Lumbar muscle structure and function in chronic versus recurrent low back pain : a cross-sectional study

Lumbar muscle structure and function in chronic versus recurrent low back pain:

a cross-sectional study

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ABSTRACT

Background context

Heterogeneity exists within the low back pain population. Some patients recover after every pain episode, whereas others suffer daily from LBP complaints. Until now, studies rarely make a distinction between recurrent low back pain (RLBP) and chronic low back pain (CLBP), although both are characterized by a different clinical picture. Clinical experiences also indicate that heterogeneity exists within the CLBP population. Muscle degeneration, like atrophy, fat infiltration, alterations in muscle fiber type and altered muscle activity, compromises proper biomechanics and motion of the spinal units in low back pain (LBP) patients. The amount of alterations in muscle structure and muscle function of the paraspinal muscles, might be related to the recurrence or chronicity of LBP.

Purpose

The aim of this experimental study is to evaluate differences in muscle structure (cross-sectional area and lean muscle fat index) and muscle activity of the multifidus (MF) and erector spinae (ES) during trunk extension, in patients with RLBP, non-continuous CLBP and continuous CLBP.

Study design and setting

This cross-sectional study took place in the University hospital of Ghent, Belgium. Muscle structure characteristics and muscle activity were assessed by magnetic resonance imaging (MRI).

Patient sample

Fifty five adults with non-specific low back pain (24 RLBP in remission, 15 non-continuous CLBP, 16 continuous CLBP) participated in this study.

Outcome measures

Total cross-sectional area, muscle cross-sectional area, fat cross-sectional area, lean muscle fat index, T2-rest and T2-shift were assessed.

Methods

A T1-weighted Dixon MRI scan was used to evaluate spinal muscle cross-sectional area and fat infiltration in the lumbar MF and ES. Muscle functional MRI was used to evaluate the muscle activity of the lumbar MF and ES during a lumbar extension exercise. Before and after the exercise, a pain assessment was performed. This study was supported by grants from the Special Research Fund of Ghent University (DEF12/AOP/022) without potential conflict of interest-associated biases in the text of the paper.

Results

Fat cross-sectional area and lean muscle fat index was significantly higher in MF and ES in continuous CLBP compared to non-continuous CLBP and RLBP ($p<0.05$). No differences between groups were found for total cross-sectional area and muscle cross-sectional area in MF or ES ($p>0.05$). Also no significant differences between groups for T2-rest were established. T2-shift, however, was significantly lower in MF and ES in RLBP compared to respectively non-continuous CLBP and continuous CLBP ($p<0.05$).

Conclusion

These results indicate a higher amount of fat infiltration in the lumbar muscles, in the absence of clear atrophy, in continuous CLBP compared to RLBP. A lower metabolic activity of the lumbar muscles was seen in RLBP replicating a relative lower intensity in contractions performed by the lumbar muscles in RLBP compared to non-continuous and continuous CLBP. In conclusion, RLBP differ from continuous CLBP for both muscle structure and muscle function, whereas non-continuous CLBP seem comparable with RLBP for lumbar muscle structure and with continuous CLBP for lumbar muscle function. These results underline the differences in muscle structure and muscle function between different LBP populations.

Key words

Low Back Pain, Magnetic Resonance Imaging, trunk muscles, muscle atrophy, fat infiltration, muscle activity.

1. INTRODUCTION

People with a history of low back pain (LBP) are known to have increased risk for recurrence [1,2], but little is known why some LBP patients transit to chronicity and others recover after every episode. Degeneration in muscle structure and alteration in muscle function of the lumbar erector spinae and multifidus might play a role in this feature. The paraspinal muscles play a crucial role in the dynamic control of the lumbar spine. Both the multifidus (MF) and erector spinae (ES) muscles are important in controlling segmental motion, by generating a compressional force on the lumbar spine and producing a lumbar extension movement when contracting bilaterally [3].

Degeneration of these lumbar muscles compromises proper biomechanics and motion of the spinal units [4]. Muscle degeneration is characterized by a decrease in ***cross-sectional area (CSA)*** and an increase in ***fat infiltration*** [5,6]. The influence of pain on degeneration of the lumbar muscles is frequently investigated in LBP patients compared to healthy controls (HC). Remarkably, results in patients with chronic low back pain (CLBP) seem to differ from patients with recurrent low back pain (RLBP).

In non-specific CLBP, studies established that MF muscle size is decreased [6–10], whereas CSA of ES is not altered [6,11]. In non-specific RLBP however, no decrease in CSA is found in the lumbar spinal muscles [11,12], suggesting CSA is either not reduced during a pain flare or recovery of muscle size occurred during pain remission.

Results on fat infiltration in non-specific CLBP remain conflicting: one study found increased fat infiltration in non-specific CLBP in MF [8] or ES [11], whereas others could not find increased fat infiltration in any paraspinal muscles in CLBP [6]. In non-specific unilateral RLBP patients in remission, no fat infiltration is established. Notable is however the increased muscle fat index (MFI), in the absence of alterations in muscle size or macroscopic fat infiltration. This enhanced MFI reflects an increased relative amount of intramuscular lipids in lean muscle tissue and resembles therefore deterioration of muscle quality in RLBP in remission [12].

Among studies, a lot of different evaluation techniques are used to assess muscle structure characteristics: computed tomography [6,9,11], ultra sound imaging [7,8,10,13] or magnetic resonance imaging (MRI) [12,14] are frequently used techniques. Recent interest arises in chemical shift-based water-fat separation methods, like the multi-point DIXON fat mapping MRI technique. This method uses the phase difference between water and fat to separate these two components. The result is a quantitative measurement of the signal fraction of water and fat. This way, the DIXON

method produces an accurate estimation of fat fraction and is shown to be a useful quantitative evaluation technique for fatty degeneration in patients with lumbar disc pathology [15–17].

Besides degeneration in muscle structures, the presence of LBP also affects ***muscle function*** of the lumbar muscles [18,19]. A lot of research on muscle function has been done by surface [20–25] and fine-wire [20,23,26–28] electromyography, measuring the myoelectric activity. An alternative way to assess muscle function is the muscle functional MRI (mfMRI) technique which evaluates exercise-related metabolic muscle activity. In this technique, the amount of metabolic activity in muscle tissue before and after exercise is recorded and the change in signal intensities, due to the relaxation time of tissue water following exercise, is measured. This non-invasive technique is a reliable and valid tool for resting and exercise measurements in deep and superficial muscles [21,29–33]. Both techniques show a linear association for the lumbar paraspinal muscles [21].

In RLBP, contradictory results concerning muscle function in remission of pain are reported. Some studies found decreased muscle activity in MF during pain remission periods [20,28], whereas others found the opposite [34]. Besides, after experimental pain induction, a decrease in muscle activity is seen, indicating an inhibitory muscle response due to pain [35,36]. Apparently, after pain onset, a combination of reflex inhibition and disturbance in coordination of trunk muscles causes changes in the MF [6,37] and despite a state of remission, the muscle function of RLBP patients remains altered.

Patients with CLBP examined by electromyography exhibit higher global trunk muscle activity compared to asymptomatic subjects as a compensatory strategy to enhance the reduced spinal stability [38]. This increased muscle activity results in increased paraspinal muscle fatigability [39]. As far as we know, few research concerning metabolic activity was performed in CLBP. The only study evaluating muscle activity by mfMRI in CLBP compared to HC, found an increased muscle activity in CLBP after surgery [40]. No previous research investigated differences in metabolic activity between RLBP and CLBP.

In conclusion, results concerning muscle structure are scarce and inconsistent in RLBP. Also research concerning muscle activity by mfMRI remains ambiguous in RLBP and is, as far as we know, non-existent in non-specific CLBP. In most studies, a (sub)group of LBP was compared with healthy controls. Little research is however done on the differences in lumbar muscle structure and muscle activity between RLBP and CLBP, although each subgroup of LBP patients is marked by its own characteristics. Moreover, clinical experience indicates heterogeneity within the CLBP population: some patients suffer daily from LBP, whereas others have pain days alternated with days of being pain free. Possibly, the amount of alterations in muscle structure and muscle function of the paraspinal muscles is related to the degree of recurrence or chronicity of LBP.

Therefore, this experimental MRI-study evaluates the differences in muscle structure (CSA and fat infiltration), muscle quality (MFI) and muscle activity during trunk extension in the lumbar MF and ES between RLBP in remission, non-continuous CLBP and continuous CLBP. In this way, the influence of the continuation of pain complaints on muscle structure and muscle function can be examined. We hypothesize more fat infiltration, a smaller CSA and decreased muscle quality in continuous CLBP patients, compared to non-continuous CLBP and RLBP. We also hypothesize that muscle activity in continuous CLBP is dysfunctional compared to RLBP and non-continuous CLBP.

2. METHODS

a. Participants

All subjects were recruited through advertisement in the University hospital of Ghent and through social media. Males and females between 18 and 65 years old with non-specific LBP were eligible for the study. Patients with neurological, respiratory, circulatory, continuous orthopaedic diseases or pregnancy in the previous year were excluded. Also subjects using antidepressants or analgesics (except for NSAID's or paracetamol) taken two weeks prior to the testing, were excluded. Patients who underwent cognitive exercise therapy were also excluded from this study.

To be included in the ***RLBP*** group, 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., an episode of LBP is defined as a pain flare of at least 24 hours, followed by a pain free episode of at least 1 month [41]. Because this definition is not based on quantitative evidence, concomitant parameters of LBP recurrence were added: a pain flair is characterized by an increase of at least 2 on a NRS for pain and/or at least 5 on the Roland Morris Disability Questionnaire [42] and a pain free episode is characterized by a 0/10 on an NRS for pain and/or a score of less than 2 on the Roland Morris Disability Questionnaire [43]. The Roland Morris Disability Questionnaire measures the amount of disability for daily activities due to LBP. The scale ranges from 0 (no disability) to 24 (severe disability). Subjects in the RLBP group suffered from non-specific recurrent LBP during at least 6 months, with a frequency of at least 2 episodes in the past year [44]. In addition, subjects in the RLBP group are in a state of remission.

Conform the definition of CLBP, subjects in the CLBP group are characterized by LBP complaints for at least 3 months [45]. During the anamnesis, prior to the acceptance for participation in this study, the researchers detected 2 major groups in this CLBP population: a group suffering daily from LBP complaints and a group characterized by 3 to 4 pain days per week. The CLBP group was therefore subdivided into a group with ***non-continuous CLBP*** (3 to 4 pain days a week) and ***continuous CLBP*** (7 pain days a week). All in- and exclusion criteria can be found in table 1.

On the day of testing all subjects were asked to refrain from alcohol, nicotine, caffeine and all medication (including NSAID's and paracetamol). Subjects were also instructed not to perform exhausting physical activities the day before. All subjects were provided with MRI-safety instruction and gave written informed consent prior to participation. The examinations took place in the University hospital of Ghent between September 2013 and November 2014. This cross-sectional study was part of a larger study, which was approved by the local ethical committee (EC UZ 22012/791).

GROUP	SPECIFIC INCLUSION CRITERIA	GENERAL INCLUSION CRITERIA	GENERAL EXCLUSION CRITERIA
RLBP	- in remission - ≥6 months - a frequency of ≥2 episodes in the past year - a pain flare of ≥24 hours, characterized by an increase of ≥2 on a NRS and/or ≥5 on the Roland Morris Disability Questionnaire - followed by a pain free episode of ≥1 month, characterized by a 0/10 on an NRS and/or <2 on the Roland Morris Disability Questionnaire	- non-specific - males and females - 18-65 years old - ≥1 years post-natal	- use of antidepressants or analgesics (except for NSAID's or paracetamol), taken two weeks prior to the testing - neurological, respiratory, circulatory or severe orthopaedic diseases - pregnancy - cognitive exercise therapy
Non-continuous CLBP	- ≥3 months - 3 to 4 pain days a week		
Continuous CLBP	- ≥3 months - 7 pain days a week		

Table 1: In- and exclusion criteria of the study

b. Procedure

A 3-Tesla Siemens Trio-Tim whole-body MRI system (Siemens AG ®, Erlangen Germany) was used to acquire all T1-weighted and T2-weighted images. First, a T1-weighted Dixon scan was used to evaluate spinal muscle CSA, fat infiltration and MFI. Afterwards, mfMRI was used to evaluate the

muscle activity of the lumbar MF and ES. For the T2-weighted mfMRI protocol, an image after 20' of rest in a comfortable chair (T2-rest) and an image immediately after exercise (T2-exercise) were taken. Before and after the exercise, a pain assessment was performed. After the exercise, also the rate of perceived exhaustion was examined.

c. Exercise protocol

A static-dynamic, standardized, low-load lumbar extension exercise was performed to activate muscle activity of the MF and ES muscles [32,35]. Subjects were installed in prone position on a variable angle chair, which was positioned at 45° of trunk flexion. The hands of the subject were placed on the ipsilateral shoulders and the legs were strapped to the chair. Subjects had to raise the upper body from the start position in 2 seconds, hold it for 5 seconds at the horizontal position and again lower the upper body to the start position in 2 seconds. Tactile feedback was used to adjust the performance. To ensure appropriate timing, a metronome was used (60 beats/minute). Exercise volume and load were set at 10 repetitions of 40% of the subjects' personal one repetitions maximum (1RM) (figure 1). The individual 1RM was indirectly determined from the maximum amount of trunk extensions performed with their own upper body weight, which was assessed on a separate day 3-10 days before. The Holten diagram was used to calculate the exercise weight corresponding to the personal 40% of 1RM. If this exercise weight was lower compared to the subject's trunk weight, a load-pulley system assisted in performing the trunk extensions [21,31].

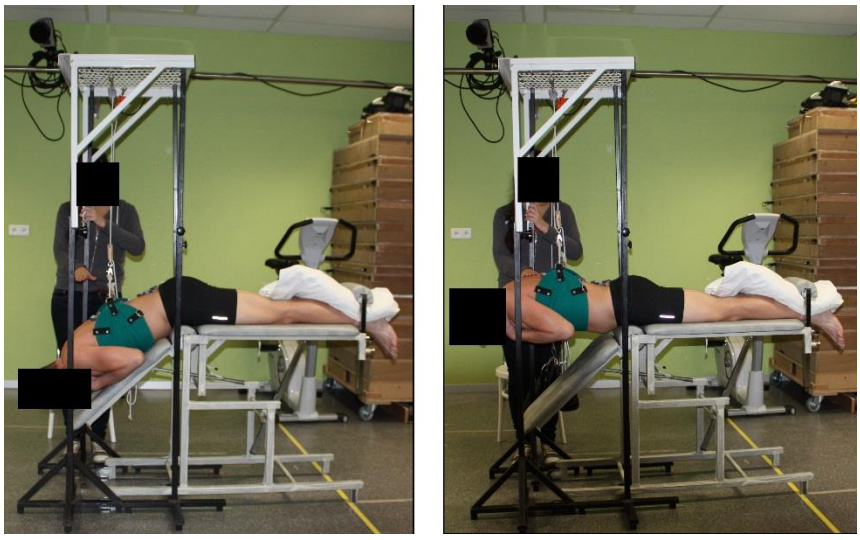

Figure 1 Static-dynamic extension exercise at 40% of 1 RM

d. Assessment of pain and exhaustion

Before the exercise, subjects were asked to rate their current pain and expected pain after the exercise on a numeric rating scale for pain (NRS: '0'=no pain, '10'=the worst pain imaginable). After the exercise, subjects were asked again to rate their current pain, the actual amount of pain during exercise and the perceived fatigue/exertion during exercise (BORG: scale to 20) [46,47].

e. Dixon MRI

For the MRI-scan, patients were installed supine on the MRI table, knees supported by a cushion making the hips flexed (30°). A flexible 6-element body-matrix coil was centered ventrally at L4, covering the complete lumbar region. A standard phased-array spine coil dorsally acted as a receiver coil [12]. A neck coil was installed to standardize the patients position (both shoulders positioned solid against the coil), but was not operational.

On a sagittal localizing scan, a slap group of 36 slices, (3mm slice thickness and 22.2% oversampling) was positioned at the upper endplate of L4. Measurement parameters for this two-point DIXON fat/water separation were: 320mm FOV read, 6.59ms TR, 2.45ms TE1, 3.675ms TE2 with 5.01s acquisition time and a 0.7x0.7matrix. Signal intensities of the MRI-data were calculated in the Siemens environment, blind to the participant's LBP status.

The DIXON-scan resulted into a fat-image and a water image. To estimate the CSA of the total MF and ES **(total CSA),** the regions of interest (ROI) of each separate muscle were drawn on the fat images (figure 2A). MF and ES were bilaterally outlined on 2 slices at the height of L4. The total CSA of each muscle was calculated as the number of voxels in the respective region of interest, multiplied by voxel size. A mean value of both slices was calculated respectively for right and left ES and MF. The signal intensity for fat (SIfat) and the signal intensity for water (SIwater) of both the total MF and ES were also obtained on these regions of interests.

The CSA of lean muscle tissue **(muscle CSA)** was calculated by the formula: "total CSA*(1-total MFI)" [48]. To estimate total MFI, the following formula was applied: "SIfat*100/(SIfat + SIwater)" [17,49].

Muscle CSA subtracted from total CSA resulted in the CSA of fat tissue in the spinal muscles **(fat CSA).**

To estimate an indication of the amount of fat in lean muscle tissue **(lean MFI)**, the fat fraction in homogenous muscle tissue was estimated (Figure 2B). Therefore, the procedure above was repeated but in a homogenous muscle region instead of the total muscle region.

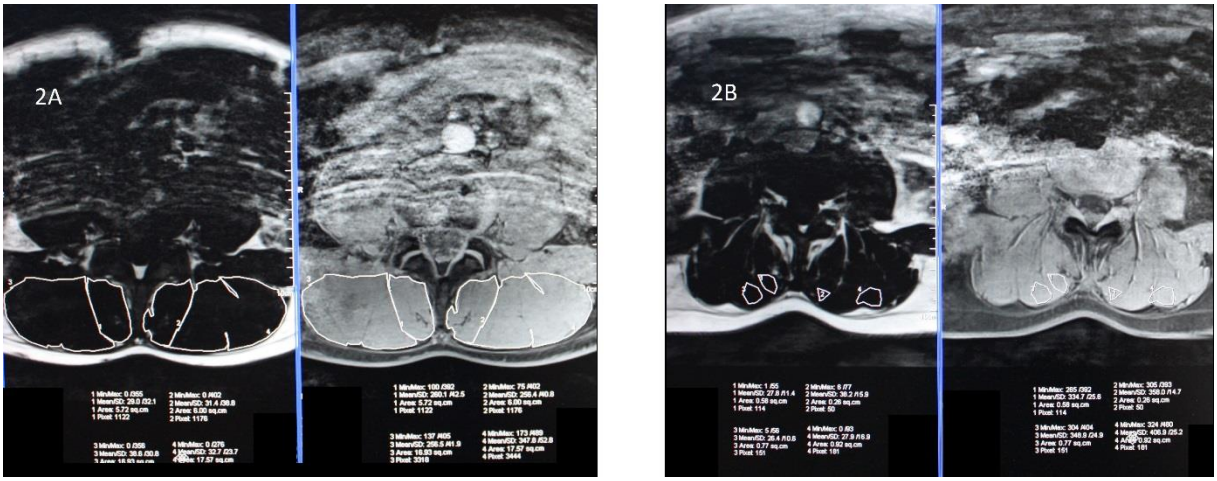

Figure 2A and 2B. Illustration of a DIXON fat and water image. 2A illustrates the ROI to define total muscle CSA and the belonging fat index. 2B illustrates the ROI to define lean muscle fat index.

f. Muscle functional MRI

On a sagittal localizing scan, 3 transversal slices were positioned equal with the upper endplate of L3, upper endplate of L4 and lower endplate of L4. A spin-echo multi-contrast sequence (SE_MC) was used for the acquisition of T2-weighted images. The following parameters were applied: repetition time (TR) 1000ms; echo train of 16 echoes ranging from 10 to 162ms; acquisition matrix 256*176mm^2; field of view (FOV) 340 mm; voxel size 1.3*1.3*5.0 mm^3; scan-time 5min52s. The T2-weighted images were obtained before (T2-rest) and immediately after exercise (T2-exercise).

The MRI images were converted into T2-maps for calculation of the mean transverse relaxation times of the muscle tissue within the selected ROI using the T2-Processor software (copyright P. Vandemaele, Eng., GIFMI UZ Gent). A T2-value per voxel (in ms) was calculated out of 15 echoes. Subsequently, regions of interest were manually traced on the T2-maps bilaterally for MF, ES, avoiding visual fat, connective tissue, or blood vessels (figure 3). Finally, for each ROI, the mean T2-value was calculated. The researcher processing the data was blinded to the participant's LBP status.

The change recorded between T2-rest and T2-exercise is referred to as the **T2-shift**, which relates to the amount of performed activity [33]. In order to estimate the T2-shift, the formula of "((T2-exercise -T2rest)/T2-rest)*100" was used.

Besides information on muscle function, T2-rest reflects the molecular proton content of tissue by quantitative measurement of the transverse relaxation time at T2-rest and thus gives information about muscle characteristics [31].

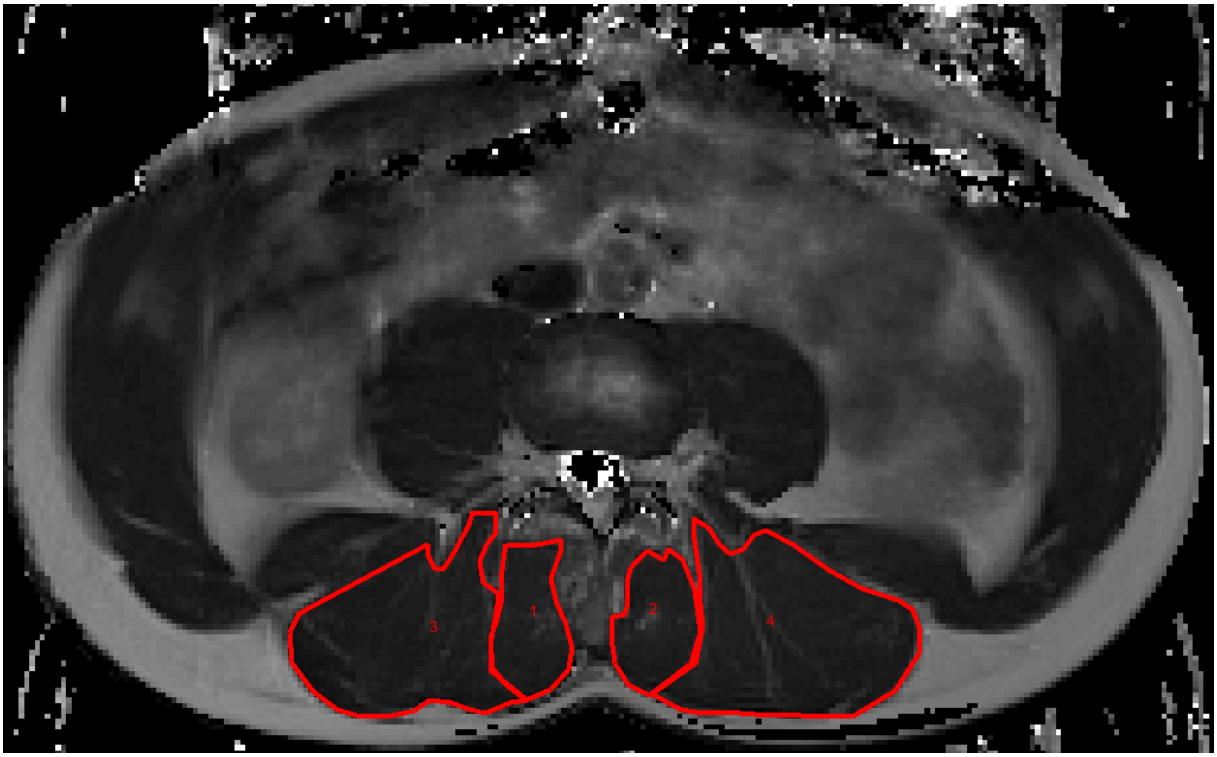

Figure 3. Illustration of an T2-weighted axial MRI image at the level of upper L4 endplate demonstrating regions of interest of MF and ES.

g. Statistical analysis

First, the distribution of data was analyzed. If the data was observed to be not normally distributed, a transformation was applied in order to approximate normality. Data for which transformation offered no solace, non-parametric testing methods were applied. Subject characteristics (age, body mass index) were tested by Kruskal-Wallis. A Mann-Whitney U test was used for post-hoc pairwise comparison. Gender was tested by chi-square test.

Analysis for DIXON outcome

To analyze group differences between total CSA, fat CSA, muscle CSA and lean MFI, an analysis of covariance (ANCOVA) was applied which included important covariants. The dependent variables in the analyses were total CSA, fat CSA, muscle CSA, and lean MFI, analyzed respectively for left and right MF and ES. The covariates in this model were body mass index and the logarithm of age, which were both mean centered. Prior to building the model, bivariate relations were depicted using a scatter plot. Only if a linear fit was deemed appropriate, the model was constructed. After building the model, homoscedasticity was analyzed by plotting the squared residual terms. In addition, normality of the error terms was analyzed together with the influence of a particular data point on the model (Cook's Distance > 4/55). Each estimated model fulfilled these required assumptions. Post-hoc testing was done with the Tukey's HSD test.

Analysis for mfMRI outcome (T2-rest and T2-shift)

To address dependency between data, mixed model analyses was performed to analyze differences in T2-rest and T2-shift between LBP patients, with patients as a random factor. Model selection and model validation was based on statistical tests for parameter estimates, comparison of Akaike's Information Criterion values and inspection of residual plots. These mixed models account for correlated measures by including a random intercept for "patients" and were adjusted for "group" (RLBP, non-continuous CLBP and continuous CLBP) and "vertebral level" (L4 lower endplate, L4 upper endplate and L3 upper endplate). Age and BMI were taken into account as covariates, but only age appeared influential on the outcome for T2-rest. Parameter estimation was performed by restricted maximum likelihood. Results were represented by muscle (MF or ES). After building the model, linearity, homoscedasticity, normality of the error terms was analyzed. Each estimated model fulfilled these required assumptions.

Analysis of pain measurements

To evaluate differences between groups for pain measurements (pain before exercise, pain during exercise, pain after exercise, expected pain after exercise and the rate of perceived exhaustion), one way ANOVA analysis were performed. Post-hoc testing was done with the Tukey's HSD test.

Analysis of correlations

The relationship between structural and functional characteristics, pain measures and rate of perceived exhaustion was analyzed by the Pearson correlation tests.

ANCOVA-models were built in R (statistical software, version 3.2.4; in R-studio, version 0.99.893). All other analysis were performed in SPSS (IBM SPSS statistics, version 23.0). A priori power calculations (By GPower) indicated 24 subjects in each group was needed to reach a power of 0.80. Statistical significance was set at $p<0.050$.

3. RESULTS

Demographics

A total of 55 subjects (26 RLBP, 15 non-continuous CLBP, 16 continuous CLBP), between 20 and 64 years of age, fulfilled the complete test protocol. In the RLBP group, 2 subjects reported being in a pain flare and were therefore excluded from the analysis. No significant difference in gender was seen between groups. The mean age was significantly higher in continuous CLBP compared to respectively RLBP and non-continuous CLBP ($p=0.002$; $p=0.021$). The body mass index was significantly higher in continuous CLBP compared to respectively RLBP and non-continuous CLBP ($p=0.014$; $p=0.041$). All descriptive information on the demographic variables and outcome measures can be found in table 2. Since there were no differences in left and right MF or ES for CSA or MFI and almost all participants suffered from central or bilateral LBP complaints, a mean value for left and right was used in all analyses.

Muscle structure: cross-sectional area, fat infiltration, muscle quality and T2-rest

Differences between groups were found for fat CSA in MF ($p<0.001$) and ES ($p=0.003$) and for MFI in MF ($p<0.001$) and ES ($p<0.001$). However, no significant differences between groups were found for total CSA in MF ($p=0.417$) or ES ($p=0.395$) or muscle CSA in MF ($p=0.511$) or ES ($p=0.241$). For T2-rest, a significant differences between groups was seen in MF ($p=0.047$) whereas a borderline significant difference was found in ES ($p=0.052$) when corrected for age.

Fat CSA was significantly higher in continuous CLBP compared to respectively non-continuous CLBP and RLBP in MF ($p<0.001$; $p<0.001$) and ES ($p=0.007$; $p=0.006$). Also lean MFI was significantly higher in continuous CLBP compared to respectively non-continuous CLBP and RLBP in MF ($p=0.006$; $p<0.001$) and ES ($p=0.001$; $p<0.001$). No significant differences between groups were established post hoc. All parameter estimates can be found in table 3.

Muscle function

Differences between groups were found for T2-shift in MF ($p=0.010$) and ES ($p=0.002$).

T2-shift was significantly lower in RLBP compared to respectively non-continuous CLBP and continuous CLBP in both MF ($p=0.032$; $p=0.030$) and ES ($p=0.025$; $p=0.005$). No differences between spine levels were seen (table 3).

		RLBP (n=24)	Non-continuous CLBP (n=15)	Continuous CLBP (n=16)
Demographic variables	***Age (years)***	30.6 ± 9.8; [21 - 53]	33.9 ± 10.4; [20 - 54]	46.1 ± 14.5; [23 - 64]
	BMI (kg/m²)	22.8 ± 2.3; [18.6 - 28.8]	23.3 ± 1.6; [19.8 - 26.1]	25.0 ±3.1; [19.7 - 31.7]
	Gender	9m; 15f	7m; 8f	8m; 8f
Muscle structure	***Total CSA MF (cm²)***	5.92 ± 1.38; [4.20 – 8.98]	5.41 ± 1.15; [3.17 – 7.47]	5.98 ± 1.41; [3.54 – 8.14]
	Total CSA ES (cm²)	16.56 ± 3.90; [12.08 – 24.34]	14.98 ± 3.06; [8.57 – 21.44]	15.71 ± 3.10; [11.45 – 22.20]
	Fat CSA MF (cm²)	0.80 ± 0.27; [0.49 – 1.66]	0.77 ± 0.19; [0.49 – 1.13]	1.06 ± 0.26; [0.62 – 1.41]
	Fat CSA ES (cm²)	2.60 ± 0.79; [1.70 – 4.58]	2.31 ± 0.62; [1.14 – 3.51]	2.15 ± 1.01; [1.89 – 5.88]
	Muscle CSA MF (cm²)	5.12 ± 1.21; [3.41 – 7.45]	4.65 ± 1.08; [2.35 – 6.47]	4.92 ± 1.39; [2.76 – 6.80]
	Muscle CSA ES (cm²)	14.06 ± 3.46; [10.34 – 21.12]	12.67 ± 2.65; [6.64 – 17.93]	12.46 ± 2.83; [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]	12 ± 4; [7 - 19]
	T2-rest MF	42829 ± 4294; [35014 - 60450]	40459 ± 4152; [31254.00 - 55746]	42116 ± 5685; [32127 - 63624]
	T2-rest ES	41427 ± 3159; [36166 - 52038]	39583 ± 2763; [31691 - 47460]	41925 ± 4998; [33447 -62330]
Muscle function	***T2-shift MF***	8 ± 9; [-12 - 34]	14 ± 11; [-3 - 39]	14 ± 9; [0 - 39]
	T2-shift ES	7 ± 8; [-15 - 30]	13 ± 12; [-1 - 55]	15 ± 10; [-9 - 38]
Pain measurements	***Pain before exercise***	0.091 ± 0.43 [0 - 2]	2.36 ± 2.02; [0 - 8]	2.41 ± 1.93; [0 - 7]
	Pain during exercise	1.68 ± 1.32; [0 - 5]	2.93 ± 2.06; [0 - 7]	3.13 ± 1.86; [0 - 8]
	Pain after exercise	1.14 ± 1.08; [0 - 3]	2.36 ± 1.60; [0 - 6]	3.44 ± 1.90; [0 - 8]
	Expected pain	2 ± 1.63; [0 - 6]	3.36 ± 2.24; [0 - 8]	3.25 ± 1.77; [1 - 8]
	RPE	9.27 ± 1.86; [7 - 13]	10 ± 1.47; [7 - 12]	10.94 ± 1.57; [8 - 13]

Table 2: Descriptive details of the demographic variables and outcome measurements for ***pain measurements*** (expressed pain before exercise, during exercise and after exercise, the expected pain after exercise and the rate of perceived exhaustion), ***muscle structure*** (total cross-sectional are, fat cross-sectional area, muscle cross-sectional are, muscle fat index and T2-rest) and ***muscle function*** (T2-shift) of the multifidus and erector spinae muscle. (BMI=body mass index; CLBP=chronic low back pain; ES=erector spinae; f=females; m=males; MF=multifidus; n=number of; NRS=numeric rating scale; RLBP=recurrent low back pain; RPE=rate for perceived exhaustion). All values, except gender, are expressed by mean, standard deviation and range.

Assessment of pain and exhaustion

Differences between groups were found for pain before exercise ($p<0.001$), pain during exercise ($p=0.024$), pain after exercise ($p<0.001$) and the rate of perceived exhaustion ($p=0.015$). No significant difference between groups was found for "expected pain after exercise" ($p=0.052$).

RLBP indicated significantly lower pain ratings compared to continuous CLBP before ($p<0.001$), during ($p=0.035$) and after exercise ($p<0.001$). Before exercise, RLBP also experienced significantly lower pain intensities compared to non-continuous CLBP ($p<0.001$). The rate of perceived exertion was significantly lower in RLBP compared to continuous CLBP ($p=0.011$) (table 3).

Correlations

Pain parameters

In continuous CLBP, mainly the NRS-score after the exercise was positively correlated with T2-rest for MF and ES at the upper L4 and lower L4 level. The expected pain caused by the exercise in continuous CLBP was positively correlated with T2-shift in both MF and ES but only at the upper L3 level. The T2-shift at upper L3 was also positively correlated with the NRS-score after exercise for MF but not for ES (table 4).

Considering the complete population, a positive correlation was found between the MFI in MF and ES with the NRS-score after exercise. Also positive correlations between the T2-shift in MF and ES at the upper L3 level and respectively the NRS-score after exercise, the expected NRS-score and the rate of perceived exhausting were found (table 4).

Structural and functional characteristics

In the ES muscle of the total population, positive correlations between the T2-rest and fat CSA on the one hand and T2-rest and MFI on the other hand were revealed. Furthermore, a positive correlation was found between T2-shift and MFI in ES. To a lesser extent, some correlations in MF were found between MFI and T2-rest on the one hand and T2-shift on the other hand. Also a single positive correlation was found between the fat CSA and T2-rest in MF (table 5)

	Δ continuous CLBP – non-continuous CLBP		Δ RLBP – non-continuous CLBP		Δ RLBP –continuous CLBP	
	Estimates [CI]	**p-value**	**Estimates [CI]**	**p-value**	**Estimates [CI]**	**p-value**
Total CSA MF (cm²)	5.64 [-5.99 ; 17.27]	P=0.475	5.12 [-5.36 ; 15.60]	p=0.470	-0.52 [-11.01 ; 9.96]	p=0.992
Total CSA ES (cm²)	7.29 [-23.24 ; 37.82]	P=0.833	15.77 [-12.23 ; 43.76]	P=0.368	8.48 [-19.52 ; 36.47]	P=0.745
Fat CSA MF (cm²)	2.89 [1.10 ; 4.69]	P<0.001*	0.38 [-1.23 ; 1.99]	P=0.837	-2.51 [-4.13 ; -0.90]	P<0.001*
Fat CSA ES (cm²)	9.36 [2.27 ; 16.45]	P=0.007*	0.73 [-5.67 ; 7.12]	P=0.959	-8.63 [-15.03 ; -2.24]	P=0.006*
Muscle CSA MF (cm²)	2.75 [-8.15 ; 13.64]	P=0.816	4.74 [-5.08 ; 14.6]	P=0.479	1.99 [-7.83 ; 11.81]	P=0.876
Muscle CSA ES (cm²)	-2.07 [-29.53 ; 26.39]	P=0.982	13.82 [-11.37 ; 39.00]	P=0.387	15.89 [-9.30 ; 41.07]	P=0.288
MFI MF (%)	0.02 [0.01 ; 0.04]	P=0.006*	-0.01 [-0.02 ; 0.01]	P=0.322	-0.03 [-0.04 ; -0.02]	P<0.001*
MFI ES (%)	0.03 [0.01 ; 0.05]	P=0.001*	-0.01 [-0.03 ; 0.01]	P=0.324	-0.04 [-0.05 ; -0.02]	P<0.001*
T2-rest MF	491.13 [-2756.37 ; 3738.627]	P=1.000	2685.74 [-87.29 ; 5458.77]	P=0.061	2194, 61 [-924.41 ; 5313.63]	P=0.263
T2-rest ES	804.69 [-1861.02 ; 3470.94]	P=1.000	2261.258 [-15.21 ; 4537.73]	P=0.052	1456.30 [-1104.21 ; 4016.81]	P=0.496
T2-shift MF	-0.00 [-0.06 ; 0.06]	P=1.000	-0.06 [-0.12 ; -0.00]	P=0.032*	-0.06 [-0.11 ; -0.00]	P=0.030*
T2-shift ES	0.01 [-0.05 ; 0.07]	P=1.000	-0.06 [-0.12 ; -0.01]	P=0.025*	-0.07 [-0.13 ; -0.02]	P=0.005*
Pain before exercise	0.05 [-1.29 ; 1.39]	P=0.996	-2.26 [-3.52 ; -1.01]	P<0.001*	-2.32 [-3.52 ; -1.11]	P<0.001*
Pain during exercise	0.20 [-1.32 ; 1.71]	P=0.947	-1.25 [-2.66 ; 0.17]	P=0.094	1.44 [-2.80 ; -0.08]	P=0.035*
Pain after exercise	1.08 [-0.26 ; 2.42]	P=0.134	-1.22 [-2.47 ; 0.03]	P=0.056	-2.30 [-3.50 ; -1.10]	P<0.001*
Expected pain	-0.11 [-1.75 ; 1.53]	P=0.986	-1.36 [-2.89 ; 0.17]	P=0.092	-1.25 [-2.72 ; 0.22]	P=0.110
RPE	0.94 [-0.54 ; 2.42]	P=0.286	-0.73 [-2.11 ; 0.66]	P=0.418	-1.67 [-2.99 ; -0.34]	P=0.011*

Table 3: Parameter estimates of **muscle structure** variables (total cross-sectional area, fat cross-sectional area, muscle cross-sectional area, muscle fat index and T2-rest) of the multifidus and erector spinae muscles, **muscle function** (T2-shift) of the multifidus and erector spinae muscles and pain measurements (CI=confidence interval; CLBP=chronic low back pain; CSA=cross-sectional area; ES=erector spinae; MF=multifidus; MFI=muscle fat index; RLBP=recurrent low back pain; RPE=rate of perceived exhaustion). Significance level is set at p<0.050 (*).

	NRS AFTER EXERCISE	NRS EXPECTED	RPE
Fat CSA MF			
Fat CSA ES			
MFI MF	Total: P=0.003; R_p=0.406		
MFI ES	Total: P=0.011; R_p=0.355		
T2-rest low L4 MF	Continuous: P=0.02; R_p=0.565		
T2-rest low L4 ES	Continuous: P=0.04; R_p=0.517		
T2-rest up L4 MF	Continuous: P=0.04; R_p=0.521		
T2-rest up L4 ES	Continuous: P=0.03; R_p=0.549		
T2-rest up L3 MF			
T2-rest up L3 ES			
T2-SHIFT up L3 MF	Total: P<0.050; R_p=0.531 Continuous: P=0.005; R_p=0.665	Total: P=0.007; R_p=0.368 Continuous: P=0.028; R_p=0.548	Total: P=0.010; R_p=0.355
T2-SHIFT up L3 ES	Total: P<0.050; R_p=0.483 Continuous: P=0.048; R_p=0.501	Total: P=0.015; R_p=0.335 Continuous: P=0.034; R_p=0.532	Total: P=0.026; R_p=0.308

Table 4: Correlations between ***pain measurements*** (the NRS taken after the Biering-Sörensen exercise, the NRS representing the expected pain after the Biering-Sörensen exercise and the rate of perceived exhausting) and ***muscle structure/function*** (Fat cross-sectional area , MFI, T2-rest and T2-shift) in the lumbar multifidus and erector spinae muscles. (CSA=cross-sectional area; ES=erector spinae; low=lower level; MF=multifidus; NRS=numeric rating scale; RPE=rate of perceived exhaustion; up=upper level). Correlations are performed by Pearson correlation tests. Test results are represented by a significance value (P) and the Pearson Correlation coefficient (R_p). In all blanc spaces, no significant correlations were found. For MRI outcome measure not mentioned in the left column, no correlations were found.

	FAT CSA MF	FAT CSA ES	MFI MF	MFI ES
T2-rest low L4 MF	Total: p=0.041; R_p=0.280	Total: p=0.016; R_p=0.327	Total: p=0.013; R_p=0.334	Total: p=0.042; R_p=0.277
T2-rest low L4 ES	Total: p=0.001; R_p=0.441	Total: p=0.001; R_p=0.433	Total: p=0.008; R_p=0.354	Total: p=0.002; R_p=0.409
T2-rest up L4 MF		Total: p=0.006; R_p=0.368	Total: p=0.009; R_p=0.348	
T2-rest up L4 ES	Total: p=0.021; R_p=0.313	Total: p<0.050; R_p=0.464	Total: p=0.001; R_p=0.451	Total: p=0.004; R_p=0.389
T2-rest up L3 MF		Total: p=0.002; R_p=0.405		
T2-rest up L3 ES	Total: 0.005; R_p=0.380	Total: p<0.050; R_p=0.511	Total: p<0.050; R_p=0.500	Total: p<0.050; R_p=0.464
T2-shift low L4 MF		Total: p=0.042; R_p=0.277	Total: p=0.009; R_p=0.350	Total: p=0.018; R_p=0.320
T2-shift low L4 ES			Total: p=0.013; R_p=0.333	Total: p=0.023; R_p=0.308
T2-shift up L4 MF				
T2-shift up L4 ES				Total: p=0.016; R_p=0.326
T2-shift up L3 MF		Total: p=0.006; R_p=0.371		Total: p=0.011; R_p=0.343
T2-shift up L3 ES				Total: p=0.009; R_p=0.350

Table 5: Correlations between DIXON outcomes (fat cross-sectional area and muscle fat index in the multifidus and erector spinae muscle at level upper L4) and mfMRI outcome (T2-rest and T2-shift of the multifidus and erector spinae muscles at the levels lower L4, upper L4 and upper L3). (CSA=cross-sectional area; ES=erector spinae; low=lower level; MF=multifidus; up=upper level). Correlations are performed by Pearson correlation tests. Test results are represented by a significance value (P) and the Pearson Correlation coefficient (R_p). Yellow spaces are correlations in the same muscle. In all blanc spaces, no significant correlations were found.

4. DISCUSSION

This experimental study evaluated differences in muscle structure, muscle quality and muscle activity in the MF and ES muscles between RLBP in remission, non-continuous CLBP and continuous CLBP. This way, the influence of the continuation of pain complaints on muscle structure and muscle function was examined. We hypothesized that lumbar muscles in continuous CLBP are characterized by more atrophy, a higher amount of fat infiltration, less muscle quality (or an enhanced lean MFI) and a dysfunctional muscle activity compared to RLBP and non-continuous CLBP.

Results revealed indeed a smaller fat CSA and a lower amount of fat infiltration in RLBP and non-continuous CLBP compared to continuous CLBP, but no differences were seen in total CSA or muscle CSA. Previous results concerning fat infiltration in non-specific CLBP compared to HC were conflicting: increased fat infiltration in MF and ES was seen in non-specific CLBP in 2 studies [8,11], whereas another found no differences between CLBP and HC [6]. In RLBP, enhanced fat infiltration does not occur according to the current literature [11,12]. To our knowledge, only one study compared CLBP with intermittent LBP and found increased fat content and less contractile tissue in non-specific CLBP compared to intermittent LBP [11]. The current study confirms these previous results by an increased fat CSA and enhanced lean MFI in continuous CLBP compared to RLBP. Because fat CSA, in the current study, is calculated by the fat fraction of the total muscle, also invisible fat droplets were taken into account. This quantitative measurement provides a very accurate representation of fatty infiltration in the muscle compared to (semi)-qualitative measurements used in previous research. In conclusion, one can conclude that ***fat infiltration is enhanced and the muscle quality is deteriorated in continuous CLBP compared to non-continuous CLBP and RLBP patients.***

No differences in total CSA or muscle CSA between groups were found. The current results indicate that the reduction in total CSA and/or muscle CSA might be similar in RLBP, non-continuous CLBP and continuous CLBP. This is however in contrast with a unique study which compared CLBP with intermittent LBP and established a significant lower CSA in CLBP. Possibly the lack of differences in total CSA in the current study are masked by the changes in fat CSA. As Freeman proposes, the transition from muscle fibers into fat, results in fatty degeneration in CLBP [37]. A recent study of Hodges and colleagues demonstrated indeed an increase in adipose/connective tissue in the absence of muscle atrophy in the MF, 3-6 months after intervertebral disk injury in sheep [50]. If muscle tissue is replaced by fat tissue and/or connective tissue, differences in total CSA might be concealed. Another possible explanation for not finding significant differences between groups for total and

muscle CSA is the large variance of muscle CSA. To overcome this issue, a larger test population is needed in future studies.

Regarding muscle activity, the current study established a higher T2-shift in both non-continuous and continuous CLBP compared to RLBP. These results resemble an ***enhanced metabolic activity in the lumbar muscles of non-continuous and continuous CLBP compared to the RLBP patients.*** The only study evaluating lumbar muscle activity by mfMRI in CLBP, also found an increased metabolic change in CLBP who underwent surgery, compared to HC [40]. Enhanced metabolic activity is also found in RLBP patients despite their state of remission [31]. Possibly, the metabolic activity is enhanced in RLBP in remission compared to HC and even more enhanced in the non-continuous and continuous CLBP. As a consequence, the frequency of pain days, might worsen the amount of metabolic activity in the lumbar muscles.

A higher T2-shift, caused by a standardized activity, resembles an enhanced metabolic activity of the lumbar muscles. This increased metabolic activity in continuous and non-continuous CLBP, possibly replicates a relatively higher intensity in contractions performed by the lumbar muscles. Muscle characteristics might influence the efficiency of performed muscle activity and be responsible for the enhanced metabolic residuals after contractions. In the total test population of the current study, a higher MFI and fat CSA was correlated to a higher T2-shift, mainly in the ES muscle. Lumbar muscles with more fat or connective tissue relative to muscle tissue, contain less remaining muscle fibers able to perform muscle activity. As a result, a relatively higher workload is enforced to the remaining muscle fibers, leading to a potential faster acidification and a higher T2-shift. This strategy is maladaptive. Clinically, the lumbar muscles are fatigued more rapidly. The rate of perceived exhaustion was significantly higher in continuous CLBP compared to the RLBP patients, possibly resembling a more fatigued lumbar musculature in the continuous CLBP group. This ongoing impaired activity produces a continuous load on spinal structures and makes the spine susceptible to strain and further injuries. This process might be a contributing factor why non-continuous and continuous CLBP, unlike RLBP, don't recover after every pain episode.

An enhanced T2-shift is established also in non-continuous CLBP compared to RLBP, but no enhanced fat infiltration is seen compared to RLBP. Therefore, another feature besides fat infiltration might contribute to the enhancement of metabolic residuals in the lumbar muscles. Differences in fiber type distribution also might influence the metabolic shift. Existing literature suggest that a lowered T2-rest indicates a higher portion of glycolytic fibers, whereas a higher resting state T2-value is related to more oxidative muscle fibers (type I fibers) [31,51–53]. A higher proportion of glycolytic fibers or anaerobic fibers (type II fibers) is reported in the back muscles of people with CLBP [54]. As

a result, more metabolic substances are produced during contraction [31]. The non-continuous CLBP group indeed indicated lower mean T2-rest values compared to RLBP and continuous-CLBP, however not significantly different. Possibly the lack of power in the current study is responsible for not finding these differences. A priori power calculation revealed that 24 subjects in each group were needed. For both CLBP subgroups, this amount unfortunately was not reached. Therefore, it is possible that the sample size of LBP-subgroups in this dissertation was to small to detect additional differences between groups. Taken together, the enhanced metabolic activity seen in continuous CLBP might be due to fat infiltration, whereas the enhanced metabolic activity of the non-continuous CLBP groups might be due to a shift in fiber type towards glycolitic fibers at the expense of aerobic fibers.

Significantly ***lower pain ratings were seen in RLBP compared to continuous CLBP before, during and after exercise just as for the rate of perceived exhaustion***. Before exercise, RLBP also experienced significant lower pain intensities compared to non-continuous CLBP. These observations seem obvious since RLBP patients were in remission. The ongoing presence of pain is however not necessary for motor control changes to persist. Psychosocial factors, such as fear of movement have a similar effect and can explain changes in patients with musculoskeletal pain even when in remission [55]. In the current study, no significant differences were found between groups in the expected pain due to exercise, which indicates that all 3 included LBP populations have a similar anticipation of pain. Since no comparison was made with a control group, the current study is not able to state if the anticipation of pain due to movement is enhanced in the LBP groups, but future research could take this into account.

In summary, muscle structure and muscle quality is deteriorated in continuous CLBP compared to non-continuous CLBP and RLBP, whereas muscle function is less efficient in continuous CLBP compared to RLBP but not compared to non-continuous CLBP. Previous research established an increased MFI in the absence of clear atrophy [12] and alterations in muscle activity [20,28,31,34] in patients with RLBP in remission compared to HC. Deterioration of the lumbar muscle quality of the RLBP population is therefore present in the absence of clear atrophy. The results of the current study point out that enhanced fat infiltration, more deterioration in muscle quality and inefficient muscle work is present in the continuous CLBP group compared to the RLBP. Taken together, muscle quality starts to deteriorate in RLBP and declines further as a patient has back pain more frequently or more continuously. As a consequence, therapies concerning functional muscle regeneration could become more crucial in patients with more continuous pain.

Limitations

In the current study, some limitations should be considered. First of all, the amount of (in)activity was not investigated. Prolonged bedrest might worsen muscle degeneration, whereas physical training and/or a general physically active lifestyle might improve structural muscle conditions [56–58]. Besides, decreased general activity levels can influence the ratio between muscle and fat tissue, without affecting the CSA of the total muscle [59].

Second, the division between non-continuous and continuous CLBP was made based on the amount of pain days per week. As a consequence, the current study investigated muscle structure and muscle function in a spectrum of LBP patients. This spectrum consists of RLBP on the one end, suffering from pain episodes alternated by long pain free episodes and continuous CLBP suffering every day of LBP on the other end. All established differences in muscle structure, muscle quality, muscle function and pain measurements between groups in this study, clearly illustrate the different characteristics in RLBP, non-continuous CLBP and continuous CLBP and strengthens our choice to divide the CLBP group of this study into 2 subgroups (non-continuous and continuous CLBP). The non-continuous CLBP suffer from LBP during multiple days a week alternated by some pain free days and are therefore situated between the RLBP and the continuous CLBP patients. Because the division of the LBP groups was based on the frequency of pain flares and not on pain intensity, heterogeneity in current pain intensity exists within the study population. Pain ratings before exercise in the CLBP groups varied between 0 and 7 or 8. Therefore, a possible influence of pain on muscle structure and muscle activity cannot be ruled out. Besides a division based on the amount of pain flares, possibly other criteria are appropriate to define both groups. Future research should look into parameters which might characterize the different CLBP groups more accurate.

5. CONCLUSION

No differences in lean muscle atrophy and total atrophy between RLBP, non-continuous CLBP and continuous CLBP are seen. Enhanced fat infiltration, MFI in lean muscle tissue, and metabolic activity after exercise are present in continuous CLBP compared to RLBP. Regarding muscle activity,

increased activity induced metabolic changes are also found in the lumbar muscles in non-continuous compared to RLBP. In patients with continuous pain, lumbar muscles contain more fat infiltration and are characterized by a worse muscle quality compared to non-continuous CLBP. All these results indicate that RLBP, non-continuous CLBP and continuous CLBP are part of a complete spectrum of LBP complaints in which each subgroup is marked by different muscle characteristics.

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