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MRI Quantification of Human Spine Cartilage Endplate Geometry: Comparison With Age, Degeneration, Level, and Disc Geometry

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Abstract

Geometry is an important indicator of disc mechanical function and degeneration. While the geometry and associated degenerative changes in the nucleus pulposus and the annulus fibrosus are well-defined, the geometry of the cartilage endplate (CEP) and its relationship to disc degeneration are unknown. The objectives of this study were to quantify CEP geometry in three dimensions using an MRI FLASH imaging sequence and evaluate relationships between CEP geometry and age, degeneration, spinal level, and overall disc geometry. To do so, we assessed the MRI-based measurements for accuracy and repeatability. Next, we measured CEP geometry across a larger sample set and correlated CEP geometric parameters to age, disc degeneration, level, and disc geometry. The MRI-based measures resulted in thicknesses (0.3–1 mm) that are comparable to prior measurements of CEP thickness. CEP thickness was greatest at the anterior/posterior (A/P) margins and smallest in the center. The CEP A/P thickness, axial area, and lateral width decreased with age but were not related to disc degeneration. Age-related, but not degeneration-related, changes in geometry suggest that the CEP may not follow the progression of disc degeneration. Ultimately, if the CEP undergoes significant geometric changes with aging and if these can be related to low back pain, a clinically feasible translation of the FLASH MRI-based measurement of CEP geometry presented in this study may prove a useful diagnostic tool.

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AUTHORS' CONTRIBUTIONS

All authors have read and revised the manuscript and have contributed to the study design and data analysis.

Keywords

cartilage endplate; magnetic resonance imaging; thickness; geometry; intervertebral disc

Geometry is important to the function of the intervertebral disc and changes in geometry are associated with disc degeneration and altered disc function. For example, disc height is critical to providing load support¹ and with degeneration and loss of hydration, the disc height decreases^{2,3} and disc axial area increases.⁴ The nucleus pulposus and annulus fibrosus substructures also have well-defined geometries. For example, the nucleus pulposus occupies approximately 25% of the disc axial area⁵ and the annulus fibrosus has a well-defined lamellar structure with decreasing fiber angle from the inner annulus fibrosus to the outer annulus fibrosus.⁶ While the nucleus pulposus and the annulus fibrosus have well-known geometries, the cartilage endplate (CEP) does not. The CEP is a thin cartilaginous layer above and below the disc that separates the disc from the adjacent vertebral endplates and vertebral bodies. The CEP functions to transmit compressive loads across the disc-bone interface, pressurize the nucleus pulposus, and serve as a barrier for solute transport. The geometry of the CEP is critical to achieving these functions. The CEP must be thick enough to support the disc-bone interface by transferring compressive loads, while also being thin enough to minimize the distance solutes must travel en route to the cells in the center of the disc.⁷ The CEP also needs to cover enough axial area to reduce fluid flow and pressurize the nucleus pulposus. CEP geometry in the non-degenerate disc is presumably optimized to perform these functions.

With degeneration, however, the CEP permeability decreases, tensile modulus decreases, and it may become sclerotic, calcified, or even severely damaged by Schmorl's nodes.⁸⁻¹⁴ While many CEP mechanical and compositional changes with degeneration are known, geometry of the CEP and changes with degeneration are not known. Indeed, there are conflicting findings in the few available studies that have measured CEP geometry. Histology demonstrated a decrease in CEP thickness with age¹⁵ while resistance micrometry has shown an increase with age.¹⁶ Additionally, histologic methods for assessing CEP geometry are not suitable in a clinical setting and only provide a 2D visualization of the tissue structure.^{17,18} Measuring CEP geometry and how it changes with degeneration is important, as it may elucidate the overall disc degeneration cascade and be a predictor of disc degeneration. Consequently, a three dimensional and non-invasive method to measure CEP geometry is needed.

Magnetic resonance imaging (MRI) techniques are appropriate for assessing CEP geometry as they are non-invasive and can provide strong contrast between adjacent tissues. Although the CEP cannot be visualized in routine clinical MRI, advances in MRI methods focusing on the CEP have aimed to identify CEP biochemical composition,^{19,20} facilitate qualitative ultrastructural assessment,²¹ and quantify CEP defects.²² These improved MRI methods are derived from two MR sequences that have recently been applied to the CEP to enhance CEP visualization: Ultrashort time-to-echo (UTE)¹⁹ and fast low-angle shot (FLASH).²³ In this study, we apply the FLASH sequence because it is readily available on clinical scanners and usually requires shorter scan times for the same field-of-view and resolution.²³ Previously,

we optimized the FLASH MRI sequence for CEP contrast and 3D visualization, providing proof of concept for measuring CEP geometry.²³ While this technique provided excellent CEP visualization and was validated against an excised cylindrical punch processed histologically, the accuracy and repeatability of the measurements were not assessed and only a small number of discs were analyzed.

The objectives of this study were to quantify mid-sagittal and axial CEP geometry using an MRI FLASH imaging sequence and evaluate relationships between CEP geometry and age, degeneration, level, and overall disc geometry. Specifically, we measured CEP width and area from a mid-axial image and CEP thickness from a mid-sagittal image. Additionally, to validate the CEP thickness measurement, we evaluated the accuracy and repeatability of the MRI-based technique compared to thickness measured in paired high resolution optical images taken after sectioning the disc.

METHODS

Male lumbar motion segments ($n = 22$) from nine human cadavers (age 60.9 ± 10.2 years; range 42–75 years, levels L1–L2 to L5–S1) were imaged using a Siemens 7T MRI, as in²³ (Table 1). Both the superior and inferior CEP from each disc were imaged in 22 motion segments, although 1 segment only had 1 discernible endplate ($n = 43$ total CEP). Disc degeneration was graded using the Pfirrmann scoring system and by T2 relaxation time of the nucleus pulposus.^{14,24} Pfirrmann grade 2 was classified as non-degenerate while grades 3–4 were classified as degenerate. No grades 1 or 5 discs were present in the data set or used in this study. Enhancement of CEP contrast was achieved using a previously developed $200 \times 200 \times 200 \mu\text{m}^3$ 3D FLASH MRI technique. Imaging parameters were TR = 9ms, TE = 3.7ms, flip angle = 20° .²³

Accuracy and Repeatability of CEP Thickness Measurement

The accuracy and repeatability of the CEP thickness measurement from the FLASH MR image were evaluated using paired high-resolution optical images of the CEP morphology taken after making a mid-sagittal section. Two discs that were imaged via MRI were selected for morphology analysis. Each disc was fixed in 10% formalin for 1 week and decalcified for 2 weeks with Formical-2000, refreshing the solution every 2–3 days. The discs were bisected along their mid-sagittal plane and imaged using a stereo dissecting microscope equipped with a high-resolution digital camera (Leica Microsystems, Wetzlar, Germany). The corresponding mid-sagittal plane MRI image (Fig. 1A) and morphology image (Fig. 1B) were aligned and overlaid (Fig. 1C) using OsiriX (www.osirix-viewer.com).

The MRI-morphology image pairs were evaluated by two raters, who each independently measured CEP thickness on the MR image and the morphology image on 4 separate days. Thickness was calculated as described in the following section. To assess the accuracy of the thickness measurement, the residual difference between the MRI and morphology measurements was calculated. To compare the slope of the raters' MRI-morphology measurements to a theoretically perfect 1:1 relationship, linear correlation was used with the y -intercept fixed to 0. To assess the repeatability for an individual user the coefficient of variation (CV) was used to analyze each rater's performance. CV is defined as the ratio of

the standard deviation to the mean. The CV was calculated for each of the locations for each user. The average CV for each user was then compared. To assess inter-user error, the Bland–Altman test was used.

Measurement and Analysis of CEP Axial and Mid-Sagittal Geometry

The CEP thickness, anterior-posterior (A-P) width, lateral width, and axial area were measured in all discs by a single rater using a single measurement. CEP thickness was measured on the mid-sagittal plane of the disc using ImageJ. Thickness was calculated for five evenly sized regions across each CEP using ImageJ (NIH) (Fig. 2A). Within a region, the rater manually outlined the CEP using the polygon selection tool in ImageJ (Fig. 2B) and converted the outline to a binary mask (Fig. 2C). Thickness was calculated as the area of the mask divided by the width of the mask. Based on changes of thickness across the CEP (see results), thickness was further evaluated in three groups: center measurement, average of the anterior and posterior measurements (A/P), and the average of all five measurements. Axial CEP geometry (axial area, CEP A-P, and lateral widths) was measured in the true axial plane of each disc using the multi-planar reformatting feature of OsiriX software (Fig. 2D and E). Due to the curvature of the disc-bone interface, reformatted true-axial mean intensity images were averaged through slabs of 1.5 mm thickness and were used to calculate CEP axial geometry (Fig. 2E). Using a thick slab ensures that the full thickness of the CEP is accounted for when making measurements in the true axial plane. Furthermore, this method provides high specificity for measuring the CEP due to the high image contrast along the CEP-vertebral body boundary. In addition, total disc height and disc axial area were measured from the same sagittal and axial sections using OsiriX.

Statistics

To determine if CEP thickness varies across the five measured regions, a one-way ANOVA with Tukey multiple comparison post-hoc test was performed. Within the full data set there are many factors (age, spine level, T2 score, Pfirrmann grade, disc height, and superior-inferior location) that may affect CEP geometry parameters (CEP axial area, A-P width, lateral width, center thickness, A/P thickness, average thickness), so reverse step-wise multiple regression analysis was performed using R software²⁵ to determine the effect of each predictor on CEP geometry. First, a full model including all factors was implemented. Factors were iteratively dropped from the model until either no factors were significant or all remaining factors were significant. Factors were dropped in order of largest (most non-significant) p -value. Statistical significance was set at $p < 0.05$. This multiple regression procedure was performed for all CEP geometry measurements. To support interpretation of the correlations from the multiple regression procedure, for those factors that were significant, individual linear regressions were fit to each combination of factor and CEP geometry parameter to obtain individual r^2 and regression lines. To make comparisons between CEP geometry and disc geometry, linear regression was used to determine any significant correlations. To determine the percent of the disc covered by the CEP the ratio of (CEP geometry parameter)/(Disc geometry parameter) was computed for each CEP and averaged for the parameters of axial area, A-P width, and lateral width.

RESULTS

Accuracy and Repeatability

Overall, independent raters produced accurate measurements between morphology and MRI images that match well with a perfect 1:1 relationship (slope = 1.01, 95% confidence interval of 0.97–1.04, Fig. 3A). The average residual was 0.03 ± 0.14 mm. The standard deviation of this residual distribution was 0.14 mm, which is smaller than the 0.2 mm isotropic resolution of the MRI image, suggesting that the MRI-based method is an accurate measure of the thickness.

The repeatability, as measured by the coefficient of variation, was found to be 13.6% for rater #1 and 14.5% for rater #2. For a CEP thickness of 0.5 mm these repeatability measures equate to 0.068 and 0.073 mm, respectively, both of which are below the MRI resolution. Sub-resolution error in repeatability for both raters suggests that both raters were able to produce consistent values when measuring a particular location. Therefore only one measurement, instead of four, was used in the full dataset.

Inter-user error was assessed using the Bland–Altman test (Fig. 3B and C). The bias for MRI comparisons (Fig. 3B) was -0.049 ± 0.072 mm, with a 95% confidence interval of -0.19 to 0.09 mm. The bias for the morphology comparisons (Fig. 3C) was -0.048 ± 0.092 mm, with a 95% confidence interval of -0.23 to 0.13 mm. There was no systematic inter-rater bias, therefore, only one rater was used for the full dataset.

CEP Mid-Sagittal and Axial Geometry

CEP thickness was greater in anterior and posterior locations than in the center of the disc (Fig. 4; Table 2; $p < 0.01$). Therefore, three thickness parameters were compared to sample age, degeneration grade, and disc geometries: CEP thickness (averaged across the entire width), center CEP thickness, and A/P thickness (averaged from the anterior and posterior site).

With an established technique for measuring CEP thickness from MR images, the full dataset of 22 discs was evaluated for CEP geometry and evaluated via multiple regression. While center thickness did not correlate with age (Fig. 5A, $r = -0.04$, $p > 0.05$), the A/P thickness (Fig. 5B, $r = -0.40$, $p < 0.01$) and average thickness (Fig. 5C, $r = -0.44$, $p < 0.01$) both decreased with age. CEP axial area (Fig. 5D, $r = -0.37$, $p < 0.05$) and lateral width (Fig. 5F, $r = -0.42$, $p < 0.01$) both decreased with age while A-P width (Fig. 5E, $r = -0.25$, $p > 0.05$) did not correlate with age. No CEP geometry parameters correlated with degeneration measured by T2 (Fig. 6) or Pfirrmann grade.

No CEP thickness parameter varied with disc level. CEP axial area did not vary by disc level, except L3–L4 CEP axial area was 35% greater than the L5–S1 CEP area ($p < 0.05$). Similarly, CEP anterior-posterior width did not vary with disc level, except the anterior-posterior width was 20% greater in L3–L4 than L4–L5 ($p < 0.05$). CEP lateral width did not vary with disc level. See Supplemental Figure S1 for correlations between CEP geometry and disc level. No CEP geometry factor depended on superior-inferior location.

In comparing CEP geometry with its associated disc geometry, surprisingly, no CEP thickness parameter correlated with disc height (Fig. 7A–C). CEP axial area did correlate with disc axial area (Fig. 7D, $r = 0.47$, $p < 0.01$) and has a CEP axial area/disc axial area ratio of $30.9 \pm 7.0\%$. CEP anterior-posterior width significantly correlated with disc anterior-posterior width (Fig. 7E, $r = 0.31$, $p < 0.05$) and a CEP A-P width/disc A-P width ratio of $56.1 \pm 7.5\%$. CEP lateral width correlated with disc lateral width (Fig. 7F, $r = 0.32$, $p < 0.05$) and a CEP lateral width/disc lateral width ratio of $57.4 \pm 7.6\%$.

DISCUSSION

The objective of this study was to quantify CEP geometry in three dimensions using an MRI FLASH imaging sequence and evaluate relationships between CEP geometry and overall age, degeneration, spine level, and disc geometry. Previously we presented the MRI technique as a possible tool to visualize and measure CEP geometric features.²³ In the present study, the accuracy and repeatability of the MRI technique was determined by comparing paired MRI and morphology-based measurements. The 3D MRI technique yielded CEP thicknesses that were accurate with respect to paired morphology thickness and between raters. Importantly, there was no systematic over- or under-prediction of the CEP thickness by the MRI technique. Moreover, the validation procedure demonstrated differences in repeatability and inter-user error that were lower than the MRI resolution (<0.2 mm). Therefore, only one user making one measurement is required, enabling practical measurement of a larger data set. The excellent repeatability and low inter-user errors are likely due to the fact that this MRI technique offers significant contrast between the CEP and the surrounding bone and nucleus pulposus (Fig. 1A), a feature that is traditionally best seen in histological assessment of the disc, where the CEP and surrounding tissues stain for significantly different biochemical content. Furthermore, the validity of the MRI technique is reinforced by the fact that measurements of CEP thickness presented here, 0.3–1 mm, are comparable to previous measurements produced using histology: 0.4–0.8 mm.^{17,26,27} This FLASH MR imaging and analysis technique, if modified for clinical feasibility as previously demonstrated,²³ will be valuable for assessing CEP geometry changes in patients with disrelated disorders.

This study evaluated changes in CEP geometry with age and degeneration. There were no significant correlations between any CEP geometry parameter and measures of degeneration, either T2 relaxation time or Pfirrmann grade, although several parameters were correlated with age. A/P thickness, average thickness, axial area, and lateral width were observed to decrease with age (Fig. 5). It is unclear what processes lead to a smaller CEP and what significance a smaller CEP has on its structural, mechanical, and transport functions. A smaller CEP will provide less exchange area for transport of solutes and water, and may affect the transport cycle. Altered transport is often hypothesized to be a factor in the degenerative cascade.^{8,28–30} If smaller CEP axial area is significantly able to hinder transport, it is possible that using MRI to evaluate CEP axial area may be a valuable predictor of the efficacy of non-invasive therapies that require transport into the disc.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Furthermore, the changes in CEP geometry with aging are seen most prominently at the interface between the inner annulus fibrosus and the CEP (Fig. 5B), a site of common CEP and annulus fibrosus herniation.²⁷ In this region, the CEP is thickest, likely due to annulus fibers passing through the CEP and anchoring to the adjacent bone^{31,32} which are not present in the center of the CEP.^{14,33} This may be a mechanically important junction in the disc as it experiences high tensile strains^{34–36} and consequently, is frequently the sight of CEP and annulus fibrosus herniation.^{27,37–39} CEP thickness at this junction decreases with age which may make the CEP more susceptible to failure. CEP axial area, which is enclosed by this outer boundary, also decreases with age (Fig. 5D). These age-related, but not degeneration-related, changes in geometry at the CEP-inner annulus interface suggest that the CEP may undergo a process of degeneration that does not directly follow disc degeneration.¹⁴

Absence of significant correlations between CEP geometric parameters and measures of disc degeneration may also be due to the differences between disc degeneration and other cartilage degenerative processes like osteoarthritis. Notably, osteoarthritis results from increased wear of articular cartilage,^{40,41} culminating in bone-on-bone contact. In contrast, the disc undergoes changes that manifest in altered structure and mechanics,^{36,42,43} but not wear. Disc degeneration is typically not defined by bone-on-bone contact⁴⁴ and only in severe degeneration (Pfirrmann grade of 5) would wear possibly occur. No grade 5 discs were tested in this study and, due to fragmentation of the CEP in grade 5 discs, it would be challenging to visualize the CEP in such advanced degeneration using MRI. These different processes of articular cartilage wear and CEP changes with disc degeneration further confirm that the CEP is not a strict analog of articular cartilage.

CEP geometry correlated with disc geometry, as expected. Larger discs had larger CEP axial area and widths (Fig. 7). The CEP had an axial area that occupies about 25–35% of the disc area, corresponding to a region encompassing the nucleus pulposus (~25% disc area) and some of the inner annulus fibrosus.⁵ A larger CEP axial area than nucleus pulposus axial area is important for the CEP's functions in the disc. The CEP serves as for the interface for transport exchange as well as a load distributor between the disc and bone.⁷ Both functions are successfully achieved by having a CEP axial area that covers the entire nucleus pulposus.

Surprisingly, particularly as CEP axial geometry correlated with disc axial geometry, the CEP thickness did not correlate with disc height. This may be valuable for the transport functions of the CEP. Taller discs are already burdened with a long diffusion distance from the vertebral solute supply to the cells in the center of the disc.^{7,29,30,45} If CEP thickness increased with disc height, this burden would only increase, particularly as the CEP has a high fixed charge density and a low permeability.^{14,17}

This study is not without limitations. A small ($n = 22$) sample set was used to identify relationships between CEP geometry and disc geometry and disc degeneration factors. A priori power analysis suggested a minimum sample size of 98, at a power of $1 - \beta = 0.8$, in order to compare across six factors. It is possible that such a large dataset would identify some correlations not detected here; however, it is not likely or expected that different outcomes would emerge. For example, in this study, several CEP geometry factors, for

example, center thickness, shared no relationships ($p > 0.9$) with disc degeneration (Fig. 6), a fact that is unlikely to change with an increased sample size. In addition, no grades 1 or 5 discs were evaluated in this study.

These ends of the degeneration spectrum may significantly affect CEP and disc geometry but are not captured in this study. This study demonstrates the accuracy of measuring CEP geometry from 3D FLASH MRI. This technique was used to show a decrease in CEP axial geometry and A/P thickness with age. Age-related decreases in these geometric features may be related to commonly observed failure at the junction between the CEP and inner annulus fibrosus. The lack of relationship between CEP geometry and disc degeneration further suggests that CEP degeneration may not progress directly with disc degeneration. Consequently, it remains unclear what relationship the CEP shares with disc degeneration and low back pain. Nevertheless, as the CEP undergoes significant geometric changes with age, the MRI technique presented in this study may prove a useful diagnostic tool for clinical use.

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Figure 1.

Accuracy of the CEP MRI technique. Mid-sagittal MRI (A) and morphology (B) images were resized and overlaid (C) to ensure that regions match in both images. In the merged image, red represents the MRI image and blue represents the morphology image. Scale = 5 mm.

Figure 2.

CEP thickness measurement technique. A CEP is divided into five evenly spaced regions (A). Using the polygon tool in ImageJ, the CEP of a particular region is outlined (B) and converted to a binary mask (C). The area of the mask is calculated in ImageJ and divided by the width of the mask to obtain thickness. Mid-axial plane (D) images were used to quantify disc axial geometry while a 1.5 mm thick axial slice (E) was used to calculate CEP axial geometry. Orange lines represent anterior-posterior width measurements while blue lines represent lateral width measurements. Scale = 5 mm.

Figure 3.

Success of MRI technique and rater performance. The MRI technique successfully predicts morphology thickness (A) with a slope of 1.01 with a 95% confidence interval of 0.97–1.04. Raters consistently matched MRI (B) and morphology (C) measurements. Each point in (A) represents one measurement at one location. Each point in (B and C) represents the average of all four measurements at each location.

Figure 4.

CEP thickness varied significantly across the anterior-posterior width of the disc ($p < 0.05$). CEP is thinnest in the center and thickest at the A/P ends, where the CEP interfaces with the inner annulus fibrosus. Bars represent $p < 0.05$. A, anterior; A-C, anterior-center; C, center; C-P, center-posterior; P, posterior.

Figure 5.

Relationships between CEP geometry and age. Center thickness (A, $r = -0.04$, $p > 0.05$) and CEP A-P width (E, $r = -0.25$, $p > 0.05$) did not correlate with age. A/P thickness (B, $r = -0.40$, $p < 0.01$) and average thickness (C, $r = -0.44$, $p < 0.01$) decreased with age. CEP axial area (D, $r = -0.37$, $p < 0.05$) and lateral width (F, $r = -0.42$, $p < 0.01$) decreased with age.

Figure 6.

Relationships between CEP geometry and degeneration measured by T2 relaxation time. No CEP geometry parameter correlated with degeneration.

Figure 7.

Linear regression relationships between CEP geometry and disc geometry. No CEP thickness parameter correlated with disc height (A–C). CEP axial area (D, slope = 0.23, $p < 0.01$), A-P width (E, slope = 0.24, $p < 0.05$), and lateral width (F, slope = 0.27, $p < 0.05$) all correlated with their disc counterparts.

Table 1

Summary of Sample Set

Spine Level	Non-Degenerate CEP	Degenerate CEP
L1–L2	3	0
L2–L3	4	6
L3–L4	6	10
L4–L5	2	4
L5–S1	0	8
Total	15	28

Table 2

CEP Thickness by Region

Location	Anterior	Anterior-Center	Center	Center-Posterior	Posterior	Average
Thickness (mm)	0.69 ± 0.24	0.51 ± 0.15	0.44 ± 0.10	0.55 ± 0.16	0.72 ± 0.30	0.58 ± 0.23