Femorotibial and Patellar Cartilage Loss in Patients Prior to Total Knee Arthroplasty: Heterogeneity and Correlation with Alignment of the Knee

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ABSTRACT

Objective. To analyze tibial, femoral and patellar cartilage loss in patients prior to total knee arthroplasty (TKA), and its correlation with malalignment of the knee.

Methods. Twenty-six patients (aged 58 to 86 yrs) with clinical indication for TKA were investigated. Quantitative endpoints of cartilage morphology (T-scores for cartilage volume normalized to total subchondral bone area) were determined from coronal and axial MR image data, using proprietary software. The static alignment of the knee was determined from standing full limb radiographs.

Results. The magnitude of cartilage loss (T-score of normalized cartilage volume) was highly variable within the knee, correlation coefficients ranging from $r = 0.17$ to 0.51 between cartilage plates. The correlation of cartilage loss with static alignment of the knee (as a continuous variable) was $r = -0.52$ (p < 0.05) for the medial tibia, -0.38 (not significant) for the medial femur, +0.76 (p < 0.001) for the lateral tibia, +0.31 (not significant) for the lateral femur, and -0.09 for the patella. When analyzing malalignment independent of direction (valgus or varus), the correlation for the patella increased to $r = 0.30$, but remained non-significant.

Conclusion. Cartilage loss was highly variable amongst patients and amongst cartilage plates prior to knee arthroplasty. Its correlation with alignment was stronger for the tibia than for the femur. There was some evidence for an association of malalignment and patellar cartilage loss. These findings stimulate further research on the mechanism and cause-effect-relationship of malalignment and knee OA using quantitative MR imaging technology.
Osteoarthritis (OA) represents an outstanding burden on the quality of life of elderly people and on the economics of today’s health care systems [1,2]. The disease is characterized by a loss of articular cartilage and changes in non-cartilage tissues, such as bone, ligaments, menisci, synovium etc.. Since cartilage tissue could not be quantified by non-invasive means until recently, information on cartilage loss in OA has been scarce and has been primarily based on indirect evidence from joint space width measurements in radiographs. Several studies have now established that quantitative MR imaging permits one to measure the morphology of articular cartilage with high accuracy and precision [3-6], if appropriate MR imaging protocols and image analysis tools are used. Adequate accuracy and precision has recently also been confirmed for patients prior to knee arthroplasty [4,6].

In cross sectional studies, cartilage volume has been identified to represent a relatively insensitive outcome measure of OA, due to confounding by bone size [7]. Considerable improvements in the discrimination between healthy subjects and OA patients (T-scores) have, however, been achieved by normalizing cartilage volume to the total subchondral bone area of cartilage plates, including cartilaginous and denuded surface areas [7].

Epidemiological research has identified numerous risk factors associated with OA in various joints of the body [8-10]. In the knee, malalignment (valgus/varus) appears to be associated with a higher prevalence and progression of OA changes in the relevant compartment [11,12], in particular in association with obesity [13]. This is likely due to the alteration in load distribution in the knee, with higher loads being transmitted across the medial femorotibial compartment in varus malalignment, and higher loads across the lateral femorotibial compartment in valgus malalignment [13].

Based on measurements of joint space width in radiographs, patients with varus OA have been suggested to display a 4-fold higher progression rate of cartilage loss in the medial femorotibial compartment, and patients with valgus OA a 5-fold higher progression rate in the lateral femorotibial compartment. A recent MR imaging study has found higher cartilage volume loss in the medial femorotibial compartments of patients with moderate symptomatic OA and varus malalignment, and a higher loss in the lateral compartment in patients with valgus malalignment. There has, however, been no information, to what extent patellar cartilage loss is associated with malalignment of the knee. Whereas varus malalignment may increase loading of the medial patellar facet, valgus malalignment may increase the mechanical stress at the lateral facet.

The objective of this cross sectional study was to use quantitative MRI for analyzing cartilage loss (T-scores) of tibial, femoral and patellar cartilage in patients with advanced OA, prior to knee arthroplasty and to relate cartilage loss in each plate to static alignment of the knee. We specifically addressed the following questions:

a) What is the magnitude of patellar, tibial and femoral cartilage loss with and without normalization to total bone area, body weight or body height in patients prior to TKA?
b) How strongly are tibial, femoral, and patellar cartilage loss correlated amongst each other in advanced OA?
c) To what extent is this cartilage loss associated with valgus / varus malalignment of the knee, with static alignment being expressed as a continuous variable?

PATIENTS AND METHODS
The study involved 26 patients (aged 58 to 86 yrs; mean 70.4 ± 7.6 yrs.; 6 men, 20 women) with a clinical indication for TKA. The body height was 164 ± 6cm and 175 ± 14 cm, the body weight 82.3 ± 12.9 kg and 97.2 ± 22.6 kg and the body mass index 30.6 ± 4.6 kg/cm² and 31.5 ± 3.2 kg/cm² in women and men, respectively. Informed
written consent was obtained from the patients, and the study protocol was ratified by the local ethic committee. MR imaging was performed in vivo prior to TKA as described previously [6]. In brief, coronal data sets of the femorotibial compartments and axial scans of the patellar cartilage were acquired, since these have been shown to yield high accuracy [4,6], test-retest precision [4,14], and sensitivity to change in longitudinal studies [15,16] for quantitative parameters of cartilage morphology. Analysis of the patella (P) and the medial and lateral tibia (MT and LT) involved the entire cartilage plates; analysis in the femur involved the central region of the medial and lateral aspect of the femur (cMF and cLF, respectively), that is the anterior aspect of the femoral condyles [14-16], a region that represents its weight bearing portion in the extended and slightly flexed position of the knee.

The following quantitative endpoints of cartilage morphology were determined using proprietary software [17-19]: 1) total volume of the cartilage [VC], 2) mean thickness of the cartilage, as averaged of the cartilage-covered area of bone, and not accounting for denuded areas yielding 0 mm cartilage thickness) [ThCcAB.Me], 3) the maximal thickness of the cartilage [ThCcAB.Max], and 4) the total subchondral bone area of the cartilage plates, including cartilaginous and denuded areas, but not peripheral osteophytes [6,7] [tAB]. Because a previous study has indicated that cartilage volume provides insufficient discrimination between healthy subjects and OA patients due to confounding of bone size, we normalized cartilage volume to body height, body weight, and tAB [VCtAB] [7]. Values were compared with a reference data base that involved 50 young healthy subjects aged 19 to 35 years (23 women aged 25.7 ± 3.6 years; 27 men aged 26.0 ± 4.0 years) without symptoms or signs of OA, history of knee pain, trauma, surgery, ligament and meniscal injury, or other diseases of the musculoskeletal system.

T-scores for cartilage morphology (difference between patient value and mean value in young healthy subjects of the same gender, divided by the standard deviation in healthy subjects of the same gender) were computed for all cartilage plates as described previously [7]. The association between patellar, tibial and femoral T scores, and that between T-scores and the static alignment of the knee was determined by linear regression analysis. An average medial femorotibial T score was computed by averaging the T-scores in the medial tibia and medial femoral condyle, and the same was done laterally.

The static alignment of the knee was determined from standing full limb radiographs in 22 of the 26 patients. To this end, we determined the medial angle between an axis drawn through the middle of the femoral head and intercondylar notch of the distal femur, and an axis through the middle of the intercondylar area of the proximal tibia and the middle of the talocrural joint. Fourteen patients displayed varus malalignment (range +4° to +14°), 6 patients had valgus malalignment (range – 3° to -19°), and 2 patients displayed neutral alignment (0°).

RESULTS
The T-scores of all cartilage plates were higher for cartilage volume [VC] normalized to total area of subchondral bone [tAB] than for VC alone or VC normalized to body weight and height (Table 1). These findings show that normalization to tAB is the most effective means to evaluate cartilage volume loss in cross sectional studies. Patellar T-scores were highest amongst the knee cartilage plates before normalization to tAB, but the scores were highest in cMF after normalization. T-scores were higher for cMF than for MT and as high for cLF as for LT laterally, suggesting that the femoral region of interest (anterior condyle) is a sensitive region to change in OA (Table 1). The combined medial T score (VCtAB) in the medial femorotibial compartment was – 4.2 ±
2.1, the combined lateral femorotibial T score – 2.8 ± 2.2, and the patellar T score -3.2 ± 1.4 in the TKA patients.

**Table 1: T scores for quantitative cartilage parameters in advanced knee OA**

<table>
<thead>
<tr>
<th>VC</th>
<th>MT.</th>
<th>cMF.</th>
<th>LT.</th>
<th>cLF.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MT</td>
<td>2.2</td>
<td>-2.4</td>
<td>-2.0</td>
<td>-0.5</td>
<td>-2.6</td>
</tr>
<tr>
<td>cMF</td>
<td>-1.4</td>
<td>-4.0</td>
<td>-2.3</td>
<td>-1.6</td>
<td>-3.1</td>
</tr>
<tr>
<td>LT</td>
<td>-0.6</td>
<td>-2.8</td>
<td>-2.3</td>
<td>-0.8</td>
<td>-2.4</td>
</tr>
<tr>
<td>cLF</td>
<td>2.9</td>
<td>-2.8</td>
<td>-3.1</td>
<td>-1.2</td>
<td>-2.4</td>
</tr>
<tr>
<td>ThCcaB.Me</td>
<td>2.1</td>
<td>-2.3</td>
<td>-2.0</td>
<td>-0.4</td>
<td>-2.4</td>
</tr>
<tr>
<td>ThCcaB.Max</td>
<td>-3.2</td>
<td>-5.2</td>
<td>-3.0</td>
<td>-2.6</td>
<td>-3.2</td>
</tr>
</tbody>
</table>

MT = medial tibia; cMF = central medial femur = anterior part of the medial femoral condyle; LT. = lateral tibia; cLF = central lateral femur; VC= total volume of the cartilage; ThCcaB.Me = mean thickness of the cartilage in cartilage covered areas, but not accounting for denuded areas as being 0 mm cartilage thickness; ThCcaB.Max = maximal cartilage thickness; tAB = total area of subchondral bone, including cartilaginous and denuded areas, but excluding peripheral osteophytes.

**Table 2: Correlation of T scores (ToVolBi) in knee cartilage plates in advanced OA**

<table>
<thead>
<tr>
<th>MT</th>
<th>cMF</th>
<th>LT</th>
<th>cLF</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>+0.51**</td>
<td>-0.30</td>
<td>+0.23</td>
<td>+0.17</td>
<td></td>
</tr>
<tr>
<td>cMF</td>
<td>-0.17</td>
<td>+0.24</td>
<td>+0.26</td>
<td></td>
</tr>
<tr>
<td>LT</td>
<td>0.46*</td>
<td>+0.46*</td>
<td>+0.29</td>
<td></td>
</tr>
<tr>
<td>cLF</td>
<td>-</td>
<td>-</td>
<td>+0.28</td>
<td></td>
</tr>
</tbody>
</table>

* p < 0.05; ** p < 0.01; for abbreviations please see Table 1

The correlation of cartilage loss (T-scores for VCTAB) amongst the cartilage plates of the knee was weak (Table 2). Only the correlation coefficients between the medial tibia and medial femur, and between the lateral tibia and lateral femur reached statistical significance (Figure 1). Even the correlation between femoral and tibial cartilage loss of the same compartment was only moderate (r = 0.51 and 0.46 respectively), suggesting that the proportion of femoral and tibial cartilage loss is highly variable in advanced femorotibial OA.

Figure 2 summarizes T-scores for patients with valgus malalignment (n=14), varus malalignment (n=6), and those with a neutral knee axis (n=2). When taking the knee axis as a continuous variable (negative = valgus, positive values = varus) we found a moderate association of the (average) medial T-scores (r = -0.54; p < 0.01) and of the lateral T-scores (r = +0.66; p < 0.001) with the alignment of the knee. There was no significant association of the T-scores with obesity (BMI). Interestingly, tibial T-scores displayed a stronger association with alignment than femoral T-scores: Correlation coefficients were – 0.52 (p < 0.05) for the medial tibia, - 0.38 (not significant) for the medial femur, +0.76 (p < 0.001) for the lateral tibia, and +0.31 (not significant) for the lateral femur.

When studying the association of patellar cartilage loss with knee alignment of the knee, there was no correlation when entering valgus as negative and varus as positive values into the regression (r = -0.09). When transforming negative (valgus) into positive values and thus treating both forms of malalignment equally (independent of
direction), correlation between patellar cartilage loss and static alignment increased to $r = 0.30$, but did not reach statistical significance.
DISCUSSION
In this study we have analyzed the magnitude of cartilage loss throughout cartilage plates of the knee in patients with advanced OA, prior to TKA, using quantitative MR imaging technology. In addition, we studied the relationship between tibial, femoral and patellar cartilage loss and valgus / varus malalignment of the knee in advanced OA.

Limitations of this study include the modest sample size and its cross sectional nature. However, to investigate cartilage loss and its relationship with alignment longitudinally in advanced OA (prior to knee arthroplasty), observations periods of 10 years and more are required. The strength of the study is that the accuracy of the measurements has been confirmed in the same study sample by applying established invasive measurements postoperatively [6], and that, in contrast with radiography [20] quantitative MR imaging allowed us to accurately differentiate tibial, femoral, and patellar cartilage loss in advanced OA.

Previous MRI studies have focused on cartilage volume as a quantitative endpoint. However, cartilage volume scales strongly with bone size and this therefore coincides with a large intersubject variability, both in healthy volunteers and in patients. This variability severely limits the capability to effectively differentiate between healthy subjects and patients in cross sectional studies. Albeit cartilage volume can be normalized to body weight, body height, age and other factors [21], the correlation with anthropometric variables is relatively week [22,23], rendering this approach relatively ineffective. As the individual subchondral bone area (tAB) can be reliably determined from MR image data [6,7,19] and correlates more strongly with cartilage volume than other parameters, normalization to tAB can be used to effectively enhance T-scores of cartilage morphology for OA patients in cross sectional studies [7].

Note, however, that this requires a different approach to cartilage segmentation, as not only cartilage, but also the denuded bone interface area of each cartilage plate needs to be traced in each slice. This tracing must exclude peripheral osteophytes which render the bone interface area larger than prior to the onset of OA.

The current data confirm that normalization to total subchondral bone area is more effective than normalization to other parameters, such as body weight and height, when trying to discriminate between healthy subjects and patients with OA. This applied without exception to all cartilage plates of the knee examined here.

When comparing cartilage loss in different cartilage plates of the knee, we found a substantial amount of heterogeneity and only a weak correlation between femoral and tibial cartilage loss. These findings are important as they clearly suggest that femoral and tibial cartilage plates should be measured separately and that measuring cartilage loss in just one of them is insufficient for estimating cartilage loss in the other [14]. Cicuttini et al [24] described correlation coefficients around 0.75 between femoral and tibial cartilage volume in healthy subjects and patients with moderate OA. The authors concluded that it may therefore be sufficient to measure only tibial cartilage in femorotibial OA. Note that a similar correlation was observed in our current study (r = 0.65 between medial tibial and femoral cartilage volume), but that the correlation became weaker when cartilage volume was normalized to tAB (r = 0.51). This effect is readily explained by the fact that the intersubject variability of cartilage volume was reduced when normalizing it to bone size. Our findings suggest that, in advanced OA, only approximately 25% of the variability in femoral cartilage loss is explained by the cartilage loss measured in the tibia and vice versa, and the correlations are even weaker between the medial and lateral femorotibial compartment, and with the patella. This suggests that the proportion of femoral and tibial cartilage loss is highly variable between OA patients, and that it is essential to measure both cartilage plates separately. Other studies have determined an aggregate value for cartilage volume in the tibia and
femur [25,26]. As the factors determining the proportion of femoral and tibial cartilage loss in femorotibial OA are currently unknown and need to be explored further, we suggest that both cartilage plates should be determined separately.

As expected, we found a significant correlation between femorotibial cartilage loss and malalignment of the knee and this result is in agreement with previous longitudinal studies employing radiography [11] and MR imaging [12]. We cannot determine retrospectively to what extent malalignment was the cause or effect of cartilage loss, but the range in static alignment of the knee amongst the subjects was large (14° varus to 19° valgus). Also, a recent longitudinal study has confirmed that the degree of malalignment at baseline was associated with prospective cartilage loss in the relevant femorotibial compartments [12].

An interesting finding of our study is that, in patients with severe OA, the correlation of cartilage loss and malalignment was higher for the tibia than for the femur. This observation has not been made in patients with moderate OA [12]. Given the moderate sample size, this finding should be interpreted with caution and will need to be confirmed in larger cohorts. However, the current result indicate that malalignment may represent a stronger determinant of tibial cartilage loss than femoral cartilage loss, and this may be one potential reason for the heterogeneity in femoral versus tibial cartilage loss in advanced OA.

When considering malalignment independent of valgus and varus, there was a weak correlation with patellar cartilage loss. Although this correlation did not reach statistical significance in this sample, it was almost as strong as that between malalignment and femoral cartilage loss. These findings indicate that patellar cartilage loss may also be associated with malalignment of the knee, potentially because of the higher pressure in the medial and or lateral patellar facet, respectively. Future studies should thus investigate the cartilage in the medial and lateral facet separately, to investigate whether valgus malalignment is specifically correlated to lateral facet cartilage loss, and varus malalignment to medial facet cartilage loss.

In summary, this study shows that quantitative MR imaging is most discriminative between healthy subjects and patients when cartilage volume is normalized to the total subchondral bone area. Cartilage loss was found to be highly variable in patients with advanced OA, this also applying to the femur and tibia of the same compartment. Femorotibial cartilage loss was associated with malalignment of the knee, but the association was found to be considerably stronger for the tibia than for the femur. The study also provides some evidence that patellar cartilage loss may be weakly associated with malalignment, the correlation being in the same order of magnitude as for femoral cartilage. The current data show that, in cross sectional studies, cartilage volume must be normalized to bone interface area to provide useful T scores of cartilage loss in OA. Patellar, tibial and femoral T scores should be measured separately, due to the larger heterogeneity of tibial cartilage loss in advanced OA. Our findings further suggest that the mechanism and cause-effect-relationship of malalignment and tibial, femoral, and patellar cartilage loss should be examined more closely in larger cohorts of OA patients, using quantitative MR imaging technology.

Competing interest statement: None of the authors has a competing interest with regard to publication of the study, because no organisation may gain or lose financially from the results of conclusions published here. Felix Eckstein works as a consultant for Virtualscopics Inc., Pfizer Inc, and Glaxo Smith Cline Inc., and is CEO of Chondrometrics GmbH, a company providing MR image analysis services. Martin Hudelmaier has a part time appointment with Chondrometrics GmbH.
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Ethics approval: Informed written consent was obtained from the patients, and the study protocol was ratified by the local ethic committee (Univ. of Frankfurt, Germany)

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Figure 1: Bivariate scattergram showing the correlation between T-scores for cartilage volume normalized to total subchondral bone area in the medial tibia and medial femur, and in the lateral tibia and lateral femur, respectively.

Figure 2: Bar graph showing T-scores for cartilage volume volume normalized to total subchondral bone area in the medial tibia, medial femur, lateral tibia, and lateral femur for patients with varus OA (n = 14), those with neutral alignment of the knee (n = 2), and those with valgus OA (n = 6). Error bars display the one-fold standard deviation.
Fig. 1: v. Eisenhart et al.: top ▲
Fig. 2: v. Eisenhart et al.: top
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