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Magnetic Resonance Imaging–Based Assessment of Cartilage Loss in Severe Osteoarthritis

Accuracy, Precision, and Diagnostic Value

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Objective. **To examine the in vivo accuracy and precision of magnetic resonance imaging (MRI)–based assessment of cartilage loss in patients with severe osteoarthritis (OA) of the knee.**

Methods. **High-resolution MRI images of the tibial cartilage were obtained in 8 patients prior to total knee arthroplasty, using a water-excitation gradient-echo MRI sequence (acquisition time 6 minutes 19 seconds; spatial resolution $1.2 \times 0.31 \times 0.31$ mm^3). The MRI measurements were repeated after joint repositioning. The precision of the cartilage volume and thickness computations was determined after 3-dimensional reconstruction. During surgery, the tibial plateaus were resected, and the MRI data were compared with water displacement of surgically retrieved cartilage.**

Results. **The standard deviation (coefficient of variation) of repeated tibial cartilage volume measurements was 56 mm^3 (5.5%) medially and 59 mm^3 (3.8%) laterally. The deviation from surgically removed tissue was −13%, on average, with a high linear correlation between both methods ($r = 0.98$). In patients with varus OA, the tissue loss was estimated to be 1,290 mm^3 in the medial tibia and 1,150 mm^3 in the lateral tibia, compared with the data in healthy volunteers.**

Conclusion. **Noninvasive quantitative MRI-based analysis of cartilage morphometry in severe OA is accurate, precise, and displays high potential diagnostic value.**

Magnetic resonance imaging (MRI) is the only imaging modality that can delineate articular cartilage directly and noninvasively. It is therefore a very promising tool for quantitatively analyzing cartilage tissue loss in osteoarthritis (OA). In particular, quantitative analyses of articular cartilage are potentially useful outcome measures for epidemiologic and clinical studies in OA. Since cartilage degeneration and clinical symptoms are often weakly correlated, objective parameters of disease status are required in the context of monitoring the progression of joint involvement, defining the optimum stage for initiating therapy, selecting the most appropriate type of treatment, and evaluating the success of different (competing) therapeutic approaches. This is of particular interest since novel therapeutic strategies and structure-modifying compounds for treating cartilage disorders are being developed (e.g., metalloproteinase inhibitors and their upstream regulators, homologous or autologous cartilage transplants, osteochondral grafts, cell transplantation, artificial matrices, growth factors, gene therapy, and others [1]) which will require clinical "proof of concept" trials.

Radiography has been shown to produce relatively accurate results only in the medial, and not the lateral, compartment of the femorotibial joint (2). Measurements of joint space width on radiographs cannot differentiate between femoral and tibial cartilage loss and do not reveal the distribution pattern of tissue degradation throughout the joint surface. Moreover, highly standardized positioning procedures and, ideally, fluoroscopic control of the exact position of the joint are

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required to obtain reproducible data on joint space narrowing, which is used as a surrogate measure of cartilage degeneration and disease progression (3,4).

Fat-suppressed gradient-echo MRI (5) in conjunction with 3-dimensional (3-D) image postprocessing has been shown to provide an accurate 3-D representation of the cartilage volume (6,7) and the thickness distribution throughout cartilage surfaces of the knee in healthy (nonarthritic) individuals (7–10). Moreover, these analyses have been shown to display good precision in normal joints (10,11). In a recent study, we have applied a T1-weighted, high-resolution, 3-D gradient-echo MRI sequence, which does not require a prepulse for fat suppression, but makes use of binomial pulses, resulting in net excitation of non–fat-bound protons (12). The contrast between the tightly hydrogen-bound water protons in the interstitial cartilage matrix and the protons of the free water in the synovial fluid results from the combination of T1 weighting and fat suppression. Using a coronal section orientation, we were able to improve the precision in healthy volunteers to 48 mm^3/2.5% (SD/coefficient of variation [CV%]) in the medial tibia and to 66 mm^3/2.6% in the lateral tibia, despite the relatively short imaging time (12).

So far, however, there have been no systematic studies on the accuracy and precision of quantitative MRI-based cartilage analyses in moderate and severe OA with this technique. It is unclear whether results obtained in volunteers also apply to OA patients, since the delineation of the cartilage may suffer from fraying of the cartilage surface, effusion, repair tissue, osteophytes, etc.

The objectives of the present study were therefore 1) to analyze the in vivo precision (reproducibility) of MRI-based volume and thickness measurements in patients with severe femorotibial OA by repositioning the joint between replicate acquisitions, 2) to determine the accuracy of quantitative cartilage imaging in these patients by comparing the in vivo MRI data (obtained immediately before knee joint arthroplasty) with physically retrieved tissue from the surgically resected tibial plateau, and 3) to compare results in the medial and lateral tibial compartment in patients with varus, valgus, and mediolateral gonarthritis, and to estimate the amount of cartilage tissue loss by relating these values to those obtained previously in healthy volunteers.

PATIENTS AND METHODS

Patient population. We examined the knee joints of 8 patients (2 men and 6 women; ages 60–85 years, mean age 70.6 years) who subsequently underwent total knee joint arthroplasty with a bilateral resurfacing prosthesis. Six patients presented with varus gonarthritis. The average knee angle, defined as the angle between the biomechanical axes of the femur and tibia, was 11.7° of varus (SD 4.0°; range 8–18°). One patient displayed valgus gonarthritis (knee angle 6° of valgus), and one had mediolateral gonarthritis (knee angle 2° of varus). Written informed consent was obtained from the patients, and the study protocol was approved by the local ethics committee.

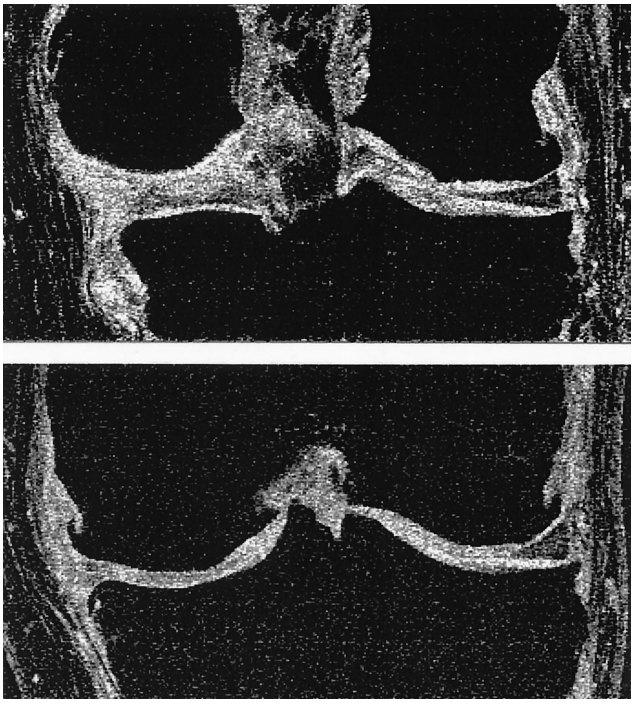

Figure 1. Coronal magnetic resonance images of the posterior (**top**) and central (**bottom**) aspect of the femorotibial joint of the left knee of a patient with varus gonarthritis. The central slice shows severe cartilage loss in the medial compartment (left side of the figure). Water-excitation gradient-echo sequence; spatial resolution 1.2 × 0.31 × 0.31 mm^3.

MRI. MRI was performed with a 1.5T magnet (Magnetom Vision; Siemens, Erlangen, Germany) and a circular, polarized transmit–receive extremity coil. To obtain high-contrast and high-resolution images of the cartilage within a short imaging time, we used a spoiled 3-D gradient-echo sequence (fast low-angle shot) with selective water excitation (radiofrequency amplitude ratios 1:2:1; repetition time 17.2 msec, echo time 6.6 msec; flip angle 20°) (Figure 1). The acquisition time for 1 coronal data set of the tibia was only 6 minutes 19 seconds, at a spatial resolution of 1.2 × 0.31 × 0.31 mm^3 (field of view 160 mm; matrix 512 × 512 pixels). This imaging sequence has previously been shown to provide accurate measurements of cartilage volume and thickness in comparison with computed tomography arthrography and A-mode ultrasound, even in joints with very thin cartilage layers (13).

Four data sets were obtained on each of 6 patients; the joint was repositioned in the magnet and the shim adjustment

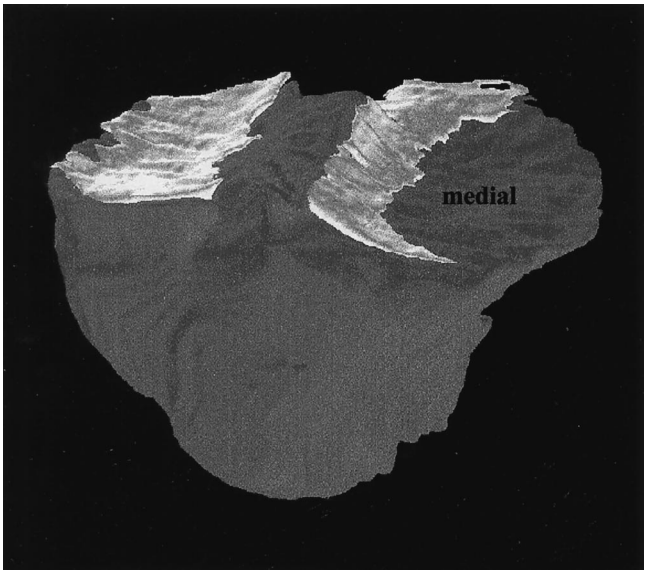

Figure 2. Three-dimensional reconstruction of tibial cartilage **(white)** on the proximal tibia **(gray)** of a patient with varus gonarthritis.

repeated between replicate examinations. In 2 patients, only 2 sequential data sets could be obtained because the patients began to feel discomfort during the imaging session.

The MRI data were transferred digitally to a workstation (Octane Duo; Silicon Graphics, Mountain View, CA). A semiautomated B-spline snake algorithm was used for the segmentation of the medial and lateral tibial cartilage, which has been shown to yield a higher precision than manual segmentation (14). The accurate performance of the algorithm was controlled visually in each section. The volume of the tibial cartilage was computed by numerical integration of the voxels assigned to the medial and lateral cartilage during the segmentation process (Figure 2). The mean and maximum thickness of these cartilage plates were determined 3-dimensionally, independent of the original section orientation. A previously validated 3-D Euclidean distance transformation algorithm (10) was applied, and the mean cartilage thickness was computed from ~1,000 measurements per square centimeter of joint surface.

From the replicate data sets obtained in each patient, the mean value, SD, and CV% (CV% = SD divided by the mean value × 100) were determined for the volume and the mean and maximum thickness as a measure of the technical precision. The average SD and CV% for the computations were determined as the root mean square (RMS) average (15) and as the median of the individual CVs, respectively.

The accuracy was evaluated by comparing the values obtained with MRI with those from volume displacement of surgically retrieved cartilage tissue (6,16). In 5 patients, an intact tibial plateau could be excised distal to the bone cartilage interface of the medial tibial cartilage, and in 4 cases, the lateral tibial cartilage as well. At these 9 surfaces, the cartilage tissue was surgically removed by an investigator (RB) who was unaware of the results of the MRI analysis. The volume of the tissue (not including the fibrous cartilage covering the osteophytes) was determined by water displacement in a pipette graded with 10-mm^3 increments. We then computed the pairwise differences, the correlation coefficient, and the standard error of the estimate (SEE) between the 2 methods, using linear regression analysis. The difference between the MRI analysis and the surgically removed tissue was tested for statistical significance with the Wilcoxon signed rank test.

To estimate the amount of tissue loss in these patients, the data from the medial and lateral tibia were compared with previously published data in 28 healthy individuals (12,17) who had no history or signs of joint involvement. The difference was given both in absolute values and in SDs from the mean of the healthy individuals (T score).

RESULTS

The SD of the 4-fold determination of the medial tibial cartilage volume in the patients ranged from 17 mm^3 to 123 mm^3 (CV% 1.5–8.5%); the RMS average was 56 mm^3 (5.5%) (Table 1 and Figure 3). For the mean cartilage thickness, the average (RMS) precision was 77 μm (6.2%), and for the maximal thickness to 170 μm (5.8%) (Table 1). The SDs of the lateral tibia were similar, and the CVs were smaller than those in the medial tibia (Table 1).

The cartilage volumes determined with MRI were somewhat lower than those obtained from water displacement of surgically removed tissue, the deviation ranging from −7% to −27% (average −150 mm^3 and −13%; $P < 0.01$). The largest deviation was observed in

Table 1. Precision of magnetic resonance imaging–based analysis of tibial cartilage in OA*

	Volume (mm^3)		Cartilage thickness (μm)			
			Mean		Maximum	
	SD	CV%	SD	CV%	SD	CV%
Medial tibia						
Varus OA (n = 6)	40	5.0	80	6.4	170	6.1
Mediolateral OA (n = 1)	29	4.6	60	5.9	100	4.6
Valgus OA (n = 1)	123	8.5	76	5.5	200	4.9
RMS average (n = 8)	56	5.5	77	6.2	170	5.8
Median (n = 8)	43	5.2	57	5.2	160	5.8
Lateral tibia						
Varus OA (n = 6)	66	4.1	62	4.0	240	6.7
Mediolateral OA (n = 1)	12	1.2	20	1.4	70	2.3
Valgus OA (n = 1)	40	3.9	10	0.8	30	1.0
RMS average (n = 8)	59	3.8	55	3.5	210	5.8
Median (n = 8)	43	3.2	40	2.6	120	3.1

* The values for the varus osteoarthritis (OA) patients are root mean square (RMS) averages of the individual SDs and coefficients of variation (CV%). The RMS average represents all 8 patients. Four data sets were obtained on 6 patients, and 2 data sets were obtained on the other 2 patients. See Patients and Methods for details of the data sets, the RMS, and the CV calculations.

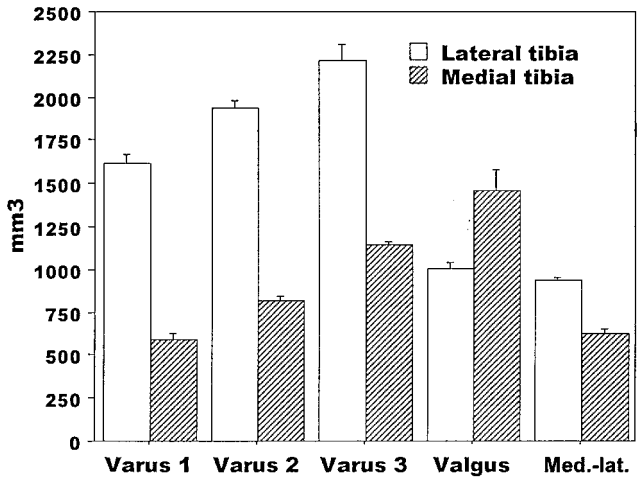

Figure 3. Precision and volume data from the medial and lateral tibia of 3 patients with varus osteoarthritis (OA), 1 patient with valgus OA, and 1 patient with mediolateral (Med.-lat.) OA. Values are the mean and SD of repeated measurements (with repositioning of the knee joint in the scanner).

the patient with mediolateral OA; the range in the other 7 patients was −7% to −12% (average −10%). There was a high linear relationship between the results from both methods: the correlation coefficient was r = 0.98 (SEE 7%) when including the patient with mediolateral OA, and r = 0.99 (SEE 2.9%) without the patient with mediolateral OA (Figure 4).

Table 2 shows the absolute values for cartilage volume and mean and maximum thickness in the patients and healthy volunteers, as well as the estimated tissue loss in the medial and lateral tibia. The tissue loss in the medial tibia was estimated to be 1,290 mm^3 in the patients with varus OA (Table 2 and Figure 5). The estimated loss was higher in the patient with mediolateral OA and lower in the patient with valgus OA (Table 2). When expressed in terms of SDs of the normal population (T score), the changes were most pronounced for the cartilage volume (Table 2 and Figure 5). T scores were −2.4 SD for the medial tibia in the varus OA patients and >3 SD in the lateral tibia of the mediolateral and valgus OA patients (Table 2).

DISCUSSION

This study demonstrates that accurate and precise information on articular cartilage volume and thickness can be obtained noninvasively with MRI, not only in healthy volunteers, but also in patients with OA. A potential limitation of the current study is the relatively modest sample size, and the data will have to be confirmed in larger clinical trials. However, the present data are promising and demonstrate the feasibility of the current approach.

The accuracy was confirmed in relation to the water displacement of surgically retrieved tissue, a method successfully used by other investigators (6,16). Although small systematic differences were noted, there was a very high linear relationship between the two methods. This confirms that quantitative assessment of articular cartilage can be reliably performed with MRI, both in moderate (lateral compartment of patients with varus OA) and severe (medial compartment prior to total knee arthroplasty) stages of OA. There was a relatively consistent underestimation relative to surgically removed tissue, but those differences were small compared with the estimated tissue loss in the patients versus the healthy volunteers.

The SDs of repeated measurements were in the same range as those in normal volunteers (12). In contrast, the relative SDs (CV%) were somewhat higher because the absolute values were substantially smaller. Comparing the precision error in the patients with varus OA with the estimated tissue loss, the ratio is >30:1. This suggests that the technique is highly effective in staging the progression of OA to its clinical end point prior to total knee arthroplasty. Although the early

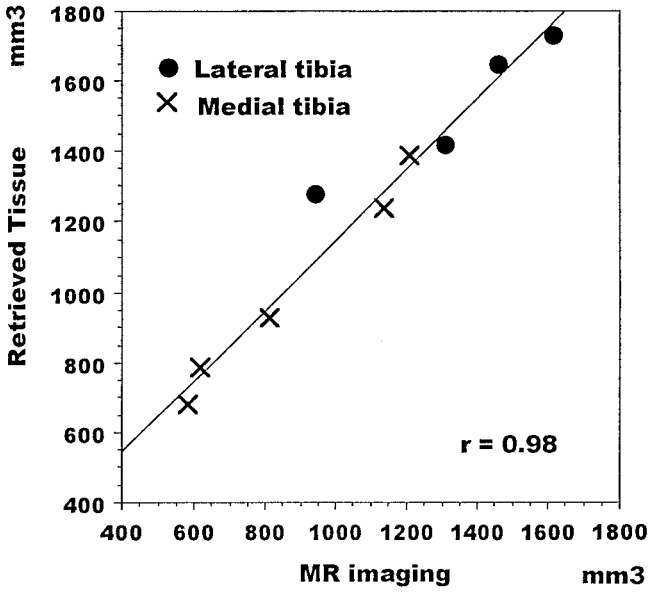

Figure 4. Correlation between cartilage volume derived from preoperative magnetic resonance (MR) imaging and from water displacement of cartilage tissue retrieved from the excised tibia after surgery.

Table 2. Absolute values of magnetic resonance imaging–based tibial cartilage analysis in 8 OA patients and 28 healthy volunteers, and estimated tissue loss in OA patients*

	Medial tibia			Lateral tibia		
	Volume (mm^3)	Cartilage thickness (mm)		Volume (mm^3)	Cartilage thickness (mm)	
		Mean	Maximum		Mean	Maximum
Patients						
Varus OA	880	1.2	2.8	1,640	1.6	3.7
Mediolateral OA	620	1.0	2.3	940	1.5	3.2
Valgus OA	1,460	1.4	4.1	1,010	1.3	2.9
Healthy subjects						
Mean	2,170	1.56	3.3	2,780	2.13	4.7
SD	540	0.24	0.55	580	0.29	0.80
Estimated tissue loss						
Absolute						
Varus OA	−1,290	−0.35	−0.56	−1,150	−0.51	−1.0
Mediolateral OA	−1,550	−0.55	−1.1	−1,840	−0.60	−1.5
Valgus OA	−710	−0.18	0.7	−1,780	−0.83	−1.8
T score						
Varus OA	−2.4	−1.5	−1.0	−2.0	−1.8	−1.3
Mediolateral OA	−2.9	−2.3	−1.9	−3.2	−2.1	−1.8
Valgus OA	−1.3	−0.8	1.3	−3.1	−2.9	−2.3

* The values for the varus osteoarthritis (OA) patients are the mean of all 6 patients. The T score is the difference between patients and healthy volunteers, expressed as the number of SDs of the values in the healthy volunteers.

biochemical and structural changes in OA (before the occurrence of quantitative tissue loss) may not be detectable with this method, the technique constitutes a potentially useful tool for monitoring noninvasively the progression of tissue loss in OA. Such quantitative data can be used for more objectively defining the optimum stage for initiating therapy, for selecting the most appropriate type of treatment, and for evaluating the success of various therapeutic approaches in moderate to severe stages of the disease in clinical trials.

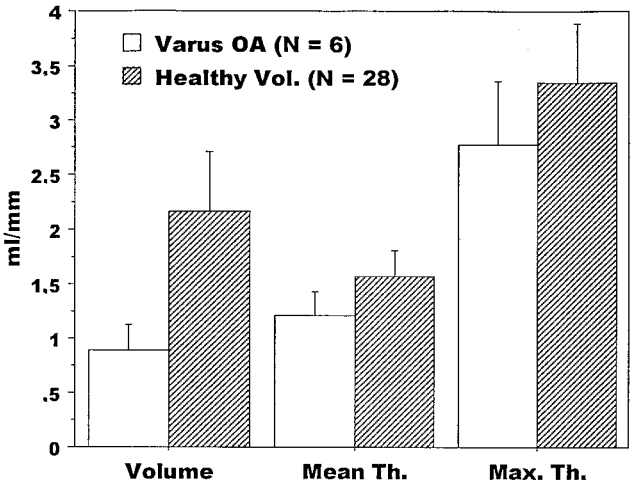

Figure 5. Absolute values of cartilage volume (in ml), mean cartilage thickness (Mean Th.; in mm), and maximum cartilage thickness (Max. Th.; in mm) in the medial tibia of 6 patients with varus osteoarthritis (OA) and 28 healthy volunteers (Vol.). Error bars indicate the variability between subjects (1 SD).

The cartilage volume loss in the medial and lateral compartments of the tibia varied between patients and reflected the differences in expected disease status in varus, valgus, and mediolateral OA. To allow for individual quantitative estimates of cartilage tissue loss, the data in the patients need to be compared with those in normal volunteers. By pooling the data from 2 previous studies (12,17) with a total of 28 normal subjects, we found that the cartilage volume of the medial tibia of the patients was reduced by 2.4 SDs in varus OA patients, and by >3 SDs in the lateral tibia of mediolateral and valgus OA patients. The T scores obtained for the thickness computations were lower because the tissue loss occurs inhomogeneously throughout the tibial surfaces. The remaining cartilage covers only parts of the surface, but retains a relatively high thickness.

A disadvantage of MRI compared with radiography is the substantially higher costs (both financially and in the logistics of the examination). By using an optimized MRI sequence (12), however, we were able to keep the acquisition time short (6 minutes 19 seconds), despite the high spatial resolution (1.2 × 0.3 × 0.3

mm^3). The cost for MRI and 3-D postprocessing may be currently too high to justify regular examination of OA patients in routine clinical practice. However, considering the costs for drug development (~$500 million per new compound), the technique can be a very powerful tool for both selecting appropriate patients and following them longitudinally in clinical trials. Another important field of application is in epidemiologic studies, in which high-resolution 3-D MRI data can clarify the risk factors and the natural history of the disease in different compartments of the knee.

Among the potential advantages of MRI as a 3-D technique over radiography is that it is less prone to errors resulting from joint malpositioning. More specific information on the disease status can be gained (e.g., distribution pattern of cartilage loss throughout the joint surface, differentiation between femoral versus tibial cartilage loss), and the number of patients required to demonstrate the structure-modifying effect of a new therapeutic agent can be potentially reduced. The results of this study suggest that changes as low as 40–60 mm^3 can be detected with 95% confidence in a sample size of 10 patients (18). Future MRI-based studies will have to examine longitudinally the rate of cartilage tissue loss in large patient groups and in specific subsets of OA patients in order to allow for statistical sample size calculations for clinical trials.

In conclusion, we show that quantitative MRI-based measurements of tibial cartilage in patients with severe OA are highly precise and accurate. In comparison with healthy normal volunteers, patients with OA display a substantial reduction of cartilage volume, a finding which demonstrates the potentially high diagnostic value of this method. Quantitative analyses of articular cartilage may therefore become powerful outcome measures for epidemiologic and clinical studies in OA.

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