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ORIGINAL ARTICLE

Expression of lipid metabolism and cartilage degeneration-related factors in lumbar vertebral endplate Modic changes

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ABSTRACT

Objectives: This study aims to investigate the relationship between the expression of lipid metabolism and cartilage degeneration-related factors and Modic changes (MCs) of lumbar vertebral.

Patients and methods: This prospective study included a total of 10 patients (6 males, 4 females; mean age: 60.4±8.7 years; range 51 to 82 years) who underwent lumbar interbody fusion surgery due to degenerative lumbar diseases (MC group), and 10 control patients (4 males, 6 females; mean age: 49.7±9.8 years; range, 42 to 76 years) with lumbar burst fractures (non-MC group) between January 2020 and December 2022. Clinical imaging data and cartilage tissues were collected to observe cartilage characteristics and pathological changes. The relative expression levels of lipid metabolism-related inflammatory factors matrix metalloproteinase-1 (MMP-1), a disintegrin and metalloproteinase with thromboSpondin motifs-5 (ADAMTS-5), and aggrecan in cartilage were detected by quantitative polymerase chain reaction (qPCR). The relative expression levels of MMP-1 and ADAMTS-5 proteins in cartilage tissues were detected by Western blotting.

Results: There were no significant differences in the baseline characteristics between the two groups. The color and transparency of the endplate cartilage in the control group were significantly better than those in the MCs group. Radiographic and hematoxylin-eosin (HE) staining of the endplate cartilage tissues showed that the extracellular matrix was higher in the control group than in the MCs group ($p<0.05$). Compared to the control group, qPCR analysis showed higher expression of MMP-1 and ADAMTS-5 in the MCs group, while aggrecan expression was lower ($p<0.05$). Western blot analysis showed that both MMP-1 and ADAMTS-5 expression were higher in the MCs group than in the control group ($p<0.05$).

Conclusion: Lipid metabolism and cartilage degeneration-related inflammatory factors exist in the vertebral endplate of the patients with degenerative lumbar diseases, and the upregulation of MMP-1 and ADAMTS-5 may be related to MCs and endplate degeneration.

Keywords: A disintegrin and metalloproteinase with thromboSpondin motifs-5, aggrecan, lumbar vertebral endplates, modic changes, matrix metalloproteinase-1.

The lumbar vertebral endplate is a soft tissue structure that connects adjacent vertebral bodies, and its health status is crucial for spinal stability and function. However, with age, many people develop degenerative diseases of the lumbar vertebral endplate.[1] Clinical manifestations mainly include symptoms such as low back pain, sciatica, and radiating leg pain, with intervertebral disc degeneration being a key factor.[2] The degeneration of intervertebral discs leads to a reduction in the intervertebral space and increases the risk of compromised spinal stability. This loss of stability can result in spinal deformity and functional impairment, leading to symptoms such as low back pain. Additionally, disc degeneration can also cause disc herniation or protrusion, compressing

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the surrounding nerve roots or spinal cord, thereby resulting in symptoms such as sciatica and radiating leg pain, severely affecting patients' quality of life.[3]

Among them, Modic changes (MCs) in the lumbar spine are an important characteristic that affects lumbar health.[4] Epidemiological studies have shown a growing trend of MCs worldwide.[5-7] It has been reported that the prevalence of MCs in asymptomatic individuals is approximately 0.5 to 6%, while it is higher at 43% in individuals with low back pain.[8-10] This condition is not only common among middle-aged and elderly populations but also shows a trend of onset at younger ages. The harm of MCs is primarily manifested in causing chronic low back pain, affecting patients' quality of life, and increasing the burden on healthcare systems. The etiology and pathophysiological dynamics of MCs are complex. Currently, it is still unclear why some patients with disc herniation and degeneration develop MCs, while others do not. Possible factors may include biomechanics, autoimmune factors, low-grade bacterial infection, and genetic factors.[10]

The occurrence mechanism of MCs is a complex process influenced by multiple factors.[11,12] Lipid metabolism-related factors include enzymes, transport proteins, receptors, hormones, transcription factors, and cytokines, among others.[13] These factors play crucial roles in regulating lipid metabolism processes, participating in key steps such as synthesis, breakdown, transport, and storage of lipids. Through their interactions, they collectively regulate the balance of lipid metabolism, which affects the overall health status of the body. A deeper understanding of the relationships between these factors can reveal the pathogenesis of MCs and provide important insights for their prevention and treatment.[14] Initiation of collagen breakdown in plaques requires matrix metalloproteinase (MMP) family members including MMP-1, MMP-8, and MMP-13. The MMP-1 is considered to be involved in lipid metabolism.[15] In addition, previous studies have confirmed that a disintegrin and metalloproteinase with thromboSpond motifs-5 (ADAMTS-5) play critical roles in cartilage endplates degeneration.[16] It has also been shown that decreased expression of aggrecan leads to degeneration of endplate chondrocytes.[17] However, the expression pattern of lipid metabolism and cartilage degeneration-related factors in the cartilage endplates of intervertebral discs has not been understood yet. Therefore, in the present study, we aimed to explore the relationship between the expression of lipid metabolism and cartilage degeneration-related factors and MCs of lumbar vertebral.

PATIENTS AND METHODS

Study design and study population

This single-center, prospective study was conducted at Affiliated Hospital of Hebei University Department of Orthopaedic Surgery, between January 2020 and December 2022. A total of 10 patients (6 males, 4 females; mean age: 60.4±8.7 years; range 51 to 82 years) who underwent lumbar interbody fusion surgery for lumbar degenerative disease were included. Inclusion criteria were as follows: patients who underwent lumbar interbody fusion surgery due to degenerative lumbar diseases, including lumbar spinal stenosis with or without mild degenerative spondylolisthesis, lumbar degenerative deformity, or adjacent segment degenerative diseases; and availability of complete clinical data. Exclusion criteria were as follows: having a history of cervical trauma or surgery; previous use of hypoglycemic or lipid-lowering drugs; and concomitant systemic diseases such as spinal tumors, spinal infections, or rheumatoid arthritis. A written informed consent was obtained from each patient. The study protocol was approved by the Affiliated Hospital of Hebei University Ethics Committee (date: 25.10.2022, no: Ke2022-115-1). The study was conducted in accordance with the principles of the Declaration of Helsinki.

These 10 patients constituted the MC group, while the control group consisted of 10 patients (4 males, 6 females; mean age: 49.7±9.8 years; range, 42 to 76 years) with lumbar burst fractures (non-MC group). The control group underwent anterior bone graft fusion and internal fixation surgery, with the removal of intervertebral disc tissue. Moreover, they were matched to the MCs group for age, sex, or comorbidities. Magnetic resonance imaging (MRI) examination indicated normal vertebral endplate signals and the degree of disc degeneration was classified as Grade 1-2. The degree of disc degeneration was determined by the Pfirrmann grading system established by Pfirrmann et al.[18] based on MRI, which classifies the degree of disc degeneration into five grades based on the sagittal T2-weighted images of the lumbar discs. Modic changes were determined with reference to the criteria proposed by Michael T. Modic et al.[19] The intervertebral discs of the patients were collected during the surgery. Clinical information, imaging

TABLE I
Primer sequences

Primer	Primer sequence (5'to3')
MMP-1-F	GGGGCTTTGATGTACCCTAGC
MMP-1-R	TGTCACACGCTTTTGGGGTTT
ADAMTS5-F	GGCCTCCATCGCCAATAGG
ADAMTS5-R	GGATAGCTGCATCGTAGTGCT
Aggrecan-F	GTGCCTATCAGGACAAGGTCT
Aggrecan-R	GATGCCTTTCACCACGACTTC
GAPDH-F	GGAGCGAGATCCCTCCAAAAT
GAPDH-R	GGCTGTTGTCATACTTCTCATGG

MMP-1: Matrix metalloproteinase-1; ADAMTS-5: A disintegrin and metalloproteinase with thromboSpondin motifs-5; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

data, and residual cartilage tissue after surgery were collected for all patients.

Specimen collection

Under sterile conditions, the excised lumbar cartilage tissue from the surgery was collected and washed with sterile saline. The samples were fixed in 4% paraformaldehyde for more than 12 h, followed by decalcification and dehydration and, then, embedded in paraffin for continuous sectioning at a thickness of 5 μm. Subsequently, hematoxylin-eosin (HE) staining was performed.

Quantitative polymerase chain reaction (qPCR)

The tissue fragments were ground to pieces in a glass homogenizer on ice and, then, centrifuged at 4°C and 6,000 rpm for 2 min, and the supernatant was discarded. Then, 1 mL of TRIzol™ (Tengen Biochemical Technology Co., Beijing, China) and 200 μL of chloroform were added and incubated before centrifugation at 4°C and 12,000 rpm for 15 min. The supernatant was transferred to pre-cooled isopropanol (500 μL) and incubated for 10 min, followed by centrifugation at 4°C and 12,000 rpm for 10 min. The supernatant was discarded and 1 mL of 75% ethanol was added. The mixture was inverted, centrifuged, and incubated on ice for 2 to 5 min to allow ethanol evaporation. The ribonucleic acid (RNA) pellet was dissolved in RNAase-free water, and 1 μL of RNAase inhibitor was added. Complementary deoxyribonucleic acid (cDNA) was synthesized using the FastKing One Step Genomic DNA Removal Kit (Tengen Biochemical Technology Co., Beijing, China) and the cDNA First Strand Synthesis Premix Kit (Tengen Biochemical Technology Co., Beijing, China). The quantitative polymerase chain reaction (qPCR) reactions were performed using the SuperReal Fluorescence Quantitative Premix Kit (Tengen Biochemical Technology Co., Beijing, China). The StepOnePlus™ real-time PCR system was used, and the relative quantification analysis of the data was performed using the $2^{-\triangle\triangle CT}$ method. The primer sequences are shown in Table I.

Western blot analysis

Total protein was extracted from the tissues using radioimmunoprecipitation assay (RIPA) lysis buffer (Thermo Scientific, MA, USA) supplemented with a protease inhibitor cocktail. The total protein was quantified using the BCA method (Thermo Scientific, MA, USA). Subsequently, 10% SDS-PAGE was used to separate the total protein. The proteins were, then, transferred onto a polyvinylidene difluoride (PVDF) membrane. After blocking the PVDF membrane with 5% BSA at room temperature for 2 h, the membrane was incubated overnight at 4°C with primary antibodies targeting β-actin (Huabio, 1:5000), ADAMTS-5 (Abcam, 1:250), and MMP-1 (affinity, 1:1000). After washing with TBST, the membrane was incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies at room temperature for 2 h. Following another round of TBST washing, the membrane was visualized and imaged using an ECL reagent (Thermo Scientific, MA, USA) and a

TABLE II
Baseline characteristics of patient and control groups

	MC group		Non-MC group		
	n	Mean±SD	n	Mean±SD	*p*
Age (year)		60.4±8.7		59.7±9.8	0.875
Sex					0.419
Male	5		4		
Female	5		6		
Pfirrmann grade		4.6±0.49		1±0	**0.000**

MC: Modic change; SD: Standard deviation.

chemiluminescence imaging system. Quantitative analysis was performed using ImageJ version 1.8.0 software (National Institutes of Health, USA).

Statistical analysis

The sample size of this study was calculated as described by Zhang et al.[20] Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Continuous data were presented in mean ± standard deviation (SD) or median (min-max), while categorical data were expressed in number and frequency. Graphs were generated using the GraphPad Prism version 6.0 software (GraphPad Software Inc., CA, USA). The t-test was used to analyze continuous data, and the chi-square (χ^2) test was used for categorical data. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 20 patients were included in this study, with 10 patients in the MC group and 10 patients in the non-MC group. In this study, the patients in MCs group belonged to Modic II and there were no patients with Modic I and III. There were no statistically significant differences in age distribution or sex between the two groups (p>0.05). However, there was a statistically significant difference in Pfirrmann grades between the two groups (p>0.05) (Table II).

Pathology of cartilage tissue

The final cartilage samples from both the non-MC group and the MC group exhibited a clear and translucent color. Imaging and HE staining of the final cartilage tissue in both groups showed that the extracellular matrix (ECM) was higher in the non-MC group compared to the MC group (p<0.05). The non-MC group had a uniform ECM and small round chondrocytes, while the MC group showed a fibrotic and sclerotic ECM with fewer chondrocytes (p<0.05) (Figure 1).

Changes in lipid metabolism-related factors

In this study, qRT-PCR was used to measure the expression of MMP-1, ADAMTS-5, and aggrecan in the final cartilage samples from both groups. The results showed that MMP-1 and ADAMTS-5 were upregulated in the MC group compared to the non-MC group, while aggrecan was downregulated in the MC group compared to the non-MC group. Additionally, Western blot results confirmed the upregulated expression of MMP-1 and ADAMTS-5 in cartilage tissue (Figure 2).

DISCUSSION

The current understanding of the etiology of osteoarthritis involves how genetic, metabolic, biomechanical, and lifestyle factors contribute to the development of the disease.[21] In this study, we specifically investigated the expression of

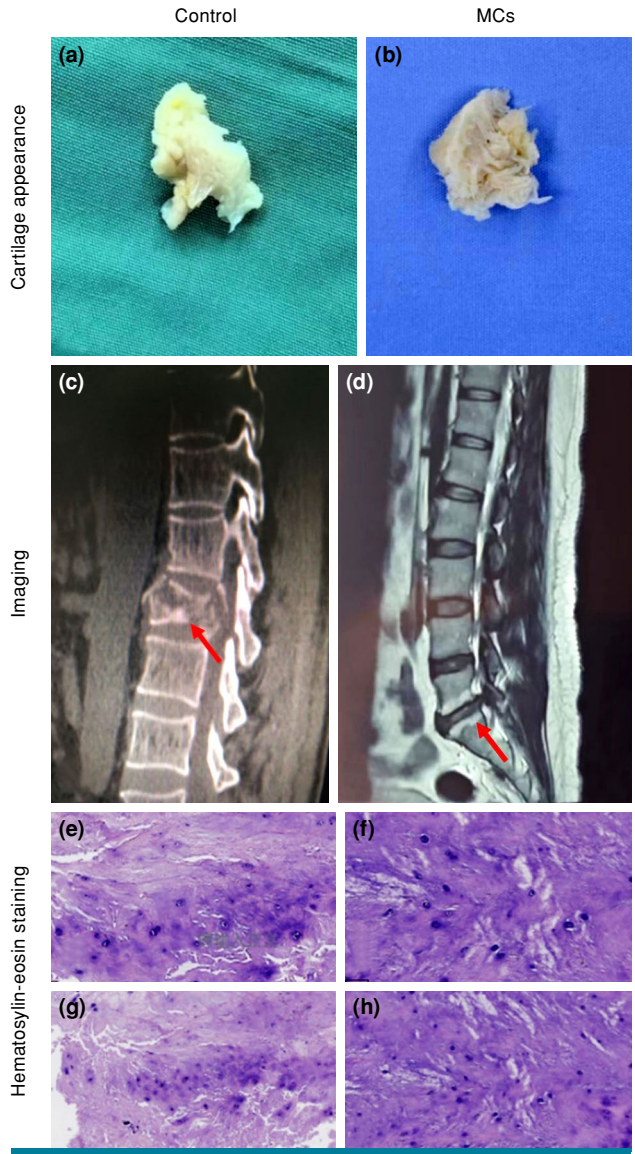


FIGURE 1. (a, b) Cartilage macroscopic photos of non-MCs and MCs groups. **(c, d)** CT image of non-MCs patient and MRI image of MCs patient. Red arrows indicate sites of fracture and disc Modic changes. **(e, f)** 50× HE staining of the cartilage tissue. **(g, h)** 100× HE staining of the cartilage tissue. The non-MC group had a higher extracellular matrix than the MC group. The non-MC group had a homogeneous extracellular matrix and small round chondrocytes, whereas the MC group showed a fibrotic and sclerotic extracellular matrix with fewer chondrocytes.
MCs: Modic changes; CT: Computed tomography.

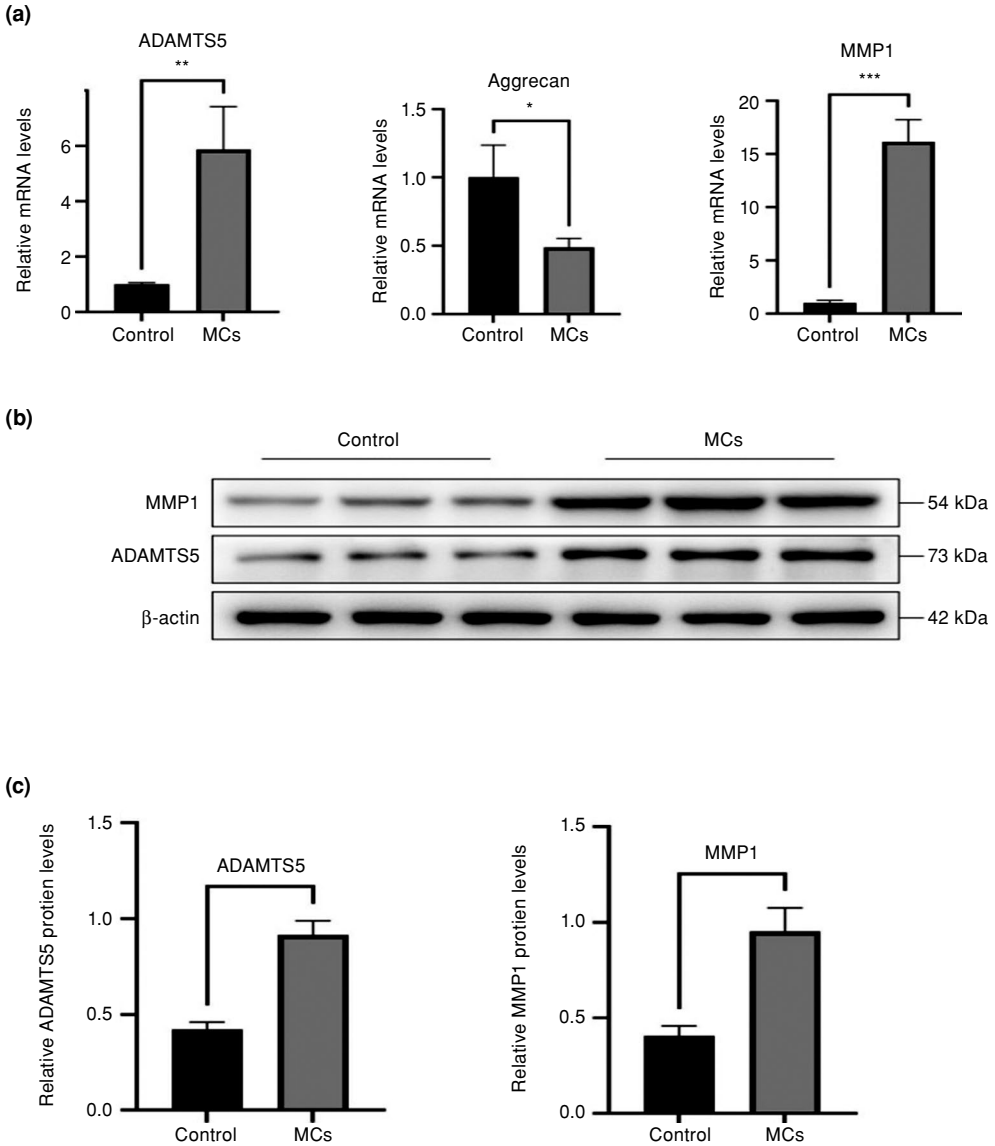


FIGURE 2. Changes in metabolism-related factors. **(a)** qPCR results; **(b)** Representative Western blot bands; **(c)** Statistical analysis of Western blot results.

qPCR: Quantitative polymerase chain reaction; ADAMTS-5: A disintegrin and metalloproteinase with thromboSpondin motifs-5; MMP-1: Matrix metalloproteinase-1; MCs: Modic changes.

lipid metabolism-related factors in the vertebral endplate and their relationship with MCs. Based on the HE-stained photographs of cartilage tissue in both groups, we observed that the cartilage of the vertebral endplate in the non-MC group appeared more translucent and had a richer ECM compared to the MC group; and these findings suggest that cartilage endplate ECM degradation is an important process of degeneration.[22]

At the molecular level, the present study found higher expression levels of MMP-1 and lower expression levels of aggrecan in the MC group. This indicates that the expression of lipid metabolism-related factors in the vertebral endplate may be associated with the occurrence of MCs. The MMP-1 is an important protease that plays a critical role in tissue repair and inflammation processes.[23,24] The MMP-1 promotes degenerative changes in intervertebral disc tissue by degrading collagen and is involved in the regulation of inflammatory responses. The ADAMTS-5 is another important protease associated with MCs, and it participates in the degenerative changes of intervertebral disc

tissue through the degradation of proteoglycans.[25] Furthermore, ADAMTS-5 may further exacerbate the development of MCs by regulating the expression of inflammatory factors.[26] Aggrecan, which is highly expressed in cartilage and intervertebral disc tissue, is crucial for maintaining the structure and function of the intervertebral disc.[27] Degradation and loss of aggrecan are common phenomena in patients with MCs. Additionally, MMP-3, MMP-9, tissue inhibitor of metalloproteinase-3 (TIMP-3), interleukin (IL)-1α, and IL-1β have been considered to play a role in the process of cartilage endplate degeneration.[20] Combining other research findings with the results of this study, lipid metabolism-related factors such as MMP-1 and ADAMTS-5 may promote the degradation of aggrecan, thereby leading to further degenerative changes in intervertebral disc tissue and exacerbating the development of MCs. A study of blood metabolism in a southern Chinese population[28] found that the mean diameter of very-low-density lipoprotein (VLDL)/low-density lipoprotein (LDL) particles and cholesteryl esters/phospholipids in large LDL were important biomarkers of MCs, and that a decrease in the mean diameter of VLDL may contribute to the development of MCs. In line with our finding, this study also suggested the potential associations of lipids and MCs.

The mechanism of MCs involves biomechanical and biochemical alterations resulting from degeneration and rupture of the intervertebral disc, which stimulate inflammation, lipid metabolism, and sclerosis processes in the adjacent vertebral bone marrow.[29,30] The structural and functional decline of the intervertebral disc, particularly damage to the annulus fibrosus, leads to abnormal loading on the vertebral body, causing changes in the bone marrow environment.[31] Additionally, degeneration of the intervertebral disc can lead to the release of inflammatory cytokines and enzymes (such as MMPs and ADAMTS-5), which further degrade cartilage and intervertebral disc tissue, exacerbating inflammation and degenerative changes in the bone marrow.[32] Specifically, degeneration of the annulus fibrosus and nucleus pulposus leads to the degradation of ECM components such as proteoglycans and collagen, which is facilitated by MMPs and ADAMTS family enzymes.[33] Among them, ADAMTS-5 is known to be upregulated and active in degenerated intervertebral discs, specifically degrading proteoglycan aggrecan, leading to the loss of nucleus pulposus hydration characteristics and mechanical properties. This degradation of ECM further promotes inflammation and functional decline in the cellular environment. As for other histological alterations of MCs, Okano et al.[34] analyzed the intervertebral discs of patients with quantitative computed tomography (QCT) and found that MCs were significantly associated with an increase in vertebral trabecular volumetric bone mineral density (vBMD). Wang et al.[35] found that bone tissue macrophages were involved in the pathological process of endplate osteosclerosis in MCs by studying 30 patients with MCs and animal experiments, and there were increased macrophages in the subchondral bone tissue of the endplates of patients with MCs.

Despite achieving some preliminary results, there are certain limitations that need to be addressed. First, the sample size of this study is relatively small and derived from a single center; therefore, the generalizability of the results needs to be validated in larger studies. Second, this study is purely observational, and the specific mechanisms of lipid metabolism-related factors have not been thoroughly investigated. Subsequent studies can further validate and explore their mechanisms through cellular experiments or animal models.

In conclusion, to the best of our knowledge, this is the first study to investigate the expression of factors related to lipid metabolism and cartilage degeneration in lumbar vertebral endplate MCs. The results of this study indicate that lipid metabolism-related factors such as MMP-1 and ADAMTS-5 may contribute to the down-regulation of aggrecan expression, leading to degradation of ECM components and further degenerative changes in disc tissues, exacerbating the development of MCs. These findings provided additional useful information to clarify the specific expressions of factors related to lipid metabolism and cartilage degeneration in the cartilage endplates of intervertebral discs among patients with degenerative lumbar diseases. Our study contributes to further understanding of the pathogenesis of lumbar degenerative diseases and provides accurate molecular targets for the treatment of these diseases. In future research, we can further investigate the regulatory mechanisms of lipid metabolism-related factors in the vertebral endplate and explore potential interventions, such as pharmacological treatments targeting lipid metabolism-related factors, to delay or reverse the process of endplate degeneration. Additionally, considering the interaction with other factors such as genetics and environment can provide a more comprehensive understanding of the pathogenesis of endplate degeneration in the lumbar spine.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Study conception and design: L.C.J., L.D.; Data collection: Y.X.W., S.S.S.; Data analysis and interpretation: R.B., H.Y.; Drafting of the article: all authors. Critical revision of the article: all authors.

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