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Original Research Article

Cervical Multifidus Morphology and Quality Are Not Associated with Clinical Variables in Women with Fibromyalgia: An Observational Study

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Abstract

Objective. Some studies have reported the presence of histological alterations, such as myofiber disorganization and abnormalities in the number and shape of mitochondria, in patients with fibromyalgia syndrome (FMS). Although Ultrasound imaging (US) is used to quantitatively characterize muscle tissues, US studies in patients with FMS are lacking. Therefore, we aimed to describe morphological and qualitative cervical multifidus (CM) muscle US features in women with FMS and to assess their correlation with clinical indicators. **Design**. Observational study. **Setting**. AFINSYFACRO Fibromyalgia Association (Madrid, Spain). **Subjects**. Forty-five women with FMS participated. **Methods**. Sociodemographic variables (e.g., age, height, weight, body mass index) and clinical outcomes (e.g., pain as assessed on a numerical pain rating scale, evolution time, pain-related disability as assessed by the Fibromyalgia Impact Questionnaire) were collected. Images were acquired bilaterally at the cervical spine (C4–C5 level) and measured by an experienced examiner for assessment of muscle morphology (e.g., cross-sectional area, perimeter, and shape) and quality (mean echo intensity and intramuscular fatty infiltration). Side-to-side comparisons and a correlational analysis were conducted. **Results**. No significant side-to-side differences were found for morphology or quality features ($P > 0.05$). None of the clinical indicators were associated with US characteristics (all, $P > 0.05$). **Conclusion**. Our results showed no side-to-side differences for CM morphology and quality as assessed with US. No associations between CM muscle morphology or quality and Fibromyalgia Impact Questionnaire, pressure pain threshold, numerical pain rating scale score, or evolution time were observed. Our preliminary data suggest that muscle morphology is not directly related to pain and pain-related disability in women with FMS.

Key Words: Fibromyalgia; Ultrasound Imaging; Neck; Echo Intensity; Fatty Infiltration

Introduction

Fibromyalgia syndrome (FMS) is characterized by generalized chronic pain, hyperalgesia and allodynia, overwhelming fatigue, sleep disturbance, alteration in mood, and impaired quality of life and daily function [1]. It is estimated to affect about 2–4% of the entire population [2–4], being the second most prevalent condition assessed by rheumatologists after osteoarthritis [2]. It seems that females (female:male ratio ranging from 7:1 to 9:1) and

people 30–55 years of age are the most affected [5]. In addition to gender and age, several risk factors, including childhood difficulties, smoking, high body mass index (BMI), alcohol abstinence, and preexisting medical disorders in adulthood, have been proposed to be associated with FMS [6].

Changes in skeletal muscle morphology and quality (e.g., reduced cross-sectional area [CSA], side-to-side asymmetry, or increased adipose tissue accumulation) [7] can contribute to the chronification of pain symptoms and can assist in determining treatment decisions. Although FMS is characterized by muscular fatigue, few studies have assessed muscular characterization in FMS, contrary to idiopathic or whiplash-associated disorders, for which this topic has been widely assessed [8].

With regard to muscle histology in individuals with FMS, a previous study observed Z-band disorganization (e.g., ragged red fibers in both trapezius and deltoid muscles, disorganization of myofibers and actin filaments), increased DNA fragmentation, and abnormalities in the number and shape of mitochondria (finding inconstant abnormalities in ATP and phosphocreatine levels) [9]. However, no current studies analyzing muscle morphology in FMS are available.

Ultrasound imaging (US) is a pragmatic, accessible, noninvasive, and safe method that, in addition to the assessment of muscle morphology features, is currently used to quantitatively characterize tissues [10]. Recent US studies reported excellent reliability in the imaging scan and the image measurement procedures [11,12], as well as normative CSA values of cervical extensor musculature in a healthy population with the use of panoramic US [13]. Furthermore, the development of US technology has permitted the quantification of muscle quality, e.g., echo intensity (EI), as an indicator of muscle function in the cervical spine [14].

EI consists of the mean pixel intensity of a muscle calculated by measuring the darkness of a region, where a darker mean EI represents high muscle quality and a whiter mean EI represents more adipose and intramuscular connective tissue [14]. This technology makes possible the quantification of fatty infiltration (FI) by isolating these white pixels to determine their area. Current evidence shows a negative correlation between EI and muscle strength independent of muscle size or age in the neck muscles [15].

The rationale for this specific US deep neck extensor assessment is based mainly on current evidence with regard to US validity and reliability [11–14] and findings in other clinical populations suggesting changes in muscle morphology and quality [16–19]. In addition, a previous study assessing pain intensity and pressure sensitivity [20] described how female patients with FMS perceived those tender points located in the cervical spine as among the most painful. Therefore, the objectives of the present study were 1) to describe morphological and qualitative muscle characteristics of cervical multifidus (CM) in women with FMS and 2) to assess the correlation between US features and demographic (e.g., age, height, weight, BMI), clinical (e.g., pain and pain-related disability), and psychophysical (pressure pain threshold [PPT]) variables.

Methods

Study Design

An observational cross-sectional study assessing ultrasonographic features (e.g., morphology and quality) in the CM muscle in female patients with FMS was conducted. This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [21]. This study was approved by the Institutional Ethics Committee of Camilo José Cela University (UCJC 20-10-2020). All participants signed written informed consent before their inclusion in the study.

Participants

The sample size was calculated by the use of the formula $n = \frac{Z_\alpha * P * (1-P)}{d^2}$ [22], setting a 95% confidence interval, where $Z_\alpha = 1.96$ is the standard score, given that $\alpha = 0.05$, $P = 2.45\%$, is the estimated prevalence of FMS in Spain [3], and $d = 5\%$ is the precision limit or proportion of sampling error that is usually the 5% confidence limit. On the basis of these data, a sample size of at least 37 women with FMS was considered appropriate.

Accordingly, this study included 45 women between 20 and 70 years of age who voluntarily responded to local announcements between July 2020 and September 2020 in the AFINSYFACRO Fibromyalgia Association located in Móstoles (Madrid, Spain). To be eligible for participate, patients had to be females with a medical diagnosis of FMS and an age between 20 and 70 years. Exclusion criteria included previous history of cervical trauma (i.e., whiplash), previous cervical surgery, neuropathic conditions (e.g., radiculopathy or myelopathy), radiological findings (e.g., severe degenerative findings), other underlying medical conditions (e.g., tumor), or pharmacological treatment affecting muscle tone or pain perception on the day of data collection.

Clinical Features

Sociodemographic data, including age, gender, height, and weight, were collected. The severity of FMS was assessed with the Spanish version of the Fibromyalgia Impact Questionnaire (FIQ). This questionnaire is a reliable, valid questionnaire that is responsive to changes for the measurement of health status and physical function in Spanish-speaking patients with FMS [23]. It independently measures physical functioning and work status on a 4-point Likert scale, from "always" to "never," as well as depression, anxiety, morning tiredness, pain, stiffness, fatigue, and well-being. The score ranges from 0 to 80, where higher scores indicate greater impact of FMS [24].

The intensity of pain was assessed on an 11-point numerical pain rating scale (NPRS; 0–10). The mean of the worst pain during the prior week, the least pain during the prior week, and the current pain level was calculated and analyzed [25].

Pressure Pain Thresholds

The assessment of PPTs has shown acceptable reliability in the cervical area (Intraclass Correlation Coefficient [ICC] 0.854–0.906) [26] and is considered a valid tool for the assessment of sensitivity to pressure pain. With patients in a prone position, PPTs were bilaterally measured over the cervical spine. An analogic algometer (FPN100, Wagner Instruments®, Greenwich, USA) was placed perpendicularly to the skin, and a progressive force of 1 kg/cm^2 was applied. All procedures were performed by the same clinician with more than 10 years of experience. Participants received standardized instructions as follows: "I am going to press on your neck. When you start to feel pain, not pressure, say 'now,' and the pressure will be stopped." The mean of three consecutive trials was calculated and used in the analysis.

Ultrasound Assessment

All images were acquired with Alpinion eCube i8 (Alpinion Medical Systems Co., Anyang-si, Gyeonggi-do, Ltd.; Korea) US equipment with a 3- to 12-MHz linear probe (L3–12T) by an assessor with 10 years of experience. The procedure was similar to that described by Valera-Calero et al. [11, 14]. Participants were in a prone position with neutral cranio-cervical position, their shoulders abducted 90°, and their elbows flexed 90°. All the images were acquired bilaterally at the C4–C5 level by following the procedure described by Valera-Calero et al. [11]. All images were acquired under the same conditions to be able to determine EI features. Frequency was set to 12.0 MHz, gain to 55 dB, dynamic range to 85, brightness to 17, and depth to 40 mm (Figure 1).

After imaging acquisition, codification, and randomization procedures, all images were transferred to the offline DICOM ImageJ software v.1.42 (National Institutes of Health, Bethesda, MD, USA) for assessment of morphological and quality values of the CM. Before the analysis, all images were transformed from RGB (red-green-blue) to a 32-bit, 256-grayscale image.

After the CM had been contoured, the intramuscular infiltrates were isolated by reducing the range from 255 (maximum EI score) until the subcutaneous tissue was covered. All pixels included in this selection (cutoff point to 255) were interpreted as fatty infiltrates and calculated as a percentage of the previous muscle selection (Figure 2). CSA, perimeter, shape descriptors, mean EI, and fatty infiltrate muscular percentages were calculated [14].

Statistical Analysis

Statistical analyses were performed in SPSS (IBM, Armonk, NY, USA) v.25 software for Mac OS. Normal distribution of the data was verified with the Shapiro-Wilk test. Descriptive data by total sample and by side were calculated. The Student t test for independent samples was used to determine side-to-side differences for normal variables. Pearson's r correlation coefficient was used for conducting a correlation analysis between sociodemographic, clinical, PPT, and US features. The association strength of r scores was considered as poor ($r < 0.30$), fair ($0.30 < r < 0.60$), moderate ($0.60 < r < 0.80$), or strong ($r > 0.80$). The level of significance was set as a P value <0.05.

Results

From a total of 51 female volunteers responding to the announcements, six were excluded because of previous cervical surgery (n = 3) or severe degenerative findings (n = 3). Forty-five women with FMS were finally included. Table 1 summarizes sociodemographic, clinical, and PPT data of the sample. No PPT side-to-side differences were observed ($P > 0.05$).

Table 2 shows CM morphology and quality features assessed with US. No side-to-side differences were found for morphology (CSA, perimeter, and shape descriptors) or quality features (mean EI and intramuscular FI) in our sample of women with FMS.

Table 3 summarizes Pearson's correlation coefficients between sociodemographic, clinical, and US characteristics. No clinical variables (FIQ, NPRS, or evolution time) were associated with US features (all, $P > 0.05$). Some associations between sociodemographic and clinical variables were found. The evolution time was negatively correlated with age and BMI and positively correlated with height; PPTs were positively correlated with BMI and negatively correlated with FIQ; and FIQ was negatively associated with BMI (Table 3).

Although CM morphology and quality were not associated with clinical severity indicators, greater mean EI scores were observed in overweight participants. In addition, weight was found to be negatively correlated with intramuscular FI (see Table 3).

Discussion

This study found that US muscle quality and morphology characteristics were not associated with clinical severity or sensitization in women with FMS. To the best of the authors' knowledge, this is the first study to assess muscle morphology and quality and to develop a correlation matrix including sociodemographic and clinical data in FMS.

Because US is a valid method of measuring muscle morphology, several studies have used this imaging method for the assessment of neck muscles [11] as a

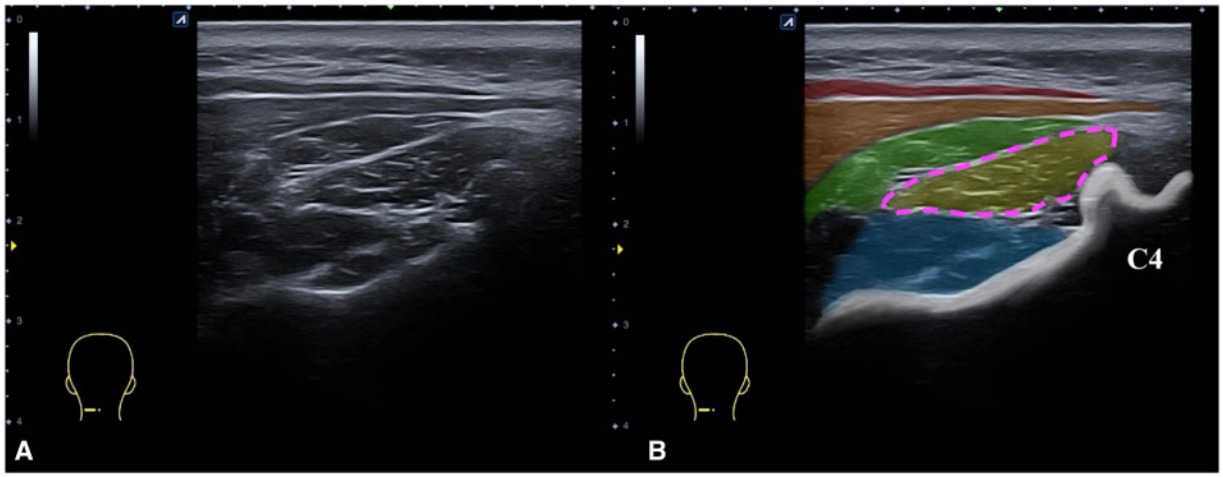

Figure 1. (A) Ultrasound image capture at the C4/C5 level. **(B)** Upper trapezius (red), splenius (orange), semispinalis (green), CM (yellow), and short rotator (blue) muscle areas. Region of interest area contouring (pink).

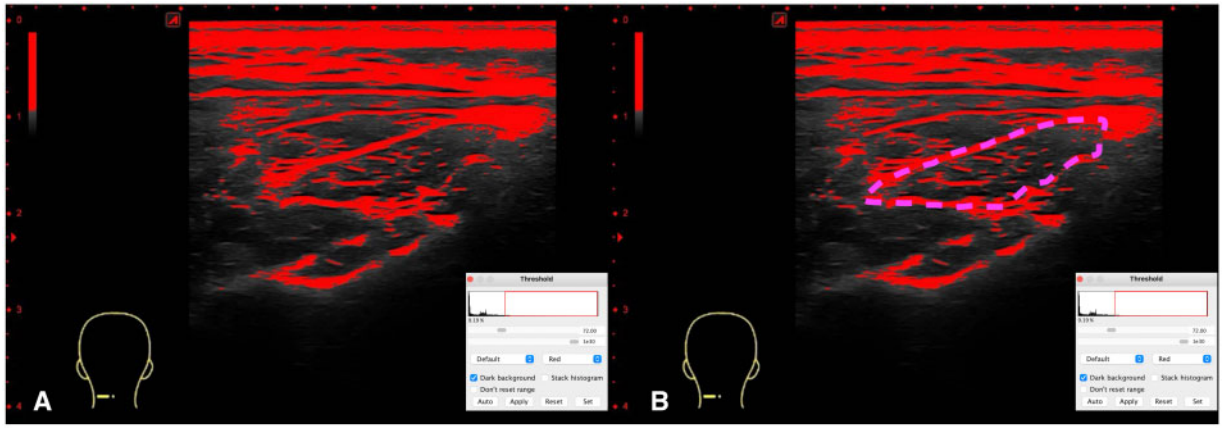

Figure 2. (A) Pixels evaluating intramuscular FI of CM at the C4/C5 level. **(B)** Region of interest area delimitation (pink).

Table 1. Participants' sociodemographic and clinical characteristics

Characteristic	Value
Sociodemographic characteristics	
Age, years	52.2 ± 10.6
Height, cm	1.61 ± 0.07
Weight, kg	67.6 ± 11.3
BMI, kg/m^2	25.8 ± 3.8
Clinical characteristics	
Fibromyalgia Impact Questionnaire (FIQ, 0–80)	63.6 ± 14.3
Evolution time, years with symptoms	11.2 ± 9.1
Pain intensity (NPRS, 0–10)	6.3 ± 2.1
PPTs, kg/cm^2	
Mean PPT	1.28 ± 0.37
Left side PPT	1.25 ± 0.36
Right side PPT	1.32 ± 0.37
Between-side PPT difference, kg/cm^2	0.06 ± 0.07 (−0.08 to 0.22)

Values are expressed as mean ± standard deviation.
Between-side PPT differences are expressed as mean ± standard deviation (95% confidence interval).

more accessible alternative to magnetic resonance imaging. Although changes in neck muscle performance and morphology have been proposed as a potential mechanism related to chronicity and disability, at least in patients with neck pain [27], the literature is still controversial [7]. In fact, higher CSA of the CM has been reported in individuals with whiplash-associated disorders, but smaller CSA has been reported in patients with

Table 2. Ultrasound features of the CM in women with fibromyalgia

	Mean	Right Side	Left Side	Side Difference
Area, mm^2	70.99 ± 16.58	71.84 ± 13.49	70.14 ± 19.30	1.70 ± 3.51 (−5.27 to 8.67)
Perimeter, cm	40.78 ± 4.19	40.58 ± 4.14	40.98 ± 4.28	0.40 ± 0.88 (−1.36 to 2.16)
Circularity (0–1)	0.55 ± 0.07	0.54 ± 0.07	0.55 ± 0.07	0.00 ± 0.01 (−0.02 to 0.03)
Aspect ratio	2.81 ± 0.66	2.76 ± 0.67	2.86 ± 0.66	0.09 ± 0.14 (−0.18 to 0.37)
Roundness	0.40 ± 0.33	0.38 ± 0.10	0.43 ± 0.46	0.05 ± 0.07 (−0.09 to 0.19)
Solidity	0.94 ± 0.03	0.94 ± 0.03	0.95 ± 0.03	0.01 ± 0.00 (0.00 to 0.02)
EI (0–255)	46.42 ± 13.60	47.35 ± 12.89	45.50 ± 14.36	1.85 ± 2.87 (−3.86 to 7.56)
FI, %	28.23 ± 11.00	29.44 ± 11.68	27.03 ± 10.27	2.40 ± 2.31 (−2.20 to 7.01)

Table 3. Pearson product–moment correlation matrix

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Area															
2. Perimeter	0.445**														
3. Circularity	n.s.	−0.498**													
4. Aspect ratio	n.s.	0.638**	−0.672**												
5. Roundness	n.s.	n.s.	n.s.	−0.258*											
6. Solidity	0.340**	n.s.	0.460**	n.s.	n.s.										
7. Mean EI	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.									
8. FI	n.s.	n.s.	n.s.	−0.227*	n.s.	n.s.	0.735**								
9. Age	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.							
10. Height	n.s.	n.s.	−0.287**	n.s.	n.s.	n.s.	n.s.	n.s.	−0.216*						
11. Weight	n.s.	n.s.	n.s.	0.214*	n.s.	n.s.	−0.222*	−0.245*	0.288**	0.385**					
12. BMI	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.395**	n.s.	0.865**				
13. FIQ	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	−0.272**	n.s.	n.s.	−0.257*			
14. PPT	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.241*	−0.312**		
15. Evolution time	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	−0.617**	0.225*	n.s.	−0.217*	n.s.	n.s.	
16. Pain intensity	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	−0.253*	n.s.	n.s.	n.s.	0.405**	−0.423**	n.s.

Note: 1–15 are the same as the numbers/item of the *y*-axis; values are Pearson's *r* score. Abbreviation: n.s.= nonsignificant.
*$P < 0.05$.
**$P < 0.01$.

nonspecific chronic neck pain than in healthy controls [28, 29].

Our results revealed no side-to-side differences in females with FMS, in accordance with previous studies aiming at identifying structural muscle/tendon alterations by the use of other imaging methods [30]. One possible reason is that FMS is a complex syndrome characterized by generalized pain (explained by increased activation in areas of the brain dedicated to pain, altered connectivity, and altered function in endogenous pain-inhibitory signals), and chronic neck pain is a less widespread pain condition [31]. Therefore, functional magnetic resonance imaging of the brain, and not muscle structural changes, would remain the most sensitive tool for explaining the neurophysiological nature of FMS.

A recent study reported reliability estimates for US quantification of intramuscular FI and preliminary EI scores in a healthy population [14]. Although age seems to be not associated with muscle morphology or quality, other sociodemographic features (e.g., BMI, sex, height, weight) are associated with CM CSA and EI [11–14], and therefore, as this sample presented significant BMI and weight differences compared with previous studies, a comparison of CM characteristics between studies is not possible.

The present findings suggest that US assessment of the cervical muscles provides no additional value as a screening tool for identifying those patients who are most at risk of developing more severe FMS. We do not currently know whether muscle morphology or quality of other musculature will reveal different results.

Some limitations should be recognized. First, we included a sample of only females with FMS; therefore, the present data should not be extrapolated to men. Although we found no correlation between US and clinical severity, we do not know whether significant differences would be observed between FMS patients and healthy controls. Second, the reliability and validity of US imaging procedures used in this study for the assessment of muscle morphology and quality have been tested in healthy subjects and other clinical populations; hence, we do not know whether this procedure would be equally reliable for FMS populations. Finally, future research should assess other areas (e.g., lumbar multifidus and abdominal wall muscles), as FMS is a widespread musculoskeletal pain condition.

Conclusion

This study describes the association between muscle morphology and quality of the CM, as assessed with US

imaging, and clinical severity features in a sample of females with FMS. Our results showed no side-to-side differences for any of the US imaging features. No associations were found between muscle morphology or quality and FMS impact, PPTs, or evolution time.

Authors' Contributions

The authors contributed as follows: conception and design: JAV-C and EÚ-D; data acquisition: JAV-C, EÚ-D, MC-C, and GMG-S; analysis and interpretation of data: JAV-C and JLA-B; drafting of the manuscript: JAV-C, CF-d-l-P, and JLA-B; critical revision: CF-d-l-P and JLA-B; statistical analysis: JAV-C and CF-d-l-P; and supervision: JAV-C. The authors agreed to submit this manuscript for publication. The datasets generated or analyzed during the present study are available from the corresponding author on reasonable request.

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