Quantitative 3D MR evaluation of autologous chondrocyte implantation in the knee: feasibility and initial results


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Summary

Objective: To evaluate the feasibility of quantitative magnetic resonance imaging (MRI) based follow-up of cartilage volumetric data in patients after autologous chondrocyte implantation (ACI). To provide results from a 1-year follow-up study.

Methods: From 21 ACI patients sagittal FS 3D FLASH (50/11/30; 0.6 × 0.6 × 1.5 mm³) MRI knee data sets were obtained pre and 1-year post-ACI surgery in the femoral condyles. After semi-automated segmentation and 3D reconstruction of the cartilage plates, cartilage volume, mean thickness and size of the cartilage—bone interface were calculated. Susceptibility artifacts were evaluated in all, intra-observer reproducibility was evaluated in six of the patients. Volumetric parameters were compared during follow-up and sensitivity to change was assessed for the total femur vs the separately evaluated medial/lateral portions of the femur.

Results: Reproducibility error (coefficient of variation %) was 3.3%/4.4% for the med./lat. tibial and 5.1% for the femoral cartilage volume. Susceptibility artifacts led to the exclusion of three out of the 21 patients, but were moderate in the remaining 18 patients, not preventing reproduceable segmentation. In contrast to lack of significant change in the (non-operated) tibiae, a mean 6% increase of volume and thickness in the treated femora (P < 0.001 Wilcoxon) relative to the pre-OP data was observed. Sensitivity to change for the femur ranged from 0.74 to 2.69 for cartilage volume and thickness and was improved when evaluating only the treated portion of the femur in contrast to the total femur.

Conclusion: Our data indicate that despite postoperative susceptibility artifacts quantitative evaluation of cartilage volumetric parameters can be performed in ACI patients. The technique is able to describe changes of these parameters over 1 year. Volumetric follow-up may help to identify altered disease progression.

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Key words: Autologous chondrocyte implantation, MRI, Knee, Cartilage Volume, Quantification.

Introduction

Damage to articular cartilage leading to defective articular surfaces is considered to be a precursor of osteoarthritis (OA), a major socio-economic burden today. Autologous chondrocyte implantation (ACI) as one of the comparatively new techniques is designed to repair joint cartilage defects in order to restore an intact and smooth joint surface with the aim to prevent the development of OA and eventually to stop the progression of preexisting OA. The technique consists of harvesting autologous cartilage from a non-weight bearing joint surface area and culturing chondrocytes derived from this tissue sample. Subsequently, the cultured chondrocyte suspension is injected into a cartilage defect which has been prepared by debridement and then the defect area is covered, e.g., by a periosteal flap.

Mostly, success of the ACI procedure is determined from clinical observations including second look arthroscopy and histology as well as magnetic resonance imaging (MRI) studies. Due to the fact, that ACI is a new technique, data from long-term follow-up studies are not abundant. The experience that is available from qualitative MRI studies aims at demonstrating defect filling, integration of the repair tissue or reconstitution of a smooth joint surface at follow-up.

In contrast to this local assessment, a more global approach targeted at quantifying the evolution of volume and thickness of the femoral and tibial cartilage plates as a whole may provide additional insight in the long-term effectiveness of ACI. Cartilage volume and thickness and their (annual) rate of loss have been observed to be associated with early and advanced OA. T1-w Fat Sat and Water Excitation 3D FLASH sequences have been validated for cartilage volume and thickness quantifications by comparison with computed tomography-arthrography and anatomical sections for healthy
volunteers/specimen and water displacement for tissue retrieved during total knee arthroplasty in OA patients. For healthy cartilage agreement between MRI and other methods is within 4% for all cartilage plates. In OA cartilage, the data show an underestimation of 10% in cartilage volume as compared to water displacement. Studying the rate of cartilage volume and thickness change per unit time may hold potential to contribute to the evaluation of ACI treatment outcome because it may show very subtle changes of volume and thickness which may not be detected in routine MRI scans. This approach would come into play once the technical success of the ACI procedure in terms of ongoing graft, reconstitution of a smooth joint surface by filling of the initial defect and integration of the graft into the neighboring bone and/or cartilage is established. In this situation, it could constitute a measure to evaluate the effect of ACI on total (global) joint surface cartilage preservation by assessing the annual rate of cartilage loss in both, the treated as well as in the untreated joint compartments.

Yet, to date, there is no experience at all from quantitative MRI evaluation of cartilage volumetric parameters in ACI patients and it is not clear whether the technique can be successfully applied to follow ACI patients: reproducibility data are available only from healthy, untreated or non-operatively treated subjects and sensitivity to change as well as the influence of potential post-OP susceptibility artifacts presumably due to debris from the metallic instruments used during the procedure is unclear. Therefore, the purpose of the study is (I) to assess the feasibility of 3D volume and thickness measurements after ACI. This comprises (1) extent and influence on cartilage segmentability of susceptibility artifacts in post-OP data sets, (2) post-OP resegmentation precision and (3) sensitivity to change of volumetric assessment. (II) To give first results of cartilage volume evolution in the treated and in the untreated femoral and tibial joint compartments from a 1-year follow-up period.

Patients and methods

A total of 21 patients (seven females, 14 males) were investigated in this pilot study. Mean age was 36.3 ± 7.7 years (median 39.3 years, range 25–48 years), mean body weight was 79.1 ± 14.9 kg (median 81.5 kg, range 55–105 kg). All patients gave informed consent for the study. All patients had undergone ACI for cartilage loss due to either OA or osteochondral defects with concomitant OA in one femoral condyle (11 medial condyles, 10 lateral condyles). Defect size (length by width in mm) measured after surgical debridement was 23.0 ± 6.5 mm (range: 10–38 mm) by 20.7 ± 6.3 mm (range: 13–30 mm). Assuming an elliptical shape of the operatively debrided defects, their cross-sectional area was calculated as length/2 × width/2 × π yielding an average defect size of 3.7 ± 1.5 cm² (range: 1.2–7.5 cm²). Defects were located in the anterior third (3 out of 21), intermediate third (10 out of 21) and posterior third (8 out of 21) of the femur. ACI was performed in a two stage surgery. After harvesting of cartilage from low weight bearing sites in the femoral notch or the periphery of the femoral trochlea and chondrocyte culturing, the chondrocyte cell suspension was injected under a periosteal patch covering the debrided defect. In all patients 1.5-T MRI (Magnetom Vision, Siemens-Erlangen, Germany) using a circularly polarized knee coil was performed within 1 week before and again between 1 and 1.7 years after operation. Board ethics review was obtained prior to the study. Average time between the two imaging sessions was 14 ± 2 (median 13, range 12–21) months. For volumetric evaluation, a 3D FLASH fat presaturated sequence (repetition time: 50 ms/echo time: 11 ms/flip angle: 30°) was applied using a field of view (FOV) of 16 cm² or 18 cm², respectively, a 256 matrix and a slab of 90 mm composed of 60 sagittal partitions of 1.5 mm each. Spatial resolution was 1.5 × (0.625² or 0.705²) mm³. Similar sequences applying fat presaturation or water excitation techniques with spatial resolutions ranging from 1.5 × 0.3² to 2 × 0.6 × 0.8 mm³ have previously been validated for 3D knee cartilage volumetric assessment. A sagittal orientation was chosen to completely cover all knee joint cartilage plates. Care was taken to obtain a truly sagittal and as such reproducible section orientation of the slab perpendicular to a tangent line to the most posterior border of the femoral condyles in axial sections.

For 3D evaluation, semi-automatic segmentation using a b-spline snake algorithm with interactive visual control of the cartilage was performed (one experienced segmentator) for the distal femoral cartilage plate and the medial and lateral tibial plateau, separately and subsequently, 3D reconstruction of the cartilage plates was performed after interpolation to isotropic voxels. As global parameters cartilage volume (voxel count), 3D mean cartilage thickness as well as the distribution of local cartilage thickness (thickness plot, Euclidean distance transformation) and the size of the cartilage–bone interface were calculated for each joint surface. Areas of complete cartilage loss in thickened, thinning and areas of 0 mm thickness in cases with difficult delineation between cartilage and joint effusion, a T2-w DESS sequence was used to visually support segmentation. Values were compared between pre- and post-OP data sets (Fig. 1). In addition, interactive segmentation of the cartilage defect was performed and the defect’s volume and surface area were determined from the pre-OP data set after 3D reconstruction using the algorithm described above. Surface area was defined as the size of the (former, intact) joint surface that was destroyed by the defect. The beginning/end of a defect was visually defined as a markedly increased curvature of the femoral cartilage’s (convex) surface followed by a surface concavity in a not anatomical location. The former joint surface was interactively extrapolated from the adjacent intact cartilage. The exact border of a defect was defined as the point of separation between the extrapolated joint surface and the actual cartilage surface contour.

The reproducibility of intra-individual segmentation was assessed in six randomly chosen patients’ postoperative data sets by four consecutive segmentations in each femoral and tibial data set. Reproducibility was determined for segmentation of the total femoral cartilage, for the separated medial/lateral portion (see description in last paragraph) of the femur and for the segmentation of the cartilage defects. There was a delay of at least 2 weeks between each of the four consecutive segmentation processes. The reproducibility error was calculated as the root mean square average of the coefficient of variation (COV) in each individual patient.

The severity of postoperative susceptibility artifacts was rated in order to assess whether these artifacts affected image quality to an extent relevant for cartilage segmentation. Rating was performed by two radiologists (CG, CT) in consensus. Artifacts were defined as areas of signal
void in or adjacent to the cartilage. Five categories were defined according to the extension of the signal void relative to the cartilage boundaries ranging from minimal (0) to severe (4). Minimal artifacts were defined as small (<5 mm) purely intracartilaginous foci without any contact to the cartilage–bone interface or the surface of the cartilage. Severe artifacts were defined as areas of signal void exceeding the thickness of the cartilage and being continuous over more than 10 mm, thus preventing reliable delineation of the cartilage contours and leading to exclusion of this data set from evaluation. Table I summarizes the details of the rating scale, Fig. 2 illustrates the various grades of artifacts. In addition, the share (given in %) of the former defect's cartilaginous surface which was obscured by artifact was calculated (Fig. 3). This was achieved by segmentation of those artifacts obscuring the cartilage surface in the post-OP data sets, calculation of their surface area and normalization to the total surface of the defects segmented in the corresponding pre-OP data sets. Similar to the pre-OP data sets, in areas of the repair site where cartilage repair tissue was obscured by artifacts, the surface was extrapolated visually from the adjacent joint surface not affected by artifacts. The portion of artifact between the extrapolated cartilage surface and the subchondral bone was considered to be cartilage.

In a subset of 10 patients, additionally, evaluation was performed separately for the medial/lateral portions of the femoral cartilage plate including the medial/lateral portions of the trochlea and condyles. The anatomic landmark for separating the medial and lateral portions of the distal femur was the shortest cranio-caudad extension of the cartilage in the trochlear groove in the original sections (Fig. 1). Based on the assumption that the size of the cartilage–bone interface does not undergo relevant changes within 1 year, separation was accepted within a delta of 5% between pre- and post-OP data for the size of the cartilage–bone interface segmentations. Sensitivity to change for volume, thickness, cartilage–bone interface and volume normalized to the size of the cartilage–bone interface was estimated in this subset of 10 patients by comparing the standardized response means (SRM = mean change/standard deviation of change) between total femur and the separated med./lat. portions of the femur. It was calculated for the relative (%) change to baseline for volume and thickness.

Results

Average artifact grading was 1.8 for all patients. In all but three of the data sets relevant postoperative artifacts were present. Artifact grading led to exclusion of three out of the 21 patients' data sets from further evaluation due to severe artifacts preventing reliable segmentation. In the remaining 18 data sets, average rating was 1.4. A total of 16 out of these 18 were rated as intermediate or better (Table I). The mean share of the former defects' surface area covered by artifact was 9.3% for artifact grades 0 through 3 (Fig. 3). There was an abrupt increase in the surface area covered by artifact from 21.3% for artifact grade 3–69.3% for artifact grade 4 (Fig. 3). Linear
Regression between artifact grading and % surface area obscured by artifact was good with $R^2 = 0.73$, $P < 0.001$.

Morphologically, there was considerable variability of the outcome of the ACI procedure with only partial filling of the former defect in three patients, good reconstitution of a smooth articular surface in nine patients and considerable graft or periosteal overgrowth in six patients. Partial filling was characterized by reduced cartilage thickness in the region of the defect as compared to the adjacent cartilage and by a more irregular surface contour. Conversely, overgrowth showed higher regional thickness values and some degree of bulging of the cartilage surface contours. From the MRI sequence, differentiation between periosteum and cartilage repair tissue was not possible.

Reproducibility error (COV) as calculated from the repeat segmentations ranged from 3.7% to 5.6% with highest values for the femur (Table V). Reproducibility error for the separated portions of the femur ranged from 6.1% to 7.9% (Table V). Reproducibility error for defect volume and defect surface area was 14.7% and 9.3%.

A total of 15 out of 18 patients had a nominal increase in femoral cartilage volume (+$0.3$ to $+9.9$%). Three out of 18 patients had a nominal reduction in femoral cartilage volume (−0.4% to −2.5%). Average total femoral volume increase was $1.04 \pm 0.69$ ml corresponding to 5.8% (Table II, Fig. 2). No such tendency could be observed for the cartilage–bone interface in the femora as well as in the tibiae. There was a small nominal, statistically not significant ($P > 0.05$; Wilcoxon signed rank test), tendency to lower cartilage volume and thickness values (−0.3% for volume and −1.6% for thickness) over the 1-year period in the tibiae. Fourteen out of 18 patients had a reduction of medial tibial cartilage volume/thickness (−0.3% to −6.9%), four had an increase (0.3$\pm$ 6.8%). Eleven out of 18 patients had a reduction of lateral tibial cartilage volume/thickness (−0.1% to −5.1%), seven had an increase (0.5$\pm$ 4.8%). Standard deviations, mean and range of values are given in Table II. Average femoral defect volume based on the preoperative MRI was $0.67 \pm 0.35$ ml (range: 0.15 ml to 1.32 ml). Average defect surface area based on the preoperative MRI was $281.5 \pm 154.9$ mm$^2$ (range: 88.9$\pm$653.7 mm$^2$).

In the subset of 10 patients in whom volume and thickness were calculated separately for the medial/lateral portions of the femur, the absolute increase of cartilage volume/thickness in the operated portion of the femur was comparable...
Fig. 3. Boxplot of % surface area covered by artifact with subgroups as defined by rating scale. The encircled cross symbol corresponds to the mean, the horizontal line to the median value of each subgroup. Values show a clear increase of the percentage of the cartilage surface obscured by artifact from grade 3 to grade 4.

Discussion

The purpose of this study was to assess the feasibility of quantitative longitudinal volumetric evaluation of the cartilage in ACI and to give first 1-year follow-up results. To this end, the influence of susceptibility artifacts, the reproducibility of segmentation of the post-OP measurements and the ability to show change over time are of interest.

Gradient echo (GRE) sequences as the MRI-sequences currently used for quantitative volumetric evaluation of cartilage are comparatively susceptible to local alterations in main magnetic field strength. When too extensive, susceptibility artifacts might prevent reliable image evaluation. Although the exact reason of such artifacts is still unclear and for better prevention investigation into their cause is needed, use of non-metallic, plastic tipped suckers and non-metallic ceramic tipped surgical tools in the future may contribute to reduce such artifacts in MRI. However, rating of susceptibility induced signal voids in average revealed but moderate artifacts (mean rating: 1.8 out of max. 4 possible) allowing for segmentation in 18 out of 21 data sets. In 14% (3/21) of the data sets artifacts extended over a length of more than 10 mm and prevented reliable segmentation. In all these cases, the artifacts were so extensive that they would have impaired reliable local clinical assessment of the cartilage in the GRE sequences used in this study, too. However, ACI artifacts rarely are observed to such an extent in turbo spin echo (TSE) sequences. Therefore, routine clinical (visual) analysis would profit from acquisition of such TSE sequences in addition to GRE sequences. The high increase in the surface area of cartilage defects covered by artifact (Fig. 3) from 21.3% (grade 3) to 69.3% (grade 4) suggests that this transition is a reasonable cutoff value to decide upon acceptability of artifact grading for segmentation. The observed drop out rate in this pilot study constitutes a first estimate and may contribute to plan studies for quantitative evaluation after ACI.

The slab of 90 mm width (60 sagittal partitions at 1.5 mm) provided complete coverage of all articular joint surfaces in the examined knees. Defect locations were distributed mostly within the intermediate and posterior portions of the femoral condyles. Therefore, and despite a potential improvement of reproducibility from coronal section orientation in the tibiae and the central portions of the femur after ACI, a sagittal section orientation has been chosen in order to enable complete assessment of all defects. Unfortunately, the FOV varied between 162 cm² and 182 cm², possibly contributing to the observed precision error in this study.
The precision of segmentation has been determined as intra-observer reproducibility errors. Ethical permission was not obtained for a second data acquisition precluding a test–retest design for evaluation of reproducibility. In addition to segmentation errors, a test–retest design would incorporate partial volume averaging, which may be relevant especially with respect to the presentation of post-OP artifacts in various imaging sessions. A test–retest design could provide information whether the grading of any given artifact stays constant or whether there is transition from one grade to another grade in different imaging sessions possibly affecting the cumulative drop out rate. This, as well as the lack of inter-observer reproducibility is a limitation of this study. The results (femur and tibiae) between 5.1% and 3.9% are within the order of magnitude described in previous studies for sagittal sections which was followed in this study. The cutoff value by a strictly standardized positioning scheme of the slabs/base value. It appears, that this effect is higher than the comparable absolute change is normalized to a smaller base value. They are reported to be within 1.5–3.9% for the femur and within 2.1–4.2% for the tibiae in healthy volunteers. In patients with defective cartilage the values for resegmentation conditions are between 2.9% and 3% for the femur and between 3.2% and 7.1% for the tibia. According to the results of Hardy et al., reproducibility error is likely to increase with decreasing in plane resolution from 0.28 mm² to 0.55 mm². The slighty lower reproducibility values, present in this study for the femur are commonly attributed to the higher degree of curvature perpendicular to the orientation of the MRI partitions in the femoral condyles as compared to the tibial plateaus.

Sensitivity to change assessed as SRMs generally was higher for volume than for thickness (Table IV). This may be explained by the fact that mean thickness is calculated from thousands of local thickness values all over the respective joint surface. Consequently, the local increase in thickness due to filling of a treated focal defect may show a comparatively smaller effect on mean thickness as a global parameter.

Separation of the two portions of the femur increased the sensitivity to change (Table IV). Expectedly, this also is expressed in the higher relative rate of change in volume and thickness (9% and 13% vs 6%) for the separately evaluated medial/lateral portions of the femur (Fig. 4) as a comparable absolute change is normalized to a smaller base value. It appears, that this effect is higher than the additional inaccuracy which is introduced by the process of separating the femur (Table V). Separation of the femur was performed in the original MRI data sets in 2D and is consequently prone to bias due to inconsistent positioning of the patients. This is to be—and could be—minimized by a strictly standardized positioning scheme of the slabs/slices which was followed in this study. The cutoff value (5%) for the delta between pre- and postoperative bone cartilage interface which is mainly based on the intra-reader reproducibility for the femur (5.1%), thus, seems.

### Table III
Volumetric data of subgroups (10 patients: five medial femoral condyle operated, five lateral femoral condyle operated) given for the medial/lateral portions of the separated femoral cartilage plates and medial/lateral tibiae. The values are given depending on which portion of the femoral condyle (med/lat) was operated. Standard deviation is given in small characters.

<table>
<thead>
<tr>
<th>Subgroup according to cartilage plate</th>
<th>Pre-OP vs post-OP volumetric data: separated medial/lateral femur (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (ml)</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
</tr>
<tr>
<td>Med femur, med cond operated</td>
<td>8.49 ± 1.75</td>
</tr>
<tr>
<td>Lat femur, lat cond operated</td>
<td>10.24 ± 1.45</td>
</tr>
<tr>
<td>Med femur, lat cond operated</td>
<td>9.02 ± 3.40</td>
</tr>
<tr>
<td>Lat femur, med cond operated</td>
<td>9.02 ± 1.62</td>
</tr>
<tr>
<td>Med tibia, med cond operated</td>
<td>2.34 ± 0.85</td>
</tr>
<tr>
<td>Lat tibia, lat cond operated</td>
<td>2.86 ± 0.93</td>
</tr>
<tr>
<td>Med tibia, lat cond operated</td>
<td>2.40 ± 0.69</td>
</tr>
<tr>
<td>Lat tibia, med cond operated</td>
<td>2.85 ± 0.73</td>
</tr>
</tbody>
</table>

cond = condyle.

In contrast to the tibiae and the non-operated portion of the femur, there is a clear increase in volume and thickness in the operated portions of the femoral condyles in each group. There was no change in the size of the cartilage–bone interface in any of the cartilage plates.

### Table IV
Sensitivity to change calculated as the SRMs (SRM = mean change/standard deviation of change). Change is given for the relative (%) difference (post-OP–pre-OP) relative to pre-OP values.

<table>
<thead>
<tr>
<th>Sensitivity to change: SRM</th>
<th>Operated portion femur (n = 10)</th>
<th>Total femur (n = 10)</th>
<th>Medial portion femur (Medial op., n = 5)</th>
<th>Lateral portion femur (Lateral op., n = 5)</th>
<th>Total femur (Medial op., n = 5)</th>
<th>Lateral op., n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume</td>
<td>1.53</td>
<td>1.39</td>
<td>0.98</td>
<td>2.60</td>
<td>1.40</td>
<td>1.40</td>
</tr>
<tr>
<td>Thickness</td>
<td>1.17</td>
<td>0.74</td>
<td>0.93</td>
<td>1.34</td>
<td>0.74</td>
<td>0.78</td>
</tr>
<tr>
<td>Interface</td>
<td>0.06</td>
<td>0.16</td>
<td>−0.77</td>
<td>0.25</td>
<td>0.10</td>
<td>0.20</td>
</tr>
<tr>
<td>Vol/Interface</td>
<td>1.24</td>
<td>1.19</td>
<td>0.87</td>
<td>1.60</td>
<td>1.21</td>
<td>1.19</td>
</tr>
</tbody>
</table>

Especially cartilage thickness profits from separate evaluation of the operated portion of the femur, whereas there is only minor profit for cartilage volume. Expectedly, SRM for the cartilage–bone interface is low.
a reasonable value. Separate evaluation of the femoral condyles only (instead of med./lat. portion of the femur) may provide an additional increase of sensitivity to change. However, lesions located more anteriorly in the femur may in part extend to portions of the trochlea and then could not be fully evaluated. Moreover, although desirable, direct separation of the femur (or femoral condyles) in 3D after segmentation and reconstruction of the complete femoral cartilage plate is still hampered by lack of appropriate software.

Interestingly, the gain in sensitivity to change was much more important for cartilage thickness whereas mixed results (clear improvement only for lateral femur) were obtained for cartilage volume (Table IV). This too, may reflect the above mentioned issue of patient positioning and separation of the femoral cartilage plate which implies an interactive step by the segmentator. This process may be more problematic for the medial femoral condyles. The parameter volume results from both, the segmented area of the cartilage–bone interface and the segmented cartilage thickness. Both, cartilage–bone interface area and cartilage thickness are described as (independent) determinants of cartilage volume. Consequently, in the case of subdividing a joint surface, the parameter mean thickness is less likely to be compromised by small variations of the segmented area of the cartilage plate than would be volume.

Normalization of cartilage volume to the cartilage–bone interface area has been shown to yield higher discriminatory power in a cross-sectional study using a T-score system as a means to detect OA related changes in patients with varus/valgus misalignment alone and prior total knee arthroplasty. In this study, normalization of volume to cartilage–bone interface yielded SRM values comparable to volume and mean thickness, but there was no noticeable change following separation of medial and lateral femur. Thus, overall, normalization of volume to cartilage–bone interface did not affect the sensitivity to change (SRM) in our study (Table IV).

At present, the thickness plot projected over the 3D reconstruction of the cartilage plate gives a qualitative means to roughly control the success of therapy and it may be helpful in systematically assessing the location of the defects within the joint surface. It would be intriguing to perform pixel by pixel comparison of preoperative and follow-up data as then a much more precise analysis could be done. However, this requires an elastic matching or other coregistration techniques of the reconstructed surfaces with a precision error of not more than the dimensions of one pixel—which is not available from the literature yet.

The values for cartilage volume and thickness in our patient group overlap with values from the literature for patients and healthy volunteers showing high inter-individual variability consistent with findings in several studies identifying bone size as an important determinant of cartilage volume in the knee. Differences of volume/thickness amount to up to 38%/47% as compared to those observed in young healthy volunteers. Individual cartilage volume/thickness differences showed a continuum suggesting that a relevant range of disease severity was covered by the study group.

With 1.04 ml and 0.82 ml femoral cartilage volume increase in the 1-year follow-up period was slightly but not statistically significantly higher than pred OP defect volume (0.67 ml and 0.71 ml) for both, total and separated femur. On the one hand, this is consistent with the higher number of patients showing overgrowth than those showing partial filling, a phenomenon that has been reported previously.

On the other hand, MRI derived defect surface area was smaller than debrided defect cross-sectional area. This may be attributable to surgical excision of softened cartilage in the periphery of the defect showing (near to) normal appearance in MRI suggesting some underestimation of defect size by MRI in this study. Compositional MR imaging studies such as dGEMRIC or T2 mapping may be beneficial in view of both, pre-OP defect and post-OP repair evaluation but were beyond the scope of this study. Moreover, defect segmentation is conceptually difficult requiring assumptions about the original position of the cartilage surface which introduce additional variability in the evaluation. Also, partial volume averaging will have higher impact on the small defects as compared to the larger joint surface. This is reflected by the higher precision errors calculated for defect surface area and volume amounting up to 9% and area of the femur being 9% for volume and 10–13% for thickness.

Table V
Resegmentation precision error calculated as COV (%) from four consecutive segmentations in six patients' post-OP data sets. The higher values for femoral data probably are related to the higher degree of curvature in the femur as compared to the more even tibial plateaus.

<table>
<thead>
<tr>
<th>Reproducibility error (COV [%])</th>
<th>Volume</th>
<th>Mean thickness</th>
<th>Cartilage–bone interface</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total femur</td>
<td>5.1</td>
<td>5.6</td>
<td>4.6</td>
</tr>
<tr>
<td>Medial femur</td>
<td>7.9</td>
<td>5.9</td>
<td>6.4</td>
</tr>
<tr>
<td>Lateral femur</td>
<td>6.7</td>
<td>7.2</td>
<td>6.1</td>
</tr>
<tr>
<td>Medial tibia</td>
<td>4.4</td>
<td>4.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Lateral tibia</td>
<td>3.9</td>
<td>4.8</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Fig. 4. Comparison of the percent change in cartilage–bone interface (Area), volume (Vol) and mean thickness (mD) pre-OP to post-OP in a subset of 10 patients: total femur (tf) vs operated portions of femur and corresponding tibial plateaus. Mfma = medial femur when medial femoral condyle was operated; lfma = lateral femur when lateral femoral condyle was operated; mfla = medial femur when lateral femoral condyle was operated; lfma = lateral femur when medial femoral condyle was operated; mt = medial tibia; lt = lateral tibia. There was an average increase of cartilage volume and mean thickness from pre- to post-OP data of 6% in contrast to the (expected) absence of change in the size of the cartilage–bone interface for the total femur. In contrast, there was a tendency to volume and thickness loss of 1–3.5% in the tibial plateau. Note the higher percentage change in the operated portions of the femur being 9% for volume and 10–13% for thickness.
14%. Although assessment of focal defects may give an orientation on the plausibility of globally measured changes, to our opinion, the strength of volumetric evaluation is rather in global joint assessment of cartilage loss/repair.

Comparing femoral and tibial cartilage volume follow-up, most of this increase seems attributable to the ingrowth of cartilage into the defect. The amount of this increase is high compared to reported loss of cartilage in OA25, 27–30. The reported amount of annual femoral cartilage volume change in OA is \(-104 \pm 324\) μl (corresponding to \(-0.8 \pm 2.4\)%) for the total femur34 and \(-150 \pm 250\) μl (corresponding to \(-7.6 \pm 8.4\)%) for those portions of the femur considered to represent its contributions to the medial or lateral femoro-tibial joints27. This, lastly, can be expected from a technically successful ACI procedure with graft growth and integration once a first critical period for the graft tissue (3–9 months to 1 year) is overcome19. Nonetheless, according to Henderson (and incomplete filling) as potential confounding factors. Treatment. With the exception of one study where no significant longitudinal change is smaller than those reported in the literature46. This amount of cartilage volume increase due to the ACI procedure can be expected, hypertrophy as well as complete defect filling49 may occur later than 1 year. This illustrates that interpretation of global data including the area of the operated defects is problematic, because competing processes, i.e., growth of repair tissue on the one hand and potential decrease of native cartilage due to progression of OA on the other hand, are to be taken into account. An option that may contribute to at least reduce—surely not to completely resolve—this uncertainty in interpretation, could be, to qualitatively (in addition to the quantitative measurements) evaluate the graft area for presence of hypertrophy (and incomplete filling) as potential confounding factors. Nonetheless, according to Henderson et al.49 more than 90% of grafted areas evaluated showed near complete or complete filling50 after one year. Therefore, our 1-year follow-up data might be helpful to determine whether a technically successful ACI procedure contributes to slow the rate of femoral cartilage loss in OA in itself or whether there is ongoing loss of femoral cartilage over a longer observation time period which is only masked by the initial increase of cartilage volume due to the ACI procedure.

In contrast to the femoral data, there was no significant longitudinal change in the—untreated—tibiae during the 1-year follow-up period. Ranging from \(+0.4\)% to \(-1.8\)% these changes were smaller than the reproducibility error of this study. However, there was a tendency to smaller values and more patients numerically had a reduction rather than an increase of tibial cartilage volume and thickness as compared to the femur. The absolute volume changes in the tibiae varied between 10 and 70 μl. This amount of change is smaller than those reported in the literature from longitudinal studies in OA patients without (operative) treatment. With the exception of one study where no significant change was reported30, those changes range from \(-3.5\)% to \(-8.4\)% corresponding to \(88–164\) μl25,27–30. In contrast to the femoral data, in the tibiae as non-operated compartments, in OA cartilage volume and thickness are expected to only decrease with time. Therefore, these results may suggest a beneficial effect of the ACI procedure on cartilage loss, but may also be related to altered physical activity during the post-OP period and lastly cannot be differentiated from an incidental finding from this pilot study. Interestingly, the evolution of medial and lateral tibial cartilage volume and thickness was uniform irrespective of which (medial or lateral) femoral compartment was operated.

Lack of a follow-up period longer than 1 year is a limitation of this study and longer follow-up studies with control populations are needed to determine if ACI can help slow or prevent OA.

**Conclusion**

Our data suggest that quantitative volumetric analysis is applicable to ACI patients. Susceptibility artifacts interfered with segmentation to a variable degree in most patients, but was judged to be severe enough to preclude quantitative evaluation in only three patients (14%). Resegmentation reproducibility errors are comparable to those in untreated patients or volunteers. Separate evaluation of the operated portion of the femur increased sensitivity to change. The observed significant increase of volume and thickness in the treated femoral compartment may indicate the initial increase of cartilage substance after a technically successful ACI procedure and—although difficult to interpret—could be used as a baseline to evaluate further evolution of cartilage substance change. The lack of cartilage loss in the tibiae may help to identify altered disease progression after ACI.

**References**


