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Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females[1]

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Summary

Objective: To describe the association between early radiographic osteoarthritis of the knee (ROA), knee cartilage volume and tibial bone surface area.

Methods: Cross-sectional convenience sample of 372 male and female subjects (mean age 45 years, range 26–61). Articular cartilage volume, bone area and volume were determined at the patella, medial tibial and lateral tibial compartments by processing images acquired in the sagittal plane using T1-weighted fat saturation MRI. ROA was assessed with a standing semiflexed radiograph and the OARSI atlas for joint space narrowing and osteophytosis. Both radiographs and MRIs were performed in the right knee and read by different observers.

Results: ROA (predominantly grade 1) was present in 17% of subjects of which medial joint space narrowing was most common (14%) followed by medial osteophytes (6%). Grade one medial joint space narrowing was associated with substantial reductions in cartilage volume at both the medial and lateral tibial and patellar sites within the knee (adjusted mean difference 11–13%, all $P<0.001$) while grade one osteophytosis was associated with substantial increases in both lateral and medial tibial joint surface area (adjusted mean difference 10–16%, all $P<0.001$). In contrast, osteophytosis was not associated with a significant change in cartilage volume and joint space narrowing was not associated with a significant change in tibial bone area (all $P>0.05$).

Conclusions: Early medial compartment ROA is associated with substantial reductions in cartilage volume and increases in bone area. These large changes, when combined with similar measurement error for MRI and radiographs, suggest that MRI may be superior at detecting and hence understanding early osteoarthritis of the knee in humans.

Key words: Cartilage, Radiograph, Osteoarthritis.

Osteoarthritis is a major public health problem. The prevalence of knee osteoarthritis is approximately 30% of those over 65[1]. Currently, the definition of osteoarthritis of the knee utilizes a combination of symptoms and radiographic criteria[2]. While this definition is useful for epidemiologic studies, a number of questions remain unanswered. Radiographs have been criticized as insensitive to change[3]. In part, this will be due to measurement error, but more importantly, most radiographic grading scales are semi quantitative and, at best, provide a broad brush assessment of the joint. There is a significant correlation between radiographic change (especially joint space narrowing) and cartilage volume[4] but there is uncertainty as to what degree of cartilage loss is present in each radiographic stage. Recent reports have suggested a 60% reduction in cartilage volume in severe knee osteoarthritis[4,5]. However, there is very limited data on how much cartilage loss has to occur before early radiographic osteoarthritis is detectable. A preliminary report suggested an 18% reduction in cartilage volume but this was based on relatively small numbers with wide confidence intervals[4]. Furthermore, as far as we are aware, there are no reports relating knee compartment bone area to radiographic osteoarthritis. The aim, therefore, of this cross-sectional study was to quantitate the change in cartilage volume and bone surface area and volume of different knee compartments with early radiographic osteoarthritis either joint space narrowing or osteophytosis in both males and females.

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Materials and methods

The study was carried out in Southern Tasmania primarily in the capital city of Hobart from June 2000 until December 2001. The study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee and all subjects provided informed written consent.

A convenience sample was utilized for this study. Subjects were selected from two sources. Half of the subjects were the adult children of subjects who had a knee replacement performed for primary knee osteoarthritis at any Hobart hospital in the years 1996–2000. This diagnosis was confirmed by reference to the medical records of the orthopaedic surgeon and the original radiograph, where possible. The other half were randomly selected controls without this history. These were selected by computer generated random numbers from the most recent version of the Hobart electoral roll (2000). Controls were individually matched to cases by sex and five year age bands. Subjects from either group were excluded on the basis of contraindication to MRI (including metal sutures, presence of shrapnel, iron filing in eye and claustrophobia) while controls were included as cases if they had a parent who had received a knee replacement for osteoarthritis. Knee pain and knee injuries were allowed in both groups.

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) which 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. The protocol also assessed knee pain, physical activity, fitness, strength, employment, injury, smoking and genetic factors, but these are not relevant to the current study and, hence, are not fully described.

A standing AP semiflexed view of the right knee was performed in all subjects. The angle was kept to 10–15 degrees by a purpose built goniometer. The tube to film and tube to tibial plateau angle was 90 degrees. Daily QA was performed on equipment. Radiographs were then assessed utilizing the Altman atlas[6]. Each of the following was assessed: medial joint space narrowing (0–3), lateral joint space narrowing (0–3), medial osteophytes (femoral and tibial combined) (0–3) and lateral osteophytes (femoral and tibial combined) (0–3). Each score was arrived at by consensus with two readers (GJ, FS) simultaneously assessing the radiograph with immediate reference to the atlas. A non-zero score in either joint space narrowing or osteophytosis was regarded as evidence of ROA. Reproducibility was assessed in 50 radiographs, two weeks apart, and yielded an ICC of 0.99 for osteophytes and 0.98 for joint space narrowing. This may represent an overestimate of the actual agreement due to the high proportion of normal radiographs. However, this method also has very high reproducibility in our hands for radiographic osteoarthritis of the hands with ICC's of 0.94–0.98[7].

An MRI scan of the right knee was also performed. Knee cartilage volume was determined by means of image processing on an independent work station using the software program Osiris as previously described and validated against cadaveric specimens[8]. Knees were imaged in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Picker) with the use of a commercial transmit-receive extremity coil. The following image sequence was used: a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 55°; repetition time 58 ms; echo time 12 ms; field of view 16 cm; 60 partitions; 512×512 matrix; acquisition time 11 min 56 s; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31×0.31 mm (192×192 pixels). The image data were transferred to the workstation. The volume of individual cartilage plates (medial tibial, lateral tibial and patella) was isolated from the total volume by manually drawing disarticulation contours around the cartilage boundaries on a section by section basis. These data were then resampled by means of bilinear and cubic interpolation (area of 312 and 312 μm and 1.5 mm thickness, continuous sections) for the final 3D rendering. The volume of the particular cartilage plate was then determined by summing all the pertinent voxels within the resultant binary volume. Femoral cartilage volume was not assessed, as we have published that two tibial sites and the patella site correlate strongly with this site[4]. Using this method we had high intra- and inter-observer reproducibility. The coefficient of variation (CV) for cartilage volume measures was 2.1% for medial tibial, 2.2% for lateral tibial and 2.6% for patella[8].

Knee tibial plateau bone area and patellar bone volume were also determined by means of image processing on an independent work station using the software program Osiris (University of Geneva, http://expasy.hcuge.ch/www/UIN/UIN.html) as previously described[4]. To transform the images to the axial plane, the Analyse Software package developed by the Mayo Clinic was employed. Medial and lateral tibial plateau bone area was determined by creating an isotropic volume from the three input images closest to the joint. The bone area of the medial and lateral tibial plateau was then directly measured from the reformatted axial images. The area of patellar bone was determined by manually drawing individual contours around the target patella boundaries on a slice-by-slice basis on sagittal views. The volume of the patellar bone was then determined by summing all the pertinent voxels within the resultant binary volume. Total volume was calculated for the patellar bone because of its irregular shape, which made it difficult to identify a simpler, representative measure of patellar size. The CV for these MRI measures in our hands are 2.2–2.6%[8]. Both cartilage and bone area methods are illustrated in Fig. 1.

Statistical methods

A combination of *t*-tests and multivariate linear modelling were utilized for the analysis of this dataset as both cartilage volume and bone area are normally distributed. Matched techniques were not utilized for the current cross-sectional study as this did not relate to the primary hypothesis for the current report. However, all results were adjusted for case control status. A *P*-value less than 0.05 (two-tailed) or a 95% confidence interval not including the null point were regarded as statistically significant. All statistical analyses were performed on SPSS version 10.0 for Windows (Chicago, IL).

Results

There were 372 subjects (female 216, male 156) comprising 186 offspring and 186 matched controls. This was a young sample with an average age of 45 years (range 26–61). Characteristics of the group stratified by ROA are presented in Table I. Subjects with ROA were generally older and heavier than normal subjects. Males were under-represented in the joint space narrowing group and over represented in the osteophytosis group. ROA was uncommon in the whole group (3–14% for the various categories) and was predominantly grade 1. A total of six subjects had scores higher than grade 1 and were excluded from further analysis due to sample size considerations. There were also insufficient numbers of subjects with lateral ROA for further analysis. However, this was not associated with

Table I
*Characteristics of participants (N=372)**

Factor	No radiographic osteoarthritis (*N*=316)	Medial osteophytosis (*N*=19)	Medial joint space narrowing (*N*=50)
Age (years)	44.6 (7.1)	48.6 (4.6)	47.7 (5.4)
Weight (kg)	77 (14)	91 (20)	84 (24)
Height (cm)	169 (9)	174 (7)	169 (7)
Male:female ratio	56% female	26% female	71% female
Significant knee pain (%)	34	73	35
Knee injury (%)	19	41	18
Medial tibial cartilage volume (ml)	2.3 (0.6)	2.4 (0.6)	2.0 (0.5)
Lateral tibial cartilage volume (ml)	2.6 (0.7)	2.8 (0.9)	2.3 (0.6)
Patella cartilage volume (ml)	3.5 (1.0)	3.7 (0.9)	3.0 (0.8)
Medial tibial bone area (cm^2)	17.4 (2.7)	20.6 (2.8)	17.2 (2.8)
Lateral tibial bone area (cm^2)	11.9 (1.9)	15.0 (2.3)	12.0 (1.8)
Patella bone volume (ml)	13.7 (3.4)	16.1 (2.7)	13.8 (2.9)

*Mean (SD) unless stated. There are 13 subjects who had both osteophytosis and joint space narrowing

Table II
Knee Cartilage volume, bone area and radiographic change

	Univariate β (95% CI)	Multivariate* β (95% CI)
Medial joint space narrowing (grade one vs zero)		
Medial tibial cartilage volume (ml)	**−0.31 (−0.48,−0.13)**	**−0.27 (−0.41,−0.13)**
Lateral tibial cartilage volume (ml)	**−0.35 (−0.55,−0.15)**	**−0.28 (−0.43,−0.14)**
Patella volume (ml)	**−0.60 (−0.89,−0.32)**	**−0.45 (−0.67,−0.23)**
Medial tibial bone area (cm^2)	−0.03 (−0.11,+0.06)	−0.00 (−0.04,+0.06)
Lateral tibial bone area (cm^2)	−0.00 (−0.07,+0.06)	+0.00 (−0.04,+0.05)
Patella volume (ml)	+0.07 (−0.94,+1.08)	+0.04 (−3.2,+10.0)
Medial osteophytosis (grade one vs zero)		
Medial tibial cartilage volume (ml)	+0.14 (−0.13,+0.42)	−0.13 (−0.15,+0.43)
Lateral tibial cartilage volume (ml)	+0.29 (−0.36,+0.61)	−0.05 (−0.28,+0.19)
Patella cartilage volume (ml)	+0.26 (−0.21,+0.73)	−0.14 (−0.50,+0.21)
Medial tibial bone area (cm^2)	**+3.40 (+2.20,+4.60)**	**+1.74 (+1.03,+2.44)**
Lateral tibial bone area (cm^2)	**+3.18 (+2.37,+4.07)**	**+2.07 (+1.45,+2.59)**
Patella bone volume (ml)	**+2.52 (+1.07,+4.01)**	+0.51 (−0.48,+1.48)

*Adjusted for age, sex, height, weight and case control status. Bold indicates statistically significant. Of the explanatory variables, sex and height were statistically significant for cartilage volume while all were statistically significant for bone area.

statistically significant changes in cartilage volume or bone area at any site after taking medial ROA into account (data not shown). Results did not differ materially if groups were stratified by offspring or control status (data not shown) so both groups were combined for subsequent analyses.

Grade one medial joint space narrowing was associated with a statistically significant 11–13% reduction in knee cartilage volume at all measured sites within the knee joint in both univariate and multivariate analysis in both sexes combined (Table II). The magnitude of the reduction was similar in males and females although the results for males did not achieve statistical significance as relatively few were affected (Fig. 2). In contrast, grade one medial osteophytosis was associated with no significant change in cartilage volume (Table II).

Conversely, in multivariate analysis, grade one medial osteophytosis was not associated with a change in cartilage volume at any site but was associated with a 10–16% increase in both medial and lateral tibial bone areas but not patella volume (Table II). Results were very consistent for males and females with a trend to greater percentage increases in females (Fig. 3).

Discussion

In this young sample of male and females, medial compartment radiographic joint space narrowing (but not osteophytosis) was associated with a substantial reduction

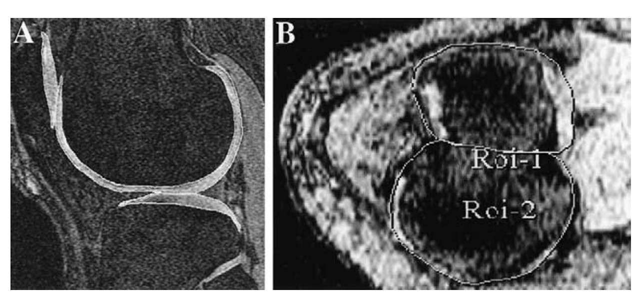

Fig. 1. MRI assessment of cartilage volume and bone area. Cartilage volume (A) is manually outlined in an average of 60 sagittal cuts and then summed giving a volume estimate. For bone area, the three reformatted axial images closest to the knee are averaged to give areas for the medial and lateral tibial plateaux. Roi-1—lateral; Roi-2—medial.

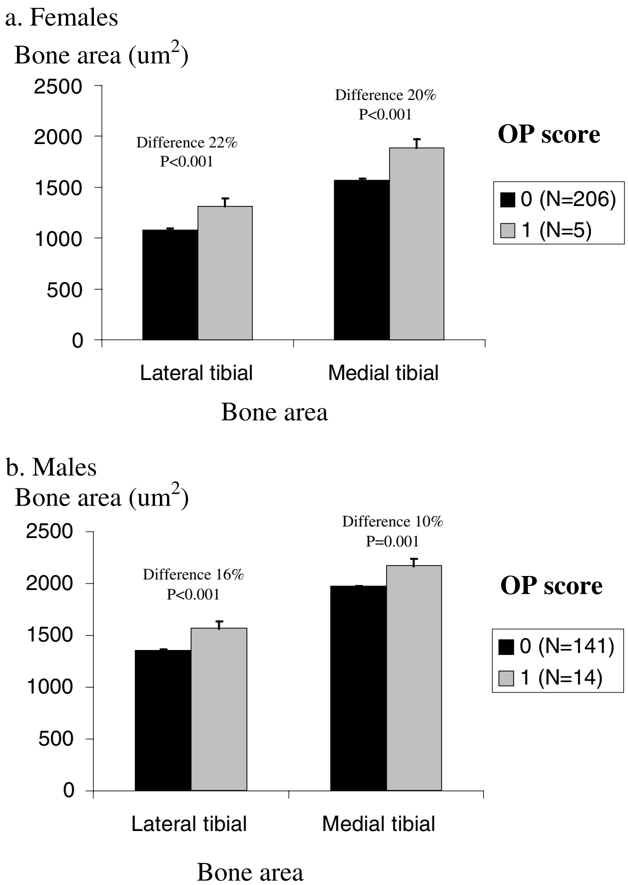

Fig. 2. Increases in tibial area with early medial osteophytosis by sex. At all sites, there is an increase in tibial areas varying from 10–22% in unadjusted analyses. All results reached statistical significance. Results are presented as mean±SE.

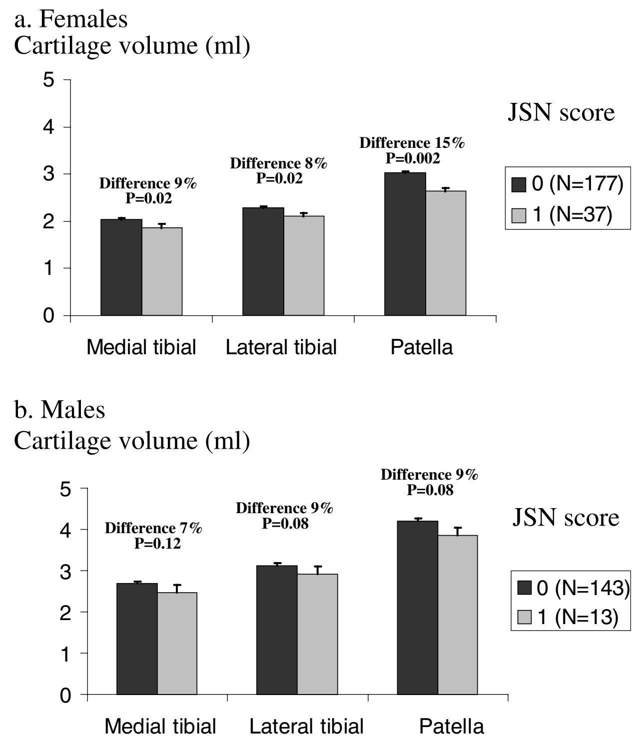

Fig. 3. Reductions in cartilage volume with early joint space narrowing by sex. At all sites there is a reduction in cartilage volume varying from 7–15% in unadjusted analysis which reaches statistical significance in females only. Results are presented as mean±SE.

in cartilage volume at all compartments within the knee but no change in tibial joint area. In contrast, medial osteophytosis was not associated with reductions in cartilage volume at any site but was associated with a substantial increase in both tibial bone areas.

The observation that an average 11–13% reduction in cartilage volume is required to detect grade one radiographic joint space narrowing in the medial compartment is important for a number of reasons. Firstly, this indicates that a considerable amount of cartilage has to be lost to detect even early ROA thus implying that the disease is likely to start well before ROA is present. The magnitude of the reduction was similar for males and females although the results were of borderline significance in males. Secondly, longitudinal data in subjects with early ROA of the knee shows that the rate of loss in cartilage volume averages 5–6% per annum and doesn't vary by severity grade[9] while studies concentrating on ROA suggest a rate of change in joint space narrowing of 2% per annum[3]. This suggests that cartilage loss is much greater than expected and also implies that a minimum of two to three years will be required to detect a grade one change in ROA but implies considerably less for MRI. This may be longer in subjects without ROA progressing to early ROA particularly when one considers that measurement error will make it more difficult to detect small radiographic changes. Longitudinal studies in subjects without ROA will be required to further delineate this relationship although MRI can detect early chondral changes in the knee[10]. In contrast to ROA where measurement error is similar to the rate of change, measurement error in the MRI assessment of cartilage volume compares very favorably to the size of the effect that can be detected although a recent study involving 16 subjects suggested no cartilage loss as assessed by MRI over 3 years in those with established knee osteoarthritis[11]. Our data would suggest that 50 subjects in each group would be sufficient to observe a 10% difference in cartilage volume cross-sectionally.

The reduction in cartilage volume was only observed with joint space narrowing and not with osteophytosis providing evidence of face validity. Intriguingly, the reduction was observed in all knee compartments despite ROA being both uncommon in the lateral compartment and not being associated with significant changes in cartilage volume. A limitation of this study is that we did not have patellofemoral views but ROA at this site in this age group is likely to be uncommon in this age group given previous prevalence estimates in older samples[12]. This observation suggests that early cartilage loss in the knee may be a global phenomenon rather than compartment specific or, alternatively, that cartilage development in the knee is highly correlated as we have documented in children[8]. Another report from our group in a different sample all with ROA measured longitudinally has suggested that tibial cartilage loss correlates strongly but not patellar loss[13]. These two observations suggest further examination of this relationship is necessary.

There have been previous reports relating to subchondral thickness, trabecular orientation and bone density generally in subjects with advanced osteoarthritis of the knee[14,15]. As far as we are aware, this is the first report of bone area changes with any ROA. In both sexes, there was a substantial 10–22% increase in lateral and medial tibial areas with grade one osteophytosis. This remained statistically significant after adjustment for age, sex and body size suggesting a true association. This also appeared to be a global tibial effect in that increases were observed in both medial and lateral tibial areas with medial osteophytosis. Our bone area measure was originally derived to adjust for bone size. It has not been validated against cadaveric specimens but its measurement is highly reproducible, has face validity and the current study provides support for content validity. Our data would suggest that 20 subjects in each group would be sufficient to observe a 10% difference in bone area. Furthermore, the finding that both age and ROA were positively associated with bone area cross-sectionally suggests that longitudinal studies of changes in bone area over time are necessary in both normals and those with ROA.

This study has a number of limitations. Firstly, the study was primarily designed to look at genetic mechanisms of knee osteoarthritis and utilized a matched design. The matching was broken for the current study but all results were adjusted for case control status and did not alter after adjustment for this variable. Indeed, while there was a reduction in power, the results otherwise did not differ if examined in offspring and controls separately (data not shown). While the sample is a convenience sample they meet the criteria for generalizability outlined by Miettinen[16] and were also ideally placed to examine the associations between MRI measures and early radiographic change due to the young age of the sample. The consistency of results also suggests that that these observations are valid and are generalizable to other subjects with early medial compartment osteoarthritis of the knee (either familial or primary but not post-traumatic). Measurement error in the assessment of both MRIs and ROA may have weakened the associations between them. However, both assessment techniques have high reproducibility in our hands suggesting this is not of major concern and which is further offset by the blinded reading of MRIs and radiographs by different observers. Other MRI protocols using gadolinium may also be able to detect early osteoarthritis[17]. Furthermore, a number of different protocols for the assessment of ROA currently exist. Our protocol used a fixed semi-flexed view which appeared very similar to the OARSI atlas. However, it is possible that each protocol may yield different results with MRI and this needs to be tested in a systematic way. Clinical trials often use change in joint space narrowing which is fully quantitative. This study has not compared these two measures as it was not the primary aim but it is possible that joint space narrowing will perform better than a semi-quantitative score. However, the majority of our subjects had normal radiographs and joint space narrowing is of uncertain significance in those without osteoarthritis. Lastly, larger numbers of subjects with lateral ROA will be required to determine if similar observations apply to this site.

In conclusion, early medial compartment ROA is associated with substantial global reductions in cartilage volume and increases in bone area. The large changes combined with similar measurement error for MRI and radiographs suggest that MRI may be superior at detecting and hence understanding early osteoarthritis of the knee in humans.

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