Correlation analysis between aromatase inhibitor and lumbar intervertebral disc degeneration: a case-control study

Xiangyu Li
The Third Hospital of Hebei Medical University
Xianda Gao
The Third Hospital of Hebei Medical University
Ruoyu Zhao
The Third Hospital of Hebei Medical University
Hengrui Chang
The Third Hospital of Hebei Medical University
Wenyuan Ding (dingwenyuan666@sina.com)
The Third Hospital of Hebei Medical University

Research Article

Keywords: low back pain, intervertebral disc degeneration, estrogen, aromatase inhibitor, breast cancer

Posted Date: April 14th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1544375/v1

Abstract

Background: Hormone level is an important factor affecting intervertebral disc degeneration (IVDD). Aromatase inhibitors (AI) can reduce the production of estrogen in peripheral tissues by inhibiting the activity of aromatase. The objective of this study is to investigate the correlation between AI as endocrine therapy and IVDD in postoperative patients with breast cancer.

Methods: Postmenopausal breast cancer patients treated in the Third Hospital of Hebei Medical University after surgery were retrospectively analyzed. Patients' age, height, weight, menstrual history, basic diseases, postoperative history, postoperative chemotherapy plan and imaging data were collected. Patients were devided into the AI group and the non-AI group according to whether AI were used or not. IVDD was assessed by measuring lumbar lordosis (LL), vertebral CT density, lumbar disc height index (DHI), and modified Pfirrmann grading system. SPSS 20 was used for statistical analysis.

Results: A total of 68 patients were included in the study, including 40 patients in the AI group and 28 patients in the non-AI group. No significant differences were present in age, body mass index (BMI), prevalence of basic diseases, postoperative history, LL and vertebral CT density between the AI group and the non-AI group. Lumbar DHI of L1/2, L2/3 and L3/4 in the non-AI group was higher than that in the AI group ($P = 0.001$, $P = 0.010$ and $P = 0.010$, respectively). But the comparisons of L4/5, L5/S1 DHI and average DHI between the two groups were not significant ($P > 0.05$). The modified Pfirrmann grading of L1/2, L2/3, L3/4 and L4/5 in AI group was higher than that in non-AI group ($P=0.001$, $P=0.017$, $P=0.005$ and $P=0.004$, respectively). However, the comparison of L5/S1 modified Pfirrmann grading between the two groups was not significant ($P > 0.05$).

Conclusions: This study indicates that there may be a positive correlation between the use of AI and lumbar IVDD, which is significant in the upper lumbar spine (L1/2-L3/4).

Background

Intervertebral disc degeneration (IVDD) is the main cause of low back pain in the elderly, and cause huge social and economic burden [1–2]. Although studies have found that IVDD is associated with inflammation, trauma, hormone, genetics and other factors, the specific mechanism of IVDD is still unclear [1–4]. Preliminary clinical studied found that ovariectomy (OVX) resulted in a significant reduction of estrogen level in patients, and promoted the lumbar IVDD in patients in a long period of time [5]. Previous studies confirmed estrogen receptor (ER) expression in intervertebral disc (IVD) tissue by immunohistochemical analysis. And further experiments proved that estrogen can through the NF-κB and PI3K-AKT signaling pathway related to enhance the nucleus pulposus cells (NPCs) against oxidative stress and anti-inflammatory ability, reduce the NPCs apoptosis, improve the survival of the NPCs and extracellular matrix (ECM) expression. At the same time, this was confirmed by the rat caudal IVD needle puncture model [4, 6–7]. Therefore, estrogen may be one of the effective molecules to delay IVDD.

Aromatase is a cytochrome P450 enzyme encoded by CYP19A1 gene, which can transform androgen into estrogen [8]. Aromatase promotes estrogen production mainly in the ovaries of premenopausal women, while in postmenopausal women, it occurs in peripheral tissues, including placenta, central nervous system, bone, muscle [8–12]. Our previous high-throughput sequencing results proved the expression of aromatase in NPCs, but there is no relevant study on the role of aromatase and aromatase inhibitors (AI) in IVD tissue. AI are commonly used in endocrine therapy for postmenopausal breast cancer patients. This study evaluated whether application of AI would affect the progression of IVDD by analyzing the clinical data of postmenopausal breast cancer patients, so as to provide clinical evidence for estrogen treatment of IVDD.

Materials And Methods

Patients

Relevant data of postoperative breast cancer patients admitted to the Third Hospital of Hebei Medical University from January 2018 to December 2021 were collected, and divided patients into AI group and non-AI group according to whether AI was used as endocrine therapy. All patients applied the AI according to the drug instructions and the doctor's medical advice.

Inclusion criteria:

1. Postoperative breast cancer patients took AI or those who did not take AI.
2. Patients have complete clinical data, including basic data, pathological data, chemotherapy plan and imaging data.

Exclusion criteria:

1. The patient failed to receive regular chemotherapy treatment after surgery.
2. The patient has a history of spinal trauma, spinal fracture and spinal surgery, which may directly affect the spinal structure.
3. The patient has a history of ovarian tumor or ovariectomy and other factors that may affect estrogen level.

Data Collection And Calculation

Patients' data included age, height, weight, menstrual history, postoperative history of breast cancer, pathological data, postoperative chemotherapy plan and history of basic diseases (including hypertension, diabetes and coronary heart disease). Imaging data included MRI, CT and X-ray. Body mass index (BMI) was calculated by the formula : BMI = weight(kg) / height(m)^2. Lumbar lordosis (LL) was measured by lumbar X-ray or CT: the angle between the tangent line of L1 and S1 vertebral upper endplate in the lateral lumbar image, as shown in Fig. 1A. Lumbar disc height index (DHI): (intervertebral

leading edge height + posterior edge height) / (intervertebral upper body width + lower body width) * 100%, as shown in Fig. 1B. The degree of degeneration of L1/2-L5/S1 IVDs was assessed by MRI t2-weighted sagittal images using the modified Pfirrmann grading system, as can be observed in Table 1 and Fig. 2. CT was used to measure the density of 5 vertebrae continuously as the average vertebral CT density. All data were measured and evaluated by two independent spinal surgeons and major disagreements were resolved by consensus. This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University and carried out in accordance with the Provisions of the Declaration of Helsinki. All data were obtained with informed consent of the patients.

Table 1
Modified Pfirrmann grading system.

	Strength of nucleus pulposus and inner annulus fibrosus	Signal difference between the inner and outer sides of the posterior annulus fibrosus	Intervertebral disc height
Grade 1	Homogeneous high signal, equivalent to cerebrospinal fluid(CSF)	Obvious	Normal
Grade 2	High signal, lower than CSF, higher than presacral fat	Obvious	Normal
Grade 3	High signal, lower than presacral fat	Obvious	Normal
Grade 4	Moderate signal, higher than the outer annulus fibrosus	Not obvious	Normal
Grade 5	Low signal, equivalent to low outer annulus fibrosus	Not obvious	Normal
Grade 6	Low signal	Not obvious	Reduced less than 30%
Grade 7	Low signal	Not obvious	Reduced 30%~60%
Grade 8	Low signal	Not obvious	Reduced more than 60%

Statistical analysis

SPSS 20 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as mean ± standard deviation (SD). The comparisons of age, BMI, postoperative history, LL,

vertebral CT density, and lumbar DHI was performed by independent sample t-test, whereas the comparisons of modified Pfirrmann grading score and basic diseases was conducted by non-parametric test. $P < 0.05$ was considered statistically significant differences.

Results

A total of 68 postoperative breast cancer patients were included in this study.All patients were postmenopausal women and divided into the AI group (40 patients) and the non-AI group (28 patients) according to whether AI were used or not.

No significant differences were present in age, body mass index (BMI) between the AI group and the non-AI group ($P > 0.05$), as shown in Table 2. And the comparisons of the prevalence of basic diseases (hypertension, diabetes, coronary heart disease) between the two groups were not statistically significant ($P > 0.05$), as can be seen in Table 3.

Table 2
Comparison of patient age, postoperative history and BMI.

	Age(year)	Postoperative history(year)	BMI(kg/m^2)
AI group (n = 40)	59.33 ± 5.42	4.38 ± 2.66	25.73 ± 3.68
Non-AI group (n = 28)	58.00 ± 6.18	4.39 ± 2.28	25.42 ± 2.34
P value	0.353	0.977	0.668

Table 3
Comparison of basic diseases between two groups.

	Hypertension(Yes/No)	Diabetes(Yes/No)	Coronary heart disease(Yes/No)
AI group (n = 40)	15/25	8/32	4/36
Non-AI group (n = 28)	16/12	6/22	4/24
P value	0.112	0.887	0.592

The LL of the AI group (29.78 ± 10.52) was lower than that of the non-AI group (31.61 ± 9.34), but the comparison was not statistically significant ($P > 0.05$). Meanwhile, no significant difference was present in vertebral CT density between the AI group (105.35 ± 40.31) and the non-AI group (119.61 ± 43.56) ($P > 0.05$), as shown in Table 4.

Table 4
Comparison of patient LL and average vertebral CT density.

	Lumbar lordosis(°)	Average vertebral CT density
AI group (n = 40)	29.78 ± 10.52	105.35 ± 40.31
Non-AI group (n = 28)	31.61 ± 9.34	119.61 ± 43.56
P value	0.453	0.170

The DHI of L1/2, L2/3 and L3/4 in the non-AI group were higher than that in the AI group (P = 0.001, P = 0.010 and P = 0.010, respectively). But the comparisons of L4/5, L5/S1 DHI and average DHI between the two groups were not significant (P > 0.05), as displayed in Table 5.

Table 5
Comparison of lumbar DHI for each lumbar disc and average value.

	L1/2	L2/3	L3/4	L4/5	L5/S1	Average
AI group (n = 40)	27.39 ± 5.95	29.26 ± 6.25	31.24 ± 8.12	29.59 ± 9.37	30.01 ± 10.12	29.50 ± 5.55
Non-AI group (n = 28)	31.81 ± 4.17	33.08 ± 5.21	35.97 ± 5.71	32.40 ± 6.25	32.18 ± 6.52	29.37 ± 4.25
P value	0.001*	0.010*	0.010*	0.137	0.322	0.921
*, indicates a significant difference(P < 0.05).						

The modified Pfirrmann grading of L1/2, L2/3, L3/4 and L4/5 in the AI group was higher than that in the non-AI group (P = 0.001, P = 0.017, P = 0.005 and P = 0.004, respectively). However, the comparison of L5/S1 modified Pfirrmann grading between the two groups was not significant (P > 0.05), as shown in Table 6.

Table 6
Comparison of modified Pfirrmann grading for each lumbar disc.

	AI group(n = 40) / non-AI group(n = 28)									
	L1/2		L2/3		L3/4		L4/5		L5/S1	
Grade 1	0	0	1	0	0	0	0	0	0	0
Grade 2	4	7	3	4	1	0	0	0	0	0
Grade 3	16	19	10	12	4	7	3	4	2	6
Grade 4	11	1	11	10	16	18	11	15	13	10
Grade 5	8	1	12	2	16	2	15	8	14	6
Grade 6	0	0	2	0	1	1	7	1	8	5
Grade 7	1	0	1	0	2	0	3	0	3	1
Grade 8	0	0	0	0	0	0	1	0	0	0
P value	0.001*		0.017*		0.005*		0.004*		0.084	
*, indicates a significant difference(P < 0.05).										

Discussion

IVDD is the main cause of low back pain in the elderly. Although IVDD is related to many factors, such as inflammation, trauma, hormones, genetics and other factors, the specific mechanism of IVDD is still unclear [1–4]. Studies have shown that oxidative stress and inflammation may play a key role in the process of IVDD. In recent years, various antioxidant and anti-inflammatory molecules or drugs have become research hotspots in the field of IVDD [3–4, 13]. Previous studies demonstrated the expression of ER in human IVD tissue and found that estrogen can enhance the antioxidant and anti-inflammatory capacity of NPCs, reduce apoptosis of NPCs, and promote the expression of ECM, such as aggrecan and type II collagen. Further studies have shown that estrogen can delay IVDD by activating NF-κB and PI3K-Akt signaling pathways [4, 6–7]. Clinical studies have found that the degree of IVDD in postmenopausal women is higher than that in premenopausal women [4]. And OVX results in a significant decrease in estrogen levels in women and promotes IVDD in a long period of time [5]. Therefore, estrogen may be one of the effective drugs to delay IVDD.

Aromatase is a cytochrome P450 enzyme encoded by the CYP19A1 gene that converts androgens into estrogens. Aromatase promotes estrogen production mainly in the ovaries of premenopausal women. In postmenopausal women, it occurs mainly in peripheral tissues. Aromatase has been found to be expressed in many tissues, including placenta, central nervous system, bone, muscle, etc. AI is currently mainly applied in endocrine therapy for postmenopausal breast cancer patients, which can effectively reduce tumor recurrence and metastasis and improve the survival of patients [8–9]. AI can also cause

side effects, such as AI associated musculoskeletal syndrome (AIMSS), whose main symptoms include aralgia, myalgia, joint stiffness, and tendinopathy. AIMSS has been proposed to be associated with estrogen deficiency in the musculoskeletal and nervous system [10–12]. Our previous high-throughput sequencing results proved the expression of aromatase in NPCs [4], but there is no relevant study on the effect of AI on IVDs. In this study, we analyzed the clinical data of postmenopausal breast cancer patients to evaluate whether application of AI could affect the process of IVDD.

We divided breast cancer patients into the AI group and the non-AI group, based on whether they received AI as endocrine therapy after surgery. No significant difference was present in basic clinical information (age, BMI, postoperative history) and basic diseases (hypertension, diabetes, coronary heart disease) between the two groups.

The physiological curvature of lumbar spine is mainly represented by LL. Previous studies on LL have found that the occurrence of low back pain is related to the reduction of LL.The reduction of LL results in changes in the biomechanical structure of the lumbar spine and exacerbates IVDD [14]. This study showed that although the comparison was not statistically significant in LL between the two groups, the LL of both groups was lower than that of normal adults in previous studies, which may be related to age increase, weight and other factors [15].

Osteoporosis is a common systemic disease in the elderly, especially in postmenopausal women, often resulting in vertebral compression fractures [11]. Bone mineral density (BMD) is an important indicator to evaluate the degree of osteoporosis, but the relationship between BMD and IVDD is not very clear so far, and most studies support the negative correlation between BMD and IVDD [11, 16]. Through autopsy, Wang et al. found that under the influence of removal of peripheral osteophytes and calcification of cartilage endplate, increased vertebral BMD would lead to more severe IVDD [17]. Kaiser et al. used quantitative computed tomography (QCT) to detect regional BMD of L3 vertebral body and evaluate the health status of adjacent L2/3 and L3/4 IVDs, and found that BMD of male and female gradually decreases with age. However, after the exclusion of age, increased BMD was found to be associated with decreased disc height [18]. AI further reduce estrogen levels in tissues by inhibiting aromatase in peripheral tissues, resulting in further bone loss [11]. We measured CT densities of 5 vertebral bodies, and the average vertebral CT density were used to evaluate vertebral BMD. We found that the average vertebral CT density in the AI group was lower than that in the non-AI group, but the comparison was not statistically significant, which may be due to the fact that anti-osteoporosis therapy (calcium and vitamin D agents) in postmenopausal women with breast cancer has somewhat slowed down the bone loss.

Intervertebral height is a parameter that reflects the height of the disc, which decreases when the disc degenerates or herniates. Previous studies have shown that the DHI of patients with lumbar disc herniation (LDH) is lower than that of patients without LDH, which may be caused by the thinning of endplate thickness and the increase of anterior and posterior extension caused by IVDD [19]. Akeda K et al. found that DHI of the elderly was significantly lower within 10 years, accompanied by an increase in Pfirrmann grading [20]. This study showed that L1/2, L2/3 and L3/4 DHI in the AI group were significantly

lower than those in the non-AI group, but No significant differences were present in L4/5 and L5/S1 DHI and average DHI. The reason may be that the lower lumbar spine (L4/5, L5/S1) is a common site of lumbar degenerative diseases such as LDH, which is affected by a variety of factors, such as trauma and strain, and hormone level may not be the dominant factor.

We can compare between the nucleus pulposus and annulus fibrosus signal change through MRI, and use the modified Pfirrmann grading system to evaluate degree of IVDD [4–5, 21]. Previous studies have proved that estrogen level is an important factor affecting IVDD. Wang et al. found that the signal in the T2 weighted imaging of MRI in postmenopausal women was significantly lower than that in premenopausal women (higher modified Pfirrmann grading), indicating more severe disc degeneration [4]. Zhao et al. compared lumbar MRI data of patients undergoing ovariectomy and normal patients, and found that ovariectomy resulted in decreased estrogen level and further accelerated IVDD, manifested by a higher modified Pfirrmann grading [5]. We found that the modified Pfirrmann grading was significantly higher in the AI group, except for L5/S1. This result is similar to that of lumbar DHI, suggesting that long-term AI promote IVDD, which is more remarkable in the upper lumbar spine.

This study also has some limitations. This study is a retrospective cross-sectional study with a small sample size and many interfering factors, which may affect the evaluation of AI for IVDD. Prospective studies with a larger sample size is needed to assess the effect of AI on IVDD with long-term follow-up.

Conclusions

This study indicates that there may be a positive correlation between the use of AI and lumbar IVDD, which is significant in the upper lumbar spine (L1/2-L3/4).

Abbreviations

AI
aromatase inhibitor
AIMSS
aromatase inhibitor associated musculoskeletal syndrome
BMD
bone mineral density
BMI
body mass index
CT
computed tomographic
CSF
cerebrospinal fluid
ER
estrogen receptor

IVDD
intervertebral disc degeneration
MRI
magnetic resonance imaging
NPCs
nucleus pulposus cells
QCT
quantitative computed tomography
LL
lumbar lordosis
DHI
disc height index
OVX
ovariectomy

Declarations

Acknowledgements

Not applicable.

Authors' Contributions

WYD conceived the study. XYL, RYZ and HRC performed data collection and statistical analysis. XYL drafted the manuscript. XYL and XDG revised the manuscript.

Consent for publication

All authors read and approved the final manuscript.

Competing interests

All the authors declare no conflicts of interest regarding this study.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Third Hospital of Hebei Medical University, Shijiazhuang, China. All data were obtained with informed consent of the patients.

Funding

No funding was used in this study.

Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

References

1. Knezevic NN, Candido KD, Vlaeyen JWS, et al. Low back pain. Lancet. 2021 Jul 3; 398(10294): 78–92.
2. Vlaeyen JWS, Maher CG, Wiech K, et al. Low back pain. Nat Rev Dis Primers. 2018 Dec 13; 4(1): 52.
3. Yang S, Zhang F, Ma J, et al. Intervertebral disc ageing and degeneration: The antiapoptotic effect of oestrogen. Ageing Res Rev. 2020 Jan; 57: 100978.
4. Wang H, Li Z, Huo Y, et al. 17β-Estradiol alleviates intervertebral disc degeneration by inhibiting NF-κB signal pathway. Life Sci. 2021 Nov 1; 284: 119874.
5. Zhao Y, Wang H, Li Z, et al. Lumbar Disk Degeneration in Female Patients with and without Ovariectomy: A Case-Control Study. World Neurosurg. 2021 Dec; 156: 68–75.
6. Bai X, Guo X, Zhang F, et al. Resveratrol Combined with 17β-Estradiol Prevents IL-1β Induced Apoptosis in Human Nucleus Pulposus Via The PI3K/AKT/Mtor and PI3K/AKT/GSK-3β Pathway. J Invest Surg. 2021 Aug; 34(8): 904–911.
7. Guo HT, Yang SD, Zhang F, et al. 17β–Estradiol protects against interleukin-1β-induced apoptosis in rat nucleus pulposus cells via the mTOR/caspase-3 pathway. Mol Med Rep. 2019 Aug; 20(2): 1523–1530.
8. Santen RJ, Brodie H, Simpson ER, et al. History of aromatase: saga of an important biological mediator and therapeutic target. Endocr Rev. 2009 Jun; 30(4): 343–75.
9. Maughan KL, Lutterbie MA, Ham PS. Treatment of breast cancer. Am Fam Physician. 2010 Jun 1; 81(11): 1339–46.
10. Hyder T, Marino CC, Ahmad S, et al. Aromatase Inhibitor-Associated Musculoskeletal Syndrome: Understanding Mechanisms and Management. Front Endocrinol (Lausanne). 2021 Jul 27; 12: 713700.
11. Rachner TD, Göbel A, Jaschke NP, et al. Challenges in Preventing Bone Loss Induced by Aromatase Inhibitors. J Clin Endocrinol Metab. 2020 Oct 1; 105(10): dgaa463.
12. Tenti S, Correale P, Cheleschi S, et al. Aromatase Inhibitors-Induced Musculoskeletal Disorders: Current Knowledge on Clinical and Molecular Aspects. Int J Mol Sci. 2020 Aug 6; 21(16): 5625.
13. Huo Y, Yang D, Lai K, et al. Antioxidant Effects of Resveratrol in Intervertebral Disk. J Invest Surg. 2021 Oct 20: 1–10.
14. Yang Z, Xie F, Zhang J, et al. An analysis of radiographic parameters comparison between lumbar spine latericumbent and full-length lateral standing radiographs. Spine J. 2017 Dec; 17(12): 1812–1818.
15. Boissière L, Takemoto M, Bourghli A, et al. Global tilt and lumbar lordosis index: two parameters correlating with health-related quality of life scores-but how do they truly impact disability? Spine J.

2017 Apr; 17(4): 480–488.
16. Khosla S, Hofbauer LC. Osteoporosis treatment: recent developments and ongoing challenges. Lancet Diabetes Endocrinol. 2017 Nov; 5(11): 898–907.
17. Wáng JQ, Káplár Z, Deng M, et al.Thoracolumbar Intervertebral Disc Area Morphometry in Elderly Chinese Men and Women: Radiographic Quantifications at Baseline and Changes at Year-4 Follow-up. Spine (Phila Pa 1976). 2018 May 15; 43(10): E607-E614.
18. Kaiser J, Allaire B, Fein PM, et al. Correspondence between bone mineral density and intervertebral disc degeneration across age and sex. Arch Osteoporos. 2018 Nov 12; 13(1): 123.
19. Schwab F, Lafage V, Patel A, et al. Sagittal plane considerations and the pelvis in the adult patient. Spine (Phila Pa 1976). 2009 Aug 1; 34(17): 1828–33.
20. Akeda K, Yamada T, Inoue N, et al. Risk factors for lumbar intervertebral disc height narrowing: a population-based longitudinal study in the elderly. BMC Musculoskelet Disord. 2015 Nov 9; 16: 344.
21. Krug R, Joseph GB, Han M, et al. Associations between vertebral body fat fraction and intervertebral disc biochemical composition as assessed by quantitative MRI. J Magn Reson Imaging. 2019 Oct; 50(4): 1219–1226.

Figures

Figure 1

Lumbar lordosis (LL) and lumbar disc height index (DHI) measurements.

(A) LL: The angle between the tangent line of the upper endplate of the L1 vertebral body and S1 vertebral body in the lateral lumbar spine. (B) DHI: (intervertebral leading edge height + posterior edge height) / (intervertebral upper body width + lower body width) * 100%, where a is the intervertebral upper body width, b is the intervertebral lower body width, c is the intervertebral anterior edge height, and d is the intervertebral posterior edge height.

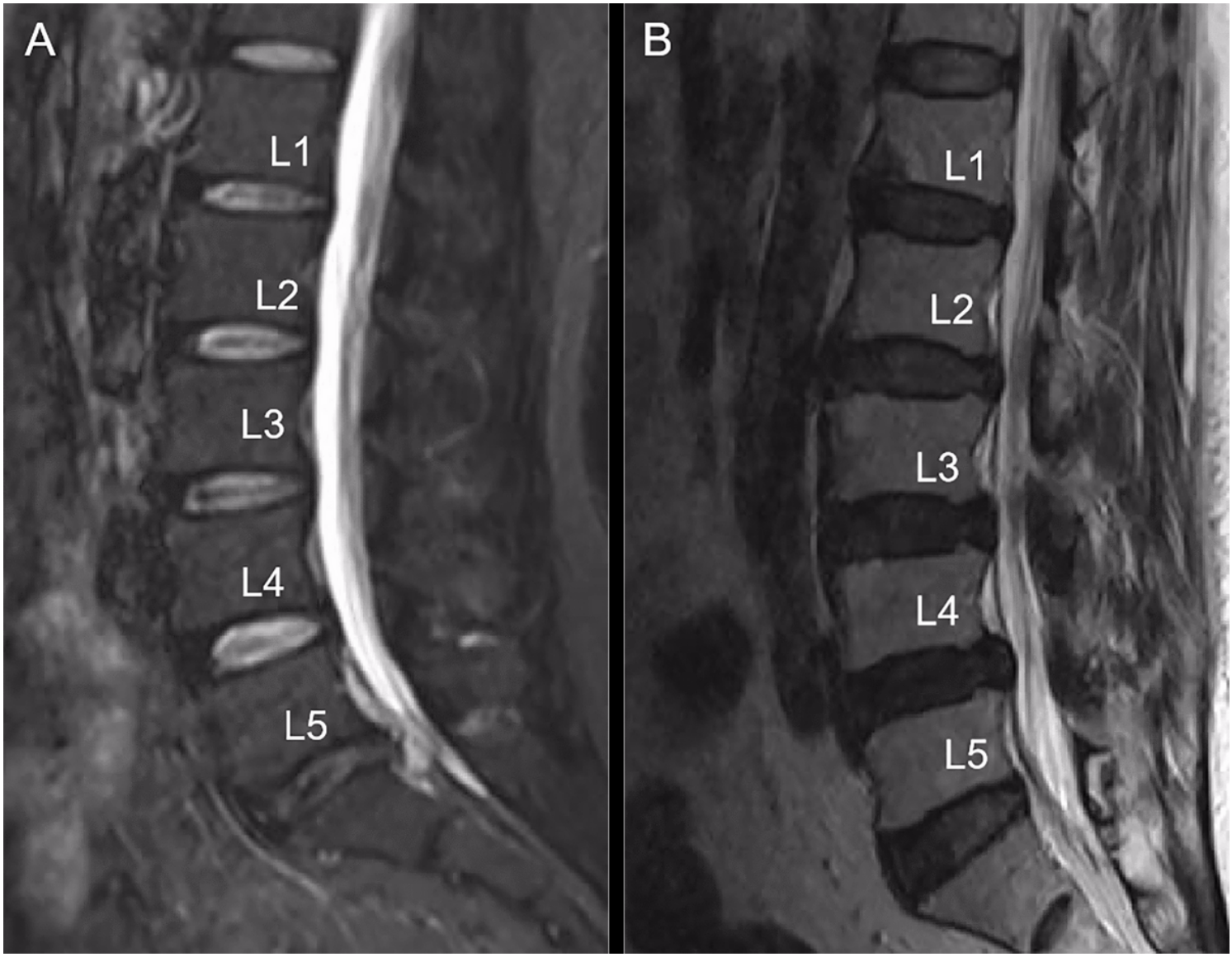

Figure 2

MRI T2-weighted sagittal images were used to assess the degree of IVDD at the L1/L2–L5/S1 levels by the modified Pfirrmann grading system.

(A) The modified Pfirrmann grading scores from L1/2 to L5/S1 were 3, 3, 3, 3, and 5 for a patient in the non-AI group. (B) The modified Pfirrmann grading scores from L1/2 to L5/S1 were 4, 4, 5, 5, and 4 for a patient in the AI group.