Osteoarthritis and Cartilage

International Cartilage Repair Society

I C R S

OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

A pilot, two-year longitudinal study of the interrelationship between trabecular bone and articular cartilage in the osteoarthritic knee[1]

Gabrielle Blumenkrantz†*, Colleen T. Lindsey†, Timothy C. Dunn†,
Hua Jin‡, Michael D. Ries§, Thomas M. Link†||, Lynne S. Steinbach¶ and
Sharmila Majumdar†§

† *Musculoskeletal and Quantitative Imaging Research Group, Department of Radiology, University of California, San Francisco, CA 94107, USA*
‡ *Department of Mathematics, South China Normal University, Guangzhou, China*
§ *Department of Orthopaedic Surgery, University of California, San Francisco, CA, USA*
|| *Department of Radiology, Technische Universität Müenchen, Munich, Germany*
¶ *Department of Radiology, University of California, San Francisco, CA, USA*

Summary

Objective: To examine the relationship between structural changes of trabecular bone and cartilage, in patients with varying degrees of osteoarthritis (OA) over 2 years, using magnetic resonance imaging.

Methods: High-resolution, axial images were acquired for assessing trabecular bone structure, using a 3-D fast gradient-echo sequence. High-resolution, fat-suppressed, sagittal images were acquired for assessing cartilage structure, using a 3-D spoiled gradient-echo sequence. In a subset of the patients, sagittal images were acquired for measuring T_2 relaxation time, using a 2-D dual-echo spin echo sequence.

Results: A large variation in bone and cartilage parameters is evident among individual subjects in each group, however, group-specific means demonstrate decreasing trends (in bone and cartilage parameters) in osteoarthritic subjects (especially in mild OA subjects). The mean T_2 increased significantly ($P < 0.05$) between the baseline and follow-up exams for all cartilage compartments except the lateral tibia. A positive relationship was established between cartilage changes and localized bone changes closest to the joint line, while a negative relationship was established between cartilage changes and global bone changes farthest from the joint line.

Conclusion: This study quantifies the changes in bone and cartilage structural parameters over time, and demonstrates a longitudinal relationship between the morphological changes in bone and cartilage structure in patients with varying degrees of OA. Although a large variation of bone and cartilage changes is apparent among subjects, significant trends are evident in a relatively small sample size, with a short follow-up duration.
© 2004 OsteoArthritis Research Society International. Published by Elsevier Ltd. All rights reserved.

Key words: Knee, Magnetic resonance imaging, Osteoarthritis, Musculoskeletal.

Introduction

Osteoarthritis (OA) is a degenerative joint disease in which bone and cartilage morphological and biochemical changes cause abnormal biomechanical loading patterns, leading to joint deformity, pain, stiffness, crepitus, and decreased mobility[1]. OA affects roughly 80% of the population over 75 years[2] and can be caused by many factors such as joint malalignment, obesity, prior surgery or trauma, meniscal abnormality, or cruciate ligament tears[3–6].

During joint loading, the tissues of the knee including cartilage, bone, muscle, and ligament interact to sustain weight-bearing stresses. Specifically, cartilage acts as a "cushion," which absorbs impacts and distributes loads along the joint surface[7]. Although it sustains less force than the surrounding bone and muscle tissues during locomotion[6], its degeneration is significant in the pathogenesis of OA. For example, previous studies have shown that joint space narrowing, an indication of OA progression, is related to cartilage degradation[8]. In addition, Wluka *et al.* showed that tibial cartilage volume decreases about 5% per year in osteoarthritic patients[9]. Such progressive osteoarthritic changes are associated with increased bone resorption[10] and abnormal trabecular architecture[11]. Moreover, increased subchondral bone stiffness has been associated with cartilage deterioration[12–14], linking bone and cartilage structural changes to the development of OA.

Given that the morphological changes occurring in bone and cartilage are interdependent[15], measurements of bone or cartilage structural parameters, individually, may be insufficient to determine the pathogenesis and implications of OA. In a previous cross-sectional study of trabecular

Table I
OA subject characteristics at baseline

	Weight (lbs)	Height (in)	BMI	Age	WOMAC pain	WOMAC stiffness	WOMAC function
OA1 (*n* = 13)							
Women (*n* = 7)							
Mean	125.57	63.14	26.04	64.43	76.71	68.43	192.73
SD	56.57	2.41	3.50	10.11	61.53	86.20	186.09
Men (*n* = 6)							
Mean	211.17	68.67	31.53	56.50	115.67	184.50	288.59
SD	31.69	3.67	4.80	12.57	72.78	87.07	358.72
OA2 (*n* = 17)							
Women (*n* = 5)							
Mean	162.75	68.00	24.83	68.00	50.67	54.67	148.00
SD	14.50	2.45	2.88	5.52	56.13	43.19	226.13
Men (*n* = 12)							
Mean	194.75	71.58	27.78	63.67	97.09	138.64	135.91
SD	28.27	2.39	4.22	12.26	45.12	79.93	86.96

bone and articular cartilage, Lindsey *et al.* used magnetic resonance imaging (MRI) to determine that cartilage degeneration in the knee joint is associated with changes in trabecular bone structure[15]. As a further investigation, it would be important to study how such a relationship changes over time. Therefore, the purpose of this study is to examine the relationship between structural changes of trabecular bone and cartilage, in patients with varying degrees of OA over 2 years, using MRI.

Materials and methods

SUBJECTS

A total of 38 subjects (mean age = 58 years, range = 28−81 years, % female = 39.5%) were scanned at baseline and 12 months. Of these subjects, 21 (mean age = 60 years, range = 28−81 years, % female = 42.8%) were scanned again at 24 months (drop-outs due to death, knee replacement, and unwillingness to continue). All patients completed a WOMAC (Western Ontario and

McMasters Universities Arthritis Index) questionnaire of pain, function, and stiffness[16]. A summary of baseline OA subject characteristics is presented in Table I. Subjects were recruited by an orthopedic surgeon based on clinical investigation and diagnosis from antero-posterior weight-bearing radiographs. All subjects (except controls) displayed symptoms of OA, as evaluated by a radiologist. The severity of each subject's OA at baseline was evaluated using the x-ray based Kellgren−Lawrence (KL) scale[17]: KL scores of 1 and 2 were considered mild OA and classified as OA1 (*n* = 13, mean age = 61 years, range = 46−81 years, % female = 53.8%); KL scores of 3 and 4 were considered severe OA and classified as OA2 (*n* = 17, mean age = 65 years, range = 43−76 years, % female = 29.4%). A summary of the OA subject cohort is presented in Fig. 1. Additionally, a group of control subjects (OA0) with no radiographic evidence of OA (*n* = 8, mean age = 39 years, range = 28−70 years, % female = 37.5%) was included in the study. This study was approved by the Committee on Human Research, and all patients signed an informed consent.
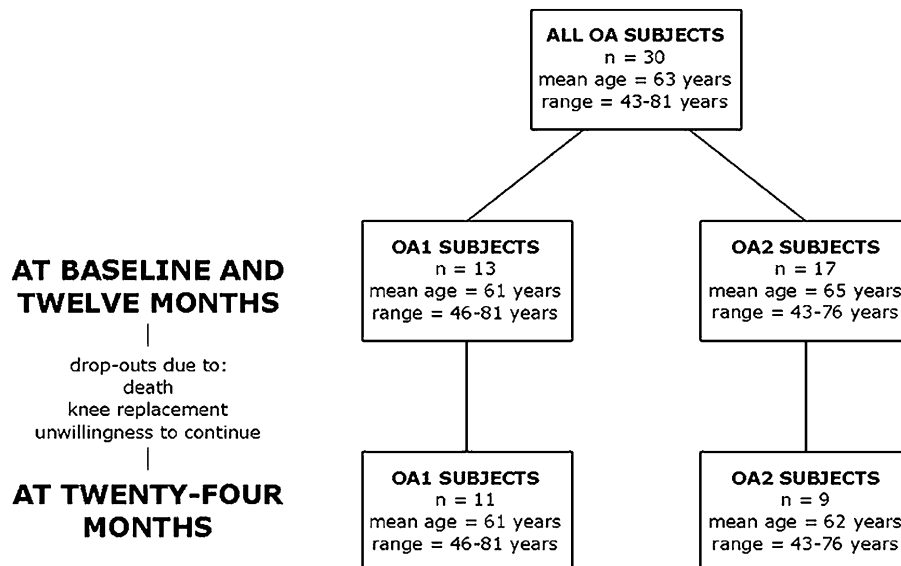

Fig. 1. A tree diagram of OA subject characteristics at baseline.

Fig. 2. A high-resolution, axial image acquired for assessing trabecular bone structure, using a 3-D fast gradient-echo sequence (TE = 4.5 ms, TR = 30 ms, flip angle = 40°, resolution = $0.195 \times 0.195 \times 1$ mm^3, FOV = 10 cm, scan time = 18:26 min). The epicondylar distance is labeled.
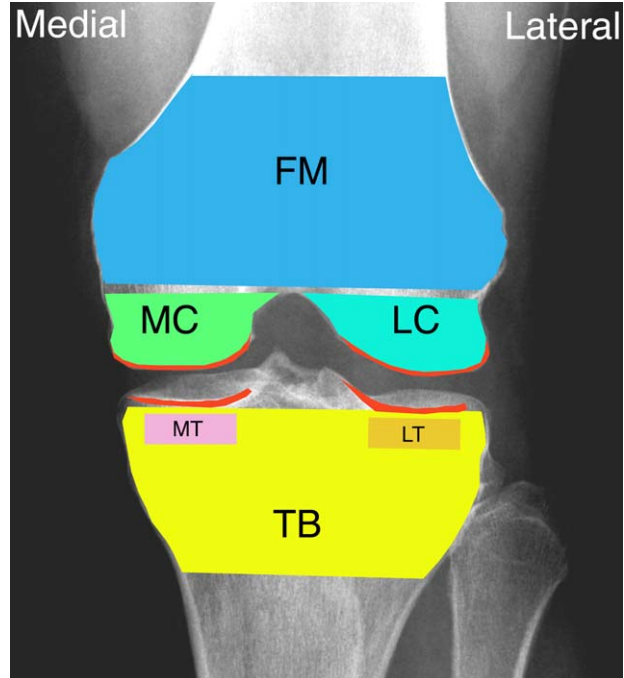

Fig. 3. A graphical representation of the segmented bone and cartilage regions. The femur (FM, blue), tibia (TB, yellow), medial condyle (MC, green), lateral condyle (LC, turquoise), medial tibia (MT, pink), lateral tibia (LT, orange) and cartilage compartments (red) are shown.

MAGNETIC RESONANCE IMAGING

A GE SIGNA 1.5 Tesla echo-speed system (GE Medical Systems, Waukesha, WI) and bilateral dual-phased array coil (USA Instruments, Cleveland, OH) were used to acquire images.

The subject was positioned supine in the scanner, and his or her knee was secured using a knee-holder (constructed in-house) that allowed the knee to flex $30 \pm 1°$. The receiver coils were secured to and centered at the knee joint, so that signal to noise ratio was maximized.

High-resolution, axial images (Fig. 2) were acquired for assessing trabecular bone structure, using a 3-D fast gradient-echo (FGRE) sequence[18] (TE = 4.5 ms, TR = 30 ms, flip angle = 40°, resolution = $0.195 \times 0.195 \times 1$ mm^3, FOV = 10 cm, scan time = 18:26 min). High-resolution, fat-suppressed, sagittal images were acquired for assessing cartilage structure, using a 3-D spoiled gradient-echo (SPGR) sequence (TE = 3.3 ms, TR = 30 ms, flip angle = 30°, resolution = $0.234 \times 0.234 \times 2$ mm^3, FOV = 12 cm, scan time = 9:31 min). In a subset of the patients ($n_{total} = 12$, $n_{OA1} = 5$, $n_{OA2} = 7$, mean age = 59 years, range = 43–76 years, % female = 33.3%), sagittal images were acquired for measuring T_2 relaxation time, using a 2-D dual-echo spin echo (SE) sequence (TE$_1$/TE$_2$ = 10/45 ms, TR = 1500 ms, resolution = $0.468 \times 0.468 \times 4$ mm^3, FOV = 12 cm, scan time = 5:24 min). All 12 subjects had a baseline and follow-up scan, averaging 680 days between scans (range = 400–1050 days).

IMAGE ANALYSIS

All images were transferred to a Sun Workstation (Sun Microsystems, Mountain View, CA), which was used to perform analysis. To correct for non-uniform signal intensity, a 3-D low pass filter was applied to the images[19].

Trabecular bone analysis was performed using an in-house program created with IDL (Research Systems, Boulder, CO)[20]. Regions of interest (ROI), consisting of

trabecular bone and marrow, were segmented (based on the axial images) in the femur, medial and lateral condyles, tibia, and medial and lateral tibia, as in a previous study (Fig. 3)[15]. The first slice was defined at the proximal end of the tibia, and the last slice was defined at the distal end of the femur. The femur was defined, beginning with the slice where the condyles meet and concluding five slices before the end of the volume, so as to minimize coil signal drop-off effects. The medial and lateral condyles were defined beginning with the slice where the condyles appear and ending at the slice where the condyles meet. The tibia was defined starting from the fifth slice and ending at the joint line. The medial and lateral tibia were segmented using a 1×3 grid that fit within the tibial plateau[15]. The first and third boxes, defined on five consecutive slices of the tibial plateau, were representative sections of the medial and lateral tibia. Figure 3 shows a representation of all the segmented regions. To adjust the ROI for variation in bone size among the subjects, the dimensions of the grid were standardized by the epicondylar distance[15]. For example, the width and height of each box were calculated using the following equation:

$$\text{Width [mm]} = \text{Height [mm]}$$
$$= \text{Epicondylar Distance [mm]} * (2/9) \qquad (1)$$

Each segmented region was analyzed to measure the following parameters: apparent trabecular number (app. Tb.N) [1/mm], apparent trabecular thickness (app. Tb.Th) [mm], apparent bone volume fraction (app. BV/TV), and apparent trabecular separation (app. Tb.Sp) [mm][21–23]. In order to distinguish the trabecular bone from the marrow, a threshold that assumed a biphasic model using a dual-reference limit, as previously described[24,25], was applied.

This threshold was employed to generate a binary image of bone and marrow phases. Reproducibility results for trabecular bone structure analysis have been previously published[20]; the coefficient of variation (CV) was 2.20% for app. BV/TV, 2.20% for app. Tb.N, 3.20% for app. Tb.Sp, and 2.90% for app. Tb.Th.

Cartilage segmentation was performed using an in-house program created with Matlab (Mathworks, Natick, MA). Based on the sagittal images, articular cartilage was segmented using a spline-based, semi-automatic technique and was defined in four distinct regions: medial and lateral tibia, and medial and lateral femur (Fig. 3). The analysis of the femur was performed by a single observer, and the analysis of the tibia was performed by a different, but single observer. The root mean square CV for intra-observer reproducibility was 2.40% for femoral thickness, 2.18% for femoral volume, 3.69% for tibial thickness, and 2.61% for tibial volume[15]. An iterative minimization process was used to calculate total cartilage volume and average thickness for each region. Following segmentation, the image was transformed into a mask in which the cartilage appeared white and the rest of the image appeared black. Second, edge detection and skeletonization were used to determine the boundaries of the cartilage so that a medial line could be generated. Finally, the cartilage thickness was determined by calculating the minimum distance from each point on the medial line to a cartilage boundary. The average thickness was calculated for each slice and then averaged for all the slices. The cartilage volume was determined by multiplying the total number of voxels encompassing the cartilage by the volume of each voxel.

Studies have shown that variations in joint size have a larger effect on cartilage volume than on cartilage thickness[26]. Therefore, cartilage volume was normalized by the epicondylar distance to minimize variation due to joint size.

Dual-echo, spin-echo images were used to generate sagittal T_2 maps, using custom software (IDL, Research Systems, Boulder, CO), assuming mono-exponential signal decay with echo time. The cartilage segmentation was re-sampled and superimposed on the T_2 map, to define the region of interest for T_2 assessment[27]. There were 12 OA subjects ($n_{OA1} = 5$, $n_{OA2} = 7$, mean age = 59 years, range = 43–76 years, % female = 33.3%) from which follow-up T_2 maps were obtained, as there was often considerable knee movement between the high-resolution scan and the dual-echo scan. The cartilage compartments were determined, as previously described, and classified as the medial and lateral tibial, and medial and lateral femoral compartments. For qualitative comparison, three normal volunteers (mean age = 44 years, range = 28–70 years, % female = 33.3%) were scanned and similarly analyzed. The intra-observer T_2 reproducibility results indicate that the CV for the femur and tibia are 1.5% and 2.0%, respectively[28].

Statistical data analysis

In this study, group-specific mean values as well as correlations between annual percentage changes of bone and cartilage structural parameters were evaluated. Partial Spearman correlations were obtained between the percentage changes in cartilage parameters in each compartment as well as between the percentage changes in trabecular bone parameters in each compartment, adjusting for age, gender, and OA group. Mixed random effects models[29] were used to compute the percentage changes from baseline to follow-up 1, and follow-up 1 to follow-up 2, for

each trabecular bone and cartilage parameter, treating the study subject as the random effect. These models properly control for correlations resulting from age, gender, repeated measurements over time, and from multiple regional measurements from the same subject. The least squares mean change of these values was calculated for each parameter, in each region based on these models.

Mean T_2 values for both osteoarthritic and control subjects were calculated at baseline and follow-up. The paired Student's *t* test was used to compare the T_2 values between the baseline and follow-up exams for each cartilage compartment, in OA subjects.

The correlations between the changes in cartilage and bone parameters were also investigated. Correlations were based on the entire longitudinal data, including the percentage changes from baseline to follow-up 1, and follow-up 1 to follow-up 2. Similar to the theory of partial correlation coefficients for normally distributed data, residuals of mixed effects models[30] were used to calculate partial Pearson's correlation coefficients between the parameters of interest and age (after removing both individual and design effects, such as repeated measurements from individual participants and different age distributions for two measurements). The corresponding *P*-value was calculated based on Fisher's *z*-transformation[31]. Effective degrees of freedom were used in calculating the significance of these correlations.

Because of the exploratory nature and limited sample size of this study, *P*-values were not adjusted for multiple tests.

Results

The following trends in baseline patient characteristics were observed (Table I): OA1 males have greater average (1) weight, (2) height, (3) BMI, (4) WOMAC pain score, (5) WOMAC stiffness score, and (6) WOMAC function score than OA1 females. (However, the average age of OA1 females was greater than that of OA1 males.) All these trends hold true for the OA2 subjects, except that the OA2 females have a greater average WOMAC function score than OA2 males.

A large variation in bone and cartilage parameters is evident among individual subjects in each group; however, group-specific means demonstrate decreasing trends (in bone and cartilage parameters) in OA subjects (representative examples are shown in Fig. 4). In OA1 subjects, a trend of decreasing mean values for apparent bone volume fraction (app. BV/TV), apparent trabecular number (app. Tb.N), and apparent trabecular thickness (app. Tb.Th) in the femur, medial and lateral condyles, and tibia, and increasing apparent trabecular separation (app. Tb.Sp) was evident over 2 years. OA2 subjects exhibited similar trends; however, they were less pronounced. Decreases in mean values of cartilage volume and thickness in all the cartilage compartments (medial and lateral tibia, and medial and lateral femur) were evident in osteoarthritic subjects over 2 years, but were more pronounced in OA2 subjects. The mean values for bone and cartilage parameters in control subjects showed mild variations, but no trends were observed.

Examination of individual OA subject data showed that 9 out of 10 OA1 subjects had reduced medial femoral cartilage thickness (mean = −19.04%, range = (−0.63% to −39.78%)), and all 10 OA1 subjects had reduced lateral femoral cartilage thickness (mean = −19.94%, range = (−6.22% to −35.52%)) over 2 years. Eight out of 10 OA1 subjects showed a reduction in medial femoral cartilage volume (mean = −32.80%, range = (−7.91% to
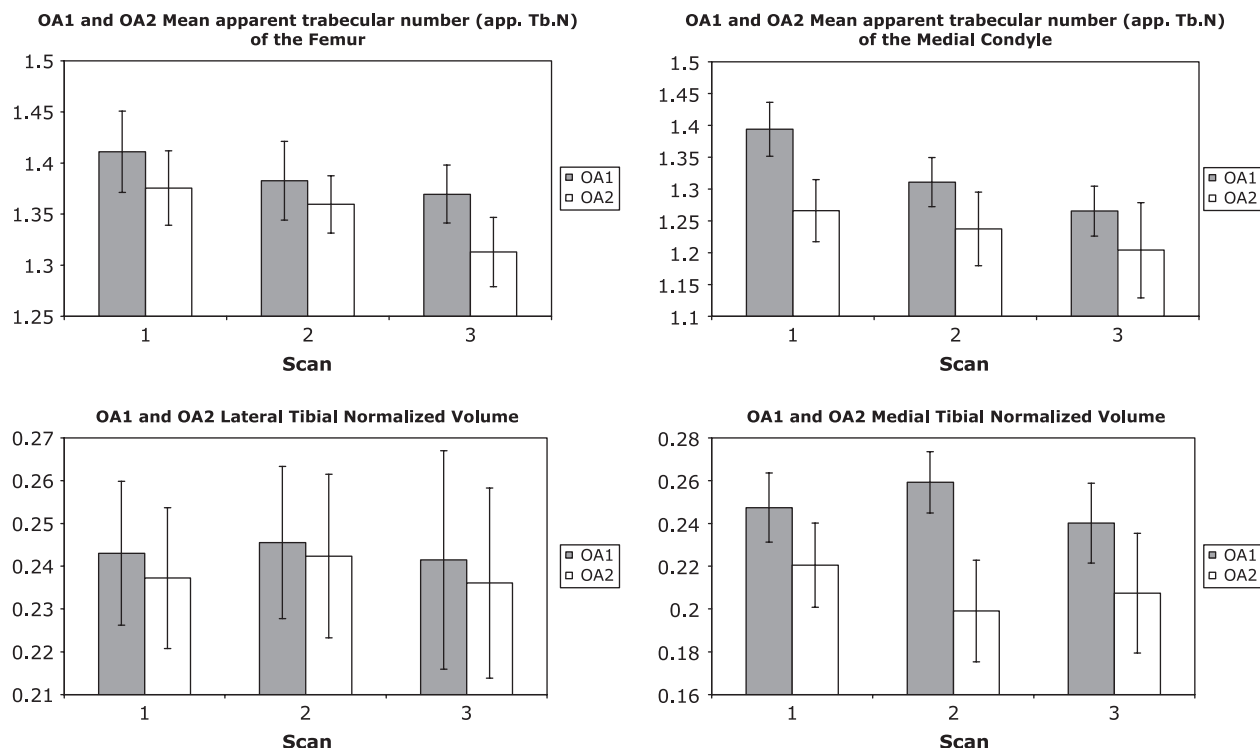
Fig. 4. A comparison of OA1 and OA2 mean bone and cartilage parameters over 2 years. The graphs show (1) a decrease in mean apparent trabecular number (app. Tb.N) of the femur, (2) a decrease in mean app. Tb.N of the medial condyle, and (3) a decrease in medial and lateral tibial normalized cartilage volume over 2 years. The error bars represent standard error of the mean.

−63.07%)), and all 10 OA1 subjects showed a reduction in lateral femoral cartilage volume (mean = −15.67%, range = (−0.88% to −40.24%)) over 2 years. Similar changes were found for OA2 subjects, but they were less pronounced. The percent changes in bone parameters varied among individual osteoarthritic subjects over 2 years; however, 9 out of 11 OA1 subjects showed decreases in apparent bone volume fraction (app. BV/TV) of the femur (mean = −12.14%, range = (−0.71% to 37.91%)) and the medial condyle (mean = −22.86%, range = (−4.72% to 46.91%)). The individual control subjects showed mild variations in bone and cartilage parameters, but no trends were observed.

Using parameter differences from baseline to follow-up 1, and follow-up 1 to follow-up 2, least squares mean percentage changes for each group were calculated, as shown in Table II. The wide range of values in the longitudinal changes between subjects in each group is demonstrated by the standard errors in Table II. A decrease in cartilage thickness and volume in the femoral condyles was evident in both osteoarthritic groups. However, the relative difference in the least squares mean change of only cartilage thickness between the osteoarthritic and control groups approached marginal significance ($P < 0.10$). The least squares mean changes of trabecular bone structural parameters for all regions, as well as cartilage structural parameters for the medial and lateral tibia were insignificant ($P > 0.10$).

The mean T_2 increased significantly ($P < 0.05$) between the baseline and follow-up exams for all cartilage compartments except the lateral tibia (Fig. 5) for both osteoarthritic groups. For qualitative comparison, the osteoarthritic subjects had a higher mean T_2 value compared to normal volunteers in all cases, except for the baseline scan of the medial tibia.

The correlation between percentage changes in medial femoral cartilage T_2 and medial tibial cartilage T_2 was $r = 0.81$ ($P < 0.05$). Additionally, a negative correlation ($r = −0.75$, $P < 0.05$) was established between percentage changes in medial femoral cartilage thickness and medial femoral cartilage T_2 (Table III).

The correlations between percentage changes in cartilage thickness, in different regions, and percentage changes in bone structural parameters, also in different regions, are shown in Tables III and IV, respectively. Significant ($P < 0.05$) correlations were evident between

Table II
Least squares mean percentage change of cartilage parameters (standard error in parenthesis) for OA0, OA1, and OA2 subjects over 2 years. A decrease in cartilage thickness and volume in the femoral condyles was evident in both osteoarthritic groups. However, the relative difference in the least squares mean percentage change of only cartilage thickness between the osteoarthritic and control groups approached marginal significance (P = 0.083 for the lateral condyle and P = 0.068 for the medial condyle)

		Cartilage thickness	Cartilage volume
Lateral condyle	OA0	2.6 (11.9)	7.2 (11.2)
	OA1	−10.5 (11.0)	−7.0 (5.8)
	OA2	−9.4 (11.2)	−5.3 (7.3)
Medial condyle	OA0	8.6 (11.6)	8.2 (16.1)
	OA1	−7.7 (10.3)	−10.2 (14.2)
	OA2	−2.5 (10.4)	−5.4 (14.5)

T2 for Baseline and Follow-up exams by compartment for OA subjects

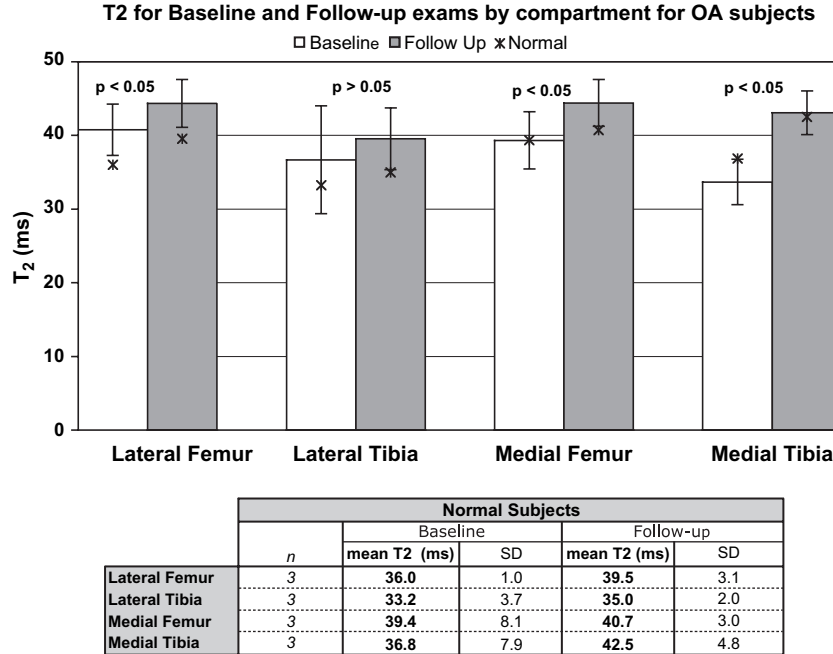|	Normal Subjects				
		Baseline		Follow-up	
	n	mean T2 (ms)	SD	mean T2 (ms)	SD
Lateral Femur	3	36.0	1.0	39.5	3.1
Lateral Tibia	3	33.2	3.7	35.0	2.0
Medial Femur	3	39.4	8.1	40.7	3.0
Medial Tibia	3	36.8	7.9	42.5	4.8

Fig. 5. A comparison of mean T_2 values (one standard deviation) across 12 patients in the knee cartilage compartments at baseline and follow-up. The T_2 was observed to significantly ($P < 0.05$) increase over time for all compartments except the lateral tibia. Mean T_2 values for three normal volunteers (standard deviations are listed in the table) are shown for qualitative comparison, and are lower in all cases except the baseline scan of the medial tibia.

the medial and lateral tibial cartilage thickness ($r = 0.49$). Similarly, a positive relationship was established between changes in bone structure in different regions. The highest correlations ($r \sim 0.65$) were established between the bone structure of the medial and lateral tibia, suggesting a strong interdependence. The remaining significant correlations of interest are moderate and are listed in Table IV.

Overall, a positive relationship was established between cartilage changes and localized bone changes closest to the joint line, while a negative relationship was established between cartilage changes and global bone changes farthest from the joint line, in both osteoarthritic groups. For example, the medial tibial cartilage volume was positively correlated with app. Tb.N of the medial ($r = 0.36$, $P < 0.05$) and lateral ($r = 0.41$, $P < 0.05$) tibia, and with app. Tb.Th of the medial ($r = 0.32$, $P < 0.10$) and lateral ($r = 0.45$, $P < 0.10$) condyles, while negatively correlated with the app. BV/TV of the tibia ($r = -0.53$, $P < 0.05$) and femur ($r = -0.50$, $P < 0.05$).

Significant positive correlations were established between changes in lateral cartilage thickness and changes in medial femoral bone structure. Furthermore, significant positive correlations were established between changes in medial cartilage thickness and changes in lateral tibial bone structure.

Table III
Significant (**0.00 < P ≤ 0.05; *0.05 < P ≤ 0.10) Spearman correlations between changes in cartilage thickness and between changes in T_2, in different regions

Parameter	Parameter	Correlation coefficient
Medial tibial cartilage thickness	Lateral tibial cartilage thickness	0.49
Medial femoral cartilage thickness	Medial femoral cartilage T_2	−0.75
Medial tibial cartilage T_2	Medial femoral cartilage T_2	0.81

Table IV
Significant (P < 0.05) Spearman correlations between percentage changes in bone parameters (apparent bone volume fraction (app. BV/TV), apparent trabecular number (app. Tb.N), apparent trabecular thickness (app. Tb.Th), and apparent trabecular separation (app. Tb.Sp)) from baseline to follow-up 1. The table shows that a positive relationship was established between bone structure changes in the femur and tibia, the femur and the medial condyle, and the lateral and medial tibia. The highest correlations were established between bone structure of the medial and lateral tibia, suggesting a strong interdependence. The * signifies that P < 0.0001

	Femur vs tibia	Femur vs medial condyle	Lateral tibia vs medial tibia
App. BV/TV vs app. BV/TV	0.47	0.44	0.63
App. BV/TV vs app. Tb.N		0.59	0.63
App. BV/TV vs app. Tb.Th	0.36		0.58
App. BV/TV vs app. Tb.Sp	−0.46	−0.49	−0.61
App. Tb.N vs app. BV/TV		0.38	0.54
App. Tb.N vs app. Tb.N		0.67*	0.57
App. Tb.N vs app. Tb.Th			0.45
App. Tb.N vs app. Tb.Sp		−0.50	−0.55
App. Tb.Th vs app. BV/TV	0.51	0.43	0.73*
App. Tb.Th vs app. Tb.N	0.39	0.39	0.70*
App. Tb.Th vs app. Tb.Th	0.42	0.44	0.71*
App. Tb.Th vs app. Tb.Sp	−0.50	−0.40	−0.69*
App. Tb.Sp vs app. BV/TV		−0.44	−0.60
App. Tb.Sp vs app. Tb.N		−0.68*	−0.61
App. Tb.Sp vs app. Tb.Th			−0.53
App. Tb.Sp vs app. Tb.Sp		0.54	0.59

Discussion

In this longitudinal study, MRI was used to track the changes in cartilage and bone structure and to determine their relationship over 2 years. Although a large variation in bone and cartilage parameters is evident in individual subjects, group-specific means show a reduction in both cartilage and (femoral, medial femoral, lateral femoral, and tibial) bone structural parameters in the OA subjects. These results indicate a loss of cartilage and a deterioration of bone structure in OA subjects over time. In addition, the correlations between changes in cartilage and bone structure demonstrate interdependence between these parameters in the progression of OA.

Previous studies have established that cartilage degeneration is one of the characteristics of OA progression[8,15]. For example, Raynaud et al. determined that tibial cartilage volume decreased 6.1% over 2 years in osteoarthritic patients and showed that the rate of cartilage depletion varies[32,33]; in their study of osteoarthritic knees, 21 patients' cartilage depleted less than 2.0% over 2 years, while 11 patients' cartilage depleted more than 15.0% over 2 years. Similarly, our study exhibited a group of fast and slow progressors: the average annual rate of change of cartilage thickness in the medial condyle was −7.7% for OA1 subjects and −2.5% for OA2 subjects. (The difference between these rates of change is not statistically significant; however, this may be attributed to a limited sample size.) In both studies, the majority of fast progressors are female; however, it is difficult to make other comparisons because Raynaud et al. based most of their categorical characterizations on clinical information such as Western Ontario and McMasters Universities Arthritis Index (WOMAC) scores, while ours were based on KL score, determined at baseline.

When examining the variation of cartilage thickness in individual subjects over 2 years, the thickness tended to increase after the baseline scan, but decreased substantially by the last scan. The initial increase of cartilage thickness can be explained by the common incidence of cartilage hydration and swelling in early stages of OA[6,34]. This initial swelling, or increase in cartilage thickness, is followed by a more pronounced decreasing trend, exhibited by the decreasing mean values and decreasing rates of change of cartilage volume and thickness.

In a subset of the study population, T_2 increased significantly ($P < 0.05$) between the baseline and follow-up scans, in all compartments (medial and lateral femur, medial tibia) except the lateral tibia. These results, along with the negative correlation established between medial femoral cartilage thickness and medial femoral T_2, concur with previous studies[35,36] and support the hypothesis that osteoarthritic cartilage has increased mobile water, and hence higher T_2[27]. When examining the correlations between changes in T_2 over time, the strongest correlation was established between the medial tibial cartilage T_2 and the medial femoral cartilage T_2 ($r = 0.81$, $P < 0.05$), suggesting that varus malalignment significantly affects the femoral and tibial cartilage of the medial compartment.

Previous studies have shown that bone and cartilage function as a unit, working together to sustain the mechanical forces associated with joint loading[15,37,38]. Thus, this study explored the relationship between cartilage degeneration and morphologic changes in bone structure. Positive correlations were established between cartilage morphology and localized bone changes closest to the joint line, while negative correlations were established between cartilage morphology and global bone changes farthest from the joint line. These relationships could be explained by the following hypothesis: osteoarthritic knees with cartilage degeneration have high incidence of subchondral plate sclerosis[39–42], which could cause osteopenia in the subarticular bone[41,43] due to decreased load transmission. This localized osteopenia may lead to reactive bone formation farther from the joint line, compensating for the localized bone loss. This hypothesis is supported by Wolff's Law, which states that tissues will adapt to changes in mechanical loading by altering their structural properties[44].

The results of this study show an association between medial tibial cartilage depletion and both medial and lateral tibial bone structure degradation. These results could be influenced by factors such as subchondral plate sclerosis and focal cartilage lesions (that may be in the vicinity of the representative slices). Therefore, these correlations show that if medial cartilage volume or thickness decreases, localized areas of tibial bone structure may degrade, however, the overall structural parameters of the femur and tibia increase significantly ($P < 0.05$).

Sharma et al.[4] showed that joint malalignment increases the probability of developing medial and lateral OA. To explore how varus and valgus alignment affects the progression of OA, this study included a subject cohort with both types of malalignment. Significant positive correlations are evident between changes in lateral cartilage and medial femoral bone structure. This relationship demonstrates that if lateral cartilage thickness decreases, the bone structure of the medial condyle is likely to degrade, while (moderately significant correlations indicate that) reactive bone structural formation will develop in the lateral condyle. Such developments may be attributed to valgus alignment, which causes greater forces in the lateral compartment and causes unloading in the medial compartment[14]. These increased forces cause bone formation in the diseased compartment[45], while the decreased forces cause bone resorption in the contra-lateral compartment[4,5,15]. Similar, but moderately significant correlations, were established in subjects with varus OA; if medial cartilage volume and thickness decreases, the lateral tibial bone structure is likely to weaken. The relationship between cartilage degeneration in one compartment and weakening of bone structure in the contra-lateral compartment further shows that alignment plays a significant role in the progression of OA.

Potential confounds of this study include long scan time, modest subject sample size, limited follow-up rate, uneven gender distribution, and wide age distribution in OA subjects. The long scan time may have influenced the quantity of follow-up T_2 data available, as knee motion between the high-resolution scan and the dual-echo scan could preclude follow-up T_2 analysis. Due to the small sample size, the trends in baseline OA subject characteristics may not be generalized to the OA subjects. Despite these confounds, this pilot study demonstrates significant trends and correlations, and therefore, substantiates the need for further longitudinal studies.

In conclusion, this study quantifies the changes in bone and cartilage structural parameters over time, and demonstrates a longitudinal relationship between the morphological changes in bone and cartilage structure in patients with varying degrees of OA. Although a large variation of bone and cartilage changes is apparent among subjects, significant correlations between changes in bone and cartilage parameters in osteoarthritic subjects are evident in a limited sample size, with a relatively short follow-up duration. This study also emphasizes the role of quantitative

MRI as a potential tool for monitoring cartilage and bone structure in degenerative joint disease.

Acknowledgments

References

1. Mollenhauer JA, Erdmann S. Introduction: molecular and biomechanical basis of osteoarthritis. Cell Mol Life Sci 2002;59(1):3–4.
2. Recht MP, Resnick D. Magnetic resonance imaging of articular cartilage: an overview. Top Magn Reson Imaging 1998;9(6):328–36.
3. Felson DT, Lawrence RC, Dieppe PA, Hirsch R, Helmick CG, Jordan JM, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. Ann Intern Med 2000;133(8):635–46.
4. Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA 2001;286(2):188–95.
5. Sharma L. Local factors in osteoarthritis. Curr Opin Rheumatol 2001;13(5):441–6.
6. Arokoski JP, Jurvelin JS, Vaatainen U, Helminen HJ. Normal and pathological adaptations of articular cartilage to joint loading. Scand J Med Sci Sports 2000;10(4):186–98.
7. Disler DG, Recht MP, McCauley TR. MR imaging of articular cartilage. Skeletal Radiol 2000;29(7):367–77.
8. Cicuttini FM, Wluka AE, Forbes A, Wolfe R. Comparison of tibial cartilage volume and radiologic grade of the tibiofemoral joint. Arthritis Rheum 2003;48(3): 682–8.
9. Wluka AE, Stuckey S, Snaddon J, Cicuttini FM. The determinants of change in tibial cartilage volume in osteoarthritic knees. Arthritis Rheum 2002;46(8): 2065–72.
10. Bettica P, Cline G, Hart DJ, Meyer J, Spector TD. Evidence for increased bone resorption in patients with progressive knee osteoarthritis: longitudinal results from the Chingford study. Arthritis Rheum 2002;46(12):3178–84.
11. Kamibayashi L, Wyss U, Cooke D, Zee B. Trabecular micro-structure in the medial condyle of the proximal tibia of patients with knee osteoarthritis. Bone 1995; 17:27–35.
12. Radin E, Rose R. Role of subchondral bone in the initiation and progression of cartilage damage. Clin Orthop 1986;213:34–40.
13. Lajeunesse D, Reboul P. Subchondral bone in osteoarthritis: a biologic link with articular cartilage leading to abnormal remodeling. Curr Opin Rheumatol 2003; 15(5):628–33.
14. Wada M, Maezawa Y, Baba H, Shimada S, Sasaki S, Nose Y. Relationships among bone mineral densities, static alignment and dynamic load in patients with medial compartment knee osteoarthritis. Rheumatology (Oxford) 2001;40(5):499–505.
15. Lindsey CT, Narasimhan A, Adolfo JM, Jin H, Steinbach LS, Link T, et al. Magnetic resonance evaluation of the interrelationship between articular cartilage and trabecular bone of the osteoarthritic knee(1). Osteoarthritis Cartilage 2004;12(2):86–96.
16. Bellamy N, Buchanan W, Goldsmith C, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip and knee. J Rheumatol 1988;15:1833–40.
17. Kellgren J, Lawrence J. Radiologic assessment of osteoarthritis. Ann Rheum Dis 1957;16:494–502.
18. Beuf O, Ghosh S, Newitt DC, Link TM, Steinbach L, Ries M, et al. Magnetic resonance imaging of normal and osteoarthritic trabecular bone structure in the human knee. Arthritis Rheum 2002;46(2):385–93.
19. Wald LL, Carvajal L, Moyher SE, Nelson SJ, Grant PE, Barkovich AJ, et al. Phased array detectors and an automated intensity-correction algorithm for high-resolution MR imaging of the human brain. Magn Reson Med 1995;34(3):433–9.
20. Newitt DC, Van Rietbergen B, Majumdar S. Processing and analysis of in vivo high resolution MR images of trabecular bone for longitudinal studies: reproducibility of structural measures and micro-finite element analysis derived mechanical properties. Osteoporos Int 2002;13(4):278–87.
21. Majumdar S, Newitt D, Mathur A, Osman D, Gies A, Chiu E, et al. Magnetic resonance imaging of trabecular bone structure in the distal radius: relationship with X-ray tomographic microscopy and bio-mechanics. Osteoporos Int 1996;6(5):376–85.
22. Majumdar S, Genant HK, Grampp S, Newitt DC, Truong VH, Lin JC, et al. Correlation of trabecular bone structure with age, bone mineral density, and osteoporotic status: in vivo studies in the distal radius using high resolution magnetic resonance imaging. J Bone Miner Res 1997;12(1):111–8.
23. Goldstein SA, Goulet R, McCubbrey D. Measurement and significance of three-dimensional architecture to the mechanical integrity of trabecular bone. Calcif Tissue Int 1993;53 Suppl 1(3):S127–32 discussion S132–S133.
24. Majumdar S, Newitt D, Jergas M, Gies A, Chiu E, Osman D, et al. Evaluation of technical factors affecting the quantification of trabecular bone structure using magnetic resonance imaging. Bone 1995;17(4): 417–30.
25. Majumdar S, Genant HK. A review of the recent advances in magnetic resonance imaging in the assessment of osteoporosis. Osteoporos Int 1995;5(2):79–92.
26. Faber SC, Eckstein F, Lukasz S, Muhlbauer R, Hohe J, Englmeier KH, et al. Gender differences in knee joint cartilage thickness, volume and articular surface areas: assessment with quantitative three-dimensional MR imaging. Skeletal Radiol 2001;30(3):144–50.
27. Dunn T, Lu Y, Jin H, Ries M, Majumdar S. MR quantification of cartilage T2 variation with severity of osteoarthritis in the knee. Radiology 2004;232:592–8.
28. Ghosh S. Magnetic Resonance Imaging based on Evaluation of Articular Cartilage in Osteoarthritis. San Francisco, CA: University of California, San Francisco 2001.
29. Diggle P, Liang K-Y, Zeger SL. Analysis of Longitudinal Data. Oxford, New York: Clarendon Press; Oxford University Press 1994.
30. Laird NM, Ware JH. Random-effects models for longitudinal data. Biometrics 1982;38(4):963–74.

31. Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences. 7th edn. New York: Wiley 1999.

32. Raynauld JP. Quantitative magnetic resonance imaging of articular cartilage in knee osteoarthritis. Curr Opin Rheumatol 2003;15(5):647−50.

33. Raynauld JP, Martel-Pelletier J, Berthiaume MJ, Labonte F, Beaudoin G, de Guise JA, et al. Quantitative magnetic resonance imaging evaluation of knee osteoarthritis progression over two years and correlation with clinical symptoms and radiologic changes. Arthritis Rheum 2004;50(2):476−87.

34. Gandy SJ, Dieppe PA, Keen MC, Maciewicz RA, Watt I, Waterton JC. No loss of cartilage volume over three years in patients with knee osteoarthritis as assessed by magnetic resonance imaging. Osteoarthritis Cartilage 2002;10(12):929−37.

35. Buckwalter JA, Mankin HJ. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. Instr Course Lect 1998;47:487−504.

36. Lusse S, Claassen H, Gehrke T, Hassenpflug J, Schunke M, Heller M, et al. Evaluation of water content by spatially resolved transverse relaxation times of human articular cartilage. Magn Reson Imaging 2000;18(4):423−30.

37. Ding M, Dalstra M, Linde F, Hvid I. Mechanical properties of the normal human tibial cartilage−bone complex in relation to age. Clin Biomech (Bristol, Avon) 1998;13(4−5):351−8.

38. Issever AS, Walsh A, Lu Y, Burghardt A, Lotz JC, Majumdar S. Micro-computed tomography evaluation of trabecular bone structure on loaded mice tail vertebrae. Spine 2003;28(2):123−8.

39. Layton MW, Goldstein SA, Goulet RW, Feldkamp LA, Kabinsky DJ, Bole GG. Examination of subchondral bone architecture in experimental osteoarthritis by microscopic computed tomography. Arthritis Rheum 1988;31:1400−5.

40. Pessis E, Drape JL, Ravaud P, Chevrot A, Dougados M, Ayral X. Assessment of progression in knee osteoarthritis: results of a 1 year study comparing arthroscopy and MRI. Osteoarthritis Cartilage 2003;11(5):361−9.

41. Buckland-Wright C. Subchondral bone changes in hand and knee osteoarthritis detected by radiography. Osteoarthritis Cartilage 2004;12(Suppl A):10−9.

42. Pastoureau P, Leduc S, Chomel A, De Ceuninck F. Quantitative assessment of articular cartilage and subchondral bone histology in the meniscectomized guinea pig model of osteoarthritis. Osteoarthritis Cartilage 2003;11(6):412−23.

43. Karvonen RL, Miller PR, Nelson DA, Granda JL, Fernandez-Madrid F. Periarticular osteoporosis in osteoarthritis of the knee. J Rheumatol 1998;25(11):2187−94.

44. Wolff J. Das Gesetz der Transformation der Knochen. Berlin: Hirschwald 1892.

45. Christensen P, Kjaer J, Melsen F, Nielsen HE, Sneppen O, Vang PS. The subchondral bone of the proximal tibial epiphysis in osteoarthritis of the knee. Acta Orthop Scand 1982;53(6):889−95.