

Observational study

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The association between back muscle characteristics and pressure pain sensitivity in low back pain patients

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Abstract

Background and aims: Some low back pain (LBP) patients recover after every pain episode whereas others develop chronicity. Research indicates that the amount of atrophy and fat infiltration differs between patients with LBP. Also enhanced pain sensitivity is present only in a subgroup of LBP patients. The relationship between pain sensitivity and muscular deformations in LBP, is however unexplored. This study examined the association between pressure pain sensitivity and the structural characteristics

of the lumbar muscles in three different groups of non-specific LBP patients.

Methods: This cross-sectional study examined the total cross-sectional area (CSA), fat CSA, muscle CSA and muscle fat index (MFI) of the lumbar multifidus (MF) and erector spinae (ES) at level L4 by magnetic resonance imaging in 54 patients with non-specific LBP (23 recurrent LBP, 15 non-continuous chronic LBP and 16 continuous chronic LBP). Pressure pain thresholds were measured at four locations (lower back, neck, hand and leg) by a manual pressure algometer and combined into one “pain sensitivity” variable. As a primary outcome measure, the association between pain sensitivity and muscle structure characteristics was investigated by multiple independent general linear regression models. Secondly, the influence of body mass index (BMI) and age on muscle characteristics was examined.

Results: A positive association was found between pain sensitivity and the total CSA of the MF ($p=0.006$) and ES ($p=0.001$), and the muscle CSA of the MF ($p=0.003$) and ES ($p=0.001$), irrespective of the LBP group. No association was found between pain sensitivity and fat CSA or MFI ($p>0.01$). Furthermore, a positive association was found between BMI and the fat CSA of the MF ($p=0.004$) and ES ($p=0.006$), and the MFI of the MF ($p<0.01$) and ES ($p=0.003$). Finally, a positive association was found between age with the fat CSA of the MF ($p=0.008$) but not with the fat CSA of the ES ($p>0.01$), nor the MFI of the MF ($p>0.01$) and ES ($p>0.01$).

Conclusions: A higher pain sensitivity is associated with a smaller total and muscle CSA in the lumbar MF and ES, and vice versa, but results are independent from the LBP subgroup. On the other hand, the amount of fat infiltration in the lumbar muscles is not associated with pain sensitivity. Instead, a higher BMI is associated with more lumbar fat infiltration. Finally, older patients with LBP are associated with higher fat infiltration in the MF but not in the ES muscle.

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Implications: These results imply that reconditioning muscular tissues might possibly decrease the pain sensitivity of LBP patients. Vice versa, therapy focusing on enhancement of pain sensitivity might also positively influence the CSA and that way contribute to the recovery of LBP. Furthermore, the amount of lumbar muscle fat seems not susceptible to pain sensitivity or vice versa, but instead a decrease in BMI might decrease the fat infiltration in the lumbar muscles and therefore improve the muscle structure quality in LBP. These hypothesis apply for all non-specific LBP patients, despite the type of LBP.

Keywords: recurrent; chronic; pressure pain thresholds; cross-sectional area; fat infiltration; magnetic resonance imaging.

1 Introduction

Low back pain (LBP) is one of the most common musculoskeletal complaints. Up to 85% of all adults deal with LBP at one point in their lives [1, 2]. Recurrence rates are high (44–78%) [3] and are related to a large amount of health care costs and reduced productivity [2]. To date, it is unknown why some people recover after an episode of LBP whereas others develop chronic low back pain (CLBP). Research on the pathogenic mechanisms that trigger and underpin LBP complaints, is essential to prevent recurrence and the progression to chronicity.

For some decades, alterations in the central nervous system are frequently reported in several chronic pain populations [4–7]. Recently, the contribution of pain processing mechanisms is also suggested in the etiology of recurrence and chronicity of LBP. In acute LBP, excitability and hypersensitivity of the peripheral nociceptors occur. This phenomenon is referred to as peripheral sensitization [8]. In case of sustained LBP, noxious input persists, which may lead to an enhanced responsiveness of the neurons within the central nervous system, termed as central sensitization. These changes in the central nervous system in some cases persist, even when the noxious input has disappeared and the initial injury is healed [8]. Central sensitization manifests through lowered pressure pain thresholds, enhanced temporal summation and decreased endogenous pain inhibition [7, 9–11]. A possible indicator of enhanced pain facilitation is hyperalgesia, or an increased response to a (painful) stimulus resulting in lowered pressure pain thresholds [8, 12]. Pressure pain thresholds are frequently measured by manual pressure algometry, both at primary pain sites and distant locations, giving an indication on local and widespread

hyperalgesia [13–16]. Based on preliminary evidence, it is expected that pain processing works properly in RLBP, enabling them to recover after every episode [17]. In CLBP however, contradicting results concerning local and widespread hyperalgesia are reported. Some studies found segmental/widespread hyperalgesia [18–21] whereas others did not [14, 22].

Recently, a contribution of alterations in muscle tissue in the development or maintenance of alterations in the central nervous system is suggested [23]. In some chronic pain populations characterized by central sensitization, peripheral alterations are established. In chronic whiplash associated disorders for example [7], enhanced fat infiltration is established in the cervical flexor and extensor muscles [24, 25]. These fatty infiltrates are more distinct in patients with greater disability and are suggested to be associated with non-recovery [26]. These recent findings suggest a possible contribution of peripheral alterations in changes in the central nervous system occurring in chronic pain populations [27–30]. An unexplored issue however, is the association between lumbar muscle alterations and pressure pain sensitivity in the LBP population. Possibly, local pressure pain sensitivity in CLBP patients, measured at the lower back, might be influenced by the muscle characteristics or vice versa.

Muscle structure alterations are frequently established in LBP patients [31]. The occurring changes in muscle structure in LBP patients differ between CLBP and recurrent low back pain (RLBP) patients. In CLBP, atrophy of the multifidus (MF) muscle is clearly established whereas results on fat infiltration remain conflicting [31]. In RLBP, no overall decrease in cross-sectional area (CSA) is present but an increased muscle fat index (MFI) is found, representing an enhanced amount of fat in lean muscle tissue and thus a decrease in lumbar muscle quality, which does not resolve when RLBP patients are in remission [32, 33].

Time aspects and the frequency of pain episodes might be involved in structural muscle alterations. One study found a relation between “the time elapsed since the last pain episode” and lean muscle CSA and total CSA in lumbar muscle tissue of RLBP patients [33]. Recovery from atrophy might therefore occur during pain remission periods. Furthermore, deterioration in muscle quality seems related to the frequency of previous pain episodes in RLBP [33]. Finally, a recent study described differences in muscle characteristics between RLBP patients, patients with continuous CLBP and patients with non-continuous CLBP [34]. As a result, the duration of pain resolution as well as the frequency of pain episodes might play a role in the alteration process of

lumbar muscle structure in LBP. Further research in this area is however needed.

Until now, the association between muscle alterations such as CSA, fat infiltration and MFI with pressure pain sensitivity remains unexplored in LBP. Understanding of this relationship however might provide insight in the recurrence and chronicity of LBP. Therefore, this explorative study examined the association between pressure pain thresholds and alterations in CSA, fat infiltration and MFI of the lumbar erector spinae (ES) and MF muscle, in three subgroups of LBP, namely patients with RLBP who are in remission, CLBP with non-continuous LBP complaints and CLBP with continuous LBP complaints. It is hypothesized that patients with the largest amount of muscle deteriorations, might be characterized by the highest pressure pain sensitivity.

2 Methods

2.1 Participants

Males and females between 18 and 65 years old, with non-specific recurrent or chronic LBP were recruited through advertisement in hospitals in Ghent, in private practices for physiotherapy and through social media.

The RLBP subjects are characterized by pain episodes alternated by pain free periods. According to the definition of a LBP episode, launched by de Vet et al. [35] an episode of LBP is defined as a pain flare of at least 24 h, followed by a pain free episode of at least 1 month. Because this definition is not based on quantitative evidence, concomitant parameters of LBP recurrence were added: a pain flare is characterized by an increase of ≥ 2 on a Numeric Rating Scale (NRS) and/or ≥ 5 on the Roland-Morris Disability Questionnaire (RMDQ) [36]. A pain free episode is characterized by a 0/10 on an NRS and/or a score of < 2 on the RMDQ [37]. Subjects in the RLBP group suffered from non-specific RLBP during at least 6 months, with a frequency of at least two episodes in the past year [38]. In addition, these subjects have a specific request for medical help concerning their RLBP but are currently in a state of remission.

CLBP is defined by symptoms of LBP for at least 3 months [39]. As described above, a large heterogeneity exists within the CLBP population and the frequency of pain flares might influence the association between muscle morphology and pain processing. Therefore, the CLBP population was subdivided into a non-continuous CLBP subgroup and a continuous CLBP subgroup.

Subjects in the continuous CLBP subgroup suffered daily from LBP, whereas those in the non-continuous CLBP subgroup suffered from LBP for 3–4 days a week.

All subjects were asked to refrain from alcohol, nicotine, caffeine and all medication (including NSAID's and paracetamol) on the day of testing. Subjects were also instructed not to perform exhausting physical activities the day before. Symptom characteristics, sociodemographic data and pain measurements were assessed on the 1st day of testing. Due to the limited availability of the MRI scanner and the subjects, the MRI assessment could vary between 3 and 10 days after the 1st day of testing. All subjects were provided with MRI-safety instructions and gave written informed consent prior to participation. This cross-sectional study took place at the University hospital of Ghent between September 2013 and November 2014 and was approved by the local ethical committee (EC UZ 22012/791). All in- and exclusion criteria for RLBP, non-continuous CLBP and continuous CLBP are summarized in Table 1.

2.2 Symptom characteristics and socio-demographic data

Sociodemographic information [age, gender, body mass index (BMI)] and symptom characteristics were obtained during a question round on the day of the pain measurements. To evaluate the impact of the LBP intensity on the day of testing, all subjects were asked to fill in the RMDQ. Greater levels of disability are reflected by higher scores on the RMDQ [40]. The current LBP intensity was recorded at the start of the experiment by use of an NRS in which “0 = no pain” and “10 = the worst pain imaginable”.

2.3 Structural muscle measurements

A 3-Tesla Siemens Trio-Tim whole-body MRI system (Siemens AG®, Erlangen, Germany) was used to acquire a T1-weighted 2-point Dixon scan, which was assessed to evaluate the CSA of MF and ES. Patients were placed supine on the MRI table, knees supported by a cushion, through which the hips were slightly flexed (30°). A flexible 6-element body-matrix coil, centered ventrally at L4 height, covered the complete lumbar region. A dorsal standard phased-array spine coil, acted as a receiver coil [33, 34].

On a sagittal localizing MRI scan, a sagittal group of 36 slices (3 mm slice thickness and 22.2% oversampling) was positioned at the upper endplate of L4 [41]. Measurement

Table 1: In- and exclusion criteria for subject selection.

Group	General inclusion criteria	General exclusion criteria	Specific in- and exclusion criteria
RLBP	– males and females – 18–65 years old – ≥ 1 years post-natal	– neurological, respiratory, circulatory or continuous orthopedic diseases – use of antidepressants or analgesics (except for NSAID's or paracetamol), taken 2 weeks prior to the testing – pregnancy – back surgery – previous exercise therapy focussing on the activation of the MF and ES muscles – current treatment for LBP	– non-specific RLBP – ≥ 6 months duration – a frequency of ≥ 2 episodes in the past year – a pain flare of ≥ 24 h, characterized by an increase of ≥ 2 on an NRS scale and/or ≥ 5 on RMDQ – followed by a pain free episode of ≥ 1 month, characterized by a 0/10 on an NRS scale and/or < 2 on RMDQ – application for medical help concerning low back complaints
Non-continuous CLBP			– non-specific CLBP – ≥ 3 months – 3–4 pain days a week
Continuous CLBP			– non-specific CLBP – ≥ 3 months – 7 pain days a week

RLBP = recurrent low back pain; CLBP = chronic low back pain; NSAID's = nonsteroidal anti-inflammatory drugs; NRS = numeric rating scale; RMDQ = Roland-Morris Disability Questionnaire.

parameters for this two-point Dixon fat/water separation were: 320 mm FOV read, 6.59 ms TR, 2.45 ms TE1, 3.675 ms TE2 with 5 min 1 s acquisition time and a 0.7×0.7 matrix. The Dixon scan resulted in a fat image and water image. Total CSA, muscle CSA and fat CSA of ES and MF were calculated from these images by the signal intensities of the MRI obtained in the Siemens environment. All data was processed by the same researcher, blinded for the participant's LBP status [34].

To estimate the total CSA of ES and MF, the region of interest (ROI) was outlined in the fat image, which was automatically copied onto the water image (Fig. 1A). ES and MF were outlined in two slices, at the height of L4, since measurements at L4 seem surrogates for the complete lumbar spine [41]. The total CSA of each muscle was

calculated as the number of voxels in the respective ROI, multiplied by voxel size. A mean value of both slices was calculated, respectively for right and left ES and MF.

In order to calculate the total fat index for MF and ES, the signal intensity for fat (SI-fat) and the signal intensity for water (SI-water) of ES and MF were also obtained from these particular ROIs. To estimate the total fat index, the following formula was applied: “SI-fat $\times 100 /$ (SI-fat + SI-water)” [34, 42, 43]. The CSA of lean muscle tissue (muscle CSA) was calculated by the formula: “total CSA $\times (1 - \text{total fat index})$ ” [44]. To calculate the CSA of fat tissue in the spinal muscles (fat CSA), muscle CSA was distracted from total CSA.

To estimate the amount of fat in lean muscle tissue (lean MFI), the fat index in homogenous muscle tissue

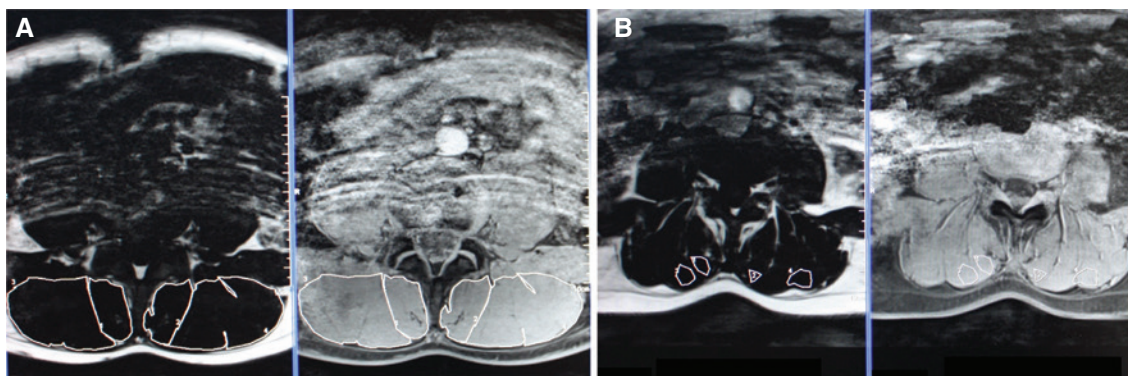


Figure 1: (A) Provides the ROI of the complete left and right ES and MF. (B) Provides the ROI for MFI in the left and right ES and MF. Therefore, an area with lean muscle tissue was selected.

was estimated (Fig. 1B). Therefore, the procedure above was repeated, but in a homogenous muscle region instead of the total muscle region.

Since there were no differences in CSA between the left and right MF and ES and the majority of subjects suffered from central or bilateral LBP complaints, a mean value of left and right measurements was used in all analyses (Table 2).

2.4 Pain measurements

A hand held manual algometer (Wagner Instruments, Greenwich, CT, USA) with a probe of 1 cm diameter was used to assess pressure pain thresholds. Therefore, pressure was applied two times, perpendicular and at a constant rate (1 kg/s) onto the tissue surface, bilaterally at four spots: lumbar ES muscle (=lower back), 5 cm lateral of the spinous process at the height of L3 [45]; quadriceps muscle (=leg) at the middle of rectus femoris muscle belly, between the anterior superior iliac spine and basis patella [46]; trapezius muscle (=neck) at the middle between acromion and spinous process at C7 height [15, 47, 48]; the web (=hand) at the dorsal hand side between index and thumb [14, 49]. Lower back represents the local pain area, whereas neck, leg and hand represents distant areas. Lower back and leg were measured, respectively in prone and supine position. The pressure pain threshold at the neck and hand were assessed when sitting on a chair. For the neck, both arms hung relaxed beside the trunk and for the hand, both hands were placed on a table (Fig. 2). The minimal amount of pressure that induced an “uncomfortable sensation” at each test side, resembles the pressure pain threshold [50]. Therefore, pressure pain thresholds were obtained by instructing the subjects to say “stop” when the sensation became “uncomfortable”. The mean of both measurements was calculated. Furthermore, the mean value of the left and right mean pressure was calculated and used in further analysis.

2.5 Statistical analyses

Statistics were performed using IBM SPSS Statistics 22 (SPP Inc., Chicago, IL, USA). Normality of the data was assessed visually and through the Shapiro-Wilk test. Comparability of groups was studied with a Pearson χ^2 test for gender distribution and symptom site. Since most of the data were not normally distributed, a non-parametric Kruskal-Wallis test was used to compare groups for age, BMI, symptom duration, disability and

Table 2: Subject characteristics.

	RLBP (n = 23)	Non-continuous CLBP (n = 15)	Continuous CLBP (n = 16)	Total (n = 54)
Gender	9 m; 14 f	7 m; 8 f	8 m; 8 f	24 m; 30 f
Symptom site	- L: 2 - R: 4 - Bilateral: 17	- R: 1 - Bilateral: 14	- L: 2 - R: 2 - Bilateral: 12	- L: 4 - R: 7 - Bilateral: 43
Age (years)	Median (IQR) 27 (12)	Median (IQR) 31 (14)	Median (IQR) 50 (28)	Median (IQR) 32 (24)
BMI	Min-Max 21–53 22.80 (2.59)	Min-Max 20–54 23.07 (1.13)	Min-Max 23–64 24.07 (3.53)	Min-Max 20–64 23.28 (2.86)
Symptom duration (months)	18.59–28.83 84 (120)	19.83–26.13 78 (138)	19.66–31.74 156 (213)	18.59–31.74 90 (141)
RMDQ (max 24)	24–300 1.00 (1)	24–240 5.00 (3)	30–552 5.00 (5)	24–552 3.00 (5)
Current LBP (NRS)	0–6 0.00 (0.00)	1–11 2.00 (1.5)	1–12 2.00 (2)	0–12 0.25 (2.00)
	0–2	0–8	0–7	0–8

IQR = Interquartile range; n = number of subjects included; m = male; f = female; L = left; R = right; no LBP = no low back pain; BMI = body mass index; RMDQ = Roland-Morris Disability Questionnaire; NRS = Numeric Rating Scale; RLBP = recurrent low back pain; CLBP = chronic low back pain.



Figure 2: Pressure pain threshold measurements at the leg, back, neck and hand by use of a manual pressure algometer.

current LBP intensity, whereas a Mann-Whitney U -test was used for post-hoc pairwise comparison. To reduce the original pressure pain threshold variables into fewer composite variables, principal component analysis was performed (pressure pain thresholds at the back, leg, neck and hand) resulting into one “pain sensitivity”-variable (pain processing) which was used in further analysis. Only components with an eigenvalue of more than one were retained. If the variance explained by the included principal components reached a value above 75%, no additional components are retained.

Multiple independent general linear regression models were performed with pain processing as independent variable, muscle structure parameters as dependent variables, patient-group as fixed factor, and age and BMI as covariates, since both factors are considered as highly relevant confounders for pain thresholds and muscle structure characteristics. After building these models, all models were individually checked via residual-analyses, analyzing the following assumptions: linearity, homoscedasticity, and randomness of error terms. In addition,

the cook’s distance for each observation was calculated to assess the influence of potential outliers on the estimated model. The significance level was set at $\alpha < 0.01$ to counteract multiple comparison.

3 Results

3.1 Demographic variables

A total of 54 LBP patients (23 RLBP, 15 non-continuous CLBP, 16 continuous CLBP) between 20 and 64 years old were included. RLBP were younger ($p = 0.002$) and had a lower BMI ($p = 0.020$) compared to continuous CLBP. RLBP experienced less disability ($p < 0.001$) and current pain intensity ($p < 0.001$) compared to both continuous and non-continuous CLBP. No significant differences between groups were found for gender, symptom site and symptom duration. All demographic variables are represented in Table 2.

Table 3: Descriptive statistics for the outcome measures.

	RLBP (<i>n</i> =23)	Non-continuous CLBP (<i>n</i> =15)	Continuous CLBP (<i>n</i> =16)
Total CSA MF (cm ²)	5.85 ± 1.40; (4.21–8.98)	5.41 ± 1.15; (3.17–7.47)	5.95 ± 1.45; (3.54–8.14)
Total CSA ES (cm ²)	16.62 ± 4.18; (12.08–24.34)	14.98 ± 3.06; (8.57–21.44)	15.84 ± 3.17; (11.45–22.20)
Fat CSA MF (cm ²)	0.83 ± 0.29; (0.53–1.66)	0.77 ± 0.19; (0.49–1.13)	1.05 ± 0.26; (0.62–1.41)
Fat CSA ES (cm ²)	2.66 ± 0.83; (1.70–4.58)	2.31 ± 0.62; (1.14–3.51)	3.27 ± 1.04; (1.89–5.88)
Muscle CSA MF (cm ²)	5.02 ± 1.21; (3.41–7.32)	4.65 ± 1.08; (2.35–6.47)	4.89 ± 1.44; (2.76–6.79)
Muscle CSA ES (cm ²)	13.96 ± 3.61; (10.34–21.12)	12.70 ± 2.65; (6.64–17.93)	12.58 ± 2.90; (8.38–17.98)
MFI MF (%)	7 ± 1; (6–10)	8 ± 2; (5–14)	10 ± 3; (6–17)
MFI ES (%)	8 ± 2; (5–15)	9 ± 2; (6–13)	11 ± 3; (7–19)
PDT leg	6.98 ± 3.23 (2.89–16.38)	6.19 ± 3.08 (2.20–14.00)	6.06 ± 2.52 (1.24–10.05)
PDT back	7.59 ± 3.22 (4.08–16.94)	6.14 ± 3.07 (1.94–14.27)	6.19 ± 3.53 (0.86–13.87)
PDT neck	4.49 ± 1.93 (1.67–9.41)	4.33 ± 2.18 (0.95–9.43)	3.77 ± 1.41 (1.00–5.87)
PDT hand	4.97 ± 2.44 (2.01–10.42)	4.78 ± 3.04 (1.45–13.88)	4.64 ± 2.45 (1.27–10.44)

Descriptive statistics of outcome measurements for muscle structure (total cross-sectional area, fat cross-sectional area, muscle cross-sectional area, muscle fat index) and pressure pain thresholds at four locations (CLBP=Chronic low back pain; CSA=cross-sectional area; ES=erector spinae; MF=multifidus; MFI=muscle fat index; n=number of subjects included; PDT=pressure pain detection threshold; RLBP=recurrent low back pain). All values are expressed by mean, standard deviation and range.

3.2 Association between pressure pain thresholds and muscle structure

The principal component analysis on the dataset of pain variables resulted in four components of which the first was retained since it explained more than 77.6% of the total variance of the dataset. The weight given to the leg, back, neck and hand variable in component 1 are, respectively 0.900, 0.887, 0.869 and 0.865, which indicates that each variable has a similar influence on the principal component.

A significant association was found between pain processing and the total CSA of MF ($p=0.006$) and ES ($p=0.001$), controlled for age and BMI and irrespective of the LBP group. In addition, a significant association was found between pain processing and the muscle CSA of MF ($p=0.003$) and ES ($p=0.001$). No association was found between pain processing on the one hand and fat CSA of MF ($p=0.876$), fat CSA of ES ($p=0.142$), MFI of MF ($p=0.274$) or MFI of ES ($p=0.231$) on the other hand.

BMI was associated with fat CSA of MF ($p=0.004$), fat CSA of ES ($p=0.006$), MFI of ES ($p=0.003$) and MFI of MF ($p<0.001$). Age was associated with fat CSA of MF ($p=0.008$) but not with MFI ES ($p=0.037$), fat CSA of ES ($p=0.115$) or MFI ES ($p=0.167$).

All descriptive details and model characteristics can be found, respectively in Tables 3 and 4.

4 Discussion

To our knowledge, this study is the first to discuss the association between pain processing measured by pressure

pain thresholds and structural changes in the lumbar muscles of patients with LBP.

This explorative study found associations between pressure pain thresholds and the total CSA of MF and ES in LBP patients, when controlled for age and BMI. This implies that higher pressure pain thresholds, which are indicative for a better pain processing, are associated with a larger lumbar CSA among all LBP patients. As a consequence, one can assume that patients with LBP who are generally more sensitive for pain (lower pressure pain thresholds in general), are more likely to have smaller total and muscle CSA and vice versa.

Larger muscles are not necessarily characterized by enlarged muscle mass. It is even recently suggested that structural remodeling occurs, rather than clear atrophy of the lumbar muscles after back injury [51]. Therefore, general atrophy in lumbar muscles might be masked by the amount of fat infiltration and connective tissue, despite the amount of healthy muscle tissue. This study however also established a positive association between pressure pain thresholds and muscle CSA for ES and MF, when controlled for age and BMI. It can therefore be hypothesized that smaller muscles are less resilient for daily impact due to lowered pressure pain thresholds. This phenomenon might play a role to the recurrence and/or chronicity of LBP complaints.

Whether alterations in pain processing mechanisms are cause or consequence of muscle alterations, remains unclear. To date, limited evidence suggests that pain results in alterations in muscle structure and muscle function [52–54], but the opposite cannot be ruled out. On the one hand, an altered control strategy, induced by

Table 4: Model characteristics and parameter estimates.

Model	df	R ² -adjusted	Sig.	Parameter estimates	β	t (sig.)	95% CI	
							Lower B	Upper B
Total CSA MF	df ₁ = 5 df ₂ = 46	14%	0.034 ^a	(Intercept)	2.826	1.490 (0.143)	-0.991	6.644
				RLBP	0.463	1.106 (0.275)	-0.380	1.306
				Continuous CLBP	0.624	1.244 (0.220)	-0.386	1.635
				BMI	0.142	1.687 (0.098)	-0.027	0.311
				Age	-0.021	-1.228 (0.226)	-0.055	0.013
				Pain processing	0.525	2.862 (0.006) ^a	0.156	0.895
Muscle CSA MF	df ₁ = 5 df ₂ = 46	14.5%	0.030 ^a	(Intercept)	3.319	1.899 (0.064)	-0.199	6.837
				RLBP	0.374	0.968 (0.338)	-0.403	1.151
				Continuous CLBP	0.479	1.035 (0.306)	-0.453	1.410
				BMI	0.099	1.280 (0.207)	-0.057	0.255
				Age	-0.028	-1.831 (0.074)	-0.060	0.003
				Pain processing	0.530	3.134 (0.003) ^a	0.190	0.871
Fat CSA MF	df ₁ = 5 df ₂ = 46	41.9%	<0.001 ^a	(Intercept)	-0.493	-1.556 (0.126)	-1.130	0.144
				RLBP	0.090	1.281 (0.206)	-0.051	0.230
				Continuous CLBP	0.146	1.739 (0.089)	-0.023	0.314
				BMI	0.043	3.042 (0.004) ^a	0.014	0.071
				Age	0.008	2.756 (0.008) ^a	0.002	0.013
				Pain processing	-0.005	-0.157 (0.876)	-0.066	0.057
MFI MF	df ₁ = 5 df ₂ = 47	44.3%	<0.001 ^a	(Intercept)	-0.024	-0.915 (0.365)	-0.077	0.029
				RLBP	-0.005	-0.755 (0.454)	-0.017	0.008
				Continuous CLBP	0.009	1.233 (0.224)	-0.006	0.024
				BMI	0.004	3.149 (0.003) ^a	0.001	0.006
				Age	0.001	2.152 (0.037)	0.0001	0.001
				Pain processing	-0.003	-1.107 (0.274)	-0.009	0.002
Total CSA ES	df ₁ = 5 df ₂ = 44	20.4%	0.009 ^a	(Intercept)	9.274	1.879 (0.067)	-0.675	19.224
				RLBP	1.257	1.174 (0.274)	-0.901	3.415
				Continuous CLBP	1.081	0.857 (0.396)	-1.461	3.622
				BMI	0.307	1.404 (0.167)	-0.134	0.749
				Age	-0.041	-0.971 (0.337)	-0.127	0.045
				Pain processing	1.685	3.599 (0.001) ^a	0.742	2.629
Muscle CSA ES	df ₁ = 5 df ₂ = 44	20.4%	0.009 ^a	(Intercept)	10.606	2.397 (0.021)	1.689	19.522
				RLBP	1.008	1.050 (0.299)	-0.926	2.941
				Continuous CLBP	0.478	0.423 (0.674)	-1.799	2.756
				BMI	0.177	0.901 (0.372)	-0.219	0.573
				Age	-0.059	-1.552 (0.128)	-0.136	0.018
				Pain processing	1.531	3.650 (0.001) ^a	0.686	2.377
Fat CSA ES	df ₁ = 5 df ₂ = 46	34.0%	<0.001 ^a	(Intercept)	-1.959	-1.581 (0.121)	-4.453	0.536
				RLBP	0.179	0.654 (0.516)	-0.372	0.730
				Continuous CLBP	0.571	1.739 (0.089)	-0.090	1.231
				BMI	0.158	2.869 (0.006) ^a	0.047	0.268
				Age	0.017	1.605 (0.115)	-0.004	0.040
				Pain processing	0.179	1.493 (0.142)	-0.062	0.421
MFI ES	df ₁ = 5 df ₂ = 46	56.6%	<0.001 ^a	(Intercept)	-0.073	-2.550 (0.014)	-0.130	-0.015
				RLBP	-0.005	-0.782 (0.438)	-0.019	0.008
				Continuous CLBP	0.015	1.804 (0.078)	-0.002	0.031
				BMI	0.006	4.964 (<i>p</i> < 0.001) ^a	0.004	0.009
				Age	0.000	1.403 (0.167)	0.000	0.001
				Pain processing	-0.004	-1.214 (0.231)	-0.010	0.002

Multiple general linear regression models for different muscle structure outcome parameters with pain processing as predictor, corrected for patient group, BMI and age. The model characteristics are situated on the left side, the parameter estimates on the right side. Non-continuous CLBP is the reference group. ^a*p* < 0.010 is significant. (df = Degrees of freedom; CI = confidence interval; B = bound; MF = multifidus; ES = erector spinae; CSA = cross-sectional area; MFI = muscle fat index).

nociceptive input, might contribute to muscle overload or disuse and thus induce adaptations at the muscle level. In contrast, pain might also be the consequence of alterations in muscle structures and/or muscle activity [55]. A longitudinal design is needed to examine this question more closely.

However, a positive association between pressure pain sensitivity and CSA for ES and MF is established in the current study, the exact interplay between pressure pain sensitivity and muscle alterations remains unclear. A possible mechanism behind this interplay is the contribution of inflammatory mediators. It is postulated that the increased production of pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukin (IL)-1, IL-6 and interferon gamma (IFN- γ) [56, 57] as well as reduced levels of anti-inflammatory mediators such as IL-10 [58] are involved in muscle wasting. In a state of acute muscle injury, a diffuse muscle degeneration results in temporary muscle atrophy which is followed by the induction of muscle regeneration [56, 57]. Chronic inflammation on the other hand, affects muscle tissue differently, by enhancing protein breakdown and impaired myogenesis, resulting in uncontrolled wound healing, fibrosis and muscle waste [56]. Peripheral inflammatory processes are also involved in the phenomenon of widespread hyperalgesia: peripheral injury or other stressors seem to trigger pro-inflammatory cytokines contributing to symptoms of central sensitization in chronic pain populations [23, 57, 59–61]. The precise working mechanisms of inflammation on both protein turnover rates and central sensitization are yet poorly understood and need further elaboration.

No associations between pressure pain thresholds and fat CSA in MF or ES are established. Also no association with the quality of muscle tissue (MFI) is observed. Possibly other factors determine the amount of fat infiltration and muscle quality deterioration in the lumbar muscles. Several personal factors e.g. are related with muscular characteristics [62, 63]. Aging processes are associated with a declined total muscle CSA [64] as the consequence of motor unit loss and muscle fiber degeneration [65]. This gradual decrease in muscle size is accompanied by a replacement of muscle tissue by fat and connective tissue [41, 65, 66]. In the current study, a significant association of age was found on fat CSA in MF, and a borderline significant association on MFI in MF, confirmed previous results. However, no association was found in the ES muscle. These results are in concordance with recent findings of Crawford and colleagues, who established muscle degeneration was more pronounced in the MF compared to the ES in asymptomatic subjects [41, 67]. BMI is also

observed to negatively influence muscle thickness [64, 68, 69] and pressure pain thresholds [21, 70]. An association between BMI and fat CSA and MFI in the current study confirms previous research reporting an influence of BMI on muscle CSA and fat infiltration [71, 72]. This finding, together with the lack of an association between fatty infiltrates and pressure pain thresholds indicate that BMI might play an explicit role in the fat infiltration of muscle tissue, and not pressure pain sensitivity.

Differences between RLBP and CLBP exist in muscle morphology [34] and are suggested in pain processing mechanisms [17]. The chronicity based classification of the LBP subgroups used in this study was of no influence on the association between pressure pain thresholds and muscle morphology in this cohort. However, given the rather small sample sizes per group, small associations might have been missed.

5 Clinical implications

An association between lumbar CSA and pressure pain thresholds in LBP patients, implies that improvement of lumbar CSA might positively affect pressure pain sensitivity. Previous studies found enhanced muscle characteristics in addition to a decrease in lumbar pain experience after exercise interventions [73, 74]. Reconditioning muscular tissues might therefore decrease the pain sensitivity of those patients. However, further research is needed to confirm this hypothesis. Also the opposite might work. Therapy focusing on enhancement of pain processing mechanisms, might positively influence muscle CSA in LBP and contribute to the recovery of LBP. These interventions intend to deactivate the pain facilitation top-down pathways, responsible for central nervous system hyperexcitability [75]. Recent interest arises for treatment approaches addressing both pain processing dysfunctions and peripheral mechanisms within a broader biopsychosocial point of view [75–77]. The results of the current study might partly explain the effectiveness of this approach. If both problem areas are addressed and positively influence each other, it is more likely that patients improve after therapy. Further research in this field is however needed.

From a clinical point of view, distant and local pressure pain thresholds could be separated. Based on the principal component analysis, an equal weight was observed from each PPT at each site. This indicates an underlying variable of pain rather than two underlying variables of distant and local pressure pain. However, one should always keep in mind that different variables could

be associated with peripheral and central processes of pain.

6 Limitations

The methodological characteristics of this study imply some limitations. First, in this study, pain processing was only assessed by pressure pain thresholds using manual algometry. Future research should incorporate additional quantitative sensory testing to fully record pain processing, amongst which temporal summation of pain, spatial summation of pain and conditioned pain modulation. Furthermore, the CSA and MFI were assessed at only level L4. The fat fraction of this level correlates best with the total lumbar fat fraction [41]. For CSA however, a full volume metrics is probably superior to single slice analysis. Future research should take this into account.

Second, it should also be highlighted that the explained variance of the multiple independent general linear regression models is limited for total CSA and muscle CSA of MF (respectively 14% and 14.5%). Besides age and BMI, also psychosocial factors may influence LBP occurrence, recurrence and chronicity [78, 79]. Therefore, an influence on the association between muscle morphology on the one hand and pain processing on the other hand can also be assumed. Addressing these psychosocial issues would dilate the theme of the current study but should be considered in future research.

Finally, the absolute observations in the cross-sectional nature of this study implies that no causal connection can be made between the explored associations. Further research on this topic in longitudinal studies is essential to provide additional insight in the association between structural characteristics, pressure pain thresholds and personal characteristics. It could be investigated whether interventions that influence muscle characteristics result in increased pressure pain thresholds and vice versa. Furthermore, the relative long-term influence of personal factors such as BMI and age on fat infiltration and MFI in lumbar muscles should be investigated in longitudinal studies to investigate whether these factors indeed play a role in the fat infiltrations of muscle tissue.

7 Conclusion

Associations between pressure pain thresholds and total and muscle CSA in the lumbar MF and ES seem to exist,

independent from the LBP subgroup. As consequence, LBP patients with generally increased pain sensitivity are more likely to have smaller muscles and vice versa. As with any novel and preliminary findings, these results need to be elaborated in future research. Longitudinal studies including more psychosocial variables are necessary to address the importance of an individual's pain threshold on muscle morphology and vice versa in LBP patients.

Authors' statements

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