ORIGINAL ARTICLE



Is preoperative fat infiltration in lumbar spine muscles associated with worse clinical outcomes after lumbar interbody fusion?

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Abstract

Purpose Lumbar musculature has a fundamental role in spine stability and spinal balance. Muscle atrophy and fat infiltration play an important role in pain pathophysiology. Accordingly, the preoperative condition of lumbar muscles may influence clinical outcomes after surgical treatment. In this context, the aim of this study was to evaluate the association between preoperative lumbar paravertebral muscle fat infiltration and clinical outcomes after lumbar interbody fusion.

Methods A retrospective study of patients with lumbar pathology submitted to lumbar transforaminal (TLIF) or posterior interbody fusion (PLIF) was performed, with a minimum of two years of follow-up. Preoperative lumbar magnetic resonance imaging (MRI) images were classified for fat infiltration in lumbar multifidus muscle and correlated with clinical outcomes. **Results** Seventy-five patients were included: 24 submitted to PLIF and 51 to TLIF. Most patients underwent surgery for spondylolisthesis (67%). Higher degrees of fat infiltration were associated with more advanced age (54.8 vs. 49.1 years old, p=0.04) and more leg pain after surgery (p=0.04). No statistically significant differences in other clinical outcomes such as Oswestry Disability Index, visual analogue scale for back and leg pain, self-reported back pain relief, return to work and overall satisfaction were found between different groups of fat infiltration. The improvement in leg pain was associated with improvement in self-reported lumbar pain (p < 0.001).

Conclusion Age and preoperative degree of fat infiltration may be important to predict improvement in leg pain after lumbar interbody fusion. The absence of solid literature on this topic and universal assessment methodologies reinforce the need for further studies.

Keywords Lumbar muscles · Muscle atrophy · Interbody fusion · Fat infiltration

Introduction

Paraspinal muscles are considered dynamic stabilizers, providing stability in spinal motion. Thereby, lumbar muscle imbalance is a frequent cause of low back pain (LBP), which is associated with disability and increased health care costs

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[1, 2]. Specific rehabilitation involving lumbar muscles can reduce LBP and prevent its recurrence [3, 4].

Histological studies have shown a change in distribution of fibre types and a reduction of muscle size in patients with chronic LBP [5, 6]. Additionally, imaging studies confirmed the relation between LBP and muscle size and fat infiltration [7, 8]. In patients with unilateral LBP, decreased crosssectional area (CSA) of lumbar muscles was reported on the painful side compared with the contralateral [9]. However, the CSA of the muscle may not be diminished, due to fatty infiltration in muscular bundle. Magnetic resonance imaging (MRI) is useful for CSA tissues differentiation due to its good soft-tissue contrast and its radiation free properties [7, 8].

Although several studies associate LBP with muscle atrophy and fat infiltration [7, 8, 10], only a few correlate preoperative fat infiltration with functional results after lumbar surgery [11, 12]. In particular, studies in patients submitted to interbody fusion are even less [13, 14].

This study aims to evaluate the prognostic value of preoperative MRI fat infiltration in paravertebral lumbar musculature and subsequent clinical outcomes after lumbar transforaminal (TLIF) or posterior interbody fusion (PLIF). The authors hypothesized that patients with fatty muscle atrophy on preoperative MRI, would have poorer clinical outcomes compared with those without these abnormal muscle changes.

Methods

A retrospective study evaluating preoperative lumbar fat infiltration and clinical outcomes in patients with lumbar pathology submitted to lumbar TLIF or PLIF was performed. The protocol was approved by the institutional review board of the hospital.

Patient selection

Patients with lumbar degenerative pathology (degenerative disc disease, lumbar spinal stenosis, spondylolisthesis and adult spinal deformity) submitted to open lumbar transforaminal or posterior interbody fusion, between 2009 and 2018, were included. Neoplasic, infectious and traumatic conditions were excluded, as well as patients with surgical site infection or submitted to implant extraction. A minimum of two years of clinical follow-up and a MRI performed 0 to 12 months before surgery were mandatory for inclusion.

Data collection

Electronic and paper medical records were retrospectively reviewed for all patients. Patient-related analysis included: demographic data (age and gender), body mass index (BMI), previous lumbar spine fractures, primary or revision surgery and type of pathology. Procedure-related analysis included: type of lumbar interbody fusion (TLIF or PLIF), interbody fusion level(s), number of instrumented levels and surgical complications.

Several classifications can be used to assess the degree of lumbar spine fat infiltration. The authors used the Tamai et al. [15] classification, which mimics the Goutallier classification of fat infiltration in shoulder rotator cuff muscles. The fat content of the lumbar multifidus muscle was graded on axial T2-weighted images according to a qualitative visual grading method. The grades were defined as follows: grade 0, no intramuscular fat; grade I, some fatty streaks present; grade II, fat evident, but less than muscle tissue; grade III, amounts of fat equal to amount of muscle; grade IV, more fat than muscle tissue (Fig. 1). Since no single-level is representative of the whole lumbar spine and a standardized multi-level evaluation of the paraspinal musculature should be used 16, three vertebral levels were evaluated: the level submitted to interbody fusion (index level) and the adjacent levels (above and below). Of these three levels analysed, the one with most fatty infiltration was considered the "worst level".

In cases with a fixation at two levels, the degree of the index level was considered the worst of the two segments. In cases with more than two levels fixed, the degree of the index level was considered the average of degrees in the fixed segments. Classification was performed by a neuroradiologist and validated by two investigators. Disagreements were solved through discussion.

Clinical outcomes were collected by telephone interview. Pain was assessed using Oswestry disability index (ODI), visual analogue scale (VAS) for back and leg pain, and selfreport improvement in back and leg pain. Patient return to previous work and overall satisfaction were also evaluated.

Statistical analysis

All data were analysed using SPSS (version 25.0, SPSS Inc., Chicago, IL, USA). A significant difference was set as p < 0.05. In order to increase statistical power and establish a relevant clinical difference, the degrees of classification were aggregated into two groups: group 1, from no intramuscular fat to evident fat, but less than muscle tissue (grade 0 to II) and group 2, from amounts of fat equal to amount of muscle to more fat than muscle tissue (grade III and IV). Once the index lumbar level and the adjacent levels were classified,

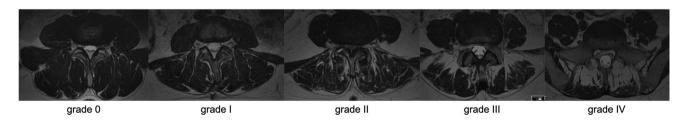


Fig. 1 Goutallier classification on axial T2-weighted images defined as follows: grade 0, no intramuscular fat; grade I, some fatty streaks present; grade II, fat evident, but less than muscle tissue; grade III, amounts of fat equal to amount of muscle; grade IV, more fat than muscle tissue statistical analysis was performed for the index level and for the "worst" of the three segments. Between-group comparisons were tested using independent samples *t*-tests for continuous dependent variables and a Chi-Square test for categorical variables. A correlation test was used for continuous variables. Multivariate logistic regression analysis was performed to identify variables associated with clinical outcomes by systematically pruning the least significant variables out of a multiple logistic regression model that initially included all variables.

Results

The description of the sample, patient and procedure related variables, as well as the clinical results are shown in Table 1.

A total of 75 patients were included: 24 (32%) submitted do PLIF and 51 (68%) submitted to TLIF. Most patients underwent surgery for spondylolisthesis (n=50, 67%), followed by degenerative disc disease (n=21, 28%), lumbar spine stenosis (n=3, 4%) and adult coronal spine deformity (n=1, 1%). In the vast majority of patients, one-level fusion was performed (n=56, 75%), followed by two-level fixation (n=17, 23%), and only one patient with three (n=1, 1%) and four (n=1, 1%) segments fixed. Almost all fused segments were at the level of L4-L5 and L5-S1. Most of the patients were female (n=51, 68%) and the mean age was 52 years old (from 22 to 76 years old).

Most of the patients had low degrees of fat infiltration at the index lumbar level (group 1-n=48, 64% vs. group 2-n=27, 36%). Patients with greater fat infiltration (group 2) at the "worst level" were significantly older compared

	Interbody fus	Interbody fusion level $(n=75)$			Worst level		
	0–II	III–IV	р	0–II	III–IV	р	
Sex							
Male	18 (38%)	6 (22%)	0.17	14 (44%)	10 (23%)	0.06	
Female	30 (62%)	21 (78%)		18 (56%)	33 (77%)		
Age	52.4	52.1	0.94	49.1	54.8	0.04	
BMI	29.9	29.0	0.94	29.0	28.8	0.86	
Pathology							
Degenerative disc disease	15 (31%)	6 (22%)	0.50	8 (25%)	13 (30%)	0.29	
Spondylolisthesis	31 (65%)	19 (70%)		24 (75%)	26 (61%)		
Lumbar spinal stenosis	1 (2%)	2 (8%)		0 (0%)	3 (7%)		
Adult scoliosis	1 (2%)	0 (0%)		0 (0%)	1 (2%)		
Revision surgery							
Yes	9 (19%)	5 (19%)	0.10	5 (16%)	9 (21%)	0.56	
No	39 (81%)	22 (81%)		27 (84%)	34 (79%)		
Previous lumbar fractures							
Yes	0 (0%)	0 (0%)	-	0 (0%)	0 (0%)	_	
No	48 (100%)	27 (100%)		32 (100%)	43 (100%)		
ODI	30.5	30.0	0.89	31.3	29.6	0.70	
VAS-lumbar	5.8	4.8	0.24	5.9	5.0	0.27	
VAS-leg	4.3	3.9	0.71	4.0	4.2	0.94	
Self-reported pain relief-lun	nbar						
Yes	44 (92%)	25 (93%)	0.89	30 (94%)	39 (91%)	0.63	
No	4 (8%)	2 (7%)		2 (6%)	4 (9%)		
Self-reported pain relief-leg							
Yes	43 (90%)	23 (85%)	0.57	31 (97%)	35 (81%)	0.04	
No	5 (10%)	4 (15%)		1 (3%)	8 (19%)		
Return to work							
Yes	24 (50%)	12 (44%)	0.15	17 (53%)	19 (44%)	0.72	
No	14 (29%)	13 (48%)		10 (31%)	17 (40%)		
not applied	10 (21%)	2 (8%)		5 (16%)	7 (16%)		
Overall satisfaction							
Yes	38 (78%)	23 (85%)	0.49	27 (84%)	34 (79%)	0.60	
No	10 (22%)	4 (15%)		5 (16%)	9 (21%)		

with patients in group 1 (54.8 \pm 11.5 vs. 49.1 \pm 12.0 years old, p = 0.04). Regarding "worst level", patients in group 2 reported less relief in leg pain after surgery (81% vs. 97% of group 1, p = 0.04). No differences were found for ODI, VAS for back pain, self-reported back pain relief, return to work and overall satisfaction between groups.

Patients who reported an improvement in leg pain after surgery were younger compared with those who did not (51.2 vs. 60.6 years old, p = 0.027) (Table 2). These patients were also more satisfied with the overall surgical result (95% vs. 57%, p = 0.001). The improvement in leg pain was associated with improvement in self-reported lumbar pain (p < 0.001) and lower post-operative VAS for leg pain (p < 0.001). This improvement was not associated with sex, BMI, type of pathology, type of surgery performed, number of levels fixed, ODI or with return to work.

 Table 2
 Characterization of factors associated with leg pain improvement

	Self-reported pain relief-leg				
	Yes	No	р		
Sex					
Male	22 (92%)	2 (8%)	0.71		
Female	44 (86%)	7 (14%)			
Age	51.2	60.6	0.03		
BMI	28.9	28.8	0.95		
Pathology					
Degenerative disc disease	19 (91%)	2 (9%)	0.84		
Spondylolisthesis	43 (86%)	7 (14%)			
Lumbar spinal stenosis	3 (100%)	0			
Adult scoliosis	1 (100%)	0			
Revision surgery					
Yes	12 (86%)	2 (14%)	0.77		
No	54 (89%)	7 (11%)			
Surgery					
PLIF	23 (96%)	1 (4%)	0.26		
TLIF	43 (84%)	8 (16%)			
ODI	28.6	42.74	0.06		
Number of levels fixed	1.32	1.11	0.305		
VAS—lumbar	5.4	6.2	0.32		
VAS—leg	3.6	8.3	< 0.001		
Self-reported pain relief-lum	bar				
Yes	65 (93%)	4 (17%)			
No	1 (6%)	5 (94%)	< 0.001		
Return to work					
Yes	32 (49%)	4 (44%)	0.25		
No	22 (33%)	5 (56%)			
not applied	12 (18%)	0			
Overall satisfaction					
Yes	57 (95%)	5 (5%)	0.001		
No	8 (57%)	6 (43%)			

A correlation was found between age and VAS for leg pain (p = 0.037). A strong correlation was found between ODI and VAS for lumbar and leg pain (both p < 0.001) and between VAS for lumbar and leg pain (p < 0.001) (Table 3). However, no correlation was found between age and ODI (p = 0.059) or between age and VAS for lumbar pain (p = 0.098).

In the multivariate logistic regression to analyse factors that independently influence pain improvement, there was no statistically significant association, when considering age (p=0.08), degree of fat infiltration (p=0.11) or type of surgery (p=0.11).

Discussion

Previous studies have consistently demonstrated the relationship between LBP and fat infiltration in lumbar spine muscles [10]. However, few studies evaluated this relationship in patients submitted to lumbar surgery and their impact in clinical outcomes. A systematic review by Jermy et al. [11], including six studies in a total of 837 patients, found an association between low multifidus fat infiltration in preoperative MRI and greater reductions of low back pain and disability following surgical treatment. However, the included studies were dissimilar in terms of fat infiltration grading technique, surgical intervention and reporting of outcomes for individual patients, so a summary statistic of effect size including all the available literature could not be calculated. A direct relationship between greater degrees of fat infiltration and less improvement in leg pain is not clear.

In this paper, the authors analysed if preoperative lumbar multifidus muscle fat infiltration is correlated with clinical and surgical outcomes. The authors found that patients with high grade of fat infiltration (grades III and IV) at "worst level" reported less improvement in leg pain after surgery and were older. These two findings may be important to predict improvement in leg pain after surgery. A study of Zhong et al. [16] found an association between positive straight leg-raising test and higher areas of fat infiltration in multifidus muscles in patients with lumbar disc herniation. Kader et al. demonstrated correlations in a cohort of patients with low back pain between the MRI appearance of the lumbar multifidus muscle and patients

Table 3 Correlation between age and clinical outcomes

	Age	VAS lumbar	VAS leg	ODI
Age				
VAS lumbar	0.098			
VAS leg	0.037	< 0.001		
ODI	0.059	< 0.001	< 0.001	

with additional leg pain [17]. Hides et al. have demonstrated that poor lumbar multifidus muscle contraction and reduced cross-sectional area of this muscle group to be associated with reduced transversus abdominis activation, and vice versa, with incompetence of these muscles linked to both back and leg symptoms [18]. By other side, Bonica et al. [19] stated an association between LBP and pain referred to the thigh. The wasting in the multifidus muscle may be caused by the Lumbar Dorsal Ramus Syndrome, which is defined as LBP with referred leg pain induced by irritation to structures innervated by the dorsal ramus nerve, e.g. facet joints, multifidus muscle and interspinous ligaments, or by myofascial injury due to acute or chronic trauma which initiates myofascial pain, spasm and ischaemia. This triggers a self-sustained vicious cycle that promotes muscle atrophy.

The authors suggest that patients with less improvement in leg pain are older, with a greater degree of fat infiltration, and therefore with a longer onset radiculopathy and, in this sense, less susceptible to improvement, compared to younger patients, with less lumbar muscle fat infiltration and less time for the onset of symptoms. Since there is no strong evidence in the literature that could support and justify this association, future studies should clarify it.

Patients in the group with greater fat infiltration in the "worst level" were older compared with the other group, which is in agreement with previous studies [7, 20]. The fact that fat infiltration is more common in adults does suggest that it is the LBP that causes muscle degeneration and that in younger patients, the LBP has not yet lasted sufficiently long to produce such changes [7]. The influence of aging on muscle mass and fat infiltration may be common regardless of the presence or absence of spinal disease, muscular type and race [21].

In this study muscle fat infiltration was not associated with BMI, which is in agreement with previous studies [7, 8, 20] stating that BMI was shown not to influence the presence of fat in the lumbar muscles. No relationship was found between fat infiltration and gender, contrary to what would be expected. According to some authors [7], the higher proportion of body fat in females is also reflected in the proportion of fat in the lumbar muscles.

This study has some limitations. Due to its retrospective nature a baseline preoperative status was missing and, therefore, a correlation between patient preoperative clinical status and fat infiltration was not possible. Furthermore, patient number was relatively small, which may have precluded some findings from being identified. Nonetheless, this study is an important addition to the literature in this topic, which lacks uniformity, due to the use of different classifications for fat infiltration and scores for clinical outcomes and to the different types of lumbar pathology and surgical approaches used.

Given that improvement in lumbar muscles trophy is related to LBP relief [22, 23], future studies should address how post-operative lumbar muscle conditioning programs can improve patients' surgical outcomes. Furthermore, it would be essential to assess the degree of fat infiltration after surgery, especially at adjacent levels. One study demonstrated adjacent-segment degeneration after L4-5 transforaminal lumbar interbody fusion for degenerative spondylolisthesis [24] and another one showed atrophy and fatty infiltration of the multifidus at the index level and below on the ipsilateral side after primary one-level minimally invasive discectomy [25]. By other side, the literature has demonstrated the advantage of minimally invasive approaches over the traditional open ones, particularly in the reduction of muscle atrophy and in lower degrees of fat infiltration [26, 27].

Conclusion

The authors found an association between high degrees of fat infiltration and age and less improvement in post-operative leg pain. Although previous studies have shown that low multifidus fat infiltration in preoperative MRI is correlated with greater reductions of low back pain and disability following surgical treatment, the absence of a standard methodology makes it difficult to draw valid conclusions. Towards the possibility of improving clinical results through this factor modification, further studies with standard methodology should be carried out to define this association.

Declarations

Conflict of interest The authors declare no conflict of interests.

Ethical approval The protocol was approved by the institutional review board of the hospital.

References

- Andersson GB (1999) Epidemiological features of chronic lowback pain. Lancet 354(9178):581–585
- Teichtahl AJ, Urquhart DM, Wang Y, Wluka AE, Wijethilake P, O'Sullivan R, Cicuttini FM (2015) Fat infiltration of paraspinal muscles is associated with low back pain, disability, and structural abnormalities in community-based adults. Spine J 15(7):1593–1601
- O'Sullivan PB, Phyty GD, Twomey LT, Allison GT (1997) Evaluation of specific stabilizing exercise in the treatment of chronic low back pain with radiologic diagnosis of spondylolysis or spondylolisthesis. Spine 22(24):2959–2967
- Hodges PW, Moseley GL (2003) Pain and motor control of the lumbopelvic region: effect and possible mechanisms. J Electromyogr Kinesiol 13(4):361–370

- Mannion AF (1999) Fibre type characteristics and function of the human paraspinal muscles: normal values and changes in association with low back pain. J Electromyogr Kinesiol 9(6):363–377
- Mannion AF, Käser L, Weber E, Rhyner A, Dvorak J, Müntener M (2000) Influence of age and duration of symptoms on fibre type distribution and size of the back muscles in chronic low back pain patients. Eur Spine J 9(4):273–281
- Kjaer P, Bendix T, Sorensen JS, Korsholm L, Leboeuf-Yde C (2007) Are mri-defined fat infiltrations in the multifidus muscles associated with low back pain? BMC Med 5:2
- Wan Q, Lin C, Li X, Zeng W, Ma C (2015) Mri assessment of paraspinal muscles in patients with acute and chronic unilateral low back pain. Br J Radiol 88(1053):20140546
- Barker KL, Shamley DR, Jackson D (2004) Changes in the cross-sectional area of multifidus and psoas in patients with unilateral back pain: the relationship to pain and disability. Spine. 29(22):E515-519
- Goubert D, Oosterwijck JV, Meeus M, Danneels L (2016) Structural changes of lumbar muscles in non-specific low back pain: a systematic review. Pain Physician 19(7):E985–E1000
- Jermy JE, Copley PC, Poon MTC, Demetriades AK (2020) Does pre-operative multifidus morphology on mri predict clinical outcomes in adults following surgical treatment for degenerative lumbar spine disease? A systematic review. Eur Spine J 29(6):1318–1327
- 12. Storheim K, Berg L, Hellum C, Gjertsen Ø, Neckelmann G, Espeland A, Keller A (2017) Fat in the lumbar multifidus muscles predictive value and change following disc prosthesis surgery and multidisciplinary rehabilitation in patients with chronic low back pain and degenerative disc: 2-year follow-up of a randomized trial. BMC Musculoskelet Disord 18(1):145
- Guan F, Bao R, Zhu L, Guan G, Chi Z, Gu J, Yu Z (2017) Risk factors of postoperative low back pain for low-grade degenerative spondylolisthesis: an at least 2-year follow-up retrospective study. World Neurosurg 107:789–794
- Gu J, Guan F, Zhu L, Guan G, Chi Z, Wang H, Yu Z (2016) Risk factors of postoperative low back pain for lumbar spine disease. World Neurosurg 94:248–254
- 15. Tamai K, Chen J, Stone M, Arakelyan A, Paholpak P, Nakamura H, Buser Z, Wang JC (2018) The evaluation of lumbar paraspinal muscle quantity and quality using the goutallier classification and lumbar indentation value. Eur Spine J 27(5):1005–1012
- Zhong Y, Liu J, Zhou W, Yu D (2020) Relationship between straight leg-raising test measurements and area of fat infiltration in multifidus muscles in patients with lumbar disc hernation. J Back Musculoskelet Rehabil 33(1):57–63

- Kader DF, Wardlaw D, Smith FW (2000) Correlation between the mri changes in the lumbar multifidus muscles and leg pain. Clin Radiol 55(2):145–149
- Hides J, Stanton W, Mendis MD, Sexton M (2011) The relationship of transversus abdominis and lumbar multifidus clinical muscle tests in patients with chronic low back pain. Man Ther 16(6):573–577
- Bonica JJ (1957) Management of myofascial pain syndromes in general practice. J Am Med Assoc 164(7):732–738
- Parkkola R, Kormano M (1992) Lumbar disc and back muscle degeneration on MRI: correlation to age and body mass. J Spinal Disord 5(1):86–92
- Hida T, Eastlack RK, Kanemura T, Mundis GM, Imagama S, Akbarnia BA (2021) Effect of race, age, and gender on lumbar muscle volume and fat infiltration in the degenerative spine. J Orthop Sci 26(1):69–74
- 22. Storheim K, Holm I, Gunderson R, Brox JI, Bø K (2003) The effect of comprehensive group training on cross-sectional area, density, and strength of paraspinal muscles in patients sick-listed for subacute low back pain. J Spinal Disord Tech 16(3):271–279
- Käser L, Mannion AF, Rhyner A, Weber E, Dvorak J, Müntener M (2001) Active therapy for chronic low back pain: part 2. Effects on paraspinal muscle cross-sectional area, fiber type size, and distribution. Spine 26(8):909–919
- Duan PG, Mummaneni PV, Guinn JMV, Rivera J, Berven SH, Chou D (2020) Is the goutallier grade of multifidus fat infiltration associated with adjacent-segment degeneration after lumbar spinal fusion? J Neurosurg Spine 34(2):190–195
- 25. Tabaraee E, Ahn J, Bohl DD, Phillips FM, Singh K (2015) Quantification of multifidus atrophy and fatty infiltration following a minimally invasive microdiscectomy. Int J Spine Surg 9:25
- Fan SW, Hu ZJ, Fang XQ, Zhao FD, Huang Y, Yu HJ (2010) Comparison of paraspinal muscle injury in one-level lumbar posterior inter-body fusion: Modified minimally invasive and traditional open approaches. Orthop Surg 2(3):194–200
- 27. Putzier M, Hartwig T, Hoff EK, Streitparth F, Strube P (2016) Minimally invasive tlif leads to increased muscle sparing of the multifidus muscle but not the longissimus muscle compared with conventional plif-a prospective randomized clinical trial. Spine J 16(7):811–819

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