Research Article

Development of a Rapid Cartilage Damage Quantification Method for the Lateral Tibiofemoral Compartment Using Magnetic Resonance Images: Data from the Osteoarthritis Initiative

Ming Zhang,1 Jeffrey B. Driban,1 Lori Lyn Price,2,3 Grace H. Lo,4,5 Eric Miller,6 and Timothy E. McAlindon1

1Division of Rheumatology, Tufts Medical Center, 800 Washington Street, P.O. Box 406, Boston, MA 02111, USA
2The Institute for Clinical Research and Health Policy Studies, 800 Washington Street, P.O. Box 63, Boston, MA 02111, USA
3Tufts Medical Center and Tufts Clinical and Translational Science Institute, Tufts University, 800 Washington Street, P.O. Box 63, Boston, MA 02111, USA
4Medical Care Line and Research Care Line, Houston Health Services Research and Development (HSR&D) Center of Excellence Michael E. DeBakey VAMC, Houston, TX 77030, USA
5Section of Immunology, Allergy, and Rheumatology, Baylor College of Medicine, 1 Baylor Plaza, BCM-285, Houston, TX 77030, USA
6Department of Electrical and Computer Engineering, Tufts University, 216 Halligan Hall, Medford, MA 02155, USA

Correspondence should be addressed to Timothy E. McAlindon; tmcalindon@tuftsmedicalcenter.org

Received 9 September 2015; Accepted 19 November 2015

Academic Editor: Yukihisa Takayama

The purpose of this study was to expand and validate the cartilage damage index (CDI) to detect cartilage damage in the lateral tibiofemoral compartment. We used an iterative 3-step process to develop and validate the lateral CDI: development (100 knees), testing (80 knees), and validation (100 knees). The validation set included 100 knees from the Osteoarthritis Initiative that was enriched to include all grades of lateral joint space narrowing (JSN, 0–3). Measurement of the CDI was rapid at 7.4 (s.d. 0.73) minutes per knee pair (baseline and follow-up of one knee). The intratester reliability is good (intraclass correlation coefficient (3, 1 model) = 0.86 to 0.98). At baseline, knees with greater KL grade and lateral JSN had a lower mean CDI (i.e., greater cartilage damage). Baseline lateral CDI is associated with both lateral JSW ($r = 0.81$ to $0.85$, $p < 0.01$) and HKA ($r = -0.30$ to $-0.33$, $p < 0.05$). The SRM is good (lateral femur SRM = $-0.76$; lateral tibia SRM = $-0.73$; lateral tibiofemoral total SRM = $-0.87$). The lateral tibiofemoral CDI quantification allows for rapid evaluation and is reliable and responsive, with good construct validity. It may be an efficient method to measure lateral tibiofemoral articular cartilage in large clinical and epidemiologic studies.

1. Introduction

Cartilage morphometry on magnetic resonance (MR) images is important for the assessment of structural progression of knee osteoarthritis (OA). However, manually obtaining accurate and reproducible cartilage data on one set of images can take many hours [1]. To reduce the time and cost of measuring cartilage on MR images, there remains a great need to design a rapid quantification method which has good reproducibility, validity, and sensitivity to change [2].

In our previous study, we developed the cartilage damage index (CDI) for the medial knee compartment and demonstrated it to be an efficient, reliable, valid, and sensitive method to measure changes of articular cartilage in the medial tibiofemoral compartment. This new study builds on our previously published paper by adapting and testing the CDI to the lateral tibiofemoral compartment. It is important to note that we needed to modify the CDI because the medial and lateral tibiofemoral compartments have different articular surface shape [3], loading [4], and distributions of
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full thickness cartilage defects [5]. Because of the differences between compartments, we needed to identify new informative locations that are specific to the lateral tibiofemoral compartment and test whether these new locations could offer an efficient, reliable, valid, and sensitive method to measure changes of articular cartilage in the lateral tibiofemoral compartment. Hence, the purpose of this study was to adapt and validate the CDI to detect cartilage damage in the lateral tibiofemoral compartment.

2. Methods

2.1. Study Design. We developed, validated, and assessed reliability of the CDI in the lateral tibiofemoral compartment. Sampling from the Osteoarthritis Initiative (OAI), we created 4 datasets: (1) a development dataset (n = 100 knees), (2) a test dataset (n = 80 knees), (3) a validation dataset (n = 100 knees), and (4) a reliability dataset (n = 20 knees).

2.2. MR Image Assessments. To deploy the CDI, we focused on the OAI 3D sagittal water-excitation dual-echo steady state (DESS) images, which were acquired using the OAI MR imaging protocol [6]. The OAI has institutional review board approval (IRB) from the coordinating centers and the four clinical centers (University of Maryland and Johns Hopkins comprise a single recruitment center, Brown University, Ohio State University, and University of Pittsburgh). All participants provided informed consent to participate in the OAI. The 3D DESS sequences were acquired using the following parameters: field of view = 140 mm, slice thickness = 0.7 mm, skip = 0 mm, flip angle = 25 degrees, echo time = 4.7 ms, recovery time = 16.3 ms, 307 x 384 matrix, x resolution = 0.365 mm, y resolution = 0.456 mm, and total slice number = 160. The acquisition time for 3D DESS sequence is 11 minutes.

2.3. Development Dataset. For the development dataset, we selected 100 knees from OAI baseline that included an equivalent number of knees with the different grades of lateral joint space narrowing (JSN, grades 0–3). We used three steps to develop the lateral tibiofemoral CDI based on areas commonly affected by denudation. (1) One reader manually marked the lateral cartilage denudation on each knee (Figure 1(a)). (2) We designed a pair of two-dimensional, rectangular, universal coordinate systems to represent the articular surface on the distal lateral femur and the proximal lateral tibia (Figure 1(b)). (3) We projected the regions of denudation onto a coordinate system and constructed a figure illustrating the frequency distribution of denudation in a three-dimensional representation of the lateral compartment. We used this to evenly select 9 informative locations on the tibia and femur (18 locations in total) in and around the regions that most frequently exhibited denudation (Figure 1(b)). We hypothesize that this region has more frequent cartilage damage.

2.4. Lateral Tibiofemoral CDI Measurement. There are three steps to measure the lateral CDI. (1) The reader determines the medial-lateral width of the femur by selecting the most medial and lateral MR image slices possessing bone. These images represent the y-axis (medial-to-lateral) of the coordinate system (Figure 1(b)). The software automatically indicates the slices that contain the informative locations based on the coordinate system. (2) The reader manually marks the bone-cartilage boundary on the selected slices (Figure 1(c)).
The software then projects the bone-cartilage to x-axis (anterior-to-posterior) of coordinate system and indicates the predefined informative location on the MR slices. (3) The reader measures the cartilage thickness at those informative locations (Figure 1(c)). The software then computed the CDI by summing the products of cartilage thickness, cartilage length (anterior-posterior), and voxel size from each informative location. To normalize for body size, the CDI for the lateral tibia and femur was divided by the individual's height.

2.5. Test Dataset. We performed preliminary tests to explore face and construct validity by selecting 80 participants from the OAI. These 80 knees all had publicly available manual cartilage segmentation on baseline and 12-month follow-up MR images (Imorphics Ltd; the dataset originally included 88 knees but we excluded 8 knees with missing height or hip-knee-ankle (HKA) angle). These participants also had height data available at each visit. One reader used customized software to measure the CDI in the lateral femur and tibia cartilage in the testing dataset.

2.6. Validation Dataset. To test the validity of the lateral tibiofemoral CDI—the main purpose of this study—we selected 100 knees with baseline and 24-month MR images from the OAI. The validation samples were chosen to represent a wide range of disease severity. The dataset was selected to include all grades of lateral JSN (n = 25 knees per lateral JSN grade) and knees with and without lateral JSN progression (JSN grade change between baseline and follow-up visit). None of these knees was included in the development or test datasets. The first ten ids were used to record the measurement time.

2.7. Reliability Dataset. In addition to the final validation set, we identified 20 other knees to assess intratester reliability (two measurements separated by at least 72 hours). The reliability set was selected based on baseline lateral JSN grade (5 knees per lateral JSN grade).

2.8. Radiographic Assessments. Participants had bilateral weight-bearing, posterior-anterior, semiflexed knee radiographs at each annual OAI visit. Central readers provided Kellgren-Lawrence (KL) grade and the modified OARSI-atlas based assessment of lateral JSN score [7, 8]. The radiographs, central readings, and protocols are publicly available at the OAI website (kxr SQ Bu 00 (version 0.5) and kxr SQ Bu 03 (version 3.5); http://oai.epi-ucsf.org/; reliability for these readings was kappa = 0.70 to 0.88).

The same bilateral knee radiographs were also used to provide central measurements of lateral tibiofemoral joint space width (JSW). We selected lateral JSW at one fixed location (x = 0.725). JSW data and descriptions of the methods are publicly available on the OAI website (kxr_gjsw_duryea_00 (version 0.5) and kxr_gjsw_duryea_03 (version 3.4); http://oai.epi-ucsf.org/; reliability for these readings was ICC > 0.93).

Finally, we used publicly available measures of static alignment (HKA angle) that was measured by a third investigator. The HKA angles were measured on full limb films primarily at the 12-month or 24-month OAI visits. The HKA data and descriptions of the methods are publicly available on the OAI website (flXR_KneeAlign_Cooke01 (version 1.2) and flXR_KneeAlign_Cooke03 (version 3.1); http://oai.epi-ucsf.org/; reliability for these readings was ICC > 0.99).

2.9. Statistical Analyses. We validated the lateral CDI by examining the Spearman correlations between baseline (month 0) lateral CDI, lateral joint space width (JSW), and static alignment (HKA angle). Scatter plots were generated using the ranking (from smallest to largest) of lateral CDI, JSW, and HKA angle measurements. Tests for trend were used to examine associations of lateral CDI with baseline JSN and KL grade. We calculated standard response mean (SRM) for lateral CDI change between baseline and 24 months. To evaluate the intratester reliability, we calculated intraclass correlation coefficients with a 3,1 model [9].

3. Results

3.1. Test Dataset (n = 80). We found a good correlation between baseline lateral CDI and lateral cartilage volume (manual segmentation) in this test dataset (lateral femur: spearman correlation = 0.74; lateral tibia: spearman correlation = 0.77; lateral tibiofemoral: r = 0.80, all p < 0.0001).

3.2. Validation Dataset Characteristics (n = 100). The final validation set included 100 knees with a mean age = 64.4 (SD = 9.3) years, 59% females, mean BMI = 28.7 (SD = 4.2) kg/m², mean JSW = 4.4 (SD = 2.3) mm, mean HKA = 3.0° (SD = 4.7°), and a diverse range of baseline lateral JSN grades (0 to 3). The distribution of baseline KL and lateral JSN grades is provided in Table 1. Forty-eight knees had lateral JSN progression over 24 months.

3.3. Measurement Time. We recorded the measurement time for the first 10 knees. The average CDI measurement time of 10 knees was 7.4 minutes (SD = 0.73) per pair of knees (baseline and 24-month scans).

3.4. Assessment of Reliability. Intratester (ICC (3, 1 model)) reliability for baseline lateral femur, lateral tibia, and total lateral tibiofemoral ranged from 0.86 to 0.98.

3.5. Relationship of Lateral CDI to Radiographic Severity. At baseline, knees with greater lateral JSN and KL had lower mean CDI (i.e., greater cartilage damage, Table 1). Baseline lateral femur CDI, baseline lateral tibia CDI, and baseline lateral tibiofemoral CDI are associated with both lateral JSW and static alignment (see Table 2 and Supplementary Figures 1 and 2 in Supplementary Material available online at http://dx.doi.org/10.1155/2015/634275).

3.6. Sensitivity to Change. The sensitivity to change is good (SRM = −0.76 for lateral femur; SRM = −0.73 for lateral tibia; SRM = −0.87 for lateral tibiofemoral total).
Lateraltibialcartilagevolume(
tibiofemoralJSW)wassignificantlycorrelatedwithbaseline
withOA[11].Forexample,Bruyereetal.foundthatlateral
atleastinpart,articularcartilagedamageamongknees
continuous).RadiographicJSNandJSWaregenerallyattributed,
globalsemiquantitativescore),lateralJSW(continuous),KLgrade(a
quantitative scale), and knee alignment (continuous). Radiographic JSN and JSW are generally attributed,
regionissmallerinthelateralcompartmentcomparedtothe
medialcompartmentregion. Thesizethedenudation
regionismoreposterior(bothfemourandtibia)than
medialcompartmentregion. Theregionsizedenudation
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medialcompartment.

The lateraltCDIhadgoodconstructvalidityrelativeto
otherestablishedradiographicmeasuresof kneeOAseverity
andriskfactorsincludinglateraltibiofemoralJSN(asemi-
quantitativescale), lateralJSW (continuous), KL grade (a
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withOA[11].Forexample,Bruyereetal.foundthatlateral
tibiofemoralJSWwassignificantlycorrelatedwithbaseline
lateral tibialcartilagevolume (r = 0.48, p < 0.01) and thick-
ness (r = 0.58, p < 0.01) [12]. Whileweonlyused18informa-
tive locations, our baseline lateral tibiofemoral CDI had
abettercorrelationwithlateralJSW (r = 0.81, p < 0.0001).
We did not look at the correlations with CDI change because
Bruyere et al. found that there were no significant correlations
between cartilage/thickness loss and lateral JSW [12]. In
additiontoverifyingthatthelateralCDIwasassociated
withradiographicOAseverity, wealsodemonstratedthatthe
lateral CDI is related to knee alignment (r = −0.30 to −0.33,
p = 0.004 to 0.01), which is a strong risk factor for knee OA
progression [2, 13].

Table1: Baseline lateraltcartilage damage index stratifiedby baseline lateralt joint space narrowing (JSN) and Kellgren-Lawrence (KL) grade.

(a)Lateralt joint space narrowing (JSN)

| Cartilage measure          | JSN = 0 (n = 25) mean | JSN = 1 (n = 25) mean | JSN = 2 (n = 25) mean | JSN = 3 (n = 25) mean | p value for trend |
|----------------------------|----------------------|----------------------|----------------------|----------------------|------------------|
| Lateral femur CDI          | 2969.3               | 3003.2               | 2184.4               | 1542.0               | <0.001           |
| Lateral tibia CDI          | 1154.9               | 889.9                | 663.8                | 392.7                | <0.001           |
| Lateral tibiofemoral CDI   | 4124.3               | 3893.0               | 2848.2               | 1934.6               | <0.001           |

(b) Kellgren-Lawrence (KL)

| Cartilage measure          | KL = 0 (n = 10) mean | KL = 1 (n = 6) mean | KL = 2 (n = 32) mean | KL = 3 (n = 26) mean | KL = 4 (n = 26) mean | p value for trend |
|----------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|------------------|
| Lateral femur CDI          | 2718.7               | 2831.5               | 3061.0               | 2254.0               | 1605.3               | <0.001           |
| Lateral tibia CDI          | 1229.3               | 994.1                | 946.3                | 690.4                | 424.7                | <0.001           |
| Lateral tibiofemoral CDI   | 3948.0               | 3825.5               | 4007.3               | 2944.4               | 2030.0               | <0.001           |

Table2: Correlation between lateralt CDI and baseline HKA and lateral JSW.

|                                    | Spearman correlation |
|------------------------------------|----------------------|
|                                    | Lateral JSW          | HKA                  |
| Femur CDI (baseline)               | 0.81 (p < 0.01)*     | −0.31 (p < 0.01)*    |
| Tibia CDI (baseline)               | 0.81 (p < 0.01)*     | −0.30 (p = 0.01)*    |
| Tibiofemoral CDI (baseline)        | 0.85 (p < 0.01)*     | −0.33 (p < 0.01)*    |

Notes: * p < 0.05; HKA = hip-knee-ankle; JSW = joint space width.

4. Discussion

This study demonstrates that the CDI can be adapted for
use in the lateraltibiofemoralcompartmentby identifying
informative locations that are unique to the lateralfemur
andtibia. This study also shows that the lateraltCDI is quick
toperform,reliable,andresponsiveandhasgoodconstruct
validity.

Testing the lateraltCDI was important because the lateralt
denudationregions were in different locations than the
medialtibiofemoralcompartment[10]. Thelateraldenu-
dation region is more posterior (bothfemur and tibia) than
medialcompartmentregion. Thesizeofthedenudation
regionissmallerinthe lateral compartment compared to the
medialcompartment.

The lateraltCDI had good constructvalidity relative to
otherestablishedradiographicmeasuresof kneeOAseverity
andriskfactorsincludinglateraltibiofemoral JSN(asemi-
quantitativescale), lateralJSW (continuous), KL grade (a
globalsemiquantitativescore), and kneealignment (con-
tinuous). Radiographic JSN and JSW are generallyattributed,
atleast in part, to articular cartilage damage among knees
withOA[11]. For example, Bruyere et al. found that lateral
tibiofemoralJSWwassignificantlycorrelatedwithbaseline
lateral tibial cartilage volume (r = 0.48, p < 0.01) and thick-
ness (r = 0.58, p < 0.01) [12]. While we only used 18 informa-
tive locations, our baseline lateral tibiofemoral CDI had
abettercorrelationwithlateralJSW (r = 0.81, p < 0.0001).
We did not look at the correlations with CDI change because
Bruyere et al. found that there were no significant correlations
between cartilage/thickness loss and lateral JSW [12]. In
addition to verifying that the lateraltCDIwasassociated
with radiographicOAseverity, wealsodemonstratedthatthe
lateraltCDI is related to knee alignment (r = −0.30 to −0.33,
p = 0.004 to 0.01), which is a strong risk factor for knee OA
progression [2, 13].

We also found that lateraltCDI is sensitive to change over
24 months. One other OAI study found that knees with lateral
JSN had more lateraltibiofemoralcartilage loss in 1 year than
knees without lateral JSN (SRM = −0.48 versus SRM = −0.09
for total lateral tibiofemoral cartilage thickness change) [14].
Our lateraltCDI had a comparable sensitivity (SRM = −0.87
for two-year lateraltibiofemoralchange).

The CDI is an efficient method of measuring cartilage
damage. The proficient operator can measure the lateralt
bipiofemoralCDI of apairofknee MRIs in about 7 minutes.
In contrast, the manual MR-based cartilage measurement
method may take up to 6 hours per knee [1]. Due to the
time and cost of measuring cartilage, most studies only focus
onmedialtibiofemoralunicompartamentalmeasurements.
Using the CDI measurement instead of full manual segmen-
tation represents substantial time and resource savings. Our
group plans to complete CDI development to include a com-
prehensiveassessmentofkneearticularcartilageincluding
medialtibiofemoral, lateraltibiofemoral, and patellofemoral
compartments. Such efforts will help develop a quantitative
understanding of OA disease progression in a compartment-
by-compartmentbasis.

This study is limited because our validation dataset did
not include lateralcartilage segmentation values. However,
we found a good correlation between baseline lateraltCDIand
lateralcartilage volume (manual segmentation) in our test
dataset (r = 0.74 to 0.80, p < 0.0001). Another limitation
ofCDIisthepossibilitythattheinformative locationsmay
not include allcartilage damage. This limitation is similar to
other methods that focus on specific articular surface regions
[6, 15]. Despite this limitation, we demonstrated that the
lateraltCDI has good construct validity with radiographic
data, which is a common strategy to assess lateraltibiofemoral
cartilage data [12, 14, 16].
In summary, the lateral tibiofemoral CDI quantification allows for rapid evaluation and is reliable and responsive, with good construct validity. It may be an efficient method to measure lateral tibiofemoral articular cartilage in large clinical and epidemiologic studies.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments
The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Pfizer, Inc., Novartis Pharmaceuticals Corporation, Merck Research Laboratories, and GlaxoSmithKline. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. The test dataset of 80 knees was provided for public access by Imorphics. Jeffrey Duryea measured JSW and HKA data. Dr. Zhang is supported by Scientist Development grant from Rheumatology Research Foundation.

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