Research Article

Multidimensional vertebral endplate defects are associated with disc degeneration, Modic changes, facet joint abnormalities and pain†

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Disclosure: The authors have no financial or competing interests to disclose.

Key Words: endplate; Modic; disc degeneration; facet, phenotypes; MRI; classification; pain

†This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1002/jor.24195]

Received 28 July 2017; Revised 24 August 2018; Accepted 25 August 2018

Journal of Orthopaedic Research®

DOI 10.1002/jor.24195

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ABSTRACT

The aim of the current study was to investigate the multi-dimensional characteristics of lumbar endplate defects in humans in relation to disc degeneration and other MRI phenotypes as well as their role with pain and disability. 108 subjects were recruited and underwent 3T MRI of the lumbar spine. Structural endplate defects were identified and their dimensions were measured in terms of maximum width and depth, and were then standardized to the actual width of the endplate and depth of the vertebral body, respectively. Both width and depth of all endplate defects in each subject were added separately and scores were assigned on the basis of size from 1 to 3. Combining both scores provided "cumulative endplate defect scores." Disc degeneration scores, Modic changes, disc displacement, HIZ and facet joint changes were assessed. Subject demographics, pain profile and Oswestry Disability Index (ODI) were also obtained. Endplate defects were observed in 67.5% of the subjects and in 13.5% of the endplates. All dimensions of endplate defects showed significance with disc degenerative scores, Modic changes, and posterior disc displacement ($p<0.05$). Maximum width ($p=0.009$) and its standardized value ($p=0.02$), and cumulative endplate defect scores ($p=0.004$) increased with narrow facet joints. Cumulative endplate defect scores showed a strong positive association with ODI ($p<0.05$) compared to disc degenerative scores. Large size endplate defects were strongly associated with degenerative spine changes and more back-related disability. Findings from this study stress the need to assess endplate findings from a multi-dimensional perspective, whose role may have clinical utility.

INTRODUCTION

The vertebral endplate is essential for maintaining the morphological and functional integrity of the lumbar intervertebral discs. The endplate provides a route for nutritional exchange and helps distribute compressive stress from the disc onto the trabecular network of the vertebral body. Despite having two components, osseous and cartilaginous, the endplate is not a perfect design. The relatively thin, perforated structure of osseous component, unable to bear compressive stresses for long, is vulnerable to fracture and defect; hence, this structure is termed as the "weak link" of the lumbar spine.

Several imaging techniques, such as plain radiographs, computed tomography (CT) scans and magnetic resonance imaging (MRI) are able to visualize the endplates.[3,6-8] Among them, MRI is considered the most sensitive and effective modality to detect even a little alteration within the structure of the endplate. It is also able to reveal the "biological reaction" to endplate defects (i.e. abnormality, breaks, damage, disruption or discontinuity of the structural endplate morphology) that have been commonly associated with and can lead to Modic changes. Modic changes are signal intensity changes in the subchondral vertebral bone marrow extending from the endplate.[14,15] It is assumed that endplate defects can facilitate communication and a constant cross-talk between the disc and vertebral body, which can lead to a persistent inflammatory state of the vertebral bone marrow; thereby, becoming an important pain generating source.[15-17]

Endplate damage is closely linked with lumbar disc degeneration. According to Mok *et al*, the presence of endplate defects was significantly associated with the severity of lumbar disc degeneration. Experimental evidences suggest that defects in the endplate cause significant reduction in the disc's proteoglycan content and can lead to elevated catabolic enzymes, pro-

inflammatory cytokines, and pro-apoptotic proteins in the disc, resulting in degenerative changes.[18,19] Furthermore, endplate defects allow nucleus material to invade the vertebral body, causing reduced pressure in the nucleus and appearance of stress peaks within the anterior and posterior annulus.[20,21] The altered mechanical stresses adversely affect the disc cell metabolism and may be a factor leading to "endplate driven disc degeneration". Such evidences suggests that endplate defects are likely involved in the initiation or progression of disc degeneration.

Owing to the highly innervated nature of the endplate, any injury or defect is highly susceptible to pain but the role of these endplate defects in discogenic back pain is still debatable. Similar controversy also exists with disc degeneration and back pain. It becomes more challenging and difficult to distinguish the potential source of back pain when both endplate changes and disc degeneration co-exist. Various studies focusing on endplate lesions determined a strong link with low back pain.[19,24] Furthermore, it has been noted that endplate pathologies perhaps are more densely innervated as compared to disc pathologies; thereby, representing an important pain generating source.[19,25] Though some endplate findings, such as Schmorl's nodes, are not strongly linked with back pain,[26,27] absence of pain may be explained by subsidence of inflammation as a part of the healing process or that there are sub-phenotypes of endplate findings that are more associated with pain. As such, variations in the size or shape of the endplate defect may cause different pain profiles. This possibility has been explored by few previous studies and they were able to demonstrate that 'large' sized endplate defects are more closely associated with disc degeneration and pain as compared to 'small' sized ones.[24,28,29] Another recent study by Farshad-Amacker *et al*[30] was able to demonstrate that endplate defects occupying ≥50% of the endplate area were more likely a risk factor for disc degeneration and

Modic changes, but all these attempts were merely a qualitative grading rather than precise measurements. A recent quantitative measurement of the cadaveric endplate defect dimensions with micro CT revealed that larger and multiple defects were significantly associated with decreased intradiscal pressure and increased severity of disc degeneration. However, how this morphological variability of the endplate defect dimensions affects other spinal phenotypes, such as high-intensity zones (HIZ), disc displacement and facet joint changes is still unknown. Likewise, the implication of such phenotypes upon the development of pain and disability is also important and needs to be explored. In light of these limitations and gap in knowledge, the current study aimed to address endplate defect size on MRI from a multi-dimensional perspective and to determine its association with other MRI phenotypes and clinical profile.

METHODS

Study participants

One hundred and eight Southern Chinese subjects were recruited. Subjects were identified from a list of volunteers of a previous cohort (approximately 3,000 subjects).[1,32-34] All the subjects of this previous cohort were found to be representative of the general Hong Kong population, the details of which have been reported elsewhere.[4,37-40] Complete medical history, detailed clinical profile, and imaging assessment were performed on all of subjects. The current study sample of 108 subjects were recruited from this cohort by stratified random sampling, after institutional review board approval, to get an equal number of males and females. This sampling was done without any bias to the presence or absence of pain. The sample size of 108 subjects was based on available funding and represents a new imaging cohort. All subjects provided written

informed consent to participate in the current study, whereby they underwent concomitant imaging and clinical assessment. Age (years), sex-type, body weight (kilograms/kg), body height (meters/m) and body mass index (BMI: kg/m^2) were noted for every individual. The visual analogue scale (VAS) was used to measure the severity of low back pain. The subjects were asked this question in a standardized manner as presented in written text form. The subjects were provided with a form having a straight horizontal line of fixed length (100 mm) with the following question: "How severe is your low back pain / sciatica today? Place a vertical mark on the line below to indicate how bad you feel your pain is today. The ends of the horizontal line are defined as the extreme limits of pain, oriented from right to left, marked as no pain---- to very severe pain."

Oswestry Disability Index (ODI) scores of all subjects were also obtained. At the same time, all subjects underwent imaging assessment via sagittal T2-weighted MRI of the lumbar spine.

MRI Parameters

All subjects underwent imaging of the lumbar spine via a 3T MRI scanner (Achieva, Philips Healthcare, Best, The Netherlands). Sagittal T2-weighted (T2W) MRI was acquired using a standard spin-echo imaging sequence with the following parameters: field of view (FoV) =28x24cm, slice thickness=5mm, acquisition matrix=400x232, and echo time/repetition time (TE/TR) =110ms/3000ms. Axial T1-weighted (T1W) MRI was also obtained with the following parameters: field of view (FoV) =18x18cm, slice thickness=4mm, and echo time/repetition time (TE/TR) =9.5ms/500ms.

MRI Assessment

The T2W MRI sagittal images of the endplates of the lumbar spine motion segments were assessed from L1/L2 to L5/S1 (n=1,080) in all subjects. Any endplate structural defects with definite margins were identified and their width and depth were measured using RadiAnat DICOM software in all the slices with defects and maximum values were considered for analysis **(Figure 1).** These values were also standardized with the actual width of the endplate and depth of the respective vertebral body to give the standardized width and depth values. Both of these values were scored 1-3 based on their size; score 1 was given to the values ≤0.2, score 2 was 0.21-0.40 and score 3 was assigned to the values >0.40. Cumulative defect scores were assigned by adding both of the scores up to a maximum value of 6 **(Table 1).** To get the cumulative endplate defect scores of the individuals with the endplate defects, width and depth of all endplate defects were added and scores were provided as; score 1 = ≤0.50, score 2 = 0.51-1 and score 3 = >1, cumulative endplate defect scores of the lumbar spine of the subjects were assigned 1 to 6 after adding both dimensions (**Table 1**).

Disc degeneration scores were assessed and based on the Schneiderman *et al*[35] grading system, which was as follows: Grade 0: normal, well hydrated hyperintense disc with normal disc space height; Grade 1: slight decrease in signal intensity in the nucleus pulposus; Grade 2: generalized hypointense nucleus pulposus (i.e. black disc) with disc space height maintained; Grade 3: generalized hypointense nucleus pulposus (i.e. black disc) with disc space narrowing. A cumulative "disc degeneration score" was obtained from a summation of individual discs scored from L1 to S1 via the Schneiderman *et al* method. The potential range of the cumulative disc degeneration score ranged from 0 to 15. The clinical relevance of this method has been

illustrated in various reports of population-based studies in relation to spinal phenotypes.[32,33,36] Other MRI changes were also observed in sagittal T2W MRI scans. For one, signal intensity changes in the subchondral vertebral bone marrow adjacent to the endplates were regarded as Modic changes, regardless of Modic type. Disc bulge/protrusion represented displacement of the annular fibers beyond the vertebral margin. High intensity zones (HIZ) were characterized as bright white signals within the annulus fibrosus of the intervertebral discs. Facet joint changes were assessed on axial MRI and noted as any presence of narrowing, irregularity or flatness to its morphology involving one or both joints.

Statistical Analyses

For statistical analyses, SPSS version 22 software (IBM, Chicago, IL) was utilized. Descriptive and frequency statistics were performed to assess the various data parameters. Mean, standard deviations (±SD) and ranges were obtained of applicable data points. Associations between defect dimensions and continuous variables, such as age, VAS, and ODI, were assessed using univariate analyses. Differences in dimension of the vertebral endplate defects with gender, lumbar level, endplate site, Modic changes, HIZ, disc displacement and facet changes were determined using independent *t* tests. For comparisons involving more than two groups, such as disc degenerative grades with different dimensions of endplate defects, one way ANOVA with Tukey Post-Hoc was used. For intra-rator reliability testing of the vertebral endplate defect measurement, the strength was noted as follows based on kappa testing: excellent ($k>0.90$), good, ($k>0.80$), fair ($k>70$) and poor ($k<0.60$). A p-value of <0.05 was considered as the

threshold for statistical significance. Inter and intra-rator reliability in the identification of the T2W MRI phenotypes were excellent (k=0.91, k=1.00, respectively).[38,39]

RESULTS

Subject Demographics

Among the 108 subjects, there were equal numbers of males and females (54:54), with a mean age of 52 years (range: 22-67, SD: 7.7 years). The mean BMI was 24.6 kg/m^2 (range: 18.1-39.5, SD: 3.5 kg/m^2). Excellent inter-rator reliability was observed in the determination of endplates with defects (k=1); in the measurement of width (mm) and depth (mm) of the endplate defects excellent intra-rator reliability was seen (k=0.84 & k=0.93, respectively). For the determination of presence or absence of defects in vertebral endplates all samples were read by two observers. For the reliability analysis of defect dimensions, measurements were repeated by a single observer on 19 subjects (n=26 endplates), randomly selected from the subjects with defects after the gap of three weeks.

Endplate Defects & Subject Characteristics

Endplate defects were observed in 67.5% (n=73) of individuals with mean age of 51.6±8.5 years. Among them 50.6% (n=37) were males. Approximately 13.5% (n=146) of the endplates had defects and 57.5% (n=84) were from males, 56.8% (n=83) belonged to the upper two lumbar levels, and 67.1% (n=98) were inferior endplates relative to the intervertebral discs.

Maximum width ranged from 1.92-18.7 mm (mean 8.5±3.3), while maximum depth values were ranged from 1.58-9.13 mm (mean 3.6±1.2). These values were standardized with the width of respective endplates and depth of the vertebral body which ranged from 0.06-0.56 (mean: 0.26±0.1) and 0.06-0.36 (mean: 0.15±0.05) respectively. Cumulative endplate defect scores ranged from 2 to 5.

Maximum and standardized values of depth were significantly positively correlated with age (r=0.24,p=0.004; r=0.20,p=0.01, respectively). All the other dimensions and cumulative defect scores did not show any significance with age (p>0.05). While comparing the sex-type differences**,** endplate defects in males were seen to have greater depth with significance seen in maximum depth values (p=0.02) but values did not reach statistical significance when standardized. Standardized width and cumulative endplate defect scores were higher in females (p=0.003 and p=0.05 respectively; **Table 2).** Standardized width of the vertebral endplate defects in the upper two lumbar levels (L1-L2 or L2-3) was significantly bigger (p=0.008; **Table 2)** compared to the lower three levels (L3-4 to L5-S1). Maximum depth and its standardized values were significantly higher in the superior endplates relative to the intervertebral discs (p=0.05, p=0.03 respectively).

Endplate Defects & MRI Phenotypes

Dimensions of the endplate defects were increased with increasing scores of disc degeneration **(Table 3).** Maximum width, depth, their standardized values and cumulative defect scores all showed significance (p=0.001, p<0.001, p=0.01, p<0.001 & p=0.001 respectively). All endplate defects were not accompanied by Modic changes (**Figure 2**) only 17.8% (n=26) of endplate defects showed Modic changes adjacent to them (**Figure 3**). All dimensions of the

defects were significantly bigger in endplates with Modic changes (maximum width p<0.001, maximum depth p=0.01, standardized width p=0.001, standardized depth p=0.003, cumulative endplate defect scores p=0.001) **(Table 3).** Intervertebral discs with posterior disc displacement had significantly larger endplate defect dimensions (maximum width p<0.001, maximum depth p=0.008, standardized width p=0.05, standardized depth p=0.005 & cumulative endplate defect scores p=0.002) (**Table 3**). Vertebral endplate defect dimensions were also seen to be increased with facet joint changes (**Table 4**) (**Figure 3**). Significance was seen with maximum width, its standardized value and cumulative defect scores with narrow facet joints (p=0.009, p=0.02 & p=0.004 respectively).

Endplate Defects & Pain

In the subjects with endplate defects, the mean cumulative endplate defect score of the lumbar spine was 2.6 (range: 2 to 6; ±0.9). These scores did not show any significant association with VAS but showed significant positive correlation with ODI (r=0.24, p=0.04) compared to disc degenerative scores, which did not show any significant relationship with ODI (r=0.08, p>0.05). Among these subjects, there were almost 54.8% (n=40) of individuals with more than one endplate that had defects. The mean value of ODI was higher in these subjects but statistical significance was not observed. When individuals with overall endplate defects were compared with individuals having no endplate defects **(Table 5)**, no significant differences were seen with age and sex-type, VAS, ODI and total degeneration scores (p>0.05). The age was slightly higher in individuals having no endplate defects (p=0.08).

DISCUSSION

This was the first study to assess the 'dimensions of endplate defects' on MRI and their relevance with various MRI spine phenotypes and the clinical profile. Vertebral endplate defects were observed in 68% of the individuals and in 14% of the endplates with almost equal distribution in male and female. Upper lumbar levels and inferior endplates relative to discs were more commonly affected. Age did not seem to have any significant effect on endplate defect dimensions except maximum and standardized depth; mean age was also not significantly different between individuals with endplate defects and individuals with no endplate defects. This is in contrast to the results of a previous study done by Wang *et al* showing association of increased age with endplate defects. The explanation behind the mismatch of results between studies is perhaps attributed to different techniques of endplate assessment between studies. Wang *et al*[40] used dried, cadaveric vertebral bodies to locate all types of endplate defects (i.e. Schmorl's nodes, fractures, erosions and calcifications) with naked eye examination. They were also able to note very small endplate defects, which cannot be visualized with MRI. The current study only measured and noted those defects having distinct margins, and calcification of the endplate was also not included within the lesion of the endplates. However this insignificant relationship with age is consistent with the findings of a previous micro CT study performed on cadaveric human samples. These results are highly suggestive of the fact that other factors, such as genetic susceptibility, mechanical loading and trauma, may play more crucial roles in the pathogenesis of discrete endplate lesions. The increase in depth of the endplate defects with age may be due to the fact that the vertebral endplate gets more porous and thinner with aging and degeneration.[41]

In our study, male endplates were seen to be slightly more affected as compared to females though significant difference could not be achieved which is consistent with previous studies.[8,31] However, we also observed that females have wider endplate defects and higher cumulative endplate defect scores, possibly a result of osteoporotic changes influencing female bones earlier than males. The osteoporosis decreases the overall strength of the vertebral endplate by causing gradual thinning of the trabecular plates, resulting in the disruption of the trabecular bone architecture underneath it and the loss of BMD may also lead to structural endplate changes.[44-46] High prevalence and size of the endplate defects at the upper lumbar levels is also in agreement with previous studies[40,47] where endplate defects were more commonly reported at the thoracolumbar and upper lumbar levels. This presumably is because of the small surface area of endplate as compared to lower lumbar levels where vertebral size and compressive strength is higher to match the loading applied to them and even a minor traumatic event is enough to cause these endplate defects. The inferior endplates relative to discs are thinner and are supported by less trabecular bone explaining the higher prevalence of inferior endplate defects in the current study. Interestingly the depth of the endplate defect was greater in superior endplates this finding was consistent with a previous study and is probably due to the marked concavity observed in these endplates with aging.[40,46,49]

The MRI scores of disc degeneration were significantly associated with all endplate defect dimensions indicating that endplate defect or damage is one of the key factors linked with disc degeneration. This finding was consistent with the results of a recent study linking size of the cadaveric endplate defects with macroscopic and microscopic grades of disc degeneration. Similarly, another cadaveric endplate study reported three sizes of the endplate lesions based on

the subjective analysis and their positive link with discographic grades of disc degeneration. The current disc degenerative scores of MRI are phenotypic representation of mainly water, proteoglycan and disc height loss; the vertebral endplate acts as a barrier and limit the movement of metabolites and water between the bone marrow and disc. Hence, with bigger defects, there are increased chances of losing water and proteoglycan contents from the disc tissue thereby leaving the discs fibrous and dehydrated. This defect in the barrier may also be responsible for the unrestricted movement of the cytokines and pro-inflammatory agents to and from the disc causing bone marrow or Modic changes to appear which were also significantly associated with dimensions of the endplate defects in the current study.[16,50] All endplate defect dimensions were also in significant correlation with posterior bulging of the intervertebral discs supporting the previous observation linking lumbar disc herniation with endplate junction failure and endplate damage. There are number of studies who have reported, based from cartilaginous and bony endplates in the surgical samples of herniated discs, that the pathophysiology of lumbar disc herniation is more likely to be mechanical and the high bending movements can cause overstretching of the annular fibers which can pull off the vertebral endplate causing junctional failure and endplate damage. Another possible explanation of this phenomenon may be that dehydrated and fibrosed discs due to endplate damage are more prone to develop fissures and tears causing disc to bulge and prolapse.[54]

The facet joint changes in relation to endplate defect dimensions were another interesting finding of the current study. The facet joints were found to be increasingly irregular, flat and significantly narrowed as the dimensions of the endplate defects increased. Facet joints are the point of contact between adjacent neural arches of the vertebral bodies and small changes in

postural angle can lead to high stress concentration. It may be possible that endplate damage and resulting uneven stress distribution and disc degeneration cause much of the compressive stress to pass through the neural arch affecting the facet joints. However, it is challenging to establish a cause and effect relationship with a cross-sectional study.

The link between cumulative endplate defect scores of the lumbar spine and ODI was also an important finding in the current study. ODI is one of the most commonly used outcome measures for individuals with low back pain.[58] VAS is a valuable instrument to assess pain intensity and is found to correlate positively with other self-reporting measures of pain intensity. However, some authors suggest that it is more difficult to understand than other measurement methods and, hence, more susceptible to misinterpretations. Disability index on the other hand can be considered as a major indicator for the severity of pain conditions, allowing more comprehensive assessment of pain and related disability.[59,60] Considering the fact that ODI is very valid, reliable, and a responsive condition-specific assessment tool helping clinicians in precise estimation of level of dysfunction associated with low back pain, we can emphasize that increase in the endplate size can have a significant clinical relevance.[61,62] The lack of any significant association between disc degenerative scores and ODI strengthen the possibilities that endplate defects and their increasing dimensions are more relevant pathologies associated with low back pain. The endplate pathologies tended to have increased pain innervation and provide an open route to various cytokines and inflammatory markers to pass through, leading to sensitization of the nerve endings present in the degenerated discs, and more specifically larger endplate defects with Modic changes might cause influx of more cytokines and also irritate the bone marrow, which may cause pain.[16,63,64]

Few inherent limitations existed with our study. As this was a cross-sectional design, larger prospective studies are required to further strengthen the association findings observed, especially related to facet changes and the pain profile. For the measurements, MRI only allows us a two-dimensional assessment of the endplate defects. Furthermore, some very shallow and irregular erosive endplate defects could not be measured due to indistinct boundaries. These factors may minimize the strength of association between facet changes and endplate defects. Three-dimensional measure of the endplate defects would certainly be needed to better define and explore the association with different MRI phenotypes. Nonetheless, our study represents the first study to measure the endplate defects on MRI and assess the association with other important MRI spinal phenotypes and the clinical profile.

CONCLUSIONS

Our findings are highly suggestive that the increase in the dimensions of the endplate defects is linked with significant increase in disc changes, such as disc degenerative scores, Modic changes and disc displacement. Furthermore, our study noted a unique observation that increases in the endplate defect dimensions are in direct association with facet joint changes, which are also an important pain generating source. The increased ODI with increasing scores of endplate defects raises further and much needed awareness on the role of the vertebral endplate as either a direct or indirect pain generating source. This work further broadens the understanding of endplate defects and their relationship with the pathogenesis and cascade of degenerative spine changes. Larger, prospective studies are needed to further validate our findings and to explore in more depth the findings that we noted.

REFERENCES

1. Mok FP, Samartzis D, Karppinen J, Fong DY, Luk KD, Cheung KM. Modic changes of the lumbar spine: prevalence, risk factors, and association with disc degeneration and low back pain in a large-scale population-based cohort. *Spine J* 2016;16:32-41.

2. Moore RJ. The vertebral endplate: disc degeneration, disc regeneration. *Eur Spine J* 2006;15:333-7.

3. Samartzis D, Mok FP, Karppinen J, Fong DY, Luk KD, Cheung KM. Classification of Schmorl's nodes of the lumbar spine and association with disc degeneration: a large-scale population-based MRI study. *Osteoarthritis Cartilage* 2016;24:1753-60.

4. Adams MA, McNally DS, Dolan P. 'Stress' distributions inside intervertebral discs. The effects of age and degeneration. *J Bone Joint Surg Br* 1996;78-B:965-72.

5. Adams MA, McNally DS, Wagstaff J, Goodship AE. Abnormal stress concentrations in lumbar intervertebral discs following damage to the vertebral bodies: a cause of disc failure? *European Spine Journal* 1993;1:214-21.

6. Maatta JH, Karppinen JI, Luk KD, Cheung KM, Samartzis D. Phenotype profiling of Modic changes of the lumbar spine and its association with other MRI phenotypes: a large-scale population-based study. *Spine J* 2015;15:1933-42.

7. Hasz MW. Diagnostic testing for degenerative disc disease. *Adv Orthop* 2012;2012:413913.

8. Mok FP, Samartzis D, Karppinen J, Luk KD, Fong DY, Cheung KM. ISSLS prize winner: prevalence, determinants, and association of Schmorl nodes of the lumbar spine with disc degeneration: a population-based study of 2449 individuals. *Spine (Phila Pa 1976)* 2010;35:1944-52.

9. Samartzis D, Borthakur A, Belfer I, Bow C, Lotz JC, Wang H-Q, Cheung KMC, Carragee E, Karppinen J. Novel diagnostic and prognostic methods for disc degeneration and low back pain. *The Spine Journal* 2015;15:1919-32.

10. Samartzis D, Borthakur A, Belfer I, Bow C, Lotz JC, Wang H-Q, Cheung KMC, Carragee E, Karppinen J. Novel diagnostic and prognostic methods for disc degeneration and low back pain. *Spine J* 2015;15:1919-32.

11. Zehra U, Bow C, Lotz JC, Williams FM, Rajasekaran S, Karppinen J, Luk KDK, Battie M, Samartzis D. Structural vertebral endplate nomenclature and etiology: a study by the ISSLS Spine Phenotype Focus Group. *Euro Spine J* 2018;27:2-12.

12. Zehra U, Bow C, Lotz JC, Williams FM, Rajasekaran S, Karppinen J, Luk KDK, Battie M, Samartzis D. Structural vertebral endplate nomenclature and etiology: a study by the ISSLS Spine Phenotype Focus Group. *Euro Spine J* 2018;27:2-12.

13. Adams MA, Dolan P. Intervertebral disc degeneration: evidence for two distinct phenotypes. *Journal of Anatomy* 2012;221:497-506.

14. Modic MT, Steinberg PM, Ross JS, Masaryk TJ, Carter JR. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology* 1988;166.

15. Dudli S, Fields AJ, Samartzis D, Karppinen J, Lotz JC. Pathobiology of Modic changes. *Eur Spine J* 2016;25:3723-34.

16. Dudli S, Sing DC, Hu SS, Berven SH, Burch S, Deviren V, Cheng I, Tay BK, Alamin TF, Ith MA, Pietras EM, Lotz JC. Intervertebral disc/bone marrow cross-talk with Modic changes. *Eur Spine J* 2017.

17. Wong AY, Karppinen J, Samartzis D. Low back pain in older adults: risk factors, management options and future directions. *Scoliosis Spinal Disord* 2017;12:14.

18. Dudli S, Haschtmann D, Ferguson SJ. Fracture of the vertebral endplates, but not equienergetic impact load, promotes disc degeneration in vitro. *J Orthop Res* 2012;30:809-16.

19. Lotz JC, Fields AJ, Liebenberg EC. The role of the vertebral end plate in low back pain. *Global Spine J* 2013;3:153-64.

20. Dolan P, Luo J, Pollintine P, Landham PR, Stefanakis M, Adams MA. Intervertebral disc decompression following endplate damage: Implications for disc degeneration depend on spinal level and age. *Spine* 2013;38:1473-81.

21. Adams MA, Freeman BJC, Morrison HP, Nelson IW, Dolan P. Mechanical initiation of intervertebral disc degeneration. *Spine* 2000;25:1625-36.

22. Kokkonen SM, Kurunlahti M, Tervonen O, Ilkko E, Vanharanta H. Endplate degeneration observed on magnetic resonance imaging of the lumbar spine: correlation with pain provocation and disc changes observed on computed tomography diskography. *Spine (Phila Pa 1976)* 2002;27:2274-8.

23. Chou D, Samartzis D, Bellabarba C, Patel A, Luk KD, Kisser JM, Skelly AC. Degenerative magnetic resonance imaging changes in patients with chronic low back pain: a systematic review. *Spine (Phila Pa 1976)* 2011;36:S43-53.

24. Wang Y, Videman T, Battie MC. ISSLS prize winner: Lumbar vertebral endplate lesions: associations with disc degeneration and back pain history. *Spine (Phila Pa 1976)* 2012;37:1490-6.

25. Fields AJ, Liebenberg EC, Lotz JC. Innervation of pathologies in the lumbar vertebral endplate and intervertebral disc. *Spine J* 2014;14:513-21.

26. Williams FM, Manek NJ, Sambrook PN, Spector TD, Macgregor AJ. Schmorl's nodes: common, highly heritable, and related to lumbar disc disease. *Arthritis Rheum* 2007;57:855-60.

27. Takahashi K, Miyazaki T, Ohnari H, Takino T, Tomita K. Schmorl's nodes and low-back pain. Analysis of magnetic resonance imaging findings in symptomatic and asymptomatic individuals. *Eur Spine J* 1995;4:56-9.

28. Wang Y, Battie MC, Videman T. A morphological study of lumbar vertebral endplates: radiographic, visual and digital measurements. *Eur Spine J* 2012;21:2316-23.

29. Rajasekaran S, Venkatadass K, Naresh Babu J, Ganesh K, Shetty AP. Pharmacological enhancement of disc diffusion and differentiation of healthy, ageing and degenerated discs : Results from in-vivo serial post-contrast MRI studies in 365 human lumbar discs. *Eur Spine J* 2008;17:626-43.

30. Farshad-Amacker NA, Hughes A, Herzog RJ, Seifert B, Farshad M. The intervertebral disc, the endplates and the vertebral bone marrow as a unit in the process of degeneration. *Eur Radiol* 2017;27:2507-20.

31. Zehra U, Flower L, Robson-Brown K, Adams MA, Dolan P. Defects of the vertebral endplate: implications for disc degeneration depend on size. *Spine J* 2017.

32. Samartzis D, Karppinen J, Mok F, Fong DY, Luk KD, Cheung KM. A population-based study of juvenile disc degeneration and its association with overweight and obesity, low back pain, and diminished functional status. *J Bone Joint Surg Am* 2011;93:662-70.

33. Cheung KM, Samartzis D, Karppinen J, Luk KD. Are "patterns" of lumbar disc degeneration associated with low back pain?: new insights based on skipped level disc pathology. *Spine (Phila Pa 1976)* 2012;37:E430-8.

34. Cheung KMC, Samartzis D, Karppinen J, Mok FPS, Ho DWH, Fong DYT, Luk KDK. Intervertebral disc degeneration: New insights based on “skipped” level disc pathology. *Arthritis & Rheumatism* 2010;62:2392-400.

35. Schneiderman G, Flannigan B, Kingston S, Thomas J, Dillin WH, Watkins RG. Magnetic resonance imaging in the diagnosis of disc degeneration: correlation with discography. *Spine (Phila Pa 1976)* 1987;12:276-81.

36. Takatalo J, Karppinen J, Niinimaki J, Taimela S, Nayha S, Mutanen P, Sequeiros RB, Kyllonen E, Tervonen O. Does lumbar disc degeneration on MRI associate with low back symptom severity in young Finnish adults? *Spine (Phila Pa 1976)* 2011;36:2180-9.

37. Vavken P, Ganal-Antonio AK, Shen FH, Chapman JR, Samartzis D. Fundamentals of clinical outcomes assessment for spinal disorders: study designs, methodologies, and analyses. *Global Spine J* 2015;5:156-64.

38. Li Y, Samartzis D, Campbell DD, Cherny SS, Cheung KM, Luk KD, Karppinen J, Song Y, Cheah KS, Chan D, Sham PC. Two subtypes of intervertebral disc degeneration distinguished by large-scale population-based study. *Spine J* 2016.

39. Pang H, Bow C, Cheung JPY, Zehra U, Borthakur A, Karppinen J, Inoue N, Wang HQ, Luk KDK, Cheung KMC, Samartzis D. The UTE Disc Sign on MRI: a novel imaging biomarker associated with degenerative spine changes, low back pain and disability. *Spine* 2018;43:503-11.

40. Wang Y, Videman T, Battie MC. Lumbar vertebral endplate lesions: prevalence, classification, and association with age. *Spine (Phila Pa 1976)* 2012;37:1432-9.

41. !!! INVALID CITATION !!! .

42. Eisman J, Clapham S, Kehoe L. Osteoporosis prevalence and levels of treatment in primary care: the Australian BoneCare Study. *J Bone Miner Res* 2004;19.

43. Brandi ML. pMicroarchitecture, the key to bone quality. *Rheumatology (Oxford)* 2009;48 Suppl 4:iv3-8.

44. Pye SR, Reid DM, Adams JE, Silman AJ, O'Neill TW. Radiographic features of lumbar disc degeneration and bone mineral density in men and women. *Ann Rheum Dis* 2006;65:234-8.

45. Ferguson SJ, Steffen T. Biomechanics of the aging spine. *Eur Spine J* 2003;12 Suppl 2:S97-s103.

46. Twomey LT, Taylor JR. Age changes in lumbar vertebrae and intervertebral discs. *Clin Orthop Relat Res* 198797-104.

47. Herwig B, Weyreuther M, Heyde CE, Westphal M, Zierski J, Weber U. MRI Atlas: Orthopedics and Neurosurgery, The Spine: Springer Berlin Heidelberg; 2007.

48. Zhao FD, Pollintine P, Hole BD, Adams MA, Dolan P. Vertebral fractures usually affect the cranial endplate because it is thinner and supported by less-dense trabecular bone. *Bone* 2009;44:372-9.

49. Twomey L, Taylor J. Age changes in lumbar intervertebral discs. *Acta Orthop Scand* 1985;56:496-9.

50. Lama P, Zehra U, Balkovec C, Claireaux HA, Flower L, Harding IJ, Dolan P, Adams MA. Significance of cartilage endplate within herniated disc tissue. *European Spine Journal* 2014;23:1869-77.

51. Rajasekaran S, Bajaj N, Tubaki V, Kanna RM, Shetty AP. ISSLS Prize winner: The anatomy of failure in lumbar disc herniation: an in vivo, multimodal, prospective study of 181 subjects. *Spine (Phila Pa 1976)* 2013;38:1491-500.

52. Berger-Roscher N, Casaroli G, Rasche V, Villa T, Galbusera F, Wilke HJ. Influence of Complex Loading Conditions on Intervertebral Disc Failure. *Spine (Phila Pa 1976)* 2017;42:E78-e85.

53. Berg-Johansen B, Fields AJ, Liebenberg EC, Li A, Lotz JC. Structure-function relationships at the human spinal disc-vertebra interface. *J Orthop Res* 2017.

54. Yu SW, Sether LA, Ho PS, Wagner M, Haughton VM. Tears of the anulus fibrosus: correlation between MR and pathologic findings in cadavers. *AJNR Am J Neuroradiol* 1988;9:367-70.

55. Samartzis D, Cheung JP, Rajasekaran S, Kawaguchi Y, Acharya S, Kawakami M, Satoh S, Chen WJ, Park CK, Lee CS, Foocharoen T, Nagashima H, Kuh S, Zheng Z, Condor R, Ito M, Iwasaki M, Jeong JH, Luk KD, Prijambodo B, Rege A, Jahng TA, Luo Z, Tassanawipas W, Acharya N, Pokharel R, Shen Y, Ito T, Zhang Z, Aithala PJ, Kumar GV, Jabir RA, Basu S, Li B, Moudgil V, Goss B, Sham P, Williams R. Critical Values of Facet Joint Angulation and Tropism in the Development of Lumbar Degenerative Spondylolisthesis: An International, Large-Scale Multicenter Study by the AOSpine Asia Pacific Research Collaboration Consortium. *Global Spine J* 2016;6:414-21.

56. Samartzis D, Cheung JP, Rajasekaran S, Kawaguchi Y, Acharya S, Kawakami M, Satoh S, Chen WJ, Park CK, Lee CS, Foocharoen T, Nagashima H, Kuh S, Zheng Z, Condor R, Ito M, Iwasaki M, Jeong JH, Luk KD, Prijambodo B, Rege A, Jahng TA, Luo Z, Tassanawipas WA, Acharya N, Pokharel R, Shen Y, Ito T, Zhang Z, Aithala PJ, Kumar GV, Jabir RA, Basu S, Li B, Moudgil V, Goss B, Sham P, Williams R. Is lumbar facet joint tropism developmental or secondary to degeneration? An international, large-scale multicenter study by the AOSpine Asia Pacific Research Collaboration Consortium. *Scoliosis Spinal Disord* 2016;11:9.

57. Williams R, Cheung JP, Goss B, Rajasekaran S, Kawaguchi Y, Acharya S, Kawakami M, Satoh S, Chen WJ, Park CK, Lee CS, Foocharoen T, Nagashima H, Kuh S, Zheng Z, Condor R, Ito M, Iwasaki M, Jeong JH, Luk KD, Prijambodo B, Rege A, Jahng TA, Luo Z, Tassanawipas W, Acharya N, Pokharel R, Shen Y, Ito T, Zhang Z, Aithala PJ, Kumar GV, Jabir RA, Basu S, Li B, Moudgil V, Sham P, Samartzis D. An International Multicenter Study Assessing the Role of Ethnicity on Variation of Lumbar Facet Joint Orientation and the Occurrence of Degenerative Spondylolisthesis in Asia Pacific: A Study from the AOSpine Asia Pacific Research Collaboration Consortium. *Global Spine J* 2016;6:35-45.

58. Vianin M. Psychometric properties and clinical usefulness of the Oswestry Disability Index. *J Chiropr Med* 2008;7:161-3.

59. Haefeli M, Elfering A. Pain assessment. *Eur Spine J* 2006;15:S17-24.

60. Vavken P, Ganal-Antonio AK, Quidde J, Shen FH, Chapman JR, Samartzis D. Fundamentals of clinical outcomes assessment for spinal disorders: clinical outcome instruments and applications. *Global Spine J* 2015;5:329-38.

61. Fritz JM, Irrgang JJ. A comparison of a modified Oswestry Low Back Pain Disability Questionnaire and the Quebec Back Pain Disability Scale. *Phys Ther* 2001;81:776-88.

62. Lu Y-M, Wu Y-Y, Hsieh C-L, Lin C-L, Hwang S-L, Cheng K-I, Lue Y-J. Measurement precision of the disability for back pain scale-by applying Rasch analysis. *Health and Quality of Life Outcomes* 2013;11:119.

63. Burke JG, Watson RW, McCormack D, Dowling FE, Walsh MG, Fitzpatrick JM. Intervertebral discs which cause low back pain secrete high levels of proinflammatory mediators. *J Bone Joint Surg Br* 2002;84:196-201.

64. Burke JG, Watson RWG, McCormack D, Fitzpatrick JM, Stack J, Walsh MG. MR Endplate Changes Are Associated With Increased Disc Inflammatory Mediator Production. *J Bone Joint Surg [Br}* 2003;85-B:164.

65. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. *Nature reviews Rheumatology* 2013;9:216-24.

66. Gellhorn AC, Katz JN, Suri P. Osteoarthritis of the spine: the facet joints. *Nature Rev Rheumatol* 2013;9:216-24.

FIGURE LEGENDS

Figure 1: Sagittal T2-weighted magnetic resonance images illustrating the dimensions taken through RadiAnat DICOM software noting: **(A)** width of the vertebral endplate defect, **(B)** depth of the vertebral endplate defect, **(C)** width of the vertebral endplate and **(D)** depth of the vertebral body.

Figure 2: (A) Sagittal T2-weighted magnetic resonance images (MRI) of the lower three lumbar levels demonstrating relatively small endplate defects without any Modic change at L3-L4 and L4-L5 (red arrows). **(B)** Axial T1-weighted MRI of L3-L4 and **(C)** L4-L5 of the same individual showing normal facets on both sides.

Figure 3: (A) Sagittal T2-weighted magnetic resonance images (MRI) of the lumbar spine illustrating an endplate defect with Modic change at L1-L2 (red arrow). **(B)** Axial T1-weighted MRI of L1-L2 of the same individual showing irregular (red arrows) facet joint changes on both sides.

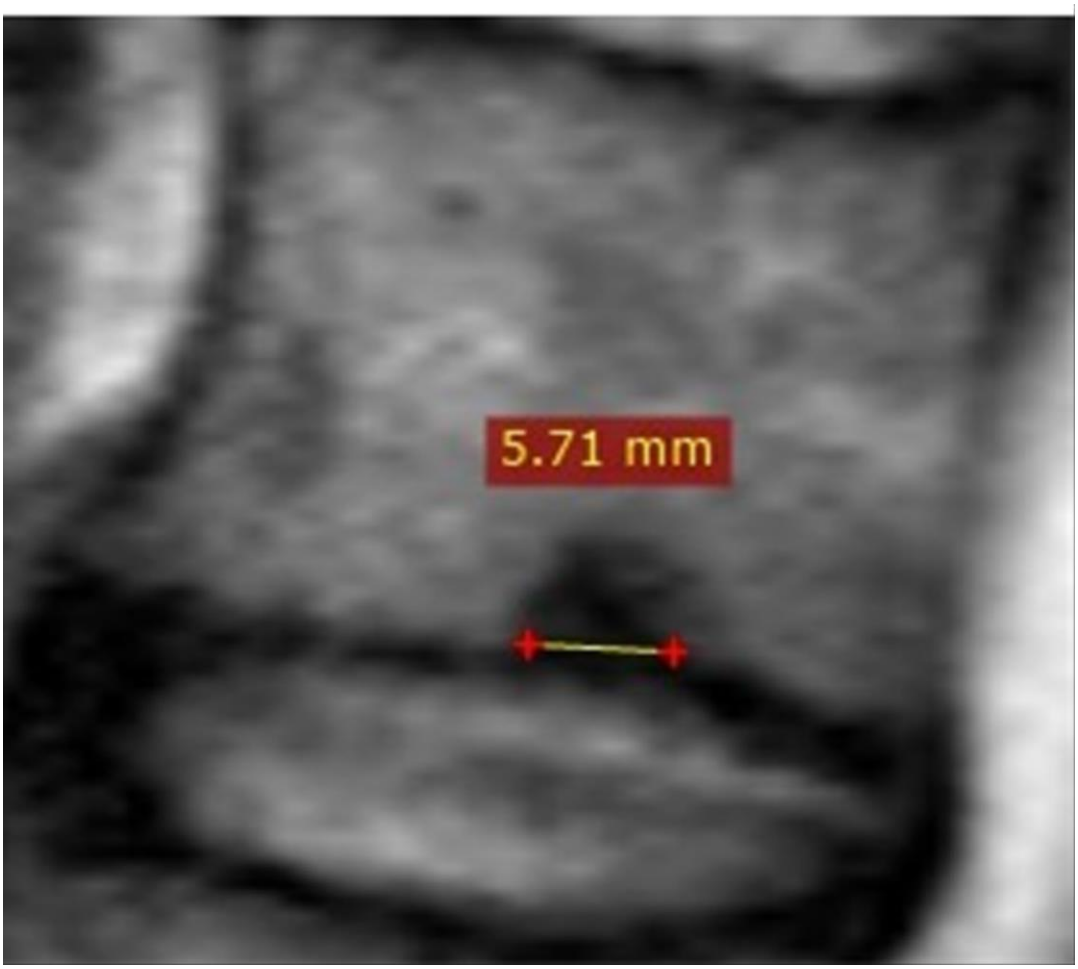
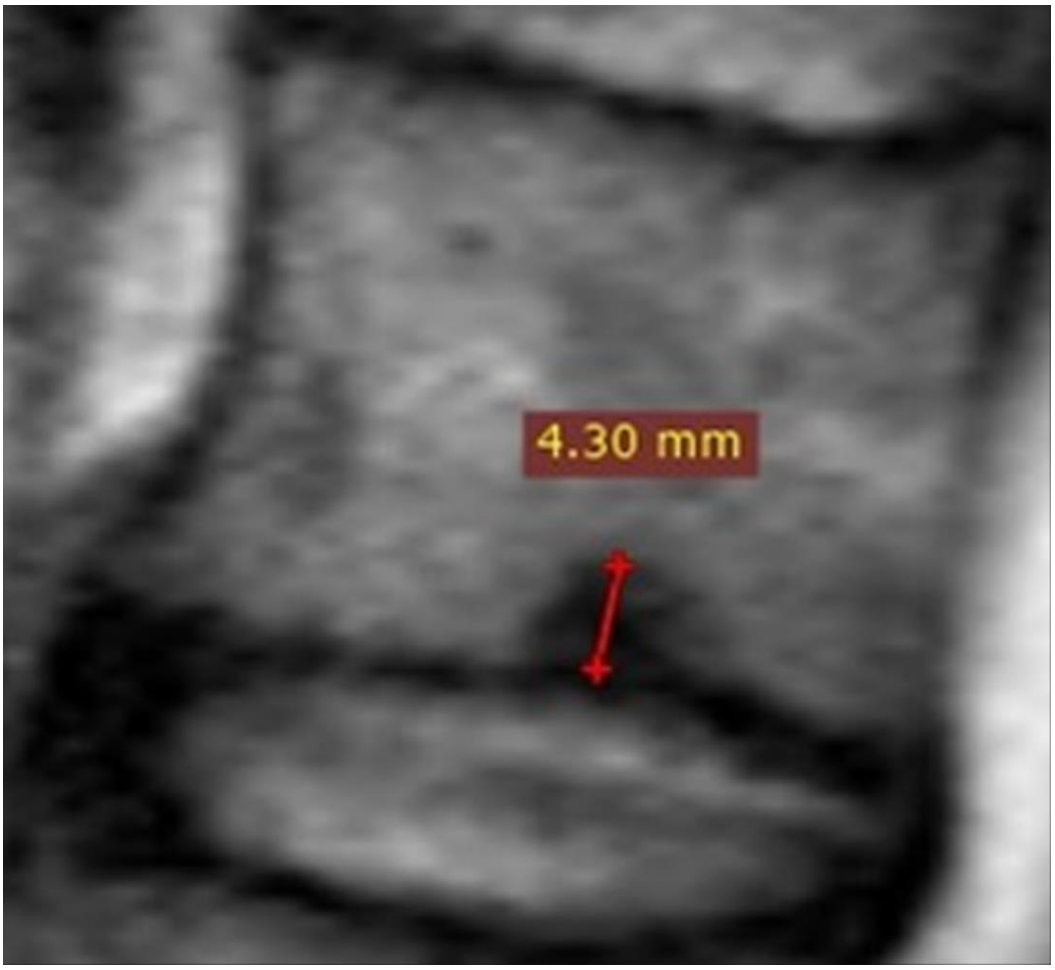


Figure 1A



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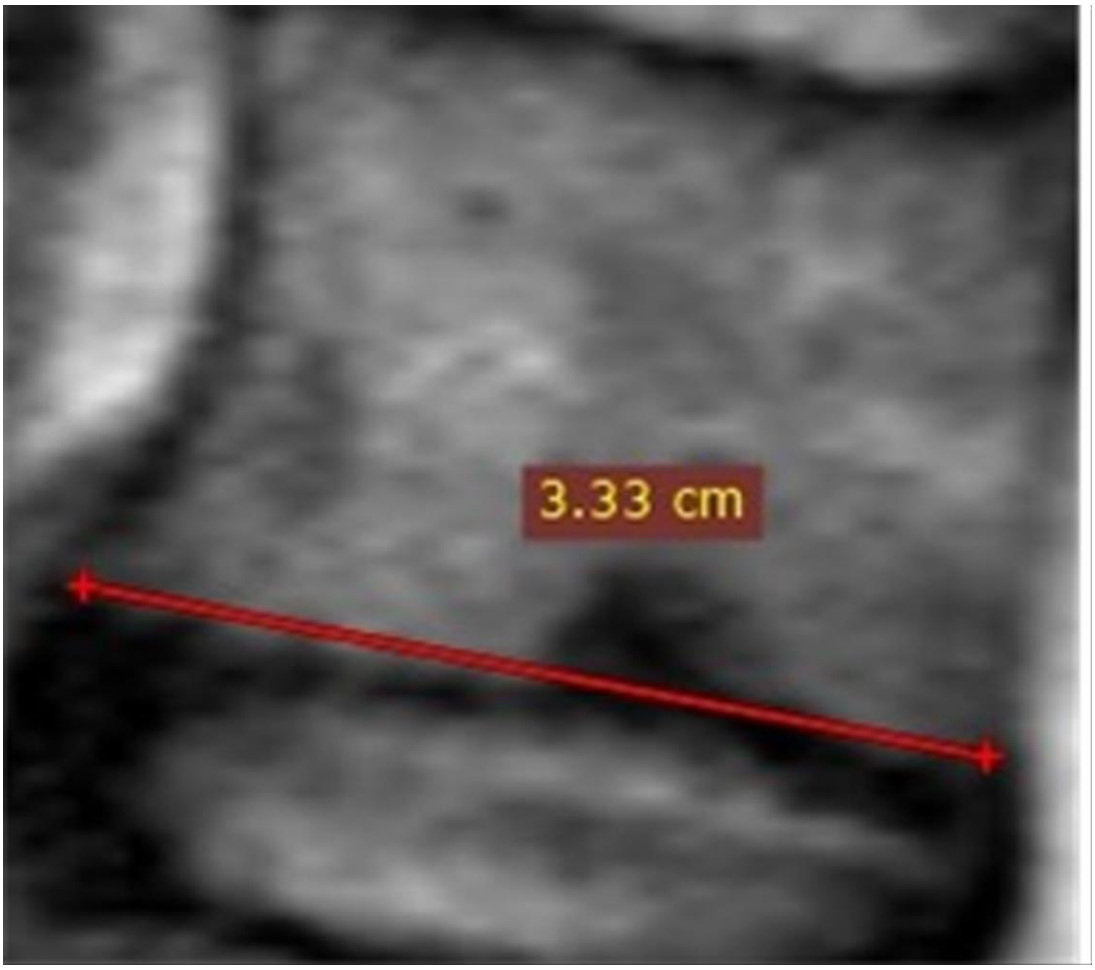


Figure 1C

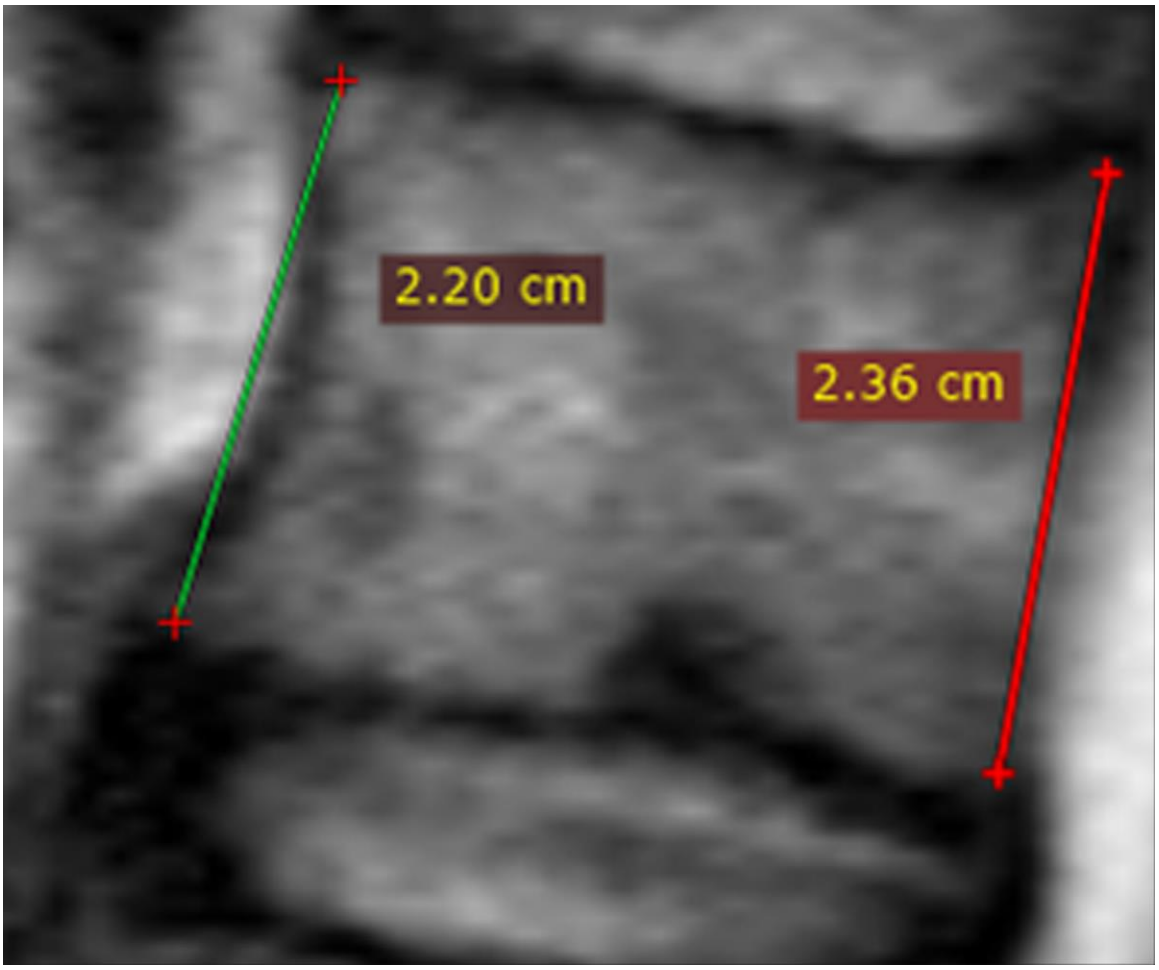


Figure 1D

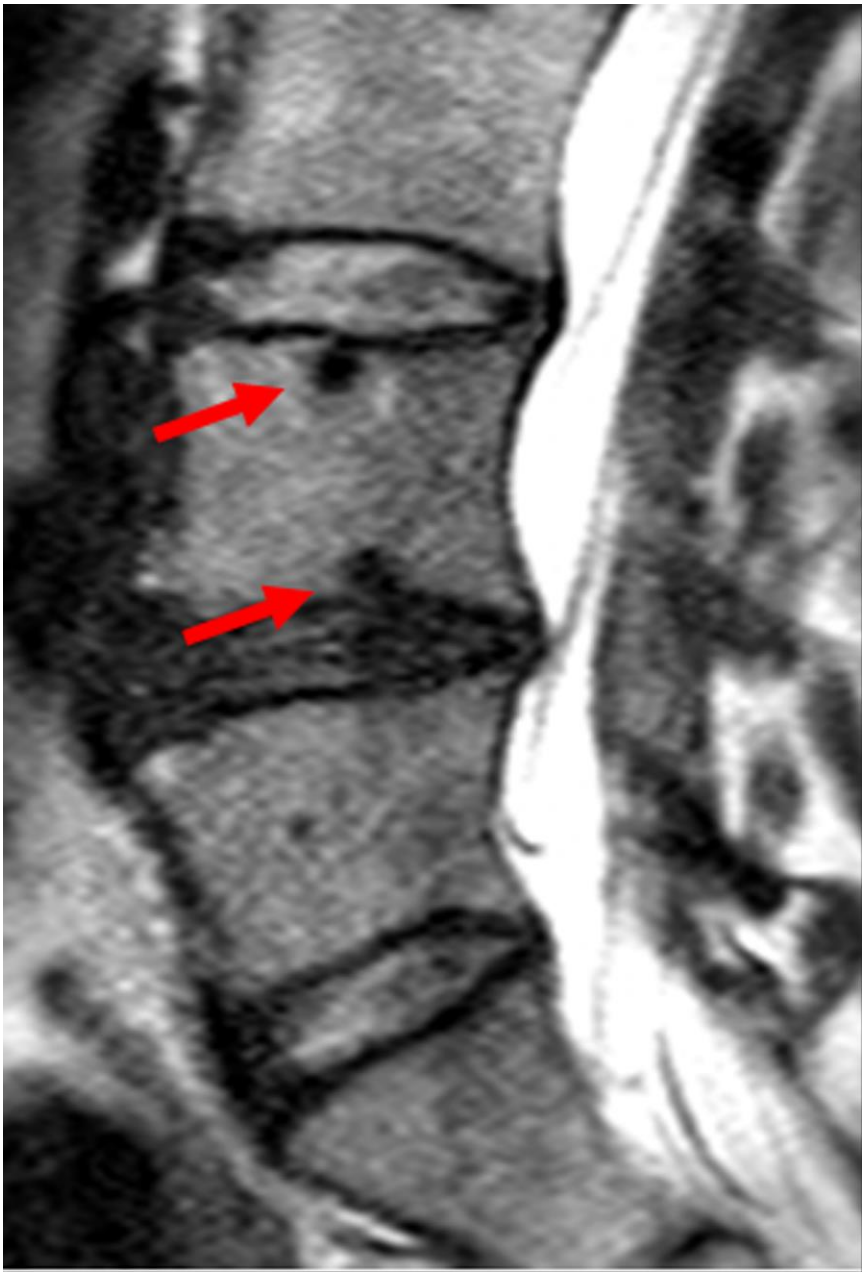
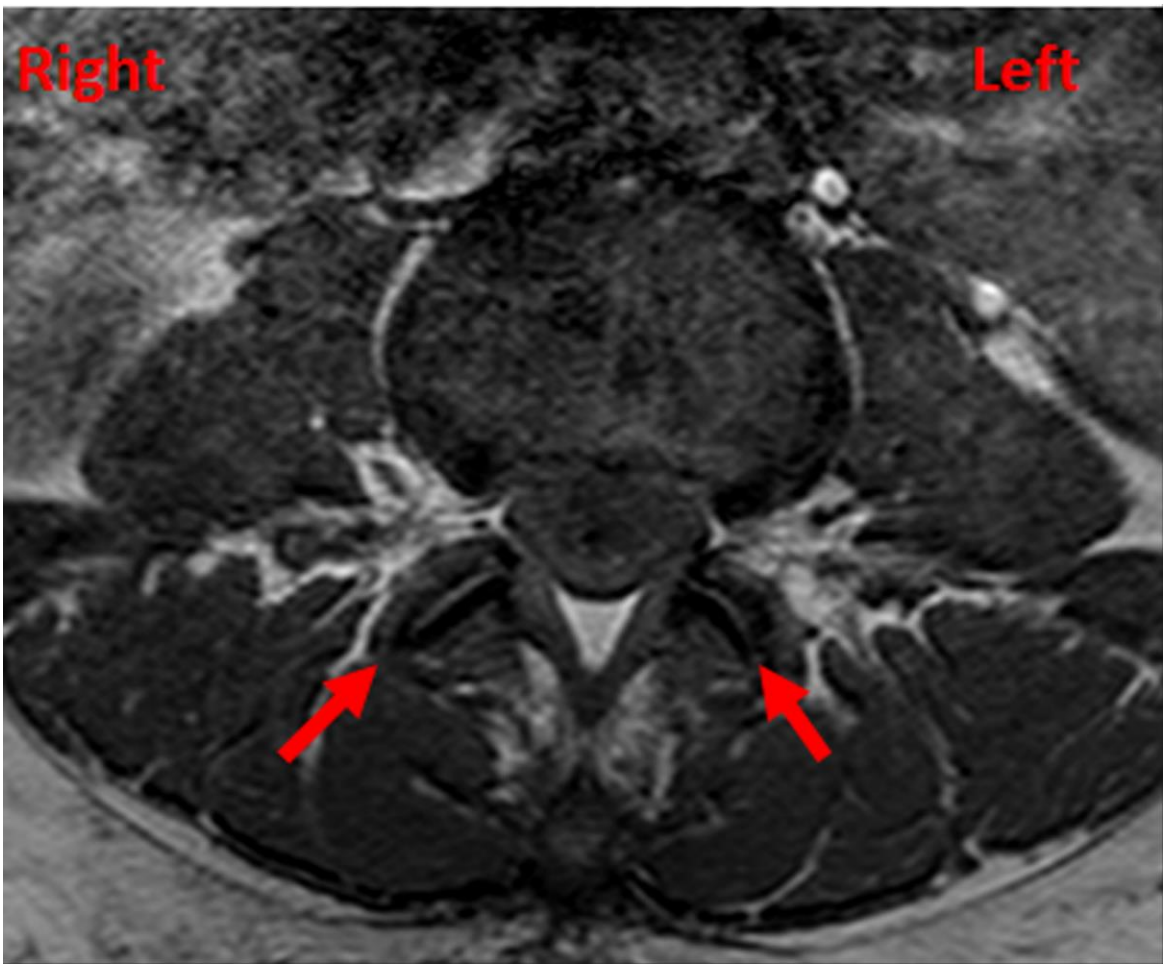


Figure 2A



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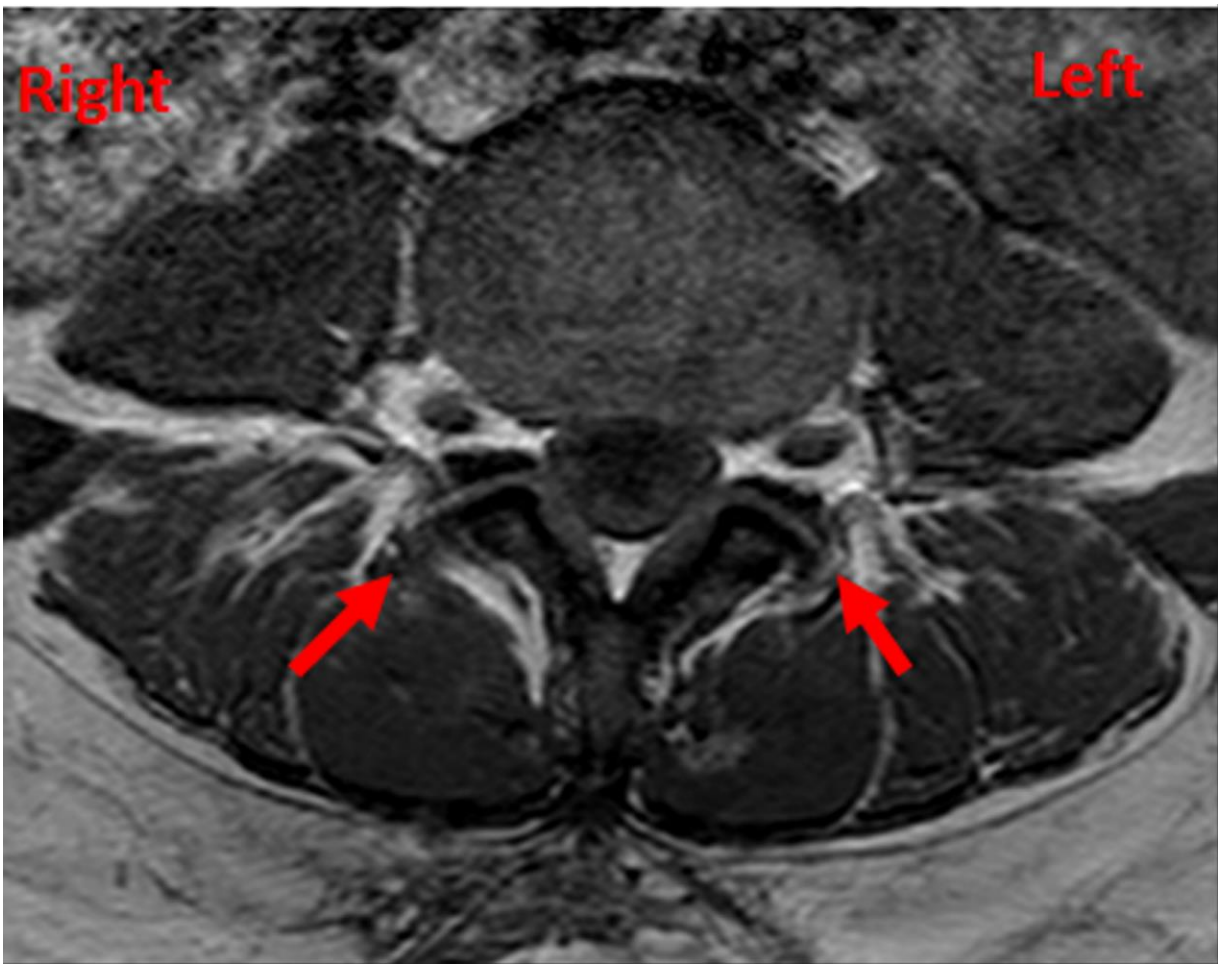

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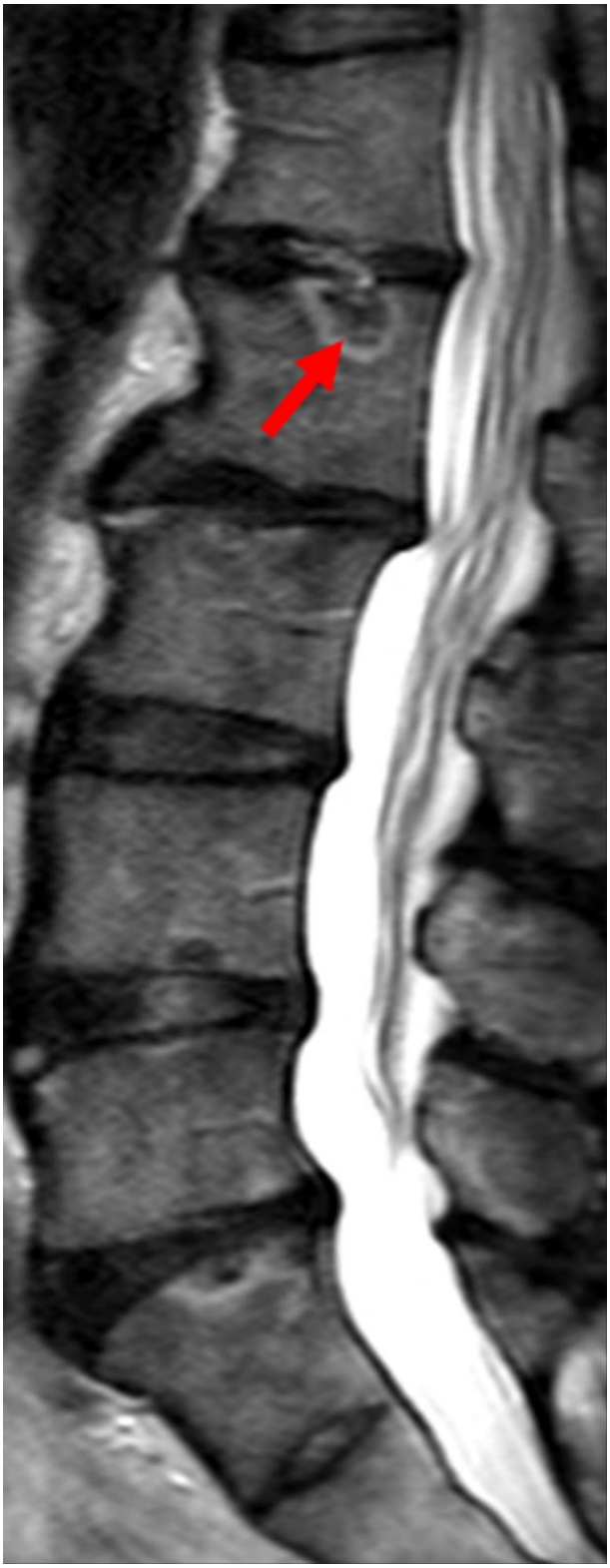

Figure 3A

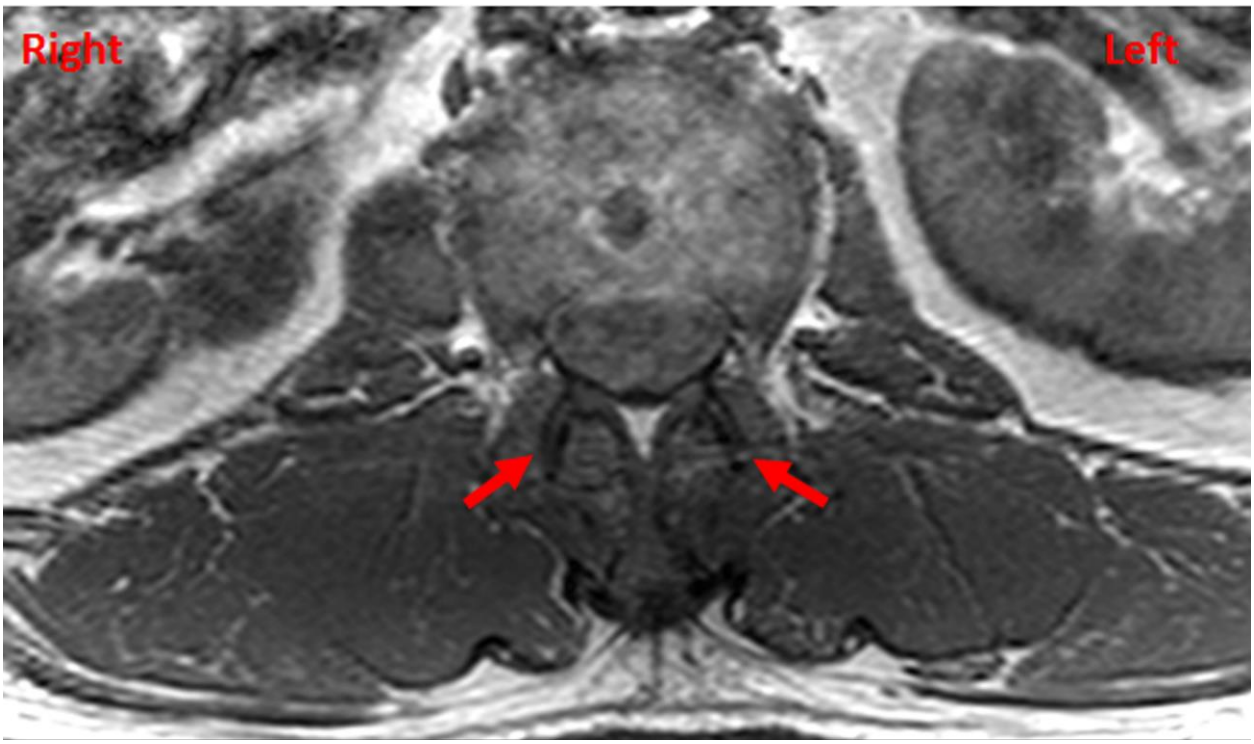

Figure 3B