Whole Knee Cartilage Quantification Based on Informative Locations

Ming Zhang [1, 2, *], Juan Shan [3, *], Yaodong Du [3], Rania Almajalid [3], Iris Su[4], Joseph DelVecchio [2]
[1] Division of Rheumatology, Tufts Medical Center, Boston, USA
[2] Department of Computer Science & Networking, Wentworth Institute of Technology, Boston, USA
[3] Department of Computer Science, Pace University, NYC, USA
[4]Newton North High School, Newton, MA, USA
MZhang@tuftsmedicalcenter.org, jshan@pace.edu, yd67578n@pace.edu, ra56319p@pace.edu, iris.anna.su@gmail.com, delvecchioj@wit.edu

***Abstract*— Knee osteoarthritis (OA) is the most common form of arthritis and the major cause of activity limitation and physical disability in older people. Quantitative measures of cartilage on MRI (Magnetic Resonance Imaging) represent potentially powerful surrogate endpoints in knee OA. However, manual segmentation and measurement of the knee cartilage are time-consuming tasks and are not sensitive to detect progression change. In this paper, we proposed a novel whole knee cartilage quantification method based on informative locations called Cartilage Damage Index (CDI). Instead of labeling the entire 3D MR sequence, we focused on the informative locations which are more likely characterized by cartilage loss. We conducted statistical studies for CDI, compared them with traditional manual segmentation, and found that CDI has high correlations with manual segmentation. CDI also shows other promising characteristics: good measurement reliability (ICC 0.90~0.98), a significantly shorter measurement time (~15 mins VS 6 hours), and better sensitivity to detect the slow progression of cartilage loss (SRM: -0.65 VS -0.11). We compared the correlation of CDI and manual segmentation with other severity measurements (joint space width and knee alignment) of OA disease and the results demonstrated that CDI is comparable or better than manual segmentation as a novel biomarker to detect the progression of knee osteoarthritis.**

Keywords: cartilage damage index; knee osteoarthritis; cartilage volume quantification; informative locations; MRI

I. INTRODUCTION

Knee Osteoarthritis (OA) affects more than 10% of the people over 55 years of age in the US and is a major cause of work loss, early retirement, and joint replacement [1-4]. Furthermore, OA is a leading cause of morbidity and disability, and thus carries high socioeconomic costs. In 2004, arthritis was estimated to cost the United States $336 billion, or 3% of the gross domestic product, with OA cited as the most common form of arthritis [5]. OA typically develops over decades (the annual cartilage change detected on manual segmentation usually is less than 1%), offering a long window of time to potentially alter its course [6]. The slow evolution of this structural disease has been thought to be a major impediment to the evaluation of treatments since such studies require large numbers of people followed for 2 years or more to detect cartilage effect on the disease progression [7-12]. Therefore, a sensitive technique for detecting the early structural and functional changes would be valuable for monitoring disease progression and for evaluating the efficacy of treatment [13]. Cartilage morphometry on magnetic resonance (MR) images is important for the assessment of the structural progression of knee OA [11]. To promote the evaluation of OA biomarkers on Magnetic Resonance Imaging (MRI), the National Institutes of Health (NIH) and private industries initiated the Osteoarthritis Initiative (OAI) database. The OAI includes four clinical centers that recruited approximately 4,800 men and women (ages 45-79 years) with knee OA or were at risk for it. The participants underwent annual knee radiography and MR scans during the first four years and then biannually for the subsequent four years. However, facing the huge amount of data, manually obtaining accurate and reproducible quantitative measurements from MRI scans is burdensome and time-consuming due to the structure and morphology of the knee, as well as the nature of MR imaging [14]. Each 3-dimensional (3D) knee MR sequence typically includes up to 160 slices and may take up to 6 hours for a radiologist to manually segment. In order to improve our understanding of OA (especially in a large cohort of patients), speed up the development of new therapies, and reduce development costs, we need to develop a rapid quantification method which has good reproducibility, validity, and sensitivity to change [15].

In this paper, a novel and efficient cartilage quantification method for the whole knee is proposed. Instead of measuring all the slides of the MR sequence, the method measures the cartilage only at certain informative locations and computes the volume of cartilage at those locations. In total, 60 informative locations are identified from the off-line study. The method greatly reduces the measurement time to quantify cartilage and enables researchers to conduct studies on large databases. The rest of the paper is organized as follows. In Section II, we described the data used in this research, the details of the measurement method, and statistical studies to evaluate the method. In Section III, we presented and analyzed the results from the statistical studies described in Section II. Finally, in Section IV, we drew conclusions and discussed future work.

*Corresponding Authors: Ming Zhang, mzhang@tuftsmedicalcenter.org and Juan Shan, jshan@pace.edu

II. Materials and Methods

A. Data

In this study, we used data and MR images from the OAI. We selected 300 knees as the development dataset to detect the cartilage informative locations on the whole knee joint (femur, tibia, and patella). In the validation dataset, we obtained a convenience sample of 88 pairs of knees (both baseline and 12-month MR scans) that had complete data (i.e., clinical, static knee alignment, semi-quantitative radiographic grading, and joint space width) and manual cartilage segmentation on the femur, tibia, and patella.

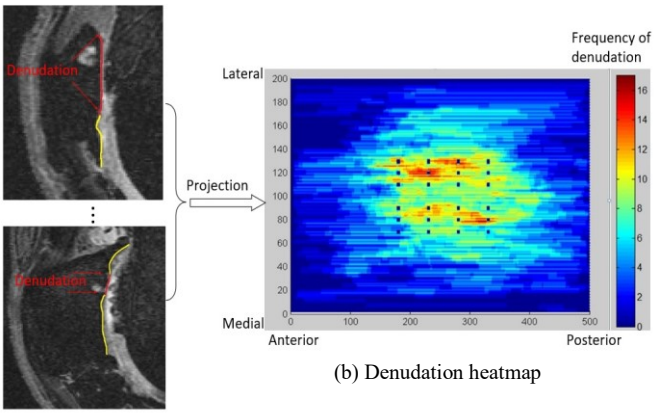
B. Cartilage Damage Index

The Cartilage Damage Index (CDI) is an innovative osteoarthritis cartilage damage quantification method that utilizes the informative locations on knee MR images. Our previous work has implemented the CDI on some parts of the knee cartilage but has not developed the CDI for the whole knee []. In this work, we are going to measure the CDI on the whole knee and evaluate how the CDI can quantify the cartilage. The procedure to measure the CDI is described as follows. The selection of informative locations is based on the statistical analysis of the denuded cartilage areas. We hypothesized that areas near or around common locations of denudation were likely to be areas characterized by cartilage loss. Because the knee joint is the most complex human joint which includes femur, tibia, and patella cartilages and each piece of cartilage is divided into medial and lateral compartments, we need to detect the informative locations in each compartment. The procedure is composed of three iterative steps to detect the informative locations on each cartilage compartment. We take the patella as an example in the following description. The same procedure is run for the femur and tibia to obtain the whole set of CDIs.

Step 1: We selected 100 knees from the OAI's baseline year that included an equivalent number of knees with each OA severity grades (Kellgren and Lawrence [KL] grade, 0-4). The patella cartilage denudation on each knee was manually marked by an expert. Fig. 1(a) shows two examples of denudation marked by red color on the patella.

Step 2: We designed a two-dimensional, rectangular, universal coordinate system to represent the articular surface on the patella. The x-axis of the coordinate system represents the length of cartilage on each MR slide, and the y-axis represents the number of MR slides for each patient. After normalization, the denudation regions of all patients were projected and accumulated on the heat map, which illustrated the frequency distribution of denudation. Fig. 1(b) shows the coordinate system and heat map of the 100 selected knees, where red color represents the highest frequency of denudation and blue color represents lowest frequency denudation.

Step 3: 12 informative locations on the medial patella and 12 informative locations on the lateral patella were evenly selected from the regions where denudation most frequently happened (Fig. 1(b)). These 24 informative locations were marked on the patella. The CDI is computed by summing the products of cartilage thickness, cartilage length, and voxel size from each of the informative location.



(a) Patella denudation mark

(b) Denudation heatmap

Fig. 1. Development of patella informative locations

We repeated the three steps above on other two compartments (femur and tibia), and detected 18 informative locations on each. In total, 300 knees were used and 60 informative locations for the whole knee joint were detected to compute the CDI for a whole knee. Fig. 2 illustrates the informative locations on the three compartments using yellow stars.

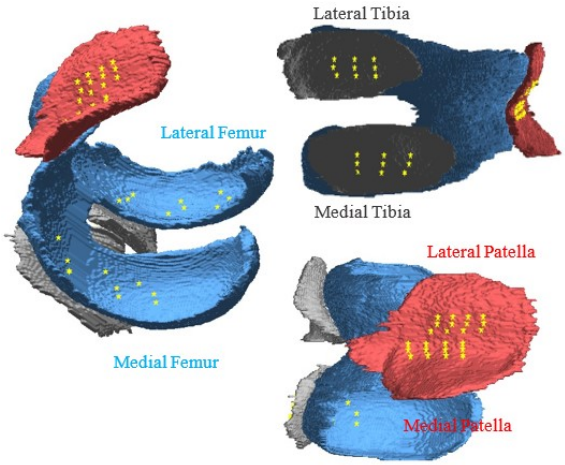
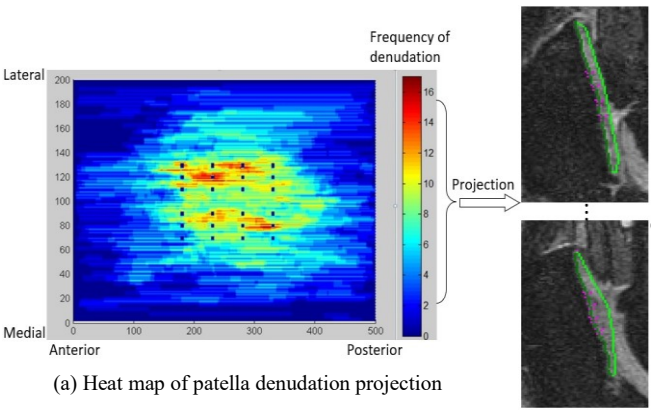


Fig. 2. Whole knee informative locations

As discussed earlier, the idea of the CDI is using informative locations to trace the volume change of cartilage, instead of using manual segmentation on the entire cartilage layer. To compute the CDI on MR images, we developed a customized software to translate a given knee MR scan into the same two-dimensional coordinate system which is defined in Step 2 (Fig. 3 (a)). Then using the predefined informative locations, we can identify the corresponding slides in the given MR sequence where the informative locations sit on. On these identified slides, we measured the cartilage length and thickness at the informative locations, as the pink crosses in Fig. 3(b) shows. The CDI is then calculated by summing the products of cartilage thickness, cartilage length (anterior-posterior), and

voxel size from each informative location. The CDI is designed as a biomarker that can represent the cartilage information at the area of cartilage that mostly changes.



(a) Heat map of patella denudation projection

(b) Informative locations on MRI (Pink crosses)

Fig. 3. Patella CDI measurement on MRI

C. Statistical Studies of the CDI

Reliability and reproducibility are important characteristics of good biomarkers. To evaluate the intra-tester and inter-tester reliability, we selected 20 pairs of knees that covered a full range of disease severity in the validation dataset. Two experts independently measured the CDI of these 20 pairs of knees on two occasions, separated by at least 72 hours. We evaluated intra-tester and inter-tester reliability with Intraclass Correlation Coefficients (ICC) [16]. Specifically, we used an $ICC_{3,1}$ model (two-way mixed single measures) for the intra-tester reliability and an $ICC_{2,1}$ model (two-way random single measures) for inter-tester reliability. An ICC value between 0.75 and 1.00 is considered as excellent according to Cicchetti [17]. The experiment result is shown in section III. B.

OA is a slowly progressing disease, so the cartilage change is usually small and hard to detect. This makes it difficult to gauge whether new treatments/medicines have any structural effects on the disease. A technique that is sensitive to structural changes would be valuable to monitor OA progression. To evaluate the sensitivity of the CDI to cartilage change, we used the standardized response mean (SRM) between baseline and 12-month measurements, which is calculated by dividing the mean change by the standard deviation of the change. A larger absolute value of SRM indicates greater sensitivity to change. A negative SRM value indicates cartilage loss during two times' measurement, while a positive SRM value indicates that the cartilage increased in the follow-up year. The experiment results of the SRM is shown in section III. C.

To evaluate the construct validity of the CDI (i.e., how the CDI is correlated with OA severity grades), we first calculated the correlations between the CDI and manual segmentation at all cartilage compartments. Then we compared the correlation of the CDI and manual segmentation with a radiographic assessment, joint space width (JSW), and a static knee alignment measurement, hip-knee-ankle (HKA). JSW is the distance measured between the femoral condyle and tibial plateau on radiographs and articular cartilage loss is indirectly inferred based on the loss of JSW [18]. JSW is measured separately for the medial compartment and the femur compartment. Static knee alignment is another commonly used measurement of OA progression and a well-established risk factor for cartilage damage. It is proved to be associated with progression of OA by previous works [19-21]. Experiment results are shown in sections III. E and III.F.

III. Experiment and Results

A. Measurement Time

It takes about 15 minutes to measure and compute the CDI for one knee joint using 3D MR images while around 6 hours is needed to manually segment and measure one knee joint, in order to obtain the cartilage volume. The huge time cost difference is mainly because the manual segmentation requires manual delineation of the cartilage layer of every single MR slide and there are about 160 slides for one knee joint. On the other hand, the CDI only requires processing a few slides which are chosen based on the informative locations. Given the large size of the OAI database (MR images from 4800 patients), the significantly faster CDI measurement method makes it possible to involve a large number of samples in future research to explore useful information from the data and better understand the OA disease.

B. Reliability

The CDI shows good reproducibility in our experiment, which is described in section II. C. The intra-tester ($ICC_{3,1}$) reliability of CDI ranges from 0.96 to 0.98 and the inter-tester ($ICC_{2,1}$) reliability of CDI ranges from 0.90 to 0.96. Both ICC values fall within the excellent range [0.75, 1.00].

C. Sensitivity to Change

The comparison of the SRM between the CDI and manual segmentation is shown in Figure 4. The SRM values of femur, tibia, patella, and whole knee CDI (-0.43, -0.60, -0.39, -0.64) are much better than that of manual segmentation (-0.06, -0.14, -0.17, -0.10), indicating that CDI is more sensitive to change than manual segmentation (Table I). Be noted that we plotted the absolute values of the SRM in Fig. 4.

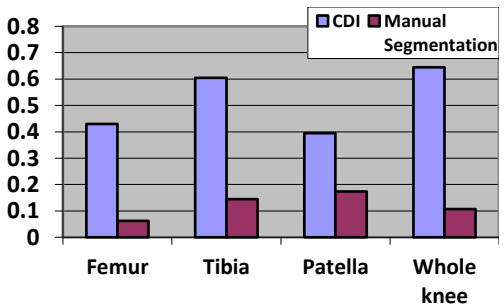


Fig. 4. SRM values of the CDI and cartilage volume obtained from manual segmentation.

Table I. SRM of the CDI and manual segmentation

	Femur	Tibia	Patella	Whole knee
CDI	-0.43	-0.60	-0.39	-0.64
Manual	-0.06	-0.14	-0.17	-0.10
Note: A larger absolute value of SRM indicates greater sensitivity to change				

D. Correlation Between the CDI and Manual Segmentation

The CDI is correlated with cartilage volume obtained from manual segmentation at all compartments. The correlation value of each compartment is shown in Table II, with all p-values <0.01.

Table II. Correlation between the CDI and manual segmentation

	Femur	Tibia	Patella	Total
Medial	0.60	0.63	0.73	0.67
Lateral	0.82	0.83	0.81	0.87

E. Correlation with JSW

The experiment results showed that the CDI has a stronger correlation with JSW than manual segmentation. Since JSW measures the distance between femur and tibia, and for the medial and lateral parts respectively, we computed the CDI separately for each part and evaluated the correlation with the corresponding JSW. The result of the medial compartment is shown in Fig. 5 and the results of the lateral compartment are shown in Fig. 6.

The correlation between the CDI and JSW at the medial femur, medial tibia, and medial tibiofemoral are 0.65, 0.67, and 0.76, while the correlation between manual segmentation and JSW at medial femur, medial tibia, and medial tibiofemoral are 0.29, 0.34, and 0.32, with all p-values < 0.01 (see Table III and Fig. 5).

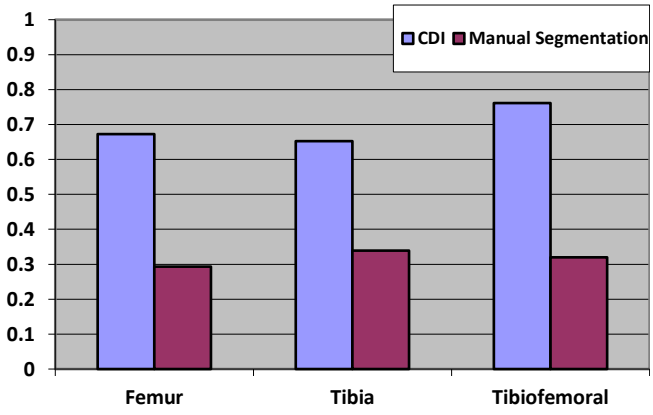


Fig. 5. Correlation with JSW at the medial compartment (all p-values < 0.01).

Table III. Correlation with medial JSW

	Femur	Tibia	Tibiofemoral
CDI	0.65	0.67	0.76
Manual	0.29	0.34	0.32

The correlation between the CDI and JSW at lateral femur, lateral tibia, and lateral tibiofemoral are 0.45, 0.72, and 0.59, while the correlation between manual segmentation and JSW at lateral femur, lateral tibia, and lateral tibiofemoral are 0.41, 0.59, and 0.49, with all p-values < 0.01 (see Table IV and Fig. 6).

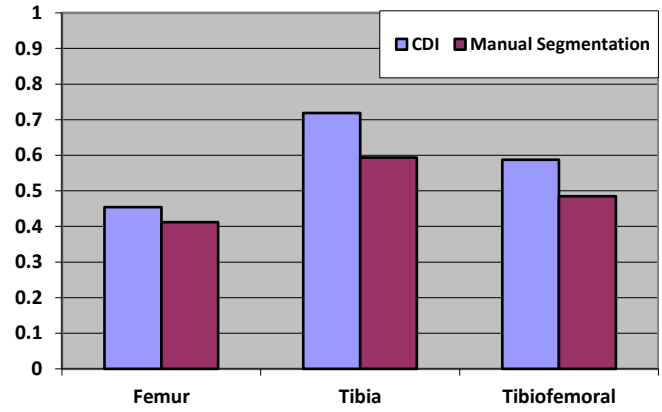


Fig. 6. Correlation with JSW at the lateral compartment (all p-values < 0.01).

Table IV. Correlation with lateral JSW

	Femur	Tibia	Tibiofemoral
CDI	0.45	0.72	0.59
Manual	0.41	0.59	0.49

F. Correlation with HKA

HKA is a measurement defined for the whole knee. We computed the whole knee's CDI as well and found its correlation with HKA is -0.30, while the correlation between manual segmentation and HKA is -0.32, with both p-values < 0.05. The CDI is comparable with manual segmentation considering the correlation with HKA.

IV. CONCLUSIONS

In this paper, a novel and efficient whole knee cartilage quantification method based on informative locations, called the CDI, is proposed and validated on an MR image dataset. Compared with the manual segmentation of cartilage, experiment results show that the CDI is easy and fast to measure, sensitive to change, reliable and reproducible, and shows good construct validity (i.e., strong correlations with OA severity grades). The CDI addresses the current barriers of measuring OA cartilage damage on a large database of knee MR images and could serve as a powerful tool to better explore and utilize large epidemiological investigation (e.g., OAI). The CDI measurement has already been successfully applied to an OA clinical trial (NIH-R01AR057802) to demonstrate the efficacy of a commonly used OA injection (Intra-articular triamcinolone) and the results have been published in JAMA [22].

In the future, we will continue the research of the CDI on a larger database and extend the methodology of using informative locations to other diseases and imaging modalities, such as brain CT.

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