Osteoarthritis and Cartilage 24 (2016) 1761–1768

Osteoarthritis and Cartilage

Facet tropism and facet joint orientation: risk factors for the development of early biochemical alterations of lumbar intervertebral discs

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ARTICLE INFO

Article history:
Received 22 September 2015
Accepted 2 May 2016

Keywords:
Glycosaminoglycan chemical exchange saturation transfer
Facet tropism
Facet orientation
Intervertebral discs
MRI

SUMMARY

Objective: To assess the glycosaminoglycan (GAG) content of lumbar intervertebral discs (IVD) in healthy volunteers with facet tropism (FT) and sagittal facet joint (FJ) orientation using glycosaminoglycan chemical exchange saturation transfer imaging (gagCEST).
Method: Seventy-five lumbar IVDs of twenty-five young, healthy volunteers without any history of lumbar spine pathologies (13 female; 12 male; mean age: 28.0 ± 4.4 years; range: 21–35 years) were examined with a 3T MRI scanner. Orientation of FT and FJ were assessed for L3/4, L4/5 and L5/S1 using standard T2 weighted images. Biochemical gagCEST imaging was used to determine the GAG content of each nucleus pulposus (NP) and annulus fibrosus (AF).
Results: Significantly higher gagCEST values of NP were found in volunteers without FT and normal FJ orientation compared to volunteers with FT and sagittal FJ orientation >45° ($P < 0.0001$). GagCEST values were significantly higher in volunteers without FT compared to volunteers with moderate or severe FT (moderate FT: $P < 0.0001$; severe FT: $P = 0.0033$). Volunteers with normal FJ orientation showed significantly higher gagCEST values compared to those with sagittal FJ orientation >45° ($P < 0.001$). We found a significant, negative correlation between gagCEST values and higher angels in sagittal FJ orientation (rho = −0.459; $P < 0.0001$).
Conclusion: GagCEST analysis indicated lower GAG values of NP in young volunteers with FT and sagittal orientated FJ, indicating that FT and sagittal orientation of the FJ represent risk factors for the development of early biochemical alterations of lumbar IVDs.

Introduction

Intervertebral disc (IVD) degeneration is a multifactorial disorder and associated with low back pain that has become one of the most common diseases with a profound individual and socioeconomic impact[1–5]. Facet tropism (FT) and increased sagittal orientation of facet joints (FJ) are proposed to be risk factors for the development of IVD degeneration, disc herniation and degenerative spondylolisthesis[6,7]. FT is defined as the asymmetry between the left and the right vertebral (apophyseal) FJ angels, with one joint having a more sagittal orientation than the other[8]. The FJ have the biomechanical function to share the spine load in compression and extension, and protect the disc against torsion forces[9]. Boden et al. demonstrated a twenty-five-fold increased risk of degenerative spine alterations in FJ with a sagittal orientation of more than 45°[10].

Large proteoglycan molecules with numerous glycosaminoglycan (GAG) side chains are a major component of IVDs, especially

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http://dx.doi.org/10.1016/j.joca.2016.05.004
1063-4584/

of the NP[11]. GAG depletion has been demonstrated to play a central part in the degenerative processes. Negatively charged carboxyl- and sulfate-groups of GAG are the driving force for hydration, thus a decrease of GAG content may lead to the morphological degradation seen on routine magnetic resonance imaging (MRI)[12,13]. Glycosaminoglycan chemical exchange saturation transfer (gagCEST) imaging allows the determination of GAG content without the application of contrast agent or dedicated additional MRI hardware[14]. It has been shown that the measurable gagCEST effect correlates directly with the underlying concentration of GAG[15,16]. Several studies using gagCEST demonstrated the sensitivity to visualize and quantify GAG in IVDs[17–19].

The aim of our study was to investigate whether FT and increased sagittal orientated FJ are possible risk factors for the development of early IVD alterations using molecular gagCEST imaging in healthy volunteers. Our hypothesis was that participants with FT and a more sagittal orientation of the FJ have significantly lower gagCEST effects and, therefore, these two characteristics can be regarded as risk factors for early IVD alterations.

Method

Study population

The study was approved by the local ethics committee. Written informed consent was obtained from all volunteers for this study. Twenty-five healthy volunteers (13 female; 12 male; mean age: 28.0 ± 4.4 years; range: 21–35 years) without any history of spine pathologies, previous acute or chronic low back pain episodes or previous surgery of the lumbar spine were enrolled in this study. The body mass index of all participants was within normal range. The data sets of the participants used here were included in a study of our research group that addressed the change of GAG content in lumbar IVDs with regard to age[17].

MR hardware, sequence protocol and gagCEST imaging

The lumbar spine of all volunteers was examined in the supine position using a clinical whole-body 3T MR system (Magnetom Trio, A Tim System, Siemens Healthcare, Erlangen, Germany). Signal reception was performed using a 24 channel spine matrix coil.

Our MR sequence protocol included morphological T2-weighted (T2w) sequences in sagittal and axial orientation. Biochemical imaging was performed using a prototype gagCEST and a water saturation shift referencing (WASSR) sequence.

Bowel movement artefacts and artefacts due to abdominal wall motion were reduced using a saturation band anterior to the spine.

The detailed parameters of biochemical and morphological sequences were selected according to the study of Müller-Lutz *et al.* (Table I)[17].

GagCEST imaging is derived from a number of images that are acquired with pre-saturation pulses at different offset frequencies around the bulk water resonance, and one reference image without saturation.

Data analysis and measurements

The L3/4, L4/5 and L5/S1 IVDs of all 25 subjects were successfully imaged and a total of 75 IVDs were included in this study.

Data analysis of biochemical imaging was performed using in-house developed MATLAB software (The Mathworks, Inc., Natick, MA, USA, R2012b). WASSR and CEST images were motion-corrected using a diffeomorphic image registration approach incorporated in the prototype software fMRLung (Siemens Healthcare, Erlangen, Germany)[20]. A reduction of image noise was performed using an in-plane 3 × 3 Gaussian filter[17]. B0 field inhomogeneities were corrected using the WASSR maximum symmetry algorithm[21]. The offset-corrected CEST-curves divided by the signal without CEST pre-saturation S0 were defined as z-spectrum Z(ω). The magnetization transfer asymmetry was determined as $MTR_{asym}(\Delta\omega) = Z(-\Delta\omega)-Z(\Delta\omega)$, where Δω is the specified frequency shift difference. The residual signal normalized to the reference image as a function of the offset frequencies (z-spectrum) can be utilized for the evaluation of GAG CEST effect[17]. GagCEST values were determined using the MTR_{asym} value in the frequency range from 0.9 to 1.9 ppm, which comprises the chemical exchange resonances of GAG hydroxyl protons[14].

A region of interest (ROI) analysis was performed to calculate the gagCEST effect of NP and AF analogue to the method used by Haneder *et al.*[19] The average size of the ROIs was 38 ± 15 pixels (NP) and 26 ± 11 pixels (AF). The ROIs were drawn by an experienced radiologist (CS, 5 years of experience in musculoskeletal segmentation analysis). He was blinded to the FT and FJ orientation measurements of the morphological sequences.

Data analysis methods and calculations of gagCEST measurements were used according the work of Müller-Lutz *et al.*[17] For reliability assessment, the analysis was repeated by the latter and by a second observer (AML) (medical physicist with four years of segmenting experience in musculoskeletal imaging).

The same radiologist (CS), blinded to the gagCEST analysis (randomly selected morphological lumbar spine images), scored the three lumbar IVDs according to FT and increased sagittal orientation of FJ[10]. Intra- and inter-reader reliability for the FJ angles were obtained by blinded first (CS) and second observer (KB, 10 years of experience in musculoskeletal radiology).

The measurements of the FJ were performed manually on axial T2w images that were aligned parallel to the end plate at the level of the inferior margin of the IVD space. FJ angel was defined as a line between the anteromedial and posterolateral margins of FJ and a horizontal line (the coronal reference plane). The reference line was assessed by marking two points on the posterior wall of the vertebral body or IVD (Fig. 1). The FJ angle in the transverse view relative to the coronal plane was calculated for both sides, left and right FJ, and the difference between both sides at each level (and therefore the FT) was analyzed.

In accordance with prior studies, three groups of FT manifestation were defined: no FT with asymmetry in the FJ orientation ≤6°, mild FT with asymmetry between the left and right FJ between >6° and ≤10° and moderate (FJ asymmetry >10° and ≤16°) to severe (FJ asymmetry >16°) FT[10]. Moderate and severe FT were placed in one group due to the small sample size.

For the graduation of FJ, a high-risk threshold of 45° for sagittal FJ orientation was used to analyze the impact on IVD degeneration[10,22]. We built four groups for sagittal FJ orientation analysis: the first group with an FJ angle <45° and no FT, the second group with an FJ angle <45° and FT, the third group with an FJ angle >45° and no FT and the fourth group with an FJ angle >45° and FT.

For the statistical analysis of gagCEST effect, MTR_{asym} values of NP and AF were used.

Statistical analysis

IBM SPSS Statistics version 22.0 for Windows (IBM Corp., Armonk, NY, USA) and SAS version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA) were used for statistical analysis. The mean, 95% confidence intervals (CIs) for the mean values, median, standard