreased to about a quarter of subjects and symptoms had improved overall. This is similar to previous studies of OA.[14 15] Despite these limitations, we showed a relationship, of consistent magnitude and direction in all measures of specific symptoms of knee OA, suggesting that cartilage loss is related to the symptoms of knee OA, albeit weakly.

That this relationship is weak is not unexpected. Although articular cartilage may be viewed as a major target tissue of OA, it is not innervated by nociceptors and the mechanism for relationship between loss of articular cartilage and deterioration of symptoms is unclear. Pain in knee OA is multifactorial, and may arise from a number of different structures related to the joint. The joint capsule, ligaments associated with the knee, the outer third of the menisci, bursae, bone and the bone marrow, and pathological structures related to OA, such as inflammatory synovitis and associated capillaries, are innervated with pain fibres and may be affected in OA.[6 44–46] These may be the source of pain in OA and may contribute to pain indirectly, secondary to abnormal forces and possible damage as articular cartilage is lost. It has been suggested that loss of articular cartilage may increase the stress on subarticular bone, inducing subchondral bony changes.[47] These may result in increased susceptibility to impact stresses, which may result in pain and bone marrow lesions.[6] In addition, pain sensation may be influenced by other unrelated factors such as culture, sex, and behavioural factors.[4 7]

In conclusion, we have shown that the severity of symptoms of knee OA is weakly and inversely associated with tibial cartilage volume and that an increase in severity of specific symptoms of knee OA is also associated with a loss of joint cartilage. However, although this finding was statistically significant, and measurable over the 2 years of follow up, it was of low magnitude. Nevertheless, it does suggest that structural change in OA measured by the more sensitive method of cartilage volume is associated with joint symptoms. Further work will be needed to confirm this in other groups, including those with asymptomatic knee OA.

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