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Tools and techniques

Fatty infiltration of the cervical multifidus musculature and their clinical correlates in spondylotic myelopathy

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ABSTRACT

Cervical spondylotic myelopathy (CSM) is among the most common spinal cord disorders of the elderly. Muscle fat infiltration (MFI), a potential pathological sign of muscle adiposity, may contribute to or be associated with pain/disability/impairments in patients with CSM. We examined the relationship between MFI and CSM's clinical manifestations by enrolling nine CSM patients and five aged-matched controls to undergo MRI imaging of the cervical spine with MFI. A blinded investigator calculated MFI for each of the bilateral multifidii muscles from C3 to C7 on the MRI images. Nurick scores, Neck Disability Index, and modified Japanese Orthopedic Association scores were collected for all patients. CSM patients and controls were equivalent with respect to age, height, weight, gender, race, smoking status, and employment status. MFI was higher in patients with CSM than in controls (31.7% v. 24.6%, respectively, $p = 0.0178$). Higher MFI was associated with increased disability on the Nurick scale ($p = 0.0371$). MJOA scores correlated linearly with MFI ($R = 0.542$, $p = 0.0453$), but not NDI ($p = 0.3125$). Increased MFI of the multifidus muscles is associated with cervical myelopathy and a clinically significant decline in sensorimotor function as measured by mJOA and Nurick scores. Spinal injury in CSM may lead to secondary muscle loss and muscle fat infiltration.

1. Introduction

Cervical spondylotic myelopathy (CSM) is a common spinal condition characterized by narrowing of the cervical spinal canal that leads to progressive pain and neurological impairment [1]. CSM is one of the most common spinal cord disorders of the elderly. Surgeries to decompress the spine in CSM patients are rising, presumably with an ever-increasing ageing population across the globe [2]. Although surgical techniques continue to advance and improve care [3], nearly 40% of CSM patients undergoing surgery achieve less than a 50% recovery using common clinical outcome metrics [4]. These key metrics include scales for myelopathy as well as scores for pain and disability associated with this condition. Therefore, there is an urgent need to better understand the pathophysiological mechanisms contributing to clinical symptoms associated with CSM, which in turn could improve assessment and management.

Muscle fat infiltration (MFI) is the pathological infiltration of muscle. MFI of the deep extensor paraspinal muscles has shown to be associated with poor outcomes in cervical injury [5,6], chronic unilateral low back pain [7,8], disc herniation [9,10], and disc disease [11]. This may occur because the deep neck extensor muscles, including the multifidus and the semispinalis cervicis, play a critical role in postural biomechanics through their deep attachments to the cervical spine [12–14]. There remain a number of mechanistic pathways for the occurrence of MFI including, but not limited to, ageing, disuses, direct injury, or denervation of skeletal muscle [15–17] While purely speculative at this stage, muscle denervation may develop at or below the level of spinal cord compression in patients with CSM. Given these findings, we hypothesize that the MFI of the multifidus plays a critical role in the development of pain and disability, and functional impairment in CSM patients and contributes to the variability in outcomes observed among patients with CSM who have undergone surgical decompression.

As CSM is common in neurosurgical practice, a more detailed understanding of factors contributing to outcomes, on a patient-by-patient basis, is warranted. The purpose of this preliminary

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study is to examine if patients with CSM demonstrate fatty infiltration in the deep muscles of the cervical spine when compared to age-matched controls without spinal cord compression [18].

2. Materials and methods

We enrolled a cohort of nine CSM patients and five aged-matched, asymptomatic controls to undergo imaging of the cervical spine for analysis of multifidus MFI. All CSM patients included were diagnosed at Northwestern Memorial Hospital (Chicago, IL) based on both clinical and radiographic findings. Inclusion criteria for entry included the following in all patients diagnosed with CSM (Table 1): classic CSM symptoms; exam findings of weakness, hyper-reflexia, or change in coordination; radiographic signs of spinal compression; Nurick grade I-IV [19]; and modified Japanese Orthopedic Association (mJOA) score 8–18 [20]. Exclusion criteria included the following: age <21 or >80, comorbid neural disease (e.g., multiple sclerosis), pregnant or nursing, active systemic rheumatological disease, active peripheral or vascular neuropathy, urgent need for surgery. In addition to the exclusion criteria for patients, controls were also screened for neck pain, or history of spinal surgery.

All participants underwent 3T MRI using a previously described protocol, detailed below [5]. Nine patients with CSM and 6 age-matched controls were consented for inclusion in the study. The study was conducted with the approval of Northwestern's Institutional Review Board (IRB). Funding was provided by the National Institute of Neurological Disorders and Stroke.

2.1. MRI measures and analysis

All imaging data were collected with a 3.0T MRI scanner (Siemens, Erlangen, Germany). Each participant underwent magnetic resonance examination of the cervical spine. A localizer scan was obtained, and a T2-weighted sagittal turbo spin echo sequence was performed to determine the location of the fat-water scan.

2.2. 3D dual-echo dixon fat-water MRI

A 3D dual-echo gradient echo acquisition was performed to collect fat and water data for the neck multifidi muscles (C3–C7) to calculate MFI. MFI measurements were taken while blinded to participant group (CSM v. control). A standard 12-channel head coil and a 4-channel neck coil were used as receiver coils to improve signal to noise. The axial FLASH dual echo, gradient echo sequence had duration of 4:23 min, an in-plane resolution of 0.7 mm using a rectangular field of view of 75% and thick-ness of 3 mm, and slab oversampling of 22% with 36 partitions to prevent aliasing in the 3D (superior-inferior) direction, TR/TE1/TE2 6.59/2.45/3.68 ms with an field of view of 190 × 320 mm. This scan covered the cephalad portion of C3 through the caudal portion of the C7 vertebral endplate.

Table 1
Entrance criteria for the current study.

Inclusion	Exclusion
Classic CSM symptoms	Age <21, >80
Exam findings of weakness, hyper-reflexia, or change in coordination	Diagnosis neural disease (ex: MS)
	Pregnant or nursing
Radiographic signs of spinal compression	Active systemic rheumatological disease
	Active peripheral or vascular neuropathy
Nurick grade I–IV and mJOA 8–18	Urgent need for surgery

2.3. Muscle fat-water quantification

Using OsiriX image processing software (Pixmeo, Geneva, Switzerland) [18], regions of interest were manually drawn within the fascial borders of the multifidus-semispinalis cervicis from C3 to C7, on the co-registered fat and water images. The software obtains the mean signal intensity within each region of interest, for fat and water. MFI was calculated as the fat signal/(fat + water signal) * 100. This method has been demonstrated to have excellent inter- and intra-rater reliability [14 ,21]. MFI for the left and right multifidus were measured for each participant. Total MFI was defined as the mean of the left and right multifidus MFI at that level. Average of total MFI of all the cervical levels for each patient was calculated. Total cervical MFI percent measurement were compared between CSM patients and controls.

Among CSM patients, MFI percentage was compared above, at, and below the level of myelopathy. Level of myelopathy (LOM) was determined by defined by a modified Torg-Pavlov ratio, Ratio = Canal Diameter/VB Anterior-Posterior Diameter. MRI measurements are used instead of X-ray measurements and just above disk-osteophytes.

2.4. Statistical analysis

The MFI data met the assumptions of normality using Kolmogorov-Smirnov testing, mean MFI percentage was compared between CSM patients and controls using independent samples *t*-test. For each CSM patient, MFI percentage was also compared above and below the level of injury using repeated measures ANOVA. Simple linear regression analysis were performed to assess the association between MFI percent and clinical scores – mJOA and the Nurick. Significance was set at $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.) and Prism 6.0b (GraphPad Software, Inc., La Jolla, CA, USA).

3. Results

CSM patients and controls were similar with respect to most baseline demographic and clinical characteristics, other than variables relating to the diagnosis of CSM (Table 2). There was no difference between the CSM group and control with respect to age (61 ± 4.0 years v. 50 ± 4.7 years, Δ = 11.18 (2.717, 25.07), p = 0.1051), height (66.9 ± 1.3 in. v. 68.4 ± 1.9 in., p = 0.5236), weight (177.7 ± 10.1 lb v. 165.6 ± 11.8 lb, p = 0.4690), gender (44.4% male v. 40% male, p = 1.0), race (88.8% white v. 100.0% white, p = 1.0), smoking status (11.1% smokers v. 20.0% smokers, p = 1.0), or employment status (p = 0.1153). There were significant differences between CSM patients and controls with respect to mJOA score (14.6 ± 0.6, 18.0 ± 0.0, Δ = 3.44 (1.58, 5.31), p = 0.0017), NDI (18.6 ± 2.9 v. 0.80 ± 0.80, Δ = 17.76 (9.13, 26.38), p = 0.0007), Nurick score (1.9 ± 0.3 v. 0.0 ± 0.0, Δ = 1.9 (1.0, 2.8), p = 0.0008), and education level (p = 0.0171).

Of the CSM patients, six patients had C3 as their level of myelopathy, two patients had C4 as their LOM, and one patient had C5 as his/her LOM (Table 3). The mean MFI percentage was 23.5% ± 12.9% above the level of injury, 23.5% ± 7.0% at the level of injury, and 32.7% ± 10.8% below the level of injury. There was no difference in MFI above and below the level of the pathology (p = 0.12, Fig. 1). Muscle fat infiltration percentage was significantly higher in patients with CSM than in controls

Table 2
Demographic and baseline clinical characteristics of patients and controls enrolled in the study.

		CSM (n = 9)	Control (n = 5)	p-value
Age		61 ± 4.0	50 ± 4.7	0.1051
Gender				
	Men	4 (44.4%)	2 (40%)	1.0
	Women	5 (55.5%)	3 (60%)	
Height		66.9 ± 1.3	68.4 ± 1.9	0.5236
Weight		177.7 ± 10.1	165.6 ± 11.8	0.4690
Smoker		1 (11.1%)	1 (20.0%)	1.0
Level of Education				0.0171
	High School Diploma / GED	5 (55.5%)	0 (0%)	
	Technical / Associates Degree	1 (11.1%)	0 (0%)	
	Bachelors Degree	2 (22.2%)	1 (20.0%)	
	Graduate Degree	1 (11.1%)	4 (80.0%)	
Race				1.0
	White/Caucasian	8 (88.8%)	5 (100.0%)	
	Black/African American	1 (11.1%)	0 (0%)	
Employment Status				0.1153
	Retired	4 (44.4%)	0 (0%)	
	Medical Leave / Disabled	1 (11.1%)	0 (0%)	
	Currently Employed	4 (44.4%)	5 (100.0%)	
Duration of Symptoms		10.1 ± 4.8	–	–
NDI		18.6 ± 2.9	0.8 ± 0.8	0.0007
mJOA		14.6 ± 0.6	18.0 ± 0	0.0017
Nurick		1.9 ± 0.3	0.0 ± 0.0	0.0008

Table 3
Mean muscle fat infiltration measurements for all cervical spondylotic myelopathy patients enrolled in the study, stratified by whether the measurements were taken above, below, or at the level of cord compression.

Patient #	LOM*	MFI above level	MFI at level	MFI below level
1	C4	21.64	18.71	18.51
2	C4	29.79	29.03	31.25
3	C3	48.13	26.84	30.10
4	C3	–	11.01	51.09
5	C3	13.29	26.49	43.40
6	C3	7.69	22.62	19.87
7	C3	31.34	33.78	36.77
8	C5	21.86	26.43	25.22
9	C3	14.08	16.39	37.84
Mean		23.48	23.48	32.67
STD		12.85	7.03	10.76
SE		4.54	2.34	3.59

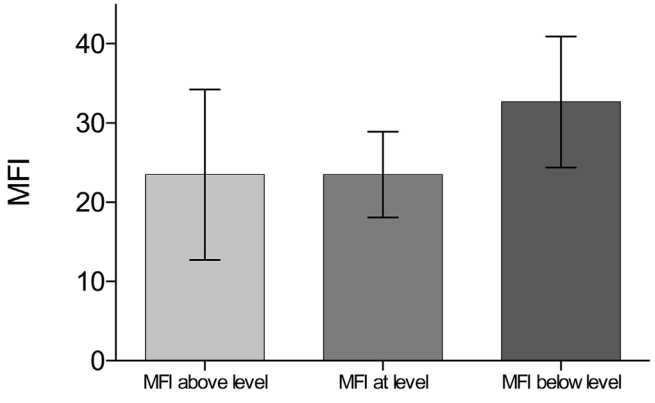

Fig. 1. Muscle fat infiltration of the multifidus muscle above, below, and at the level of stenosis for patients with cervical spondylotic myelopathy.

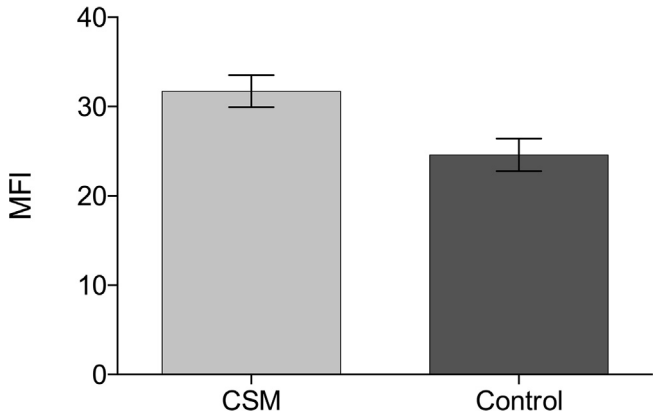

Fig. 2. Muscle fat infiltration of the multifidus muscle among patients with cervical spondylotic myelopathy and age-matched controls.

(31.7% v. 24.6%, respectively, p = 0.0178, Fig. 2). The mean difference in MFI was Δ = 7.13% (1.33%, 12.93%).

Higher MFI was associated with poorer clinical status. Patients with more MFI had more disability, as measured by Nurick scores (p = 0.0371, Fig. 3). mJOA scores were found to be linearly inversely correlated with MFI (p = 0.0453, R = 0.542, Fig. 4). NDI scores were not found to correlate with MFI (p = 0.3125, R = 0.2911, Fig. 5).

4. Discussion

Cervical spondylotic myelopathy (CSM) is a common spinal cord disorder of the elderly [2]. As CSM produces spinal cord injury, clinical presentation includes upper extremity clumsiness, upper and lower limb sensory disturbances and weakness, gait difficulty,

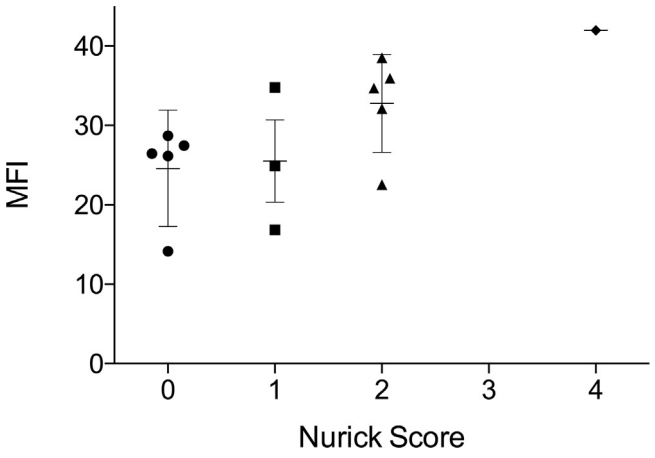

Fig. 3. Increased muscle fat infiltration of the multifidus muscle was associated with more disability, as measured by Nurick Score ($p = 0.0371$).

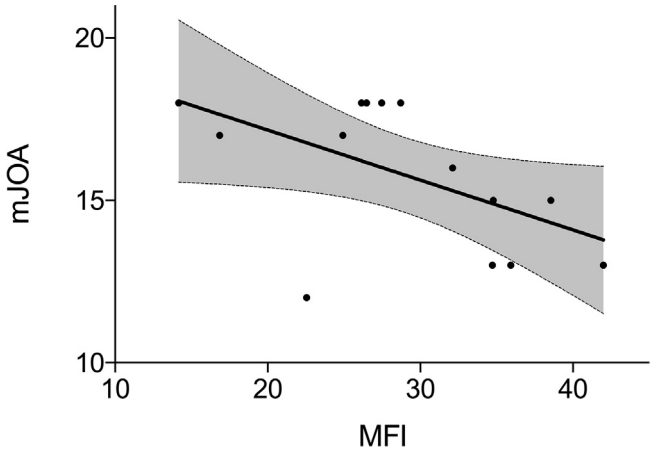

Fig. 4. Muscle fat infiltration was found to be linearly correlated with modified Japanese Orthopedic Association scores ($p = 0.0453$, $R = 0.542$). The figure depicts both the best-fit line and its 95% CI.

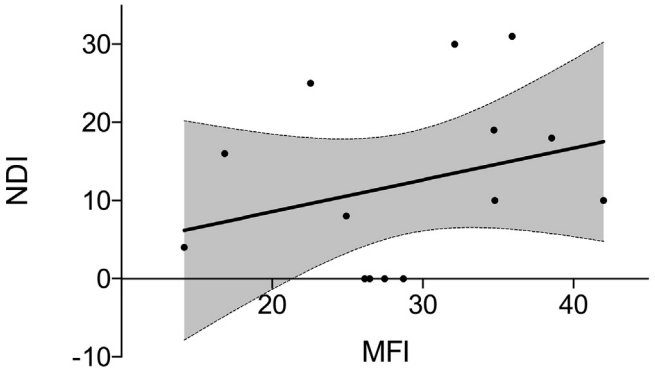

Fig. 5. Muscle fat infiltration was not found to be correlated with Neck Disability Index ($p = 0.3125$, $R = 0.2911$). The figure depicts both the best-fit line and its 95% CI.

urinary urgency, and less commonly bowel and bladder incontinence [22,23]. Moreover, the disease can lead to neck pain and fatigue [24,25,26]. The exact etiology of neck-associated symptoms in CSM is unknown. Possible explanations include poor cervical alignment and muscular denervation secondary to myelopathy, leading to muscular atrophy and microinstability [27]. Moreover, denervated musculature would likely fatigue easily [28], which may be compounded by the daily demands of upright and dynamic posture. As CSM patients likely have muscular neck pain, we examined cervical musculature in CSM patients versus controls to assess muscular changes in the CSM population.

Muscle fat infiltration is not a new marker of potential pathology, but surprisingly it's presence on MRI is likely thought of as an emerging marker of injury, and associated physiologic degeneration, of the spinal musculature [29]. MFI is associated with poor outcomes in a variety of spinal pathologies [5–11], including chronic unilateral low back pain [7,8], disc herniation [9,10], and disc disease [11]. It is known to occur following the denervation of skeletal muscle [15–17], including muscle denervation due to CSM [30]. This is hypothesized to occur as spinal compression limits efferent output to these muscle motor units. In this report, we demonstrate that MFI percentage is significantly higher among patients with CSM than among age-matched controls. In addition, we observe a trend toward significance comparing MFI percentages below the level of pathology to MFI percentages at or above the level of pathology.

Our finding that there is a trend toward increased MFI below the level of myelopathy is consistent with existing studies [31]. The multifidus originates at the articular process and inserts into the spinal process to or three levels below its innervating nerve root [32], making multifidus atrophy most pronounced below a level of neurological injury. Multifidus muscle atrophy and increased fatty infiltration at and below the level of the lesion has been observed in patients with cervical radiculopathy and cervical root avulsion injury [33,34]. Fortin et al. also observed increased MFI in the multifidus in CSM patients specifically [31], though notably their study did not compare their cervical myelopathy cases to age-matched controls. Our finding is therefore consistent with these prior analyses, including both CSM and non-CSM patients.

Our finding that MFI is higher in CSM patients than age-matched controls builds upon current literature, and is consistent with known effects of neurological injury on muscle. Elliott et al. demonstrated that MFI occurs rapidly in some, but not all, patients following whiplash injury [6,35], and that MFI is associated with poor functional recovery in the long-term [5]. Our findings demonstrate that MFI also occurs in patients with CSM as compared to controls, suggesting that the neuromuscular sequelae of CSM are consistent with other cervical injuries. While whiplash injury occurs as an acute injury to the neck (and possibly spinal cord in a discrete number of patients) [36,37], CSM patients may have progressive and repetitive smaller injuries to the cord parenchyma over time. However, while the chronicity of these two pathologies differ, it is possible that both whiplash and CSM could lead to decreased efferent input to the neck musculature. In tandem, the association between MFI and clinical pathology (CSM) is consistent with existing understanding of cervical biomechanics. Changing the physical properties of cervical musculature can alter its function [38]. The multifidus musculature are deep extensor muscles, and have been show to play a critical role in biomechanical stability of the spine [12]. Accordingly, dysfunction could lead to pain and microinstability. Reliable and valid measures for the latter are required before definitive diagnostic schemes can be acknowledged and recommended across the many practitioners that assess and treat these patients. Fortin et al. found a relationship between cervical muscle morphology, clinical symptoms, and functional status [31]. Our finding that CSM patients' multifidi are significantly different than controls' is therefore consistent with the existing clinicopathological framework.

Our finding that MFI is associated with clinical outcomes as measured by mJOA score is also consistent with existing literature. Among patients with degenerative cervical myelopathy, Fortin

et al. found that MFI of the semispinalis capitis (SCap) was associated with mJOA scores [31]. Notably, however, our analysis found that MFI of the multifidus was associated with mJOA scores, rather than MFI of the SCap. Fortin et al. found no association between mJOA and multifidus MFI. Nevertheless, as both muscles are deep extensors that contribute significantly to the stability of the cervical spine, their pathologies likely have overlapping clinical manifestations that are measured on the mJOA score.

We did not find an association between MFI and NDI scores. Similarly, Elliott et al.'s 2006 study of 79 chronic patients with whiplash and 34 healthy controls found no association between MFI and NDI, though this likely reflects homogeneity across that particular population with chronic pain and disability [5]. Notably, when considering the heterogeneity of the whiplash condition however, NDI scores were found to be associated with MFI in a 2015 prospective study on 36 patients enrolled immediately following whiplash injury: higher MFI was associated with higher NDI at two weeks and three months post injury, and higher MFI at two weeks was predictive of higher NDI at three months [6]. Moreover, Fortin et al. observed that asymmetrical MFI of the SCap was associated with higher NDI scores among patients with degenerative cervical myelopathy [32].

The differences between our findings and prior studies may lie in the difference in timing between studies. Indeed, as the mean duration of symptoms in our CSM population was 10.1 months, patients with a chronic pathology are likely more similar than patients with an acute presentation where patient reports of pain intensity may be reasonably expected to be much higher. Moreover, the muscle group being analyzed may explain some differences in findings, as Fortin et al.'s findings in the CSM population focused on SCap rather than the multifidus muscle. Lastly, rather than the overall percentage of MFI, the association Fortin et al. observed with NDI analyzed asymmetry of SCap MFI between sides, which may be a marker for a different pathological process than overall percentage of MFI. We also observed an association between MFI and Nurick scores, contrary to the findings of Fortin et al., an inconsistency that the aforementioned methodological differences may explain.

Our study has a number of important limitations. The small sample size included a total of only 15 patients. However, to our knowledge, a direct comparison of MFI between CSM patients and age-matched controls has yet to be reported. A variety of other changes in the cervical musculature, such as atrophy [38], asymmetry [7,8,10], have been noted in association with spinal pathology, but could not be controlled for with a study of this sample size. Moreover, while we used a well-described method of quantifying MFI in blinded fashion [6], measurement errors and variability in methods complicate comparing our methodology to other reported studies.

Here, we have demonstrated that MFI of the multifidus is significantly higher among patients with CSM than among age-matched controls, and that patients with more MFI have worse Nurick scores. Morever, MFI was found to be adversely correlated with mJOA scores, though not with NDI scores. While preliminary, this is, to our knowledge, an original examination for MFI in the CSM population using well-validated clinical metrics.

The underlying cause and persistent nature of traumatic and non-traumatic neck pain and disability remains poorly understood. While multiple drivers may exist (discogenic, anatomical deformity, nerve root compression, and muscular degeneration), the contribution of each remains unclear. We acknowledge that direct MFI applications for clinical decision making remain undefined. However, as we better understand the key drivers of symptoms, we will be able to better refine decision making prior to surgery. Further, we may be able to further build upon this work to understand the role of therapy and rehabilitation in patient recovery [39].

5. Conclusion

Cervical spondylotic myelopathy is associated with increased muscle-fat infiltration of the deep extensor neck muscles on MRI. MFI may contribute to the clinical symptoms associated with CSM, as measured by mJOA and Nurick scores.

Disclosure

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jocn.2018.03.028.

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