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FULL PAPER

Evaluation of intramyocellular and extramyocellular lipids in the paraspinal muscle in patients with chronic low back pain using MR spectroscopy: preliminary results

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Objective: To analyze the intramyocellular lipids (IMCL) and extramyocellular lipids (EMCL) in the psoas muscle (Pm) and multifidus muscle (Mm) using MR spectroscopy (MRS) in patients with chronic low back pain (CLBP) and asymptomatic volunteers.

Methods: This prospective study had institutional review board approval, and written informed consent was obtained from all individual participants. 20 patients with CLBP (mean age, 49.8 ± 12.5 years; age range, 28–66 years) with low back pain (LBP) duration of ≥ 3 months and asymptomatic volunteers (mean age, 44.0 ± 12.8 years; age range, 28–65 years) underwent MRS for the quantification of IMCL and EMCL of the right Pm and Mm in a volume of interest at the intervertebral level of L4 through L5. We compared patients with CLBP and asymptomatic volunteers for age and body mass index (BMI), IMCL and EMCL of Pm and Mm. The Mann–Whitney *U*-test was used for significant difference

testing, with *p*-value < 0.05 indicating statistical significance.

Results: No statistically significant differences were observed in the age and BMI of patients with CLBP and asymptomatic volunteers. There was no statistically significant difference in the EMCL and IMCL in Pm between the two groups. EMCL in Mm was not statistically significantly different; the IMCL of patients with CLBP was significantly higher than that of asymptomatic volunteers ($p < 0.05$).

Conclusion: MRS demonstrates that IMCL in the Mm of patients with CLBP is significantly higher than that of asymptomatic volunteers. The increase of IMCL in the Mm may be a characteristic finding in CLBP.

Advances in knowledge: We investigated the detail of the fat content in the paraspinal muscles in patients CLBP and asymptomatic volunteers. The increase of fat content in the Mm of patients with LBP on previous studies was demonstrated to be the increase of IMCL.

INTRODUCTION

Low back pain (LBP) is a common disorder, with a prevalence rate of 80% or higher^{1,2} and it is a leading cause of disability during the working years.^{3,4} LBP can be classified into the following two types: pain with a clear aetiology (e.g. trauma, spondylitis, tumours etc.) and non-specific pain, in which the source is difficult to identify. Non-specific LBP, which comprises $\geq 80\%$ of all cases,^{5–7} can be further classified into myofascial, discogenic, facet-related and sacroiliac joint-related LBP.⁵ Although various diagnostic imaging modalities and auxiliary methods are used, the cause of chronic low back pain (CLBP) can rarely be clarified in individual patients.

Suspicion regarding the involvement of the trunk muscles, such as the paraspinal muscles, in the aetiology of LBP has

been reported.^{8,9} In particular, the psoas muscle (Pm) and multifidus muscle (Mm) both provide stability to the spine and are sensitive to pathologic changes. Attention has been focused on the role of the Pm in stabilizing the spine. Biomechanical models suggest that the Pm may achieve this function by its large potential to generate compressive forces, which increase spinal stiffness.¹⁰ On the other hand, the Mm is responsible for providing two-third of the spinal segmental stability and is important for the maintenance of trunk function.^{1,11}

Previous imaging studies have examined the relationship between LBP and fat degeneration in paraspinal muscles such as the Mm.^{12–14} Diagnostic imaging techniques such as ultrasonography, CT and MRI are often used to assess fat degeneration in muscles.^{12,13,15} Among MRI techniques,

the multipoint Dixon technique^{16,17} and MR spectroscopy (MRS)^{3,18} have been used in previous studies. In recent years, MRS analysis of muscle physiology has been applied in various fields, including sports medicine;^{18–20} this has enabled the detailed analyses of muscular fat mass, such as evaluation of the presence of intramyocellular lipids (IMCL) and extramyocellular lipids (EMCL).^{3,21,22} IMCL appear as lipid droplets in skeletal muscle cells and are reportedly associated with aerobic metabolism. In contrast, EMCL exist as subcutaneous and extracellular fat in cells along the muscle fibres. To date, some reports on the relationship between fat degeneration in the paraspinal muscles and LBP have been published;^{3,14,17,23} however, the association of IMCL and EMCL with LBP remains unclear.

The aim of the present study was to analyze the IMCL and EMCL in the Pm and Mm using MRS in patients with CLBP and in asymptomatic volunteers.

METHODS AND MATERIALS

Study participants

The institutional review board approved this prospective cross-sectional study and written informed consent was obtained from the study participants. 20 patients (8 females and 12 males; age range, 28–66 years) with non-localized and non-specific CLBP were included in the study if they met the following inclusion criteria, as assessed by a routine diagnostic MRI of the lumbar spine: (a) more than 3 months of continuous or recurrent LBP, (b) visual analogue scale (VAS) score of >30 mm for LBP and (c) referral for MRI given by a spine surgeon at our institution because of LBP. The exclusion criteria were as follows: (i) prior spine surgery; (ii) systemic inflammatory disease; (iii) neurologic disorder; (iv) acute trauma, neoplasm or infection; (v) spinal deformities; and (vi) diabetes, hypertriglyceridaemia or other metabolic disorders. 20 asymptomatic age-matched volunteers with no history of prior spinal surgery or LBP were recruited (9 females and 11 males; age range, 28–65 years).

Body mass index (BMI) and VAS scores as indicators of obesity and degree of LBP, respectively, were also obtained from each group.

MRI protocol

The Signa HDx 1.5-T MRI system (GE Healthcare, Milwaukee, WI) with a spine coil was used to obtain T_2 weighted sagittal and transverse MR images. From these images, the proton MRS volume of interest (VOI) was positioned at the centre of the Pm and Mm at L4/5 on the right side (Figure 1). Single-voxel point-resolved spectroscopy sequence was performed with the following parameters: repetition time, 2000 ms; echo time, 35 ms; average number of signals, 64; VOI size, $15 \times 15 \times 15$ mm (3.4 ml); and acquisition time, 164 s.

Analysis of MR images and spectroscopic data

T_2 weighted transverse MR images were used for analyzing fat infiltration in the Pm and Mm at a similar level and on the same side by MRS. For the quantitative analysis of non-muscular fat infiltration, we used a four-grade visual scale adapted from previous reports:^{14,24} Grade 0 = no apparent non-muscular tissue, Grade 1 = minor deposits of non-muscular tissue (<25%), Grade 2 = moderate infiltration of non-muscular tissue (25–50%) and Grade 3 = severe infiltration of non-muscular tissue (>50%). The obtained spectral data were used to measure IMCL and EMCL using LCModel software (Stephen Provencher, Inc., Oakville, ON). The data were transferred from the scanners to a Linux workstation, and metabolite quantification was performed by eddy current correction and water scaling. The data for IMCL (1.3 ppm) and EMCL (1.5 ppm) corresponding to methylene protons were used for statistical analysis. Estimates of IMCL and EMCL were automatically scaled to an unsuppressed water peak (4.7 ppm). These data are graphically displayed, with chemical shifts plotted along the x-axis, thus allowing the identification of metabolites. Peak intensity is plotted on the y-axis (Figure 2). We excluded subjects in whom the Pm and

Figure 1. Positioning of the volume of interest for MR spectroscopy measurements: (a) psoas muscle (Pm) and (b) multifidus muscle (Mm) as indicated on the transverse T_2 weighted image (repetition time/echo time, 4000 ms/102 ms) at the intervertebral level L4 through L5 on the right side. At level L4/5, a $15 \times 15 \times 15$ -mm voxel was positioned at the centre of the Pm and Mm.

Figure 2. The proton MR spectrum of the multifidus muscle was analyzed using LCModel software (Stephen Provencher, Inc., Oakville, ON). The following metabolites are identified: intramyocellular lipids (IMCL) ($-CH_2$) methylene protons at 1.3 ppm; and extramyocellular lipids (EMCL) ($-CH_2$) methylene protons at 1.5 ppm.

Mm showed a standard deviation of over 15% for EMCL or IMCL on the LCModel.

Statistical analysis

The BMI, degree of fat infiltration and IMCL and EMCL values in the Pm and Mm were compared between patients with CLBP and asymptomatic volunteers. The Mann–Whitney *U*-test was used to test statistical significance, which was set at a *p*-value of <0.05 . All statistical analyses were performed with commercially available software (SPSS® software, v. 20.0; IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL). If there were significant differences between the findings for patients with CLBP and asymptomatic volunteers, we calculated the cut-off value for CLBP by receiver-operating characteristic curve analysis using MedCalc (v. 10.2.0.0; MedCalc Software, Ostend, Belgium).

RESULTS

The mean age and BMI of patients with CLBP were 49.8 ± 12.5 years and $23.9 \pm 3.6 \text{ kg m}^{-2}$ and those of asymptomatic volunteers were 44.0 ± 12.8 years and $22.4 \pm 3.6 \text{ kg m}^{-2}$, respectively. No statistically significant differences were observed in the age, gender and BMI of patients with CLBP and asymptomatic volunteers. Moreover, the average VAS scores in patients with CLBP and asymptomatic volunteers were 63.8 ± 16.5 and 0, respectively. Further, a statistically significant difference was observed between the two groups for the quantitative analysis of non-muscular fat infiltration in the Mm ($p = 0.002$). However,

no statistically significant difference was observed with regard to fat infiltration in the Pm for the two groups (Table 1).

The mean IMCL value in the Pm of patients with CLBP and asymptomatic volunteers was $1.91 \pm 1.03 (\times 10^2)$ and $2.08 \pm 1.09 (\times 10^2) \text{ mmol l}^{-1}$, respectively. Further, the mean EMCL value in the Pm of patients with CLBP and asymptomatic volunteers was $1.38 \pm 0.69 (\times 10^3)$ and $1.11 \pm 0.98 (\times 10^3) \text{ mmol l}^{-1}$, respectively. No statistically significant differences were found between patients with CLBP and asymptomatic volunteers in terms of EMCL and IMCL in the Pm (Figure 3). For the Mm, the mean IMCL of patients with CLBP and asymptomatic volunteers was $6.10 \pm 2.67 (\times 10^2)$ and $2.58 \pm 1.43 (\times 10^2) \text{ mmol l}^{-1}$, respectively. The IMCL of patients with CLBP was significantly higher than that of asymptomatic volunteers ($p = 0.017$). The mean EMCL of patients with CLBP and asymptomatic volunteers was $2.63 \pm 1.75 (\times 10^3)$ and $1.52 \pm 1.54 (\times 10^3) \text{ mmol l}^{-1}$, respectively; no statistically significant difference was found between patients with CLBP and asymptomatic volunteers for this variable (Figure 4). We analyzed the cut-off value of IMCL in the Mm, and the resulting cut-off value was $325.4 (\text{mmol l}^{-1})$, with a sensitivity of 90.0%, specificity of 85.0% and an area under the curve of 0.912 (Figure 5).

DISCUSSION

Several studies have reported an association between LBP and fat degeneration in the paraspinal muscles using various indicators and imaging techniques, and all studies revealed an increase in

Table 1. Distribution of the examinees with regard to the age, gender, body mass index (BMI), visual analogue scale (VAS) and fatty infiltration grade in the multifidus muscle (Mm) and psoas muscle (Pm)

Characteristics	Fatty infiltration grade	Patients with CLBP	Asymptomatic volunteers	<i>p</i> -value
Age (years) mean $\pm$ SD (95% CI)		49.8 $\pm$ 12.5 (42.7–56.3)	44.0 $\pm$ 12.8 (37.7–50.8)	0.223 ^a
Gender				
Female		8	9	0.744 ^b
Male		12	11	
BMI (kg m ⁻²) mean $\pm$ SD (95% CI)		23.9 $\pm$ 3.6 (22.7–25.9)	22.4 $\pm$ 3.6 (20.5–24.3)	0.390 ^a
LBP VAS (mm) mean $\pm$ SD (95% CI)		63.8 $\pm$ 16.5 (54.5–72.1)	0	0.000 ^a
Mm	0	0	2	0.002 ^a
	I	5	11	
	II	10	2	
Pm	0	2	3	0.630 ^a
	I	13	12	
	II	0	0	

CI, confidence interval; CLBP, chronic low back pain; LBP, low back pain; SD, standard deviation.

^aMann-Whitney *U*-test.

^b χ^2 test.

fat degeneration in patients with LBP.^{17,21,23,25} The majority of these studies used the fat fraction of the multipoint Dixon technique to assess degeneration and reported that atrophy and fat degeneration of the paraspinal muscles is common in adults with LBP. Histochemical and morphometric analyses have shown structural changes in the Mm of patients with LBP when compared with that of healthy volunteers.¹⁷ Conversely, studies using MRS comprehensively evaluated fat degeneration as the overall amount of fat content. Mengiardi *et al*³ used proton MRS to evaluate the changes in the fat content of the Mm. These patients with LBP exhibited a significant increase in the fat content of the Mm. Moreover, Fischer *et al*²¹ reported a strong correlation between the fat content and the fat fraction assessed by the multipoint Dixon and single-voxel MRS techniques. Although the mechanisms of fat degeneration in skeletal muscles

are not fully understood, the likely mechanisms are listed as follows: firstly, fat degeneration may occur owing to the transformation of the fibroblasts/pre-adipocytes in response to glucocorticoid-induced inflammation. Secondly, increased secretion of cell mediators, such as proinflammatory cytokines, growth factors and prostaglandins, or derivatives may stimulate adipose tissue proliferation and degeneration.¹⁷ In the present study, there was significantly more fat infiltration in patients with CLBP than in asymptomatic volunteers, as assessed using conventional *T*₂ weighted transverse images; this finding is consistent with the results of previous reports.^{17,26} Moreover, in this study, adipose tissue was distinguished from IMCL and EMCL as fat content in the Pm and Mm, whereas previous studies reported the increased fat content as total amount of adipose tissue in the Mm of patients with CLBP. Increased IMCL

Figure 3. Comparison of the mean values of intramyocellular lipids (IMCL) and extramyocellular lipids (EMCL) in the psoas muscle (Pm) in patients with chronic low back pain (CLBP) and asymptomatic volunteers: the mean value of IMCL was not statistically significantly different between patients with CLBP [$1.91 \pm 1.03 (\times 10^2) \text{ mmol l}^{-1}$] and asymptomatic volunteers [$2.08 \pm 1.09 (\times 10^2) \text{ mmol l}^{-1}$]. The mean value of EMCL was not statistically significantly different between patients with CLBP [$1.38 \pm 0.69 (\times 10^3) \text{ mmol l}^{-1}$] and asymptomatic volunteers [$1.11 \pm 0.98 (\times 10^3) \text{ mmol l}^{-1}$].

Figure 4. Comparison of the mean values of intramyocellular lipids (IMCL) and extramyocellular lipids (EMCL) in the multifidus muscle (Mm) in patients with chronic low back pain (CLBP) and asymptomatic volunteers: the mean value of IMCL in patients with CLBP was $6.10 \pm 2.67 (\times 10^2) \text{ mmol l}^{-1}$ and in asymptomatic volunteers it was $2.58 \pm 1.43 (\times 10^2) \text{ mmol l}^{-1}$. The IMCL of patients with CLBP was statistically significantly higher than that of asymptomatic volunteers ($p < 0.05$). The mean value of EMCL was not statistically significantly different between patients with CLBP [$2.63 \pm 1.75 (\times 10^3) \text{ mmol l}^{-1}$] and asymptomatic volunteers [$1.52 \pm 1.54 (\times 10^3) \text{ mmol l}^{-1}$].

content in skeletal muscles has been associated with obesity^{27,28} and ageing.^{28,29} However, in the present study, there were no statistically significant differences in the age or BMI of patients with CLBP and asymptomatic volunteers. Therefore, we believe that it is possible to obtain reliable data on the basis of increased IMCL in the Mm of patients with CLBP in this study. In addition, we demonstrated a cut-off value for IMCL in the Mm of patients with CLBP and asymptomatic volunteers, and this IMCL may be detected using a grading system of CLBP.

IMCL are stored in spheroid droplets in the cytoplasm of muscle cells in close contact with skeletal mitochondria^{30,31} and are directly used as an energy source by mitochondria. Therefore, IMCL are involved in the increase of free fatty acids in the blood, the increase in their uptake by skeletal muscles and their decreased oxidative capacity.^{18,32,33} Physical inactivity has adverse effects on skeletal muscle metabolism, manifesting

as poor oxidative capacity,^{28,34} lower glycogen storage and decreased capillary density.³⁵ We believe that these mechanisms contributed to the accumulation of IMCL in the Mm of patients with CLBP. These findings, together with those of the present study, indicate that exercise therapy to accelerate mitochondrial activity and diet therapy to control additional adipose tissue accumulation caused by excessive weight are effective measures to reduce or eliminate pain in patients with non-specific CLBP.

EMCL are defined as more or less compact areas of adipose tissue in subcutaneous layers or along fasciae and are considered to be metabolically inactive lipid deposits involved in the reduced functionality associated with obesity and a sedentary lifestyle.^{32,36,37} Lost muscle strength is associated with the accumulation of EMCL, which can interfere with sufficient muscle nutrition.^{36–38}

Figure 5. (a) A receiver-operating characteristic (ROC) curve in intramyocellular lipids (IMCL) in patients with chronic low back pain (CLBP) and asymptomatic volunteers and (b) the cut-off value. We obtained the cut-off value from the highest value both of sensitivity and specificity. The IMCL cut-off value for patients with CLBP and asymptomatic volunteers was $325.4 \text{ mmol l}^{-1}$, which corresponded to a sensitivity (Sens) 90.0%, specificity (Spec) 85.0% and area under the ROC curve 0.912 (95% confidence interval; 0.779–0.978).

With regard to fat degeneration in the Pm, some studies^{24,26} have reported that the Pm of other examinees showed minimal fat degeneration. In the present study, no significant difference was found in the fat degeneration in the Pm between patients with CLBP and controls. Consequently, this suggests that fat degeneration in the Pm has no relation to CLBP in patients.

We positioned the VOI in each muscle and measured IMCL and EMCL at the L4/5 level because pathological changes appear most often at that location based on previous reports.^{1,21,39} At this level, the paraspinal muscle is thought to be the main muscle protecting the spinal structure controlling the gliding motion at each articuli intervertebrales.^{40,41} Previous studies^{23,42} have reported that atrophy and fat infiltration of the Mm appear to occur at multiple levels and are side specific in relation to symptoms in patients with CLBP and that degenerative scoliosis is associated with the asymmetry of paraspinal muscle changes. In the present study, although we only measured IMCL and EMCL at the L4/5 level on the right side, we inferred that the atrophy and fat infiltration of the Mm at other levels would follow a similar trend to that at the L4/5 level. Moreover, we believe that the influence of these changes would be remarkably limited because the patients in the present study had non-localized and non-specific CLBP. On the other hand, EMCL signals increase drastically as soon as the VOI touches the adipose tissue because EMCL in adipose tissue is about 200 times more concentrated than IMCL in muscle tissue.³⁰ As long as the VOI comprises muscular tissue only, a shift or expansion of the VOI entails no changes in IMCL per volume. EMCL signals are very position dependent; thus, they are, at most, an indicator of the reproducibility of the VOI position and should not be interpreted physiologically. Interindividual and intraindividual reproducibility studies have indicated that the inherent error of IMCL measurements is about 6%.^{30,43} Therefore, we believe that IMCL was accurately assessed in the present study.

The present study had several limitations that should be addressed. First, the number of subjects included in the study

was small. Therefore, it was difficult to calculate the correlation between IMCL and VAS. Further investigation is required to assess whether the results in this study would be obtained with a larger number of subjects. We needed to match the BMI and age of patients with CLBP to those of asymptomatic volunteers, as the fat content in muscles correlates with these. However, it was difficult for us to recruit enough patients with CLBP to match their BMI and age to those of asymptomatic volunteers. Second, we measured the IMCL and EMCL at L4/5 on the right side only. Fat degeneration in the paraspinal muscles of individuals with LBP appears to occur at the site of pain or at multiple levels. Therefore, this should be measured at multiple levels and on both sides in future studies. Third, the daily physical activity and muscle strengths of the subjects in the present study were not assessed. Hence, it is possible that daily activity-associated changes in IMCL occurred in our subjects, who were believed to mainly lead a sedentary lifestyle because of LBP. Finally, because the present study had a cross-sectional design, it is unclear whether the increase in IMCL was the cause or the result of the CLBP. Therefore, future longitudinal studies are warranted to address these limitations.

In conclusion, MRS demonstrates that IMCL in the Mm of patients with CLBP are significantly higher than that of asymptomatic volunteers. In previous studies, the increased fat content in the Mm of patients with LBP was demonstrated to be increased IMCL. The increase of IMCL in the Mm may be a characteristic finding in CLBP.

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