Quantitative Analysis Concerning Atrophy and Fat Infiltration of the Multifidus Muscle with Magnetic Resonance Spectroscopy in Chronic Low Back Pain

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Abstract:

Introduction: Magnetic resonance spectroscopy (MRS) enables detailed analysis of the composition of muscular fat tissues such as intramyocellular lipids (IMCLs) and extramyocellular lipids (EMCLs). The aim of this study was to analyze the EMCL and IMCL of the multifidus muscle (Mm) using MRS in chronic low-back pain (CLBP) patients and identify their possible correlations with age, body mass index (BMI), low-back pain (LBP) visual analog scale (VAS) score, cross-sectional area (CSA), and fat infiltration of the Mm.

Methods: Eighty patients (32 men and 48 women; mean age, 64.7 ± 1.3 years; range, 22-83 years) with VAS scores >30 mm for CLBP were included. We analyzed the gender difference and the possible correlations of age, BMI, LBP VAS, CSA, and fat infiltration of the Mm with the IMCL and EMCL of the Mm. The subjects were divided into five groups as per their age range: < 40s, 50s, 60s, 70s, and 80s. We also analyzed the EMCL and IMCL of the Mm as per the fat infiltration classification.

Results: CSA was larger in the male group, EMCL was higher in the female group, and there was no significant difference in IMCL between the female and male groups. There was a significant positive correlation of EMCL with age (r = 0.33, $p < 0.01$) and BMI (r = 0.42, $p < 0.01$) and a significant negative correlation of EMCL with CSA (r = −0.61, $p < 0.01$). There was a significant positive correlation between IMCL and VAS (r = 0.43, $p < 0.01$). The EMCL and CSA of the Mm decreased with age, whereas fat infiltration increased with age.

Conclusions: These results suggest that EMCL could indicate Mm degeneration associated with aging, and IMCL could be an effective objective indicator of CLBP. The EMCL and IMCL of the Mm may be useful prognostic markers in rehabilitation strategies.

Keywords:
chronic low-back pain, multifidus muscle, magnetic resonance spectroscopy, intramyocellular lipids, extramyocellular lipids, cross-sectional area, fat infiltration

Introduction

Current research has emphasized the significance of sarcopenia, characterized by the impairment of skeletal muscle mass and function with aging. This state might impair physical capability, quality of life, cardiopulmonary performance, and metabolic processes and increase the risk of falls, disability, and mortality in older people[1-6]. Several mechanisms have been implicated in the occurrence and course of sarcopenia such as altered fat metabolism, reduced protein intake, enhanced oxidative stress, and physical inactivity frequently observed in aged people[3,7]. Although sarcopenia is common and has become the focus of several important health problems, a widely accepted clinical measurement method is yet to be established. Several measurement methods can be used to assess the muscle mass, strength, and function[1].

Low-back pain (LBP) is also a frequently observed condi-

Figure 1. The volume of interest for magnetic resonance spectroscopy measurements was positioned at the center of the multifidus muscle (Mm), as indicated on the T2-weighted image at the L4/5 level.

tion and one of the most serious physiological issues in the world[8-10]. Recently, the mechanism of LBP has been elucidated[11,12]. Trunk muscles are important for normal spinal function and are etiologically significant in LBP[13,14]. In particular, the multifidus muscle (Mm) provides two-thirds of spinal segmental stability[15] and is important for maintaining spinal alignment[16]. The evaluation of the Mm function forms part of the clinical assessment of LBP patients[17], and changes in Mm function are related to the outcome of conservative therapy[13,18]. The measurement of lumbar paraspinal muscle morphology using magnetic resonance imaging (MRI) is reportedly effective for the determination of atrophy and fat infiltration[19]. Recently, in addition to morphological assessments, muscles have been evaluated using MRI with the multipoint Dixon technique[20,21] and magnetic resonance spectroscopy (MRS)[22,23]. MRS analysis of muscle physiology has facilitated detailed analyses of muscular fat masses by recording the concentration of extramyocellular lipids (EMCLs) and intramyocellular lipids (IMCLs), which in turn are useful for the identification of fatty degeneration[24-30]. In our previous study, IMCL using MRS analyses in the Mm of chronic LBP (CLBP) patients was significantly higher than that in control subjects[31-33]. In addition, we identified the associations of spino-pelvic alignment (lumbar lordosis and sagittal vertical axis) with the IMCL of the Mm in CLBP[32]. The purpose of this study was to analyze the EMCL and IMCL of the Mm using MRS in CLBP and identify the possible correlations with age, body mass index (BMI), LBP visual analog scale (VAS), cross-sectional area (CSA), and fat infiltration of the Mm.

Materials and Methods

The Hospital Board of Ethics approved this study, and written informed consent was obtained from all the partici-

pants before study initiation.

Participants

Subjects comprised patients with nonspecific CLBP, which was defined as experiencing pain, stiffness, and discomfort in the lower back from the 12th rib to the lumbar or lumbosacral area and had persisted for more than 3 months and whose symptoms had persisted despite conservative treatments. We excluded patients with neurological symptoms of the lower leg or obvious instability, which could be identified as a pain generator that caused CLBP and could be improved with surgical treatment. The exclusion criteria included the following: (i) systemic inflammatory disease; (ii) neurological disorder; (iii) prior spine surgery; (iv) neoplasm, infection, or acute trauma; (v) spinal deformities such as spondylolisthesis with obvious instability, which meant sagittal translation of more than 3 mm, segmental motion of more than 20°, or posterior opening of more than 5° on flexion/extension radiographs or scoliosis (>10°); and (vi) diabetes, hypertriglyceridemia, or other metabolic and endocrine disorders. Eighty patients (32 men and 48 women; mean age, 64.7 ± 1.3 years; range, 22-83 years) fulfilled the diagnostic criteria. The numbers of men and women for each age group were 5 and 5, respectively, for < 40 years; 7 and 12, respectively, for the 50s; 8 and 12, respectively, for the 60s; 8 and 13, respectively, for the 70s; and 4 and 6, respectively, for the 80s. All subjects underwent MRI of the lumbar spine and completed the LBP VAS (0-100 mm). We calculated the BMI using the self-reported body weight (kg) divided by the height squared (m^2) to determine the prevalence of obesity associated with the fat content.

MRI protocol

We used the previously described MRI protocol[31-33]. In brief, the Signa HDx 1.5T MRI system (GE Healthcare, Milwaukee, WI, USA) with a spine coil was used to obtain the T2-weighted sagittal and transverse MR images. Using these images, the proton MRS volume of interest (VOI) was positioned at the center of the Mm at L4/5 for the right side (Fig. 1). Single-voxel point-resolved spectroscopy sequence was performed with the following parameters: repetition time (TR), 2000 ms; echo time (TE), 35 ms; average number of signals, 64; VOI size, 15 × 15 × 15 mm (3.4 mL); and acquisition time, 164 s.

Measurement of CSA and fat infiltration

The CSA and fat-infiltrated area were measured by axial T2-weighted MRI. We measured the right Mm at L4/5 (same level and side as for MRS). CSA was defined by manually tracing the fascial border of the Mm (Fig. 2a), as previously described[34]. The regions of interest were analyzed for the areas and histograms of signal intensity using digitized image-processing software (Image J; National Institutes of Health, Bethesda, MD, USA). The percentage of fat-infiltrated area was measured using a pseudo-coloring
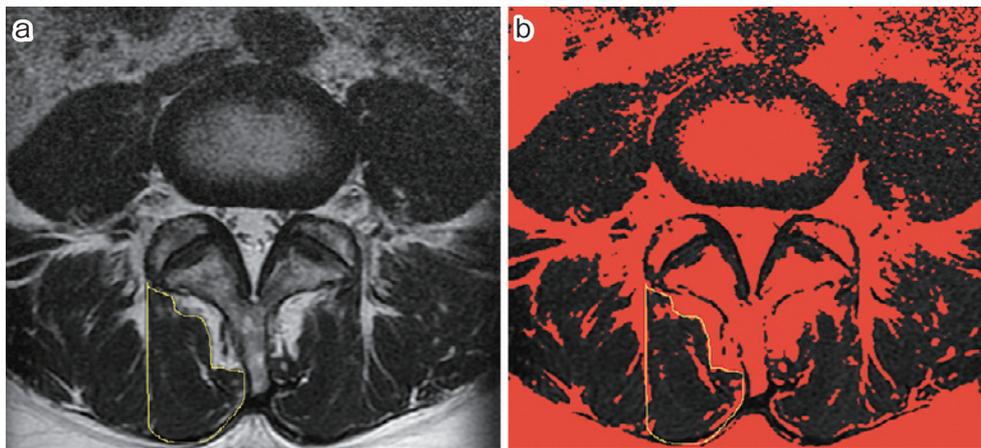
Figure 2. Axial T2-weighted magnetic resonance imaging was performed to measure the cross-sectional area (CSA) and fat infiltration rate of the multifidus muscle (Mm) at the intervertebral level L4 through L5.
(a) The CSA of the right Mm was measured using the transverse T2-weighted image.
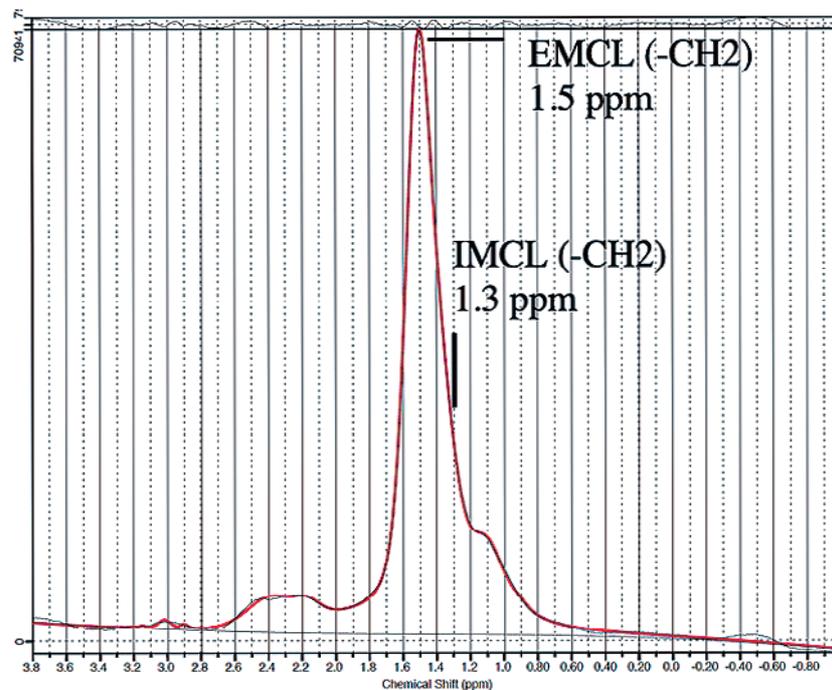(b) The fat infiltration of the Mm was measured using the transverse T2-weighted image with Image J.

Figure 3. Proton magnetic resonance spectrum of the Mm analyzed using the LC-Model software.
The following metabolites were identified: intramyocellular lipids (IMCLs) (-CH$_2$) methylene protons at 1.3 ppm; extramyocellular lipids (EMCLs) (-CH$_2$) methylene protons at 1.5 ppm.

method, according to which bright pixels of fat tissue were colored red using the pseudo-coloring tool of the software. Subsequently, the percentage of the red area in the muscle compartment was calculated (Fig. 2b). Then, we calculated the corrected CSA as the actual measurement CSA (cm^2) divided by the height squared (m^2) in order to standardize by body stature. To classify fat infiltration of the Mm, we used a three-grade visual scale adapted as previously reported[35]:

"Grade 0" for estimates of 0%-10% fat within the muscle, "Grade 1" for 10%-50% fat, and "Grade 2" for > 50% fat.

All muscle measurements were performed by two investigators (Observer 1: IO; Observer 2: HT) who were blinded to the patients' clinical details. The intra- and inter-rater reliabilities for the measurement of the paraspinal muscle were assessed, yielding similar results (Pearson's correlation coefficient; 0.92-0.93, 0.91-0.92). Finally, we adopted the data

of Observer 1.

Analysis of MRS data

Analysis of MRS data was performed by a method previously described[31-33]. The spectral data obtained were used to measure IMCL and EMCL using the LCModel software (Stephen Provencher, Inc., Oakville, Ontario, Canada). Data were transferred from the scanners to a Linux workstation, and metabolite quantification was performed by eddy current correction and water scaling. Data for IMCL (1.3 ppm) and EMCL (1.5 ppm) corresponding to the methylene protons were used for statistical analyses. Assessments of IMCL and EMCL were automatically scaled to an unsuppressed water peak (4.7 ppm) and expressed in institutional units. These data are displayed graphically with the chemical shift along the x-axis, allowing identification of the metabolites. The peak intensity is plotted on the y-axis (Fig. 3). We excluded subjects with Mm over 15% of the %SD of EMCL or IMCL on the LCModel.

Statistical analyses

We checked the gender differences for each age group with the chi-square test. We investigated the gender differences concerning CSA, EMCL, and IMCL of the Mm with the Mann-Whitney U-test. We analyzed the possible correlations of age, BMI, LBP VAS, CSA, and fat infiltration of

Table 1. Pearson's Correlation Coefficient of Age, BMI, CSA, and VAS with the EMCL and IMCL of the Mm.

	EMCL		IMCL	
	r	p	r	p
Age	0.33	<0.01	−0.02	0.83
BMI	0.42	<0.01	−0.07	0.51
CSA	−0.61	<0.01	−0.14	0.24
VAS	−0.06	0.53	0.43	<0.01

IMCL: intramyocellular lipid; EMCL: extramyocellular lipid; Mm: multifidus muscle; BMI: body mass index; CSA: cross-sectional area; VAS: visual analog scale
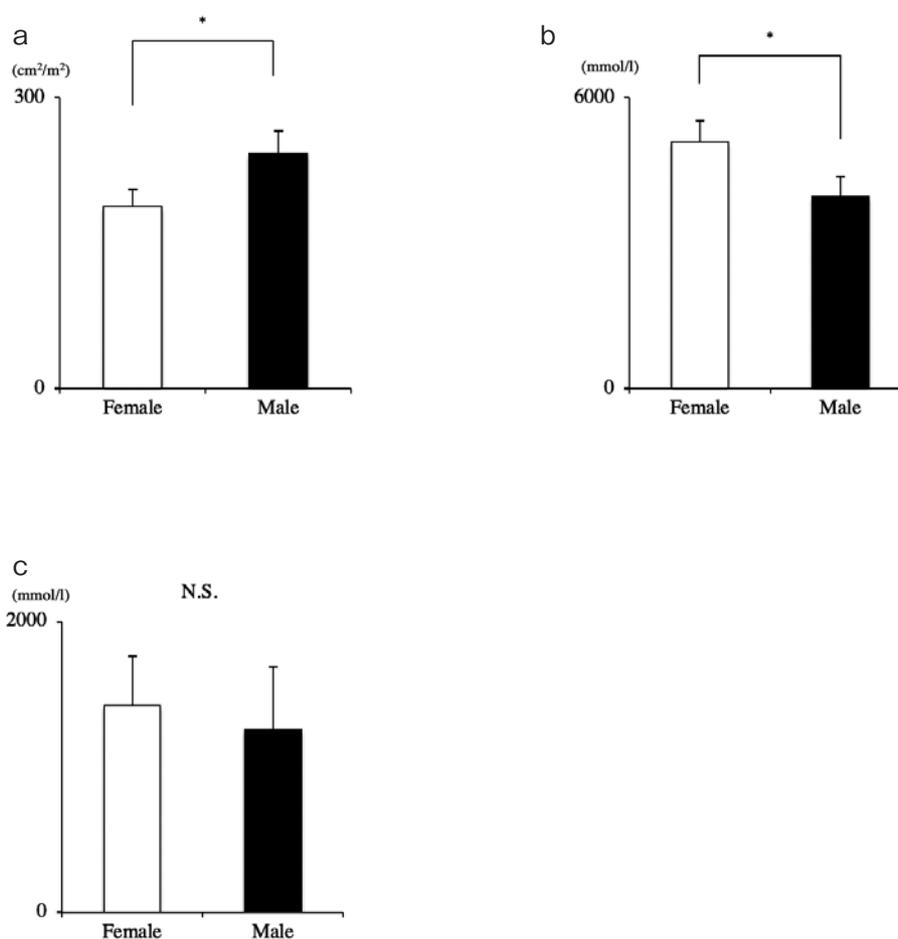
Figure 4. Comparisons of the gender difference concerning CSA (a), EMCL (b), and IMCL (c) of the Mm.
CSA were larger in the male group; EMCL was higher in the female group, and there was no significant difference between the female and male groups for IMCL.
Data are shown as the means±standard error of the mean.
$p<0.01$ female versus male: Mann-Whitney U-test.
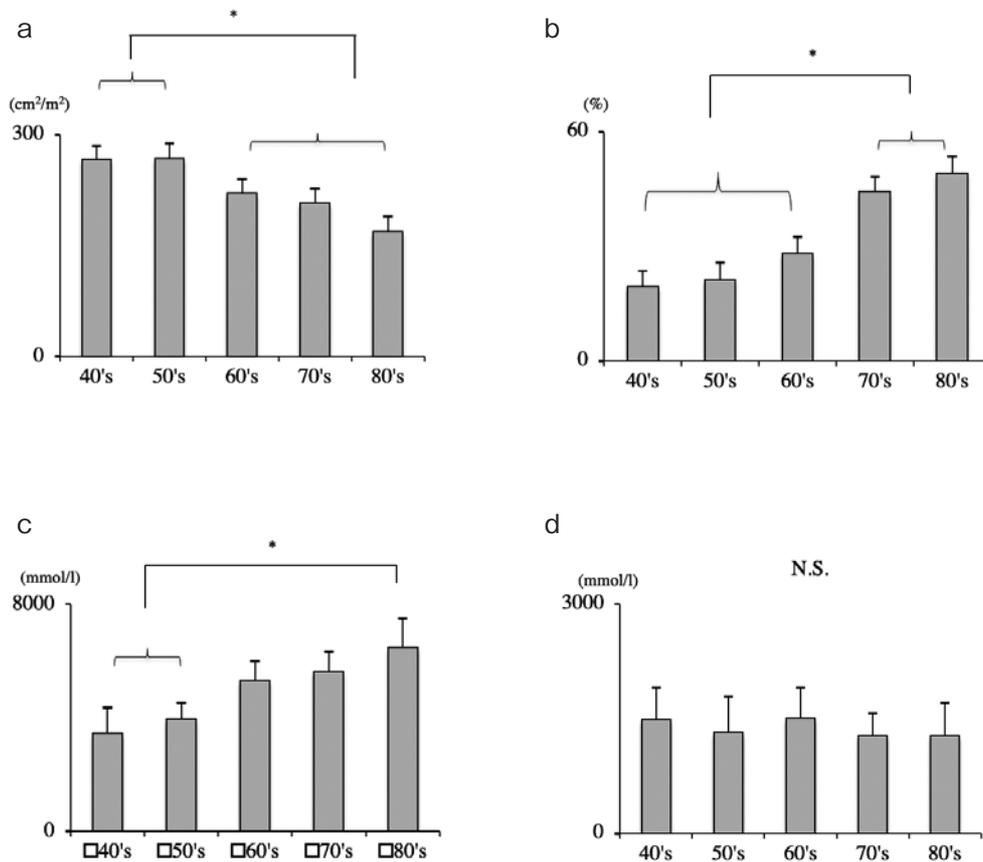
Figure 5. Comparisons of the CSA, fat infiltration, EMCL, and IMCL of the Mm among the five groups divided by age.

(a) The CSA of the Mm decreased with age; the CSA in subjects >60 years significantly decreased than in those <50 years.

(b) The fat infiltration rate increased with age; the fat infiltration rate in subjects >70 years significantly decreased than in those <60 years.

(c) The EMCL of the Mm decreased with age; the EMCL in subjects >80 years significantly decreased than in those <50 years.

(d) The IMCL of the Mm was not associated with age.

Data are shown as the means±standard error of the mean.

$*p<0.01$: one-way factorial measures of analysis of variance (ANOVA) with *post hoc* testing performed using the Bonferroni method.

the Mm with the EMCL and IMCL of the Mm using Pearson's correlation coefficient analyses. The subjects were divided into the following five groups as per their age— < 40 years, 50s, 60s, 70s, and 80s (more than 10 subjects in each group)— to identify the BMI, CSA fat infiltration, EMCL, and IMCL of the Mm by age using one-way factorial measures of analysis of variance (ANOVA) with the *post hoc* testing performed using the Bonferroni method. We analyzed the EMCL and IMCL of the Mm using the fat infiltration classification with one-way ANOVA and the Tukey-Kramer test among the three experimental groups. A probability value of < 0.05 indicated statistical significance. All the numerical data are expressed as means ± standard error of the mean (SEM).

Results

As shown in Table 1, there was a significant positive correlation of EMCL with age (r = 0.33, $p < 0.01$), BMI (r = 0.42, $p < 0.01$), and fat infiltration (r = 0.52, $p < 0.01$). There was a significant negative correlation of EMCL with CSA (r = −0.61, $p < 0.01$). There were no significant correlations between EMCL and VAS score (r = −0.06, $p = 0.53$). There were no significant correlations of IMCL with age (r = −0.02, $p = 0.83$), BMI (r = −0.07, $p = 0.51$), and CSA (r = −0.14, $p = 0.24$). There was a significant positive correlation of IMCL and VAS score (r = 0.43, $p < 0.01$).

There were no statistically significant gender differences for each age group ($p = 0.97$). CSA was larger in the male group (Fig. 4a), EMCL was higher in the female group (Fig. 4b), and there was no significant difference (Fig. 4c) between the female and male groups for IMCL.
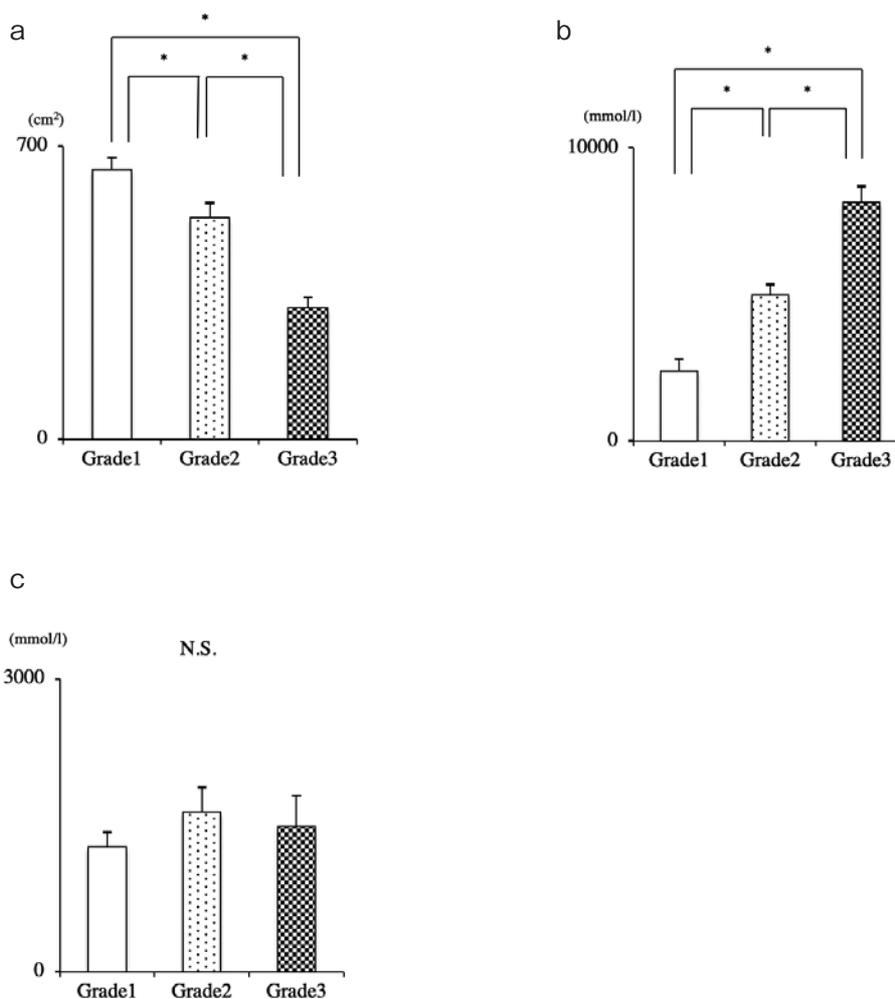
Figure 6. Comparisons of the EMCL and IMCL of the Mm among the three groups classified by the fat infiltration classification.
(a) CSA reduced significantly with fat infiltration grade.
(b) EMCL increased significantly with fat infiltration grade.
(c) IMCL was not associated with fat infiltration grade.
Data are shown as the means±standard error of the mean.
*$p < 0.01$: ANOVA and the Tukey-Kramer test.

The CSA of the Mm decreased with age; CSA in subjects ≥ 60 years decreased significantly than in those < 50 years (Fig. 5a). The fat infiltration rate increased with age and decreased significantly in subjects ≥ 70 years than in those < 60 years (Fig. 5b). The EMCL of the Mm decreased with age; EMCL in subjects ≥ 80 years significantly decreased than in those < 50 years (Fig. 5c). The IMCL of the Mm was not associated with age (Fig. 5d).

According to the fat infiltration classification, CSA reduced significantly with fat infiltration grade (Fig. 6a), and EMCL increased significantly with fat infiltration grade (Fig. 6b). In contrast, IMCL was not associated with fat infiltration grade (Fig. 6c).

Discussion

Aging is associated with an increased risk of problems related to the locomotor system. Rosenberg[36] first defined the concept of sarcopenia as a condition involving a loss of muscle mass and strength due to age. Then, some consensus on the definition and diagnosis of sarcopenia from the European Working Group on Sarcopenia in Older People[1], the International Working Group on Sarcopenia[2], and the Asian Working Group for Sarcopenia[3] was proposed. Sarcopenia is a common problem and has been well recognized as one of the relevant factors concerning a prevalence of disability[37]; however, no broadly accepted clinical measurement method has been established so far. Several methods can be used to assess the muscle mass.

The CSA and fat content used as indexes of muscle degeneration were estimated by ultrasonography[38], computed tomography (CT)[39], and MRI[19]. MRI is valuable for evaluating the muscles because of its good contrast of soft tissue. In recent years, several studies have revealed degenerative disorders of the paraspinal muscles using a variable approach related to fatty degeneration[20,22,40,41]. Most of these

studies used the fat fraction of the multipoint Dixon technique to evaluate fatty degeneration; however, studies using MRS comprehensively estimated the degeneration as the total amount of fat content. In the present study, the adipose tissue of the Mm was excellently separated as EMCL and IMCL.

In this cross-sectional study, we analyzed the EMCL and IMCL of the Mm using MRS to identify the possible correlations with atrophy and fat infiltration of the Mm. Quantitative analyses of the EMCL and IMCL in the Mm revealed correlations of EMCL with age, BMI, CSA, and fat infiltration and correlations of IMCL with LBP VAS score. EMCL locates extracellular adipose tissue around the muscle cells and provides long-term energy storage. We noted the association between EMCL and CSA as an index of muscle atrophy as stated in past reports[25,42]. In addition, EMCLs are thought to be metabolically inactive lipid deposits related to reduced functionality such as a sedentary lifestyle and lack of exercise[26,27]. Muscle weakness is related to EMCL storage interfering with sufficient muscle nutrition[24,27]. In the present study, increased EMCL levels could correlate with aging and fatty degeneration. Therefore, we believe that EMCLs can be used as a quantitative and reasonable index for evaluating the Mm degeneration associated with aging. In contrast, IMCLs are stocked as intramuscular lipid droplets in the skeletal muscle cells. They exist near the mitochondria, probably related to oxidative metabolism[25,30], and serve as a rapidly usable source of energy for muscular fatty acid oxidation[26,30,43]. IMCLs are reportedly related to the storage of free fatty acids and insulin resistance, and increased IMCL concentrations have been observed in type 2 diabetic patients[26,44]. An association has been observed between IMCL and LBP; therefore, it is possible that the mitochondrial activity of the Mm is impaired, resulting in an increased level of inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α, in the Mm of CLBP patients[45,46]. IMCL could be an effective index of CLBP.

This study has several limitations. First, we do not assess the daily physical activity of the patients. Daily activity might influence the concentration of EMCL and IMCL. Second, this was a cross-sectional study; a longitudinal study design would have been a better choice. Third, we evaluated only CLBP. We should perform detailed questioning and physical examination to accurately assess CLBP.

In summary, we analyzed the EMCL and IMCL of the Mm using the MRS in CLBP and identified the possible correlations with LBP VAS, CSA, and fat infiltration of the Mm in this cross-sectional and comparative study. The CSA of the Mm decreased with age, whereas the fat infiltration rate increased with age. Quantitative analyses of the EMCL and IMCL in the Mm revealed correlations of EMCL with age, BMI, CSA, and fat infiltration and correlations of IMCL with LBP VAS score. This may suggest that EMCL could evaluate the Mm degeneration associated with aging, and IMCL could become an effective objective indicator of CLBP.

Author Contributions: Izaya Ogon wrote and prepared the manuscript, and all of the authors participated in the study design. All authors have read, reviewed, and approved the article.

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