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RESEARCH ARTICLE

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Influence of patient-specific factors when comparing multifidus fat infiltration between chronic low back pain patients and asymptomatic controls

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Abstract

Introduction: Many studies have attempted to link multifidus (MF) fat infiltration with muscle quality and chronic low back pain (cLBP), but there is no consensus on these relationships.

Methods: In this cross-sectional cohort study, 39 cLBP patients and 18 asymptomatic controls were included. The MF muscle was manually segmented at each lumbar disc level and fat fraction (FF) measurements were taken from the corresponding advanced imaging water-fat images. We assessed the distribution patterns of MF fat from L1L2 to L5S1 and compared these patterns between groups. The sample was stratified by age, sex, body mass index (BMI), subject-reported pain intensity (VAS), and subject-reported low back pain disability (oswestry disability index, ODI).

Results: Older patients had significantly different MF FF distribution patterns compared to older controls ($p < 0.0001$). Male patients had 34.8% higher mean lumbar spine MF FF compared to male controls ($p = 0.0006$), significantly different MF FF distribution patterns ($p = 0.028$), 53.7% higher mean MF FF measurements at L2L3 ($p = 0.037$), and 50.6% higher mean MF FF measurements at L3L4 ($p = 0.041$). Low BMI patients had 29.7% higher mean lumbar spine MF FF compared to low BMI controls ($p = 0.0077$). High BMI patients only had 4% higher mean lumbar spine MF FF compared to high BMI controls ($p = 0.7933$). However, high BMI patients had significantly different MF FF distribution patterns compared to high BMI controls ($p = 0.0324$). Low VAS patients did not significantly differ from the control cohort for any of our outcomes of interest; however, high VAS patients had 24.3% higher mean lumbar spine MF FF values ($p = 0.0011$), significantly different MF FF distribution patterns ($p < 0.0001$), 34.7% higher mean MF FF at L2L3 ($p = 0.040$), and 34.6% higher mean MF FF at L3L4 ($p = 0.040$) compared to the control cohort. Similar trends were observed for ODI.

Conclusions: This study suggests that when the presence of paraspinal muscle fat infiltration is not characteristic of an individual's age, sex, and BMI, it may be associated with lower back pain.

KEYWORDS
chronic low back pain, fat infiltration, IDEAL, multifidus

1 | INTRODUCTION

Low back pain (LBP) has consistently accounted for the largest number of years lived with disability in the US population, and affects 65%–85% of the general population at some point in their lifetime.[1,2] In addition, chronic low back pain (cLBP) is among the most common non-malignant disorders associated with prescribed opioid use in primary care.[3] Many have sought to understand the root cause of cLBP, but it has proven to be quite difficult due to its multifaceted etiology.[4–6] An often overlooked factor in cLBP patients is the condition of their paraspinal muscles. Paraspinal muscles provide support and control multiaxial movement of the lumbar spine, appear symmetrical about the spinal axis, and show increased fat infiltration in people with LBP.[7] Poor paraspinal muscle quality is defined as asymmetric/atrophic size along with excessive fat infiltration, which together decrease muscle endurance and contractile strength.[8,9] Targeted paraspinal muscle therapeutics may be clinically useful only if biomarkers for paraspinal muscle dysfunction can be developed, validated, and made routinely available.

Of the paraspinal muscles, the multifidus (MF) plays a uniquely important role in providing segmental stability within the spine. The relative health of the MF can be assessed through clinical MRI imaging, with measurement of the relative amount of fat infiltration as an indicator of muscle quality. Many studies have attempted to link MF atrophy, asymmetry, and fat infiltration with muscle quality and cLBP, but there has not been any set conclusion on this relationship.[10] Lack of consensus within the literature stems mainly from differences in methodology, including discrepancies in imaging modalities, sample population composition (lack of controls, differing inclusion/exclusion criteria of cLBP), and varying definition of muscle quality. A small number of studies has investigated the differences in fat infiltration in cLBP patients and asymptomatic controls, and although there is conflicting evidence, the general consensus seems to be that cLBP patients tend to have increased fat infiltration compared to pain free controls.[11–18]

One problem of prior attempts to link fat infiltration to cLBP is the lack of understanding regarding the regional patterns of fat infiltration throughout the lumbar spine. Prior studies analyzed their cohorts either by single spinal level or by an average of measurements taken at each lumbar level. The limitation with this methodology is that MF changes along the lumbar spine are dynamic and continuous, and single level measurements do not capture potential pathologic patterns.[19] In addition, the normal intramuscular fat distribution patterns from L1-S1 as a function of age, sex, BMI, and pain and disability status are currently unknown.

We hypothesize that fat infiltration is not an independent marker for cLBP, and that the relationship between MF fat infiltration and pain is dependent on other patient-specific factors such as age, sex, BMI, and severity of pain and disability. To investigate this, we conducted a cross-sectional cohort study of 39 cLBP patients and 18 age-, BMI-, and sex-matched asymptomatic controls. Using an advanced sequence to measure fat fraction, commonly known as Dixon-MRI featuring Iterative Decomposition of water and fat with Echo Asymmetry and Least-Squares Estimation (IDEAL), we assessed the differences in fat infiltration between cLBP patients and asymptomatic volunteers.[20] In order to assess the effect of patient demographic features like age, sex, and BMI, as well as severity of pain and disability from patient-reported outcomes, our sample was further stratified to measure the effects of each variable.

2 | MATERIALS AND METHODS

2.1 | Sample

A sample of 57 individuals, 39 patients with cLBP, and 18 asymptomatic controls, were screened and enrolled to receive T1- and T2-weighted as well as IDEAL axial and sagittal MRI images. Asymptomatic controls were recruited to match the age, sex, and BMI profiles of the patient cohort. Inclusion criteria comprised of patients with more than three continuous months of LBP (VAS ≥ 4 or ODI ≥ 30), between ages 18 and 65, and with a BMI under 40 kg/m^2. Exclusion criteria comprised of pregnancy, diabetes, smoking, cancer, spondylolisthesis, scoliosis, prior lumbar surgery, disc herniation, compression fractures, and those taking osteoporosis medication. Age- and sex-matched controls were recruited locally and reported no prior history of back pain (VAS ≤ 1) or spinal pathology.

2.2 | MR imaging

Lumbar scans were performed on a 3T Discovery MR 750 scanner using an 8-channel phased-array spine coil (GE Healthcare, Waukesha, WI). Sequences included standard clinical T1- and T2-weighted MRI sequences and the IDEAL sequence (Figure 1). Specifications for the IDEAL sequence included TR = 7 ms, TE = 2.1 ms, flip angle = 3°, rBW = ±83.3 kHz, FoV = 22 cm, in-plane resolution = 1.3 mm, and slice thickness = 4 mm. Detailed methods can be found in Supplemental Information Data S1.

2.3 | Muscle segmentation

The MF muscle was manually segmented at each lumbar disc level from a combination of T1- and T2-axial images to conclude accurate fascial boundaries, and segmentation boundaries were subsequently

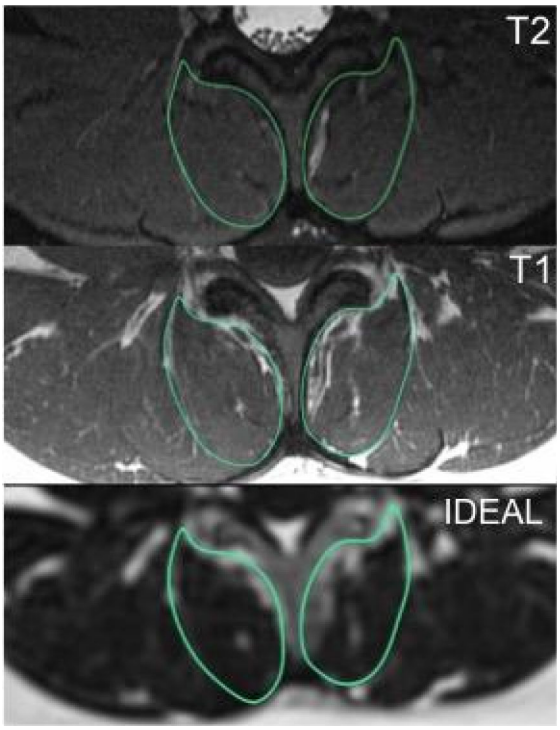

FIGURE 1 Outlining methodology. MF outlined on T1- and T2-weighted images, then segmentation boundaries were transferred to the coincident IDEAL image for measuring mean fat fraction. MF, multifidus

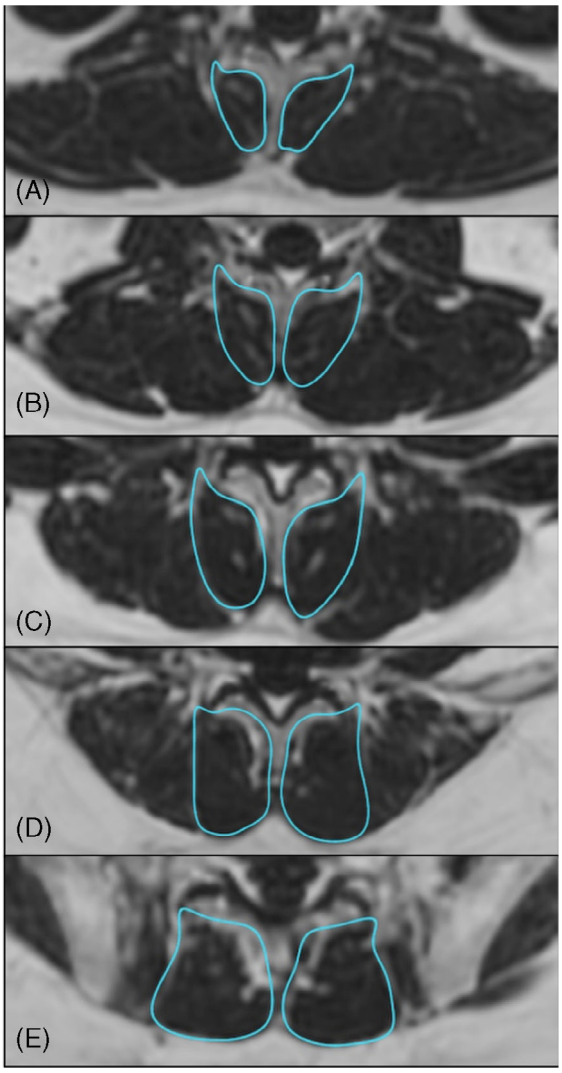

FIGURE 2 Disc-level outlines of MF for quantifying fat fraction from L1L2 (A) to L5S1 (E) on IDEAL imaging. MF, multifidus

transferred to the coincident IDEAL images to measure mean fat fraction (Figure 2). In chemical shift encoding-based water–fat imaging, water and fat signals can be separated automatically based on the chemical shift difference between water and fat,[20] and accurate fat quantification can be achieved by incorporating a multi-peak fat spectrum in the signal model.[21] In short, this technique enables spatially resolved assessments of muscle fat fraction, where each voxel has a fat fraction value between 0% and 100%, without the need to apply signal intensity thresholds. The mean fat fraction (FF) was calculated as the mean fat fraction for all of the voxels on the axial IDEAL images within the segmentation boundaries identified on the axial T1- and T2-weighted images. Bilateral measurements of MF FF were collected by two investigators using OsiriX open source MRI analysis software. Intra- and inter-rater reliability was verified from muscle segmentation measurements from five subjects (intra-rater ICC: 0.98, $p < 0.001$; inter-rater ICC: 0.99, $p < 0.001$). Mean FF values were averaged both bilaterally and between two adjacent segments per lumbar disc level. Patient-reported outcomes included ODI (0–100) and VAS for back pain (0–10).

2.4 | Statistical analyses

All statistical analyses were conducted in RStudio (Version 4.0.1). In order to assess the effect of patient demographic features like age, sex, and BMI, as well as severity of pain and disability from patient reported outcomes, our sample was stratified accordingly for statistical analysis. In particular, patients and controls above and below the average age of the cohort (46 years) were separated into younger and older groups. We also separated by male and female patients and controls to investigate sex differences. In addition, we separated patients and controls by the average BMI of the cohort (above and below 25) to compare within higher and lower BMI categories. Finally, we separated by VAS (≥6) and ODI (≥40), to compare patients with high VAS, low VAS, high ODI, and low ODI against the whole pain-free control cohort.

We developed a Gaussian family generalized linear model for univariate linear regression to see if individual demographic factors could predict mean lumbar spine MF FF (averaged between both sides and between all lumbar spine segments) in patient and control cohorts. Wald testing was performed to evaluate the effect of the weighted distance between the estimated value and the hypothesized true value under the null hypothesis on statistical parameters within each model.

Next, we conducted univariate testing to compare the mean lumbar spine MF FF between patients and controls within each of our cohorts. Mann–Whitney-U testing was performed as a nonparametric analysis to control for ordinal and ranked data elements and to control for potential outliers.

To assess differences at specific spinal levels, Welch two-sample *t*-testing was performed to compare the mean MF FF at each spinal level between patients and controls within each of our cohorts.

To compare the pattern of variation of MF FF between subjects, we conducted Kernel two-sample testing to compare the distribution of mean MF FF from L1L2 to L5S1 between patients and controls within each of our cohorts. Kernel two-sample testing (kde.test) computes all pairwise distances in our data and then use a permutation test to see if the between group distances are different from within group distances. Fitting smoothed splines through the two samples (control vs. patients) is a good way of visualizing how the groups are different on a spinal level-by-level scale. The curves that are being demonstrated represent fat fraction by spinal level for patients and controls. Fat fraction at each individual spinal level is what is being compared between patients and control using the Kernel method. Cubic smoothing spline plots were fitted for variation between levels within subjects and developed for each analysis cohort. Jackknife (studentized) residuals and standardized error were calculated to obtain 95% confidence intervals (CIs).

3 | RESULTS

3.1 | All patients versus all controls

Our study contained 39 cLBP patients (mean age: 47.43 ± 12.31 years, female: 48.7%, mean BMI: 25.70 ± 5.08 kg/m^2) and 18 controls (mean age: 42.74 ± 12.81 years, female: 44.4%, mean BMI: 24.05 ± 4.34 kg/m^2; Table 1). Patients had 21.7% higher mean lumbar spine MF FF compared to controls (patients: 24.60 ± 10.60, controls: 20.22 ± 9.48, $p = 0.0032$). At L3L4 specifically, we observed 32.4% higher MF FF in patients (patients: 22.81 ± 11.26, controls: 17.23 ± 8.00, $p = 0.038$). All other level-specific differences were not significant. When comparing the MF FF distribution patterns via Kernel two-sample testing, no significant difference was observed between patients and controls ($p = 0.076$).

3.2 | Age

In the control cohort, univariate linear regression revealed that age (OR: 1.66, 95% CI: 1.48–1.87, $p < 0.0001$) was a significant predictor of increased mean lumbar spine MF FF. In the patient cohort, univariate linear regression also revealed that age (OR: 1.61, 95% CI: 1.46–1.79, $p < 0.0001$) was a significant predictor of increased mean lumbar spine MF FF.

After stratifying by age, we identified 16 patients (mean age: 34.90 ± 6.08, female: 37.5%, mean BMI: 23.44 ± 3.40) and 11 controls (mean age: 33.91 ± 5.54, female: 45.5%, mean BMI: 23.08 ± 4.57) in our younger cohort. Younger patients had 15.1% higher mean lumbar spine MF FF compared to younger controls (patients: 18.62 ± 6.70, controls: 16.18 ± 7.21, $p = 0.0613$). Level-specific analyses did not show a significant difference in MF FF in the younger cohort any specific level. When comparing the MF FF distribution patterns via Kernel two-sample testing, no significant difference was observed between patients and controls in our younger cohort ($p = 0.916$; Figure 3).

For the older cohort, we identified 23 patients (mean age: 56.14 ± 6.56, female: 56.5%, mean BMI: 27.38 ± 5.47) and 7 controls (mean age: 56.61 ± 6.85, female: 42.9%, mean BMI: 25.40 ± 3.68). Older patients had 8.5% higher mean lumbar spine MF FF compared to older controls (patients: 28.85 ± 10.82, controls: 26.58 ± 9.19, $p = 0.231$). Level-specific analyses did not show a significant difference in MF FF in the older cohort at any specific level. When comparing the MF FF distribution patterns via Kernel two-sample testing, a significant difference was observed between patients and controls in our older cohort ($p < 0.0001$; Figure 3).

3.3 | Sex

Female controls had 56.3% higher mean lumbar spine MF FF compared to male controls (female mean FF: 25.28 ± 8.17, male mean FF: 16.17 ± 8.51, $p < 0.0001$). In addition, female patients had 26.5% higher mean lumbar spine MF FF compared to male patients (female mean FF: 27.56 ± 11.22, male mean FF: 21.79 ± 9.17, $p = 0.0001$).

After stratifying by sex, we identified 19 female patients (mean age: 48.72 ± 13.14, mean BMI: 25.30 ± 6.01) and 8 female controls (mean age: 44.10 ± 13.91, mean BMI: 25.73 ± 5.61). Female patients had 9.0% higher mean lumbar spine MF FF compared to female controls (patients: 27.56 ± 11.22, controls: 25.28 ± 8.17, $p = 0.4058$). Level-specific analyses did not show a significant difference in MF FF in the female cohort at any level. When comparing the MF FF distribution patterns via Kernel two-sample testing, no significant difference was observed between patients and controls in our female cohort ($p = 0.087$; Figure 4).

In our male cohort, we identified 20 patients (mean age: 46.20 ± 11.67, mean BMI: 26.07 ± 4.06) and 10 controls (mean age: 41.65 ± 12.52, mean BMI: 22.85 ± 2.63). Male patients had 34.8% higher mean lumbar spine MF FF compared to male controls (patients: 21.79 ± 9.17, controls: 16.17 ± 8.51, $p = 0.0006$). At L2L3 and L3L4 specifically, we observed 53.7% (patients: 21.40 ± 9.43, controls: 13.92 ± 8.24, $p = 0.037$) and 50.6% (patients: 19.95 ± 9.73, controls: 13.25 ± 7.04, $p = 0.041$) higher MF FF in male patients, respectively. All other level-specific differences were not significant. When comparing the MF FF distribution patterns via Kernel two-sample testing, a statistically significant difference was observed between patients and controls in our male cohort ($p = 0.028$; Figure 4).

3.4 | BMI

In the control cohort, univariate linear regression revealed that BMI (OR: 3.33, 95% CI: 1.95–5.68, $p < 0.0001$) was a significant predictor

TABLE 1 Demographics, VAS, ODI, and mean lumbar MF FF of each cohort

	N	Age (SD)	Female (%)	BMI (SD)	VAS (SD)	ODI (SD)	Mean MF FF (SD)
All patients	39	47.43 (12.31)	48.7	25.70 (5.08)	6.59 (1.65)	33.24 (14.07)	24.60 (10.60)
All volunteers	18	42.74 (12.81)	44.4	24.05 (4.34)	0	0.44 (1.84)	20.22 (9.48)
Patient, old	23	56.14 (6.56)	56.5	27.38 (5.47)	6.89 (1.60)	37.47 (14.06)	28.85 (10.82)
Patient, young	16	34.90 (6.08)	37.5	23.44 (3.40)	6.17 (1,63)	27.28 (11.81)	18.62 (6.70)
Control, old	7	56.61 (6.85)	42.9	25.40 (3.68)	0	0	26.58 (9.19)
Control, young	11	33.91 (5.54)	45.5	23.08 (4.57)	0	0.73 (2.32)	16.18 (7.21)
Patient, female	19	48.72 (13.14)	100	25.30 (6.01)	6.68 (1.73)	36.02 (15.48)	27.56 (11.22)
Patient, male	20	46.20 (11.67)	0	26.07 (4.06)	6.50 (1.57)	30.60 (12.08)	21.79 (9.17)
Control, female	8	44.10 (13.91)	100	25.73 (5.61)	0	0	25.28 (8.17)
Control, male	10	41.65 (12.52)	0	22.85 (2.63)	0	0.8 (2.42)	16.17 (8.51)
Patient, high BMI	22	51.24 (10.79)	38.1	29.35 (3.71)	6.67 (1.71)	33.71 (15.91)	27.59 (11.64)
Patient, low BMI	17	41.53 (11.44)	58.8	21.20 (1.95)	6.53 (1.62)	32.02 (11.62)	20.48 (7.72)
Control, high BMI	6	50.11 (14.40)	50.0	27.75 (2.99)	0	0	26.53 (10.97)
Control, low BMI	6	36.94 (5.80)	33.3	20.35 (1.04)	0	1.33 (3.03)	15.80 (6.40)
High VAS	29	48.98 (11.89)	48.3	25.97 (5.22)	7.28 (1.25)	35.38 (13.75)	25.14 (10.36)
Low VAS	10	42.93 (13.03)	50.0	24.93 (4.61)	4.5 (0.53)	26.40 (14.04)	23.02 (11.20)
High ODI	14	53.30 (9.38)	64.2	27.45 (6.21)	7.57 (1.70)	49.0 (6.60)	27.41 (10.26)
Low ODI	25	44.14 (12.68)	40.0	24.77 (4.09)	6.0 (1.35)	24.16 (8.08)	23.00 (10.49)

Abbreviations: FF, fat fraction; MF, multifidus.

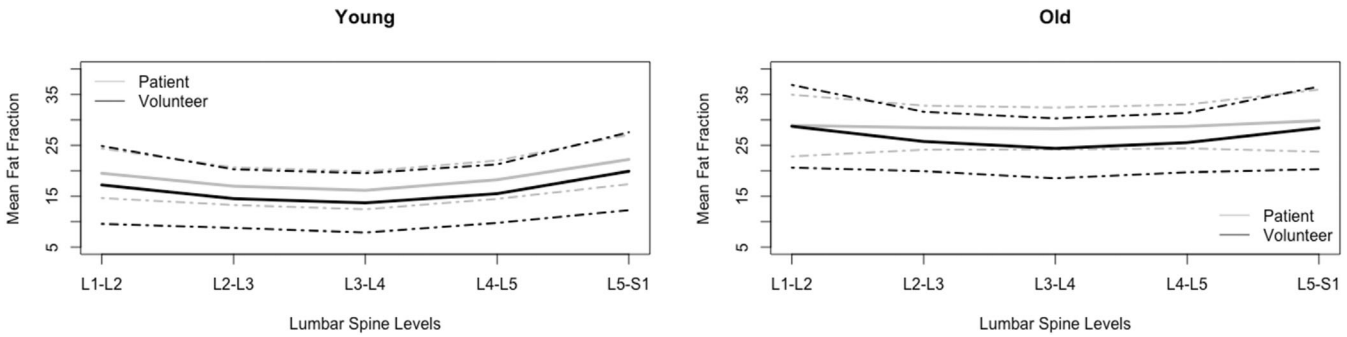

FIGURE 3 Mean fat fraction at each spinal level in young patients and young asymptomatic volunteers (left). Mean fat fraction at each spinal level in old patients and old asymptomatic volunteers (right). Dotted lines represent 95% confidence interval.

of increased mean lumbar spine MF FF. In the patient cohort, univariate linear regression also revealed that BMI (OR: 3.16, 95% CI: 2.46–4.06, $p < 0.0001$) was a significant predictor of increased mean lumbar spine MF FF.

After stratifying by BMI, we identified 17 patients (mean age: 41.53 ± 11.44, female: 58.8%, mean BMI 21.20 ± 1.95) and 6 controls (mean age: 36.94 ± 5.80, female: 33.3%, mean BMI 20.35 ± 1.04) in our lower BMI cohort. Low BMI patients had 29.7% higher mean lumbar spine MF FF compared to low BMI controls (patients: 20.49 ± 7.72, controls: 15.80 ± 6.40, $p = 0.0077$). Level-specific analyses did not show a significant difference in MF FF in our lower BMI cohort at any level. When comparing the MF FF distribution patterns via Kernel two-sample testing, no statistically significant difference was observed between patients and controls in our lower BMI cohort ($p = 0.6540$; Figure 5).

In our higher BMI cohort, we identified 22 patients (mean age: 51.24 ± 10.79, female: 38.1%, mean BMI 29.35 ± 3.71) and 6 controls (mean age: 50.11 ± 14.40, female: 50.0%, mean BMI 27.75 ± 2.99). High BMI patients had 4.0% higher mean lumbar spine MF FF compared to high BMI controls (patients: 27.59 ± 11.64, controls: 26.53 ± 10.97, $p = 0.7933$). Level-specific analyses did not show a significant difference in MF FF in our higher BMI cohort at any level. When comparing the MF FF distribution patterns via Kernel two-sample testing, a statistically significant difference was observed between patients and controls in our higher BMI cohort ($p = 0.0324$; Figure 5).

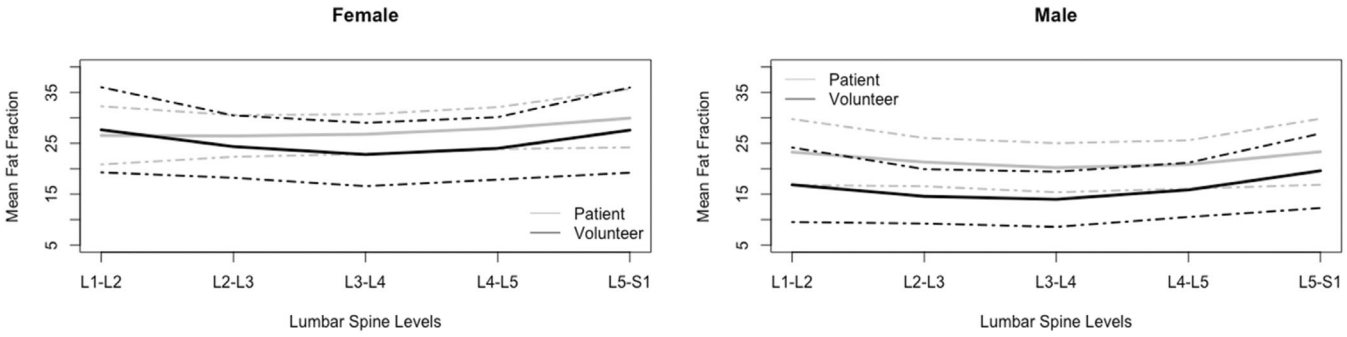

FIGURE 4 Mean fat fraction at each spinal level in female patients and female asymptomatic volunteers (left). Mean fat fraction at each spinal level in male patients and male asymptomatic volunteers (right). Dotted lines represent 95% confidence interval.

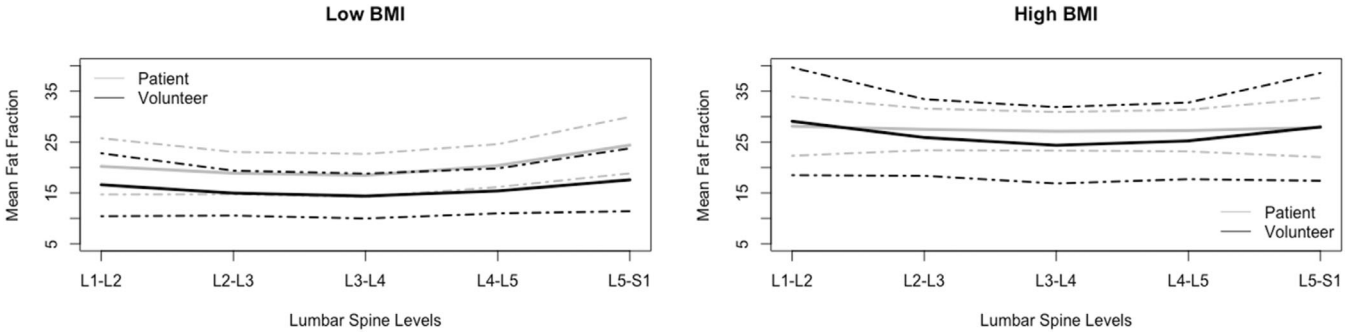

FIGURE 5 Mean fat fraction at each spinal level in low BMI patients and low BMI asymptomatic volunteers (left). Mean fat fraction at each spinal level in high BMI patients and high BMI asymptomatic volunteers (right). Dotted lines represent 95% confidence interval.

3.5 | VAS

In the patient cohort, univariate linear regression revealed that VAS (OR: 3.87, 95% CI: 1.60–9.39, $p = 0.0031$) was a significant predictor of increased mean lumbar spine MF FF.

We identified 10 patients (mean age: 42.93 ± 13.03, female: 50%, mean BMI: 24.93 ± 4.61) that have VAS back <6, and compared them to our 18 controls (mean age: 42.74 ± 12.81, female: 44.4%, mean BMI: 24.05 ± 4.34). Low VAS patients had 13.8% higher mean lumbar spine MF FF compared to all controls (patients: 23.02 ± 11.20, controls: 20.22 ± 9.48, $p = 0.2811$). Level-specific analyses did not show a significant difference in MF FF in our low VAS cohort at any level. When comparing the MF FF distribution patterns via Kernel two-sample testing, no significant difference was observed between the low VAS and control groups ($p = 0.53$; Figure 6).

We identified 29 patients (mean age: 48.98 ± 11.89, female: 48.3%, mean BMI: 25.97 ± 5.22) that have VAS back ≥6, and compared them to our 18 controls (mean age: 42.74 ± 12.81, female: 44.4%, mean BMI: 24.05 ± 4.34). High VAS patients had 24.3% higher mean lumbar spine MF FF compared to all controls (patients: 25.14 ± 10.36, controls: 20.22 ± 9.48, $p = 0.0011$). At L2L3 and L3L4 specifically, we observed 34.7% (patients: 24.72 ± 11.04, controls: 18.35 ± 9.34, $p = 0.040$) and 34.6% (patients: 23.19 ± 11.22, controls: 17.23 ± 8.00, $p = 0.040$) higher MF FF in high VAS patients, respectively. When comparing the MF FF distribution patterns via Kernel two-sample testing, a significant difference was observed between the high VAS and control groups ($p < 0.0001$; Figure 6).

3.6 | ODI

In the patient cohort, univariate linear regression revealed that ODI (OR: 1.33, 95% CI: 1.21–1.47, $p < 0.0001$) was a significant predictor of increased mean lumbar spine MF FF.

We identified 25 patients (mean age: 44.14 ± 12.68, female: 40.0%, mean BMI: 24.77 ± 4.09) that have ODI <40 and compared them to our 18 controls (mean age: 42.74 ± 12.81, female: 44.4%, mean BMI: 24.05 ± 4.34). Low ODI patients had 13.7% higher mean lumbar spine MF FF compared to all controls (patients: 23.00 ± 10.49, controls: 20.22 ± 9.48, $p = 0.1415$). Level-specific analyses did not show a significant difference in MF FF in our low ODI cohort at any level. When comparing the MF FF distribution patterns via Kernel two-sample testing, no significant difference was observed between the low ODI and control groups ($p = 0.35$; Figure 7).

We identified 14 patients (mean age: 53.30 ± 9.38, female: 64.2%, mean BMI: 27.45 ± 6.21) that have ODI ≥40 and compared them to our 18 controls (mean age: 42.74 ± 12.81, female: 44.4%, mean BMI: 24.05 ± 4.34). High ODI patients had 35.6% higher mean lumbar spine MF FF compared to all controls (patients: 27.41 ± 10.26, controls: 20.22 ± 9.48, $p < 0.0001$). At L2L3, L3L4, and L4L5

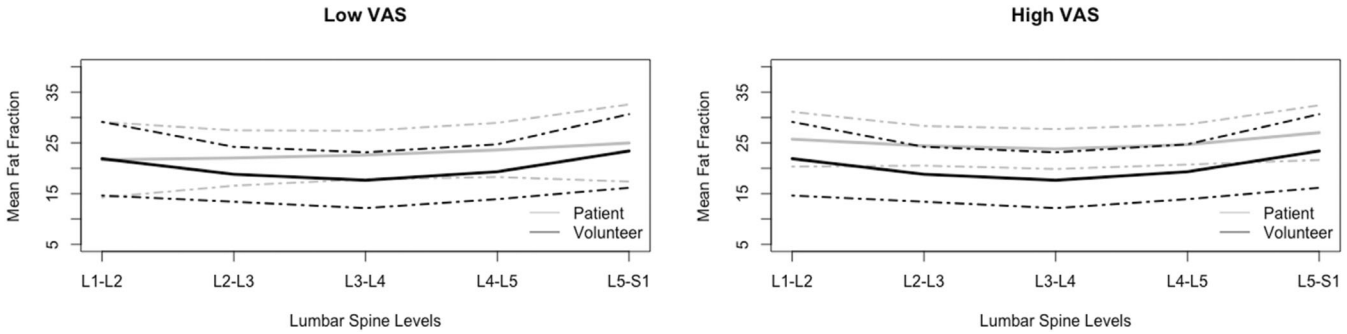

FIGURE 6 Mean fat fraction at each spinal level in low VAS patients and all asymptomatic volunteers (left). Mean fat fraction at each spinal level in high VAS patients and all asymptomatic volunteers (right). Dotted lines represent 95% confidence interval.

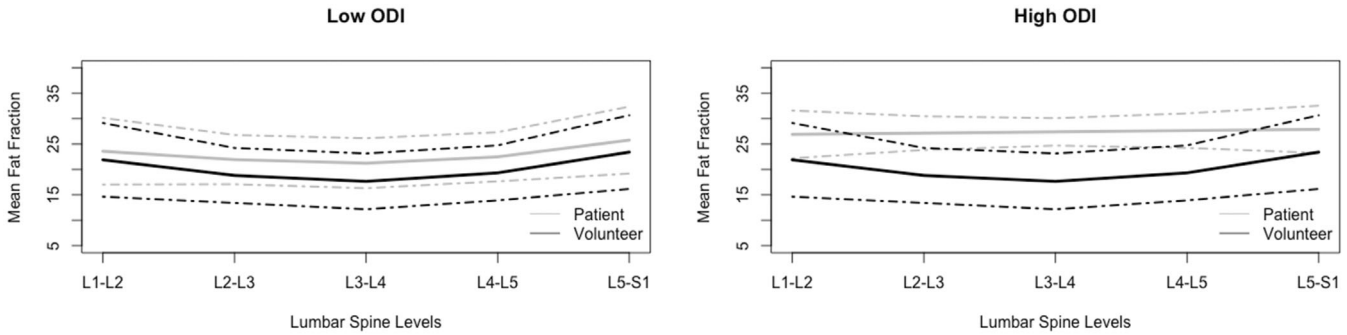

FIGURE 7 Mean fat fraction at each spinal level in low ODI patients and all asymptomatic volunteers (left). Mean fat fraction at each spinal level in high ODI patients and all asymptomatic volunteers (right). Dotted lines represent 95% confidence interval.

specifically, we observed a 48.5% (patients: 27.25 ± 11.90, controls: 18.35 ± 9.34, $p = 0.030$), 53.1% (patients: 26.38 ± 11.09, controls: 17.23 ± 8.00, $p = 0.016$), and 41.2% (patients: 25.75 ± 9.30, controls: 18.24 ± 8.84, $p = 0.025$) higher MF FF in high ODI patients, respectively. When comparing the MF FF distribution patterns via Kernel two-sample testing, a significant difference was observed between the high ODI and control groups ($p < 0.0001$; Figure 7).

4 | DISCUSSION

The purpose of the present study was to investigate how patient-specific factors, including age, sex, BMI, VAS, and ODI, may influence fat infiltration in the MF muscle and whether these relationships are different between patients with cLBP and pain-free controls. We observed that age, female sex, BMI, VAS, and ODI were significant predictors for higher mean lumbar spine MF FF in both our patient and control populations, and that these factors all uniquely play a role when comparing patients and controls within each of their respective categories.

Muscles are mechanoreceptive tissues that respond to use/disuse, and their form and composition are dictated by numerous patient-specific factors. The factors leading to the accumulation of intra- and intermuscular fat are not well understood, but evidence indicates that increases in intramuscular fat may be associated with disuse, altered leptin signaling, sex steroid deficiency, and glucocorticoid treatment.[22] There have been multiple studies conducted over the years to investigate paraspinal muscle morphology and its relationship to LBP, yet the exact relationship remains unclear. A recent systematic review of 25 LBP and paraspinal muscle studies conducted by Ranger et al. concluded that the current literature has limited or conflicting evidence for the relationship between fat infiltration of paraspinal muscles and LBP.[10] Disagreement within related literature stems mainly from differences in methodology including imaging modality, paraspinal muscles selection, study design (no controls, differing inclusion/exclusion criteria of LBP), and the definition of muscle quality.

Regional differences in the physical strain put on the MF muscle may affect focal parts of the muscle at various spinal levels.[23] With this in mind, we decided to analyze individual spinal level differences in our study. When comparing all of our patients to our controls, we observed a significant difference in fat content at the L3L4 disc level, but at no other levels. We also noted this difference in our male, high VAS, and high ODI sub-analyses. This level-specific difference across multiple groups highlights a potential association between cLBP and increased fat at the L3L4 level. However, to make this study more complete, we also conducted a detailed analysis of mean lumbar spine measurements and fat distribution patterns to emphasize the importance of methodology when analyzing cLBP patients, as single-level measurements are not representative on their own.[19]

Fat infiltration is a natural phenomenon that is understood to increase as we age, is relatively higher in females, and increases with

higher overall body fat composition.[24,25] The mechanism of fat infiltration as a biomarker of cLBP remains unclear, as numerous factors such as illness and disuse have been documented to increase the content of intramuscular fat.[22,26] Our data suggest that the presence and distribution pattern of MF fat beyond that which is characteristic of an individual's age, sex, and weight profile, may be a distinct factor related to cLBP symptoms. As seen in our results, when we separate by age, significant differences in MF fat distribution patterns were only seen when comparing our older patients to our older controls, highlighting the idea that fat infiltration may be related to pain when it is not characteristic for an individual's age. However, the young group also had differences noted that may become significant if the power of the study was increased.

Female patients with pain may be hard to distinguish from the normal characteristic profile of fat infiltration of a pain-free individual, as fat replacement of paraspinal muscles is a normal age-progressive phenomenon that is most prominent in females.[27] As shown in our results, females not only have significantly increased intramuscular fat as quantified by IDEAL imaging in both patient and control populations, but also have insignificant differences in mean lumbar spine MF FF and fat distribution patterns between female patients and female controls. This effect of sex can be helpful in the clinical understanding of imaging, as we only observed this masking effect of fat content in females, with our male patient cohort having a significantly higher mean lumbar spine MF FF and significantly different fat distribution patterns compared to male pain-free controls.

Similarly, we observed the masking effect of fat infiltration with generally higher body fat composition, as seen in our high BMI cohort. As shown in our results, we only observed significant differences in mean lumbar spine MF FF when comparing low BMI patients to low BMI controls, not in our high BMI cohort. Increased intra- and intermuscular fat has been linked to higher overall body fat composition,[28] so when attempting to understand the imaging of an individual with cLBP, higher BMI may confound meaningful conclusions.

Lastly, patient reported outcomes, such as VAS and ODI, have been shown to have an association with increased intramuscular fat of the paraspinal muscles.[29] Here, we find that individuals with higher VAS and ODI had significant differences in mean lumbar spine MF FF, fat distribution patterns and level-specific differences at L2L3, L3L4, and L4L5 only when comparing patients with high VAS and high ODI to the control population, but not in our low VAS or ODI cohorts. Therefore, patients who fall under the current classifications of cLBP with relatively lower VAS and ODI, do not have significantly different patterns of fat infiltration compared to those who are pain-free. This may mean that fat infiltration may only be a characteristic for those with severe pain. Further research is warranted to fully understand the interplay between pain scoring systems and MF fat infiltration.

5 | LIMITATIONS

In the present study, we are examining subjects at a single timepoint, as we do not have chronicity or follow-up measurements. In addition, we do not have metrics on the amount of physical activity for our population, which may affect the fat content measurements. Given that there are a greater proportion of females in the low BMI patient group compared to the low BMI control group, and that this study found that females have higher MF FF than males, the conclusions drawn from the low BMI analysis may be limited. In the future, there is a need for a larger, longitudinal study that tracks changes in age, BMI, VAS and ODI to strengthen our understanding of fat infiltration in the MF.

6 | CONCLUSION

This study provides insight on the multifactorial presentation of fat infiltration in patients, and suggests that when the presence of fat is not characteristic of an individual's age, sex, and weight profile, fat infiltration may be an indicator of painful sensation. In addition, our study highlights that cLBP patients with relatively lower VAS and ODI do not have significantly different patterns of MF fat infiltration from pain-free individuals. Finally, our study points to a potential masking effect of fat infiltration seen in female and obese patients due to the natural deposition of fat for females as they age and with obese individuals with increasing overall body fat composition. A proper understanding of the causes and significance of intramuscular fat may augment the targeted therapeutics for the subset of patients who have fat infiltration that is not characteristic of their age, sex, and weight profile.

AUTHOR CONTRIBUTIONS

Alexander M. Ballatori designed, collected and analyzed the data, and wrote the manuscript. Shane Shahrestani conducted all the statistical analyses. Priya Nyayapati collected data. Vibhu Agarwal assisted in study design and statistical analysis. Roland Krug and Misung Han developed the images for this study. Aaron J. Fields, Conor O'Neill, and Sibel Demir-Deviren aided in patient acquisition and data analysis. Jeffrey C. Lotz received funding for this work, contributed to design of the study, and aided in revising the manuscript. Jeannie F. Bailey designed, collected, and analyzed the data, as well as revising the manuscript with Alexander M. Ballatori. All authors have read and approve of the final manuscript.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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