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RESEARCH ARTICLE

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Links among MRI features in paraspinal muscles, inflammatory processes, and related back pain in patients with lumbar disc herniation

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Abstract

Background: Recent studies have provided evidence that structural changes in paraspinal muscles are associated with intervertebral disc degeneration (IDD), ubiquitous with low back pain (LBP), and potentially thought to be regulated by inflammatory processes. However, the links remain unclear.

Objective: The aims of this study were to investigate structural changes in paraspinal muscles that differed in healthy and lumbar disc herniation (LDH) patients, and LDH patients with and without LBP, and to determine the link with the expression of inflammatory marker(s).

Methods: Cross-sectional areas (CSAs) and fatty degeneration of muscles were measured in this prospective cohort study. Multifidus muscle (MM) tissue was procured from included individuals undergoing surgery. Gene expression was quantified using qPCR assays. Independent *t*-test, Chi-square, and Spearman correlation were used for evaluating the links among structural changes, expression of inflammatory markers, and clinical outcomes.

Results: Functional CSA and fatty degeneration of MM were larger in healthy group than LDH group. A significant increase in fat infiltration in MM in LBP group than in non-LBP group. TNF-alpha (TNF-α) was 28-fold greater in high-fat infiltration group than low-fat infiltration group within MM. Expression of TNF-α and IL-1β in MM was moderately correlated with functional CSA and fatty degeneration of MM, which was moderately correlated with clinical outcomes.

Conclusions: Results support the hypothesis that IDD is associated with dysregulation of inflammatory state of local MM, which provides initial evidence that inflammatory dysregulation in paraspinal muscles has the potential for a broad impact on tissue health and LBP symptoms.

KEYWORDS
fatty degeneration, inflammation, low back pain, lumbar disc herniation, paraspinal muscle atrophy

1 | INTRODUCTION

Paraspinal muscles include psoas, multifidus muscle (MM), and erector spinae muscle as the main component of trunk musculature which plays an important role in the stability and functional movements of the lumbar vertebral column. Recent studies highlight structural changes in paraspinal muscles (such as increased fatty infiltration,[1] reduced cross-sectional area (CSA),[2] and fiber-type transformation[3]) in association with intervertebral disc degeneration (such as lumbar disc herniation (LDH))[4,5] that may be considered as a significant contributor to low back pain (LBP). Disuse, denervation, and dysregulation of the inflammatory state have been revealed as the main mechanisms for the structural changes in paraspinal muscles. Research using animal models of experimental injury to the intervertebral disc (IVD)[3] and spontaneous IVD degeneration[6] has revealed dysregulation of local inflammatory activity as a novel mechanism to explain fat and connective tissue accumulation in paraspinal muscles. During the acute phase, the inhibition of paraspinal muscle activation is associated with muscle atrophy. The subacute to the chronic phase of paraspinal muscle remodeling after IVD degeneration and injury has been proposed to be regulated by inflammation processes which lead to loss of slow-twitch muscle fibers, connective tissue accumulation, and fatty infiltration.[3–6] Previous studies have observed structural remodeling of paraspinal muscles in patients with LDH, which is closely related to high-intensity pain and disability.[3,7] However, there are some controversies about the mechanisms that regulate paraspinal muscle structural changes in association with or without LBP in patients with LDH.

Interestingly, an active process mediated by a localized muscle inflammatory response has been revealed in a range of tissue pathologies. The balance between proinflammatory (M1) and anti-inflammatory (M2) macrophages in the musculoskeletal system is regarded as one of the main reasons for maintaining tissue integrity. Recently, data from animal models with IVD lesions show the expression of proinflammatory cytokine (such as tumor necrosis factor-alpha (TNF-α))[8,9] and localization and polarization of macrophages that could drive the structural alterations, including the accumulation of fibrosis and fiber-type transformation.[3,10] A recent human study supported that fatty infiltration of MM is associated with inflammatory dysregulation.[11] However, the potential links between the dysregulation of the inflammatory state and structural changes in the paraspinal muscles in patients with LDH remain unclear. Confirmation requires examination to support the mechanisms for the structural remodeling in the paraspinal muscles in the patient with LDH.

A study was performed to determine the relationship between pain and structural changes (including CSA and fat infiltration) in the paraspinal muscles of LDH patients through comparisons with healthy control subjects. Moreover, a cohort study was conducted to investigate the presence of structural changes in paraspinal muscles differed in the LDH patients with and without LBP and the associations between the expression of genes for the inflammatory marker(s) and structural changes in paraspinal muscles.

2 | MATERIALS AND METHODS

2.1 | Study design

Eighty healthy controls and 166 participants who were diagnosed with LDH were enrolled in this prospective study. All experiments were performed with the approval of our institution's Research Ethics Committee where participants had consented to use of their demographic data, radiological data, clinical scores, and tissue samples for research.

2.2 | Study design and participants

In this prospective study, healthy controls (control group: aged more than 18 years without LBP) and participants who were diagnosed with LDH (investigate group) were assessed and screened at our center from January 2020 to May 2022. In the first stage, the relationship between pain and morphological changes in the paraspinal muscles of patients with LDH through comparisons with healthy control subjects was conducted. In the second stage, all the LDH participants were enrolled into two groups in regarding with the presence of LBP. The difference in the structural changes in the paraspinal muscles between LBP and non-LBP groups were assessed. In the third stage, the participants who underwent percutaneous endoscopic lumbar discectomy (PELD) surgery were consented to use of their tissue samples for research were enrolled. The associations between the expression of genes for the inflammatory marker(s) and structural changes in paraspinal muscles differed in the LDH patients with and without LBP were investigated. All the patients in the LBP group who has LBP lasting more than 12 weeks.

The inclusion criteria were as follows: (1) aged ≥18 years old; (2) single level herniation disc at L4/5 or L5S1 on magnetic resonance imaging (MRI); (3) clinical history (such as radiculopathy with or without LBP) and physical examination (such as straight-leg-raising test) consistent with the findings on CT or MRI[12]; and (4) conservative treatment was inefficient for more than 3 months.

The exclusion criteria were as follows: (1) history of lumbar spine surgery, tumor, infection, spinal deformity, cauda equina syndrome, and using of hormones; (2) history of diabetes, systemic metabolic bone disease, lipodystrophy, severe organic disease, and neuromuscular syndromes; (3) history of physical exercise or rehabilitation; and (4) participate declined to participant in this project.

Demographic data of the patients' age, sex, body mass index (BMI), duration of symptoms, and surgical level were collected.

2.3 | Clinical assessment

The clinical outcomes included the Visual Analogue Scale (VAS) for evaluating back pain and leg pain and the Oswestry disability index (ODI) score for assessing function and disability.

2.4 | Imaging assessment

Three sequences of MRI were performed using a 3.0 T Trio Tim scanner (Siemens, Erlangen, Germany) preoperatively, including sagittal T2-weighted fast spin-echo (FSE), sagittal T1-weight FSE, and axial T2-weighted scans. The sagittal T1-weighted FSE parameters were as follows: field of view (FOV) = 310 * 310 mm, repetition time (TR)/echo time (TE) = 550 ms/9.6 ms, matrix size = 320 * 320, slice thickness = 4.0 mm, slice per slab = 11, 2 number of excitations (NEX). The sagittal T2-weighted FSE parameters were as follows: FOV = 310 * 310 mm, TR/TE = 2700 ms/97 ms, matrix size = 320 * 320, slice thickness = 4.0 mm, slice per slab = 11, 2 NEX. The axial T2-weighted FSE parameters were as follows: FOV = 210 * 210 mm, TR/TE = 3400 ms/102 ms, matrix size = 320 * 320, slice thickness = 4.0 mm, slice per slab = 15, 2 NEX. The total time taken for MR imaging ranges from 20 to 25 min. All participants' MRIs were obtained in DICOM format utilizing protocols for standard clinical lumbar spine acquisitions.

The Pfirrmann score was used to evaluate IVD degeneration which was referred as to more than grade 3 of the score.[13] The Kjaer method was utilized to determine fat infiltration in paraspinal muscles.[1] Scores were allocated as "normal/mild", "slight", and "severe" fat filtration for estimates of 0%–10%, 10%–50%, and >50% fat and fibrous tissue within the muscle, respectively. Based on the classification, all the participants were divided into low (normal/mild + slight) and high (severe) fat infiltration groups.

The software ImageJ (version 1.53, National Institutes of Health, Bethesda, MD) was used for measuring the total and functional CSAs and fatty degeneration of paraspinal muscles. The total CSAs were referred to as the total area of muscle and fat. Functional CSA was referred as to fat-free in the area of paraspinal muscles based on the method described by Fortin et al.[15] and Jeon et al.[14] The ratio of functional CSA to total CSA was used to assess the fatty degeneration. The outline of muscle fascial boundary was identified and selected as the region of interest (ROI) for the measurement using an axial T2-weighted MRI at the level of L4-5 IVD (Figure 1).

2.5 | Sample collection and quantitative polymerase chain reaction (qPCR)

The participants who are nonresponsive to at least 6 weeks of conservative treatment underwent standard PELD surgery. A standard surgical approach was used for PELD through an endoscope (SPINENDOS GmbH, Munich, Germany). After exposing the lumbodorsal fascia, the muscle samples were harvested from the transversospinal corner of the deep MM from the ipsilateral side at the lumbar spine level of L4-L5 or L5-S1 via the endoscope according to the Figure 1. All the samples were washed three times with PBS and placed in RNA later for storage at −20°C.

RNA was extracted from muscle using RNeasy Lipid Tissue Mini Kit and RNeasy Fibrous Tissue Mini Kit (QIAGEN, Germany). cDNA was synthesized and purified using QuantiTech Reverse transcription kit (QIAGEN, Germany). The expression of inflammatory and structural markers in MM samples was examined, which includes TNF-α, interleukin-1 beta (IL-1β), IL-6, IL-15, transforming growth factor beta 1 (TGF-β1), Arginase 1 (Arg-1), and nitric oxide synthase 2 (Nos-2)[11,15] (Table 1).

The expression of each gene was converted to a percentage of the house keeping gene glyceraldehyde 3-phosphate dehydrogenase (GAPDH). Data are presented as arbitrary units.

2.6 | Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD). Dichotomous data are presented as numbers and percentages. Categorical variables were compared using Fisher's exact test. Parametric and non-parametric continuous variables were compared among groups using one-way ANOVA and the Kruskal–Wallis test, respectively.

Independent *t*-tests were used to compare the total and functional CSAs and fatty degeneration of paraspinal muscles between healthy control group and investigate group and between LBP and

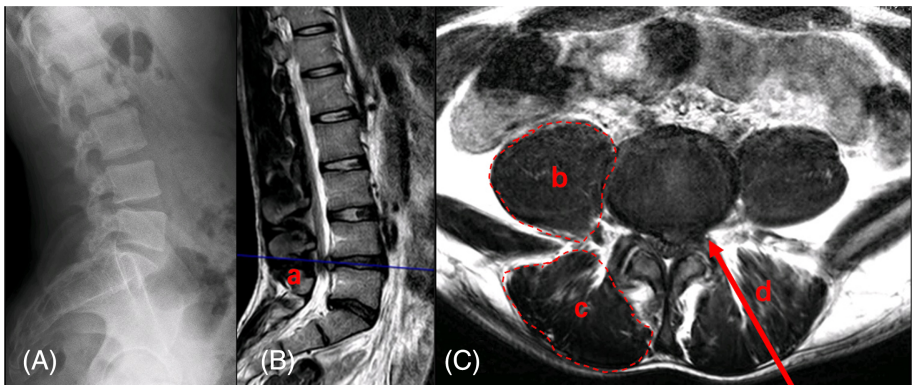

FIGURE 1 (2A) Standing lateral x-ray of the lumbar spine; (2B) The blue line (a) shows the disc herniation at the L4-L5 intervertebral disc level on sagittal T2-weighted MRI; (c) The cross-sectional area (CSA) of the paraspinal muscles was measured by drawing the outline of the muscle fascial boundary using the range of interest (ROI) at the L4-L5 intervertebral disc level on axial T2-weighted MRI. (b) ROI of psoas muscle; (c) ROI of multifidus muscle. (d) The procedure of percutaneous endoscopic lumbar discectomy (PELD) for treating the herniated disc (red arrow).

TABLE 1 Cytokines and molecules involved in muscle and primer sequences used for quantitative polymerase chain reaction (qPCR) analysis.

Gene	Full name	Primer sequences	Role
TNF-α	Tumor necrosis factor—alpha	F: 5′-GAGGCCAAGCCCTGGTATG-3′ R: 5′-CGGGCCGATTGATCTCAGC-3′	Pro-inflammatory cytokine (polypeptide cytokine)
IL-1β	Interleukin 1 beta	F: 5′-AGCTACGAATCTCCGACCAC-3′ R: 5′-CGTTATCCCATGTGTCGAAGAA-3′	Pro-inflammatory cytokine
IL-6	Interleukin 6	F: 5′-ACTCACCTCTTCAGAACGAATTG-3′ R: 5′-CCATCTTTGGAAGGTTCAGGTTG-3′	Pro- and anti-inflammatory cytokine
IL-15	Interleukin 15	F: 5′-GCCATAGCCAGCTCTTCTTCA-3′ R: 5′-CTGCACTGAAACAGCCCAAA-3′	Pleiotropic cytokine
TGF-β1	Transforming growth factor beta 1	F: 5′-GGCCAGATCCTGTCCAAGC-3′ R: 5′-GTGGGTTTCCACCATTAGCAC-3′	Anti-inflammatory mediator
Arg-1	Arginase 1	F: 5′ TGGACAGACTAGGAATTGGCA 3′ R: 5′ CCAGTCCGTCAACATCAAAACT 3′	Anti-inflammatory cytokine
Nos-2	Nitric oxide synthase 2	F: 5′ AGGGACAAGCCTACCCCTC 3′ R: 5′ CTCATCTCCCGTCAGTTGGT 3′	Pro-inflammatory cytokine

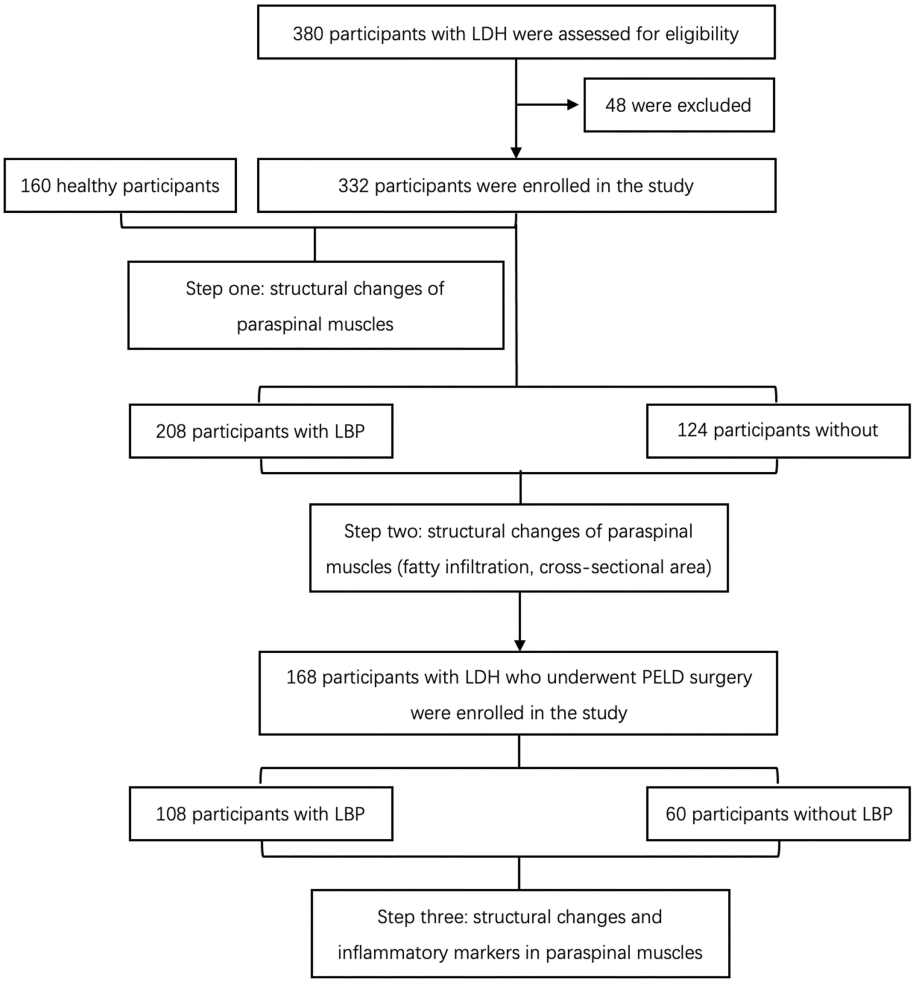

FIGURE 2 Consolidated standards of reporting trials flow diagram showing patient disposition.

non-LBP groups. The Chi-square test was used to assess the different fat filtration grades in LBP and non-LBP groups. The normality of variables has been evaluated. Spearman correlation analysis was used to test the association between the demographic data, clinical scores, the expression of inflammatory markers, and CSAs of paraspinal muscles. Intra- and inter-rater reliability was evaluated with intra-class correlation coefficient (ICC) and their 95% confidence intervals (95% CIs).[16] Statistical analysis was evaluated using SPSS v24.0 (SPSS Inc., Chicago, IL, USA) with a $p < 0.05$ considered to be statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Figure 2 shows the enrolment for three stages of this study. There are 160 health subjects (92 males and 68 females) included in the control group. Overall, 380 patients with LDH were screened and identified as eligible; 48 eligible patients declined to participate in the study. Among the remaining 332 patients for the first stage of this study, 208 were accompanied by LBP and 104 without LBP. Based on the criteria for surgical treatment, a total of 168 patients were allocated to the third stage of this study.

In the second stage, a total of 332 patients with LDH (188 males and 144 females; the age of 43.33 ± 10.08 years, ranging from 24 to 70 years;

TABLE 2 Demographic, clinical, and radiological data of included patients.

		Investigate group			
Characteristic	**Healthy control group**	**LBP**	**Non-LBP**	**Total**	***p* value[d]**
Number of patients	160	208	112	332	-
Sex (female)	68 (42.5%)	102 (49%)	42 (33.9%)	144 (43.4%)	0.075
Age (years)	44.24 ± 11.21	43.43 ± 10.68	43.16 ± 11.06	43.33 ± 10.08	0.876
BMI (kg/m^2)	26.79 ± 3.12	27.68 ± 3.52	27.75 ± 3.43	27.70 ± 3.48	0.900
Segment					
L4-L5	-	134 (64.4%)	84 (67.7%)	218 (65.7%)	0.737
L5-S1		74 (35.6%)	40 (32.3%)	114 (34.3%)	
Mean duration of LBP (weeks)	-	22.4 ± 6.42	-	22.4 ± 6.42	0.000***
VAS LBP	-	7.64 ± 1.77	-	7.64 ± 1.77	0.000***
VAS leg pain		7.43 ± 1.80	7.30 ± 1.80	7.38 ± 1.80	0.947
ODI		26.8 ± 9.72	27.3 ± 9.32	27 ± 9.57	0.626
Low fat infiltration	152 (95%)	124 (59.6%)	92 (74.2%)	216 (65.1%)	0.046*
High fat infiltration	8 (5%)	88 (40.4%)	32 (25.8%)	116 (34.9%)	
CSA of psoas muscle (mm^2)	3245.29 ± 578.21	2965.11 ± 624.71	3147.01 ± 593.16	3034.41 ± 617.48	0.369
CSA of paraspinal muscles (mm^2)	4890.34 ± 865.32[b,*]	4748.82 ± 830.24	4811.48 ± 979.43	4772.70 ± 887.67	0.249
CSA of multifidus muscle (mm^2)	1995.23 ± 324.65[a,b,c,*]	1948.91 ± 351.53	1893.64 ± 401.19	1927.86 ± 371.02	0.313
Functional CSA of multifidus muscle (mm^2)	1835.41 ± 321.22[a,b,c,*]	1601.05 ± 333.33	1655.34 ± 378.08	1621.74 ± 350.93	0.362
Fatty degeneration of multifidus muscle	0.92 ± 0.06[a,b,c,***]	0.83 ± 0.10	0.87 ± 0.06	0.84 ± 0.09	0.000***

Note: Continuous data are presented as the mean ± standard deviation (SD). Dichotomous data are presented as numbers and percentages.
Abbreviations: BMI, body mass index; CSA, cross-sectional area; LBP, low back pain; ODI, Oswestry disability index; VAS, visual analogue scale.
[a]Independent *t*-test between healthy control and investigate groups.
[b]Independent *t*-test between healthy control and LBP groups.
[c]Independent *t*-test between healthy control and non-LBP groups.
[d]Independent *t*-test between LBP and non-LBP groups.
*Significant difference $p < 0.05$. ***Significant difference $p < 0.001$.

TABLE 3 Expression of inflammatory genes in multifidus muscles between low- and high-fat infiltration groups.

Gene	**Low-fat infiltration group**	**High-fat infiltration group**	***p*-value**
TNF-α	0.00005 ± 0.00003	0.00014 ± 0.00006	0.02*
IL-1β	0.00027 ± 0.00021	0.00036 ± 0.00030	0.45
IL-6	0.015 ± 0.007	0.012 ± 0.006	0.72
IL-15	0.00036 ± 0.00011	0.00087 ± 0.00034	0.25
TGF-β1	0.10 ± 0.01	0.15 ± 0.05	0.74
Arg-1	0.0032 ± 0.0027	0.0056 ± 0.0033	0.34
Nos-2	0.0224 ± 0.032	0.032 ± 0.031	0.54

Note: Data are presented as arbitrary units. Continuous data are presented as the mean ± standard deviation (SD).
Abbreviations: Arg-1, arginase 1; IL-1β, interleukin 1 beta; Nos-2, nitric oxide synthase 2; TGF-β1, transforming growth factor beta 1; TNF-α, tumor necrosis factor alpha.
*Significant difference $p < 0.05$ (independent *t*-test).

BMI 27.70 ± 3.48 kg/m^2) were enrolled. All the patients diagnosed as single-level herniation at L4-L5 or L5-S1, including 218 herniations at L4-L5 and 114 herniations at L5-S1. The mean VAS LBP, VAS leg pain, and ODI scores of participants in the investigate group were 7.64 ± 1.77, 7.38 ± 1.80, and 27 ± 9.57, respectively. There are 168 patients (108 males and 60 females) underwent PELD surgery, including 106 herniations at L4-L5 and 62 herniations at L5-S1. The mean VAS LBP, VAS leg pain, and ODI scores were 7.66 ± 1.08, 7.40 ± 1.80, and 26.91 ± 9.55 at preoperative, respectively. There were no significant differences in the number of females, age, and BMI between control and investigate groups and between LBP and non-LBP groups (Table 2 and Table S1).

3.2 | Quantitative assessment of paraspinal muscles between healthy control and investigate groups

The CSAs of MM ($p < 0.05$), functional CSA of MM ($p < 0.05$), and fatty degeneration of MM ($p < 0.001$) were larger in the healthy group than investigate group, especially the comparisons in the healthy control and LBP group.

3.3 | Clinical outcomes and quantitative assessment of paraspinal muscles between LBP and non-LBP groups

A significant increase in the incidence rate of fat infiltration in the LBP group than in the non-LBP group ($p = 0.046$). The CSAs of psoas muscle, paraspinal muscles, MM, and functional CSA and fatty degeneration of MM in LBP group (vs. non-LBP group) were 2965.11 ± 624.71 mm^2 (vs. 3147.01 ± 593.16 mm^2), 4748.82 ± 830.24 mm^2 (vs. 4811.48 ± 979.43 mm^2), 1948.91 ± 351.53 mm^2 (vs. 1893.64 ± 401.19 mm^2), 1601.05 ± 333.33 mm^2 (vs. 1655.34 ± 378.08 mm^2), 0.83 ± 0.10 (vs. 0.87 ± 0.06), respectively. The statistically significant difference in the fatty degeneration of MM ($p = 0.000$) between LBP and non-LBP groups was indicated in Table 2. There were no significant differences in VAS leg pain and ODI scores between LBP and non-LBP groups.

3.4 | Comparison of inflammatory markers in the multifidus muscle between fat infiltration groups

TNF-α was 28-fold greater in the high-fat infiltration group than the low-fat infiltration group within the MM (Table 3). No differences in the expression of the remaining inflammatory markers were present between groups.

3.5 | Associations between quantitative data of paraspinal muscles and clinical outcomes

Age showed a moderate association with fatty degeneration of MM ($r = -0.383$, $p = 0.000$) (Table 4). There was no correlation between

TABLE 4 Correlations between continuous variables from the patients who underwent percutaneous endoscopic lumbar discectomy (PELD) surgery.

	Age	BMI	VAS LBP	VAS leg pain	ODI	TNF-α	IL-1β	IL-6	IL-15	TGF-β1	Arg-1	Nos-2
CSA of psoas muscle (mm^2)	0.038 (0.729)	−0.052 (0.637)	0.160 (0.082)	−0.031 (0.777)	−0.204 (0.063)	−0.404 (0.001**)	−0.153 (0.227)	0.139 (0.189)	0.259 (0.222)	0.209 (0.072)	0.134 (0.212)	0.141 (0.387)
CSA of multifidus muscle (mm^2)	−0.126 (0.344)	0.033 (0.763)	0.399 (0.000***)	−0.186 (0.121)	−0.209 (0.062)	−0.389 (0.002**)	−0.172 (0.229)	0.009 (0.913)	−0.008 (0.921)	−0.109 (0.221)	0.007 (0.932)	0.032 (0.772)
CSA of paraspinal muscles (mm^2)	−0.195 (0.140)	0.077 (0.484)	0.024 (0.831)	−0.206 (0.061)	0.115 (0.299)	−0.376 (0.002**)	−0.103 (0.416)	0.115 (0.297)	0.258 (0.087)	0.178 (0.234)	0.167 (0.287)	0.182 (0.202)
Functional CSA of multifidus muscle (mm^2)	−0.012 (0.915)	−0.012 (0.917)	0.113 (0.306)	−0.158 (0.150)	−0.168 (0.127)	−0.340 (0.006**)	−0.696 (0.000***)	0.213 (0.122)	0.254 (0.091)	−0.168 (0.221)	0.112 (0.322)	0.103 (0.315)
Fatty degeneration of multifidus muscle	−0.383 (0.000***)	−0.080 (0.471)	0.456 (0.000***)	0.116 (0.292)	0.083 (0.451)	−0.478 (0.002**)	−0.682 (0.000***)	0.145 (0.156)	0.103 (0.315)	0.218 (0.110)	0.056 (0.613)	0.168 (0.267)
VAS LBP	-					0.466 (0.000***)	0.537 (0.000***)	0.089 (0.563)	−0.086 (0.606)	0.051 (0.723)	0.062 (0.816)	0.121 (0.265)
VAS leg pain						0.478 (0.000***)	0.303 (0.016*)	0.074 (0.732)	0.160 (0.337)	0.083 (0.645)	0.209 (0.057)	0.189 (0.196)
ODI						0.466 (0.000***)	0.537 (0.000***)	0.032 (0.796)	−0.086 (0.606)	0.051 (0.723)	0.096 (0.335)	0.075 (0.721)

Note: Data were presented as coefficient value (*p*-value). Significant difference.
Abbreviations: BMI, body mass index; CSA, cross-sectional area; LBP, low back pain; ODI, Oswestry disability index; VAS, visual analogue scale.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$ (Spearman correlation coefficient).

demographic data (includes age and BMI) and the remaining quantitative data of paraspinal muscles.

The score of VAS LBP had a moderate negative correlation with the CSA of MM ($r = -0.399$, $p = 0.000$) and fatty degeneration of MM ($r = -0.456$, $p = 0.000$). Quantitative measurement data of paraspinal muscles were not related to pre-operative VAS leg pain and ODI (Table 4).

3.6 | Associations between quantitative data of paraspinal muscles and the expression of inflammatory markers

Expression of TNF-α in MM was moderately correlated with the total CSAs of psoas muscle ($r = -0.404$, $p = 0.001$), MM ($r = -0.389$, $p = 0.002$), and paraspinal muscles ($r = -0.376$, $p = 0.002$), and functional CSA ($r = -0.340$, $p = 0.006$) and fatty degeneration of MM ($r = -0.478$, $p = 0.002$). Expression of IL-1β in MM was strongly correlated with the functional CSA ($r = -0.696$, $p = 0.000$) and fatty degeneration of MM ($r = -0.682$, $p = 0.000$).

3.7 | Associations between the expression of inflammatory markers and clinical outcomes

Expression of TNF-α and IL-1β in MM was moderate to strongly correlated with the clinical outcomes (TNF-α with clinical outcomes: VAS LBP ($r = 0.466$, $p = 0.000$), VAS leg pain ($r = 0.478$, $p = 0.000$), and ODI ($r = 0.466$, $p = 0.000$); IL-1β with clinical outcome: VAS LBP ($r = 0.537$, $p = 0.000$), VAS leg pain ($r = 0.303$, $p = 0.016$), and ODI ($r = 0.537$, $p = 0.000$)). There was no significant correlation between the expression of the remaining inflammatory markers in MM and clinical outcomes (Table 4).

3.8 | Inter-rater reliability

There was good to excellent agreement in terms of inter-rater for the quantitative measurements (including CSA of psoas: 0.892 (0.860, 0.912), CSA of MM: 0.876 (0.842, 0.893), CSA of paraspinal muscles: 0.865 (0.832, 0.891), functional CSA of MM: 0.789 (0.764, 0.832), and fatty degeneration of MM: 0.823 (0.792, 0.861)).

4 | DISCUSSION

This prospective study provided evidence of relationships between quantitative changes of paraspinal muscles and inflammatory dysregulation in the LDH patients. Data show the reduction of CSAs of MM and functional CSA of MM and higher incidence rate of fatty degeneration in MM in the LDH patients compared with healthy control subjects, higher presence of fatty degeneration in MM in the LDH patients with LBP versus the patients without LBP, and upregulation of greater pro-inflammatory response in the MM in individuals with high-fat infiltration. These findings have potential implications for understanding the mechanisms that regulate MM structural changes in association with LBP in LDH patients.

4.1 | Comparison of quantitative data of paraspinal muscles between healthy and individuals with LDH

Compared to healthy subjects, patients with LDH are associated with morphological changes in paraspinal muscles comprising size, distribution, and type of fibers.[17] The potential mechanisms have been proposed for the structural changes in paraspinal muscles in LDH patients, including disuse, denervation, and inflammatory response.[2,10,18–20] The lesion of compressive nerve root by herniated disc leads to muscle fiber denervation or disuse of muscles which contributes to the structural remodeling of paraspinal muscles.[21] Additionally, the persistent compression of nerve roots by herniated disc is a plausible explanation for fatty infiltration and atrophy in the paraspinal muscles of muscle fibers supplied by that nerve.[17] Furthermore, increased fatty infiltration and atrophy in paraspinal muscles occurred with a consistent reduction in the CSA and/or the shift from slow to fast myosin isoforms muscle phenotypes.[10] Taken together, these actions support that structural changes in paraspinal muscles (including reduction of CSA and high fat infiltration) might be already occurred in the individuals with LDH compared to the healthy subjects,[2,10,18–20] which is consistent with our results. Of note, it is interesting to wonder what the main mechanism for causing the structural changes in paraspinal muscles is and whether the structural changes could contribute to clinical outcomes.

4.2 | Differences in the structural changes in paraspinal muscles in disc herniation related LBP and non-LBP groups

Many studies supported the potential relationships between the structural changes in paraspinal muscles and the presence of LBP, leg pain, and functional limitation, especially in MM and erector spinae.[4,5,22–24] However, paraspinal muscles dysfunction as a primary cause of LBP remains controversial. Previous review showed a positive association between the paraspinal muscles characteristics and LBP, including CSA (50%) and fat infiltration (67%) in MM.[2,24] Our data provided evidence for the reduced CSA and fatty degeneration of MM in the disc herniation-related LBP group. MM is considered to play an important part for stabilize and control of spine motion. Fat infiltration and the size of CSA are related to muscle activity and muscle strength, respectively. Taken together, individuals with LDH might have a high incidence rate in the reduction of CSA and high-fat infiltration in MM, which is a plausible explanation for LBP. Therefore, an investigation of the mechanisms that regulate MM structural changes in association with LBP in LDH patients is required.

4.3 | Expression of inflammatory and structural markers in MM

Dysregulation of local inflammatory activity has been proposed as a novel mechanism for the explanation of structural changes in MM. Our data showed that expression of the pro-inflammatory cytokine TNF-α was elevated in MM in LDH patients with high-fat infiltration and reduction in the CSA, and expression of TNF-α was correlated with LBP. Adipose tissue is the main source of pro-inflammatory cytokines which plays an important role in a range of muscle pathologies. TNF-α as a pro-inflammatory mediator is not only the product of adipose tissue, but also the driver of adipogenesis. Data from animal models with IVD degeneration/lesion showed that the increased expression of TNF-α was located in the adipose and connective tissue in MM and significantly related to polarization towards pro-inflammatory macrophages.[3,6] Human study provided the evidence for the greater expression of TNF-α in MM in individuals with high-fat infiltration rather than low-fat infiltration.[11] This supports the conclusion that TNF-α from alternate sources is promoting fat infiltration and reduction of CSA in paraspinal muscles.

Our data reveal that interleukin-1β (IL-1β) is strongly associated with functional CSA and fatty degeneration of MM. IL-1β as a pro-inflammatory cytokine plays a role in the early phases of myogenesis and muscle–adipose tissue interaction in paraspinal muscles.[25] Animal study on IVD lesion model showed that IL-1β expression accelerated fat accumulation in MM.[26] Inflammatory markers change in MM in present study provided evidence for translation of the findings from recent animal studies to humans.

Upregulation of TNF-α and IL-1β expression is associated with pain intensity, functional disability, and LBP chronicity,[27,28] which was confirmed by recent studies.[11,15] Although the upgrade TNF-α and IL-1β expression was associated with a poor recovery in LDH patients with LBP,[15] the potential underlying mechanism regulating the associations is still unknown and warrants further investigation. Understanding the links between TNF-α and IL-1β expression and clinical outcomes is critical to understanding its etiology and subsequent treatment.

4.4 | Methodological issues

Several methodological issues require consideration. First, the potential bias of fibromyalgia has been considered in the protocol. However, due to the debate on the diagnostic criteria and classification criteria of fibromyalgia, the details of fibromyalgia have not been mentioned in our exclusion criteria. Therefore, potential fibromyalgia data affect final results. Second, the comorbidities of anxiety and decompression have not been extracted which potentially affects the pain scores. Third, the potential bias still exists for the threshold for the period of physical exercise in the exclusion criteria. Fourth, despite all care in selecting areas to collect samples from, there is the likelihood to cause potential bias during the tissue samples collection from the ipsilateral side. Meanwhile, due to the lack of measuring the inflammation biomarkers in the other paraspinal muscles, the association between the physical activity levels and the change in specific paraspinal muscles cannot be analyzed. Fifth, only one image from each patient was used for measuring paraspinal muscles. Sixth, expression of the proteins has not been measured in the present study. Future prospective studies should explore the inflammatory marker(s) change in paraspinal muscles using a randomized controlled design with a larger sample size.

5 | CONCLUSIONS

The novel results from the present study support the hypothesis that reduced CSA and increased fatty infiltration in paraspinal muscles are observed in LDH patients compared with healthy subjects, which is associated with inflammatory regulation. Furthermore, the inflammatory response in the MM as a novel mechanism has been confirmed through which TNF-α promotes chronic pain and paraspinal muscles structural changes. They provide a clear and complete insight into the pathophysiology of paraspinal muscles changes in LBP and provide initial evidence.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Peng Cui, Yongjin Li, and Yu Wang. The first draft of the manuscript was written by Xiaolong Chen, and all authors commented on previous versions of the manuscript. Shibao Lu provided great comments during the revision process. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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