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An Investigation of Fat Infiltration of the Multifidus Muscle in Patients With Severe Neck Symptoms Associated With Chronic Whiplash-Associated Disorder

STUDY DESIGN: Cross-sectional study.

BACKGROUND: Findings of fat infiltration in cervical spine multifidus, as a sign of degenerative morphometric changes due to whiplash injury, need to be verified.

OBJECTIVES: To develop a method using water/fat magnetic resonance imaging (MRI) to investigate fat infiltration and cross-sectional area of multifidus muscle in individuals with whiplash-associated disorders (WADs) compared to healthy controls.

METHODS: Fat infiltration and cross-sectional area in the multifidus muscles spanning the C4 to C7 segmental levels were investigated by manual segmentation using water/fat-separated MRI in 31 participants with WAD and 31 controls, matched for age and sex.

RESULTS: Based on average values for data spanning C4 to C7, participants with severe disability related to WAD had 38% greater muscular fat infiltration compared to healthy controls ($P = .03$) and 45% greater fat infiltration compared to those with mild to moderate disability related to WAD ($P = .02$). There were no significant differences between those with mild to moderate disability and healthy controls. No significant differences between groups were found for multifidus cross-sectional area. Significant differences were observed for both cross-sectional area and fat infiltration between segmental levels.

CONCLUSION: Participants with severe disability after a whiplash injury had higher fat infiltration in the multifidus compared to controls and to those with mild/moderate disability secondary to WAD. Earlier reported findings using T1-weighted MRI were reproduced using refined imaging technology. The results of the study also indicate a risk when segmenting single cross-sectional slices, as both cross-sectional area and fat infiltration differ between cervical levels. *J Orthop Sports Phys Ther 2016;46(10):886-893. Epub 2 Sep 2016. doi:10.2519/jospt.2016.6553*

KEY WORDS: *cervical spine, magnetic resonance imaging, WAD*

As many as half of individuals with whiplash-associated disorder (WAD) secondary to a motor vehicle collision never fully recover, continuing to have a wide variety of clinical signs and symptoms.[2,16] There are only a few imaging methods providing the ability to identify pathological lesions potentially related to the common symptoms of chronic WAD, which may include neck pain, radiating arm pain, headache, and dizziness.[2,16,23] However, recent evidence has shown greater fat infiltration in the neck extensor muscles that appear unique to those individuals who transition from acute to chronic WAD.[7] These muscular changes, which appear greatest in the deeper multifidus muscles,[5,10] are not present in those with nontraumatic neck pain,[7] suggesting that trauma or related factors may play a role.

The findings of altered muscle morphometry[6,7] may be important not only for improved diagnostic criteria but also for improved medical and rehabilitative intervention strategies, which, to date, have not been shown to significantly improve functional recovery following whiplash.[14,15,18] However, in a study by Ludvigsson et al,[17] neck-specific exercises (motor control and muscle endurance training) were found to provide benefits over general physical activity, suggesting the importance of neck muscle activation. While the findings of muscle degeneration are interesting, they have, to our knowledge, only been produced in an Australian and American cohort by a

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single group of investigators.[6,7] Those 2 studies were also conducted using T1-weighted images and did not take advantage of recent developments in magnetic resonance imaging (MRI) techniques for quantification of intramuscular adipose tissue using water- and fat-separated imaging.[22]

The aim of the present study was to investigate cross-sectional area and fat infiltration of the multifidus muscle bilaterally at different cervical levels in individuals with chronic WAD compared to healthy controls, using a new imaging method using high-resolution, 2-point Dixon water- and fat-separated MRI. A secondary aim was to investigate the cross-sectional area and fat infiltration between controls and participants with WAD after dividing those with WAD into 2 subgroups: those with mild/moderate versus those with severe neck pain–related disability.

TABLE 1 Participant Demographic Data*

	Healthy Controls	WAD†		
	Total	Total	NDI<40%	NDI≥40%
Participants, n	31	31	20	11
Age, y	41.5 ± 10.6 (22-61)	41.5 ± 10.9 (20-62)	39.2 ± 11.5 (20-62)	45.7 ± 8.5 (34-58)
Body mass index, kg/m^2	24.4 ± 3.2 (19.7-34.5)	25.6 ± 3.8 (19.1-33.8)	25.5 ± 4.1 (19.1-33.8)	25.8 ± 3.4 (20.3-32.3)
NDI, %	NA	35.8 ± 14.1 (10-68)	27.3 ± 6.8 (10-38)	51.3 ± 10.2 (40-68)
Time since injury, mo	NA	18.1 ± 9.2 (6-36)	20.1 ± 9.8 (7-36)	14.5 ± 7.2 (6-32)

Abbreviations: NA, not applicable; NDI, Neck Disability Index; WAD, whiplash-associated disorder.
**Values are mean ± SD (range) unless otherwise indicated.*
†*The WAD groups (NDI<40% and NDI≥40%) are subgroups of the total WAD group.*

METHODS

Criteria for Study Participation

Right-handed individuals with varying levels of neck pain–related disability, without contraindications for MRI (previous heart or brain surgery, metallic implants, claustrophobia, obesity, pregnancy), were consecutively recruited from an ongoing randomized controlled trial[17,21] that compared 3 different exercise strategies for individuals with chronic (greater than 6 months) WAD. All participants had undergone the MRI scan, which was used for this analysis, prior to participating in the clinical trial.

WAD Cohort Inclusion Criteria To be included in the WAD cohort, participants had to have (1) an age of between 18 and 63 years, (2) Quebec Task Force WAD of grade II or III (grade II, neck complaints and musculoskeletal signs; grade III, the same findings as grade II plus neurological signs[27]), (3) time since the accident of 6 months to 3 years, and (4) pain intensity of greater than 20 mm on a 100-mm visual analog scale[12] or a score greater than 20% on the Neck Disability Index (NDI).[29]

WAD Cohort Exclusion Criteria Potential participants were excluded from the WAD cohort for (1) known or suspected serious physical pathology, including myelopathy, spinal tumor, spinal infection, or ongoing malignancy; (2) earlier fracture or luxation of the cervical column; (3) neck trauma with persistent symptoms from previous injury; (4) surgery on the cervical column; (5) neck pain that caused absence from work for greater than 1 month in the year prior to the WAD trauma; (6) signs of traumatic brain injury at the time of WAD (unconsciousness, retrograde or posttraumatic amnesia, disorientation or confusion); (7) generalized or more dominant pain elsewhere in the body; (8) diseases or other injuries that might prevent full participation in the study; (9) diagnosis of a severe psychiatric disorder; (10) known drug abuse; or (11) insufficient knowledge of the Swedish language to answer the questionnaires.

Healthy Cohort Inclusion Criteria Right-handed age- and sex-matched healthy controls were recruited from university and hospital staff as well as acquaintances.

Healthy Cohort Exclusion Criteria Exclusion criteria included the following: (1) present or past neck pain, dysfunction, or related disability; (2) history of neck trauma, neck pain, or lower back pain; (3) rheumatological or neurological disease; (4) generalized myalgia; and (5) contraindications for MRI as listed above.

Participants

All participants provided written informed consent prior to participation in the study. The protocol for the study was approved by the regional ethical review board (DNR 2011/262-32).

Thirty-one participants (14 men, 17 women; mean ± SD age, 41.5 ± 10.9 years; range, 20.7-62.7 years) with chronic (greater than 6 months in duration) clinically verified WAD and 31 healthy controls, matched for sex and age (mean ± SD age, 41.5 ± 10.6 years; range, 22.2-61.8 years), were included in this study.

The participants with WAD were divided into those with mild/moderate disability (score less than 40% on the NDI) and those with severe disability (NDI score of 40% or greater) (**TABLE 1**).[19]

Magnetic Resonance Imaging

Images were acquired with a Philips Ingenia 3.0T scanner (Royal Philips, Amsterdam, the Netherlands), using the built-in phased-array posterior coil, a 32-channel head coil, and an anterior flexible coil placed adjacent to the head coil. The participants were positioned supine for imaging. A 3-D gradient-echo sequence was used with out-of-phase and in-phase echo times of 3.66 milliseconds

and 7.24 milliseconds, respectively. The echo times were chosen to enable high resolution. The repetition time was 10 milliseconds and the flip angle was 10°, with a total acquisition time of 9.07 minutes. The images included cervical segmental levels C4 through C7 and were angled so that the in-plane images were parallel to the cervical segments. The acquired image resolution was 0.75 × 0.75 × 0.75 mm^3.

Phase-sensitive reconstruction was used to acquire fat- and water-separated images.[24,25] With dual-echo Dixon imaging it is not possible to correct for T2 effects based on the information in the images. Therefore, a literature value for T2 relaxation of 23.9 milliseconds was used for both fat and water to perform the T2 correction in this study.[11,30] The segmental levels at C4, C5, C6, and C7 were marked in all volumes. The 5 closest slices at each level were averaged for creating axial cross-sectional images. Cross-sections in 1 water- and fat-separated image volume at C4, C5, C6, and C7 are shown in **FIGURE 1**. In 1 participant (healthy control), a water-fat shift artifact was apparent at the C7 level. That cross-sectional image was not included in further data analysis.

An investigator, with approximately 6 months of experience, who was blinded to group allocation of the images manually segmented the multifidus muscles (left and right sides) at the 4 segmental levels using Analyze Version 11.0 (AnalyzeDirect, Overland Park, KS) for all 62 participants. To determine the interrater reliability of the image analysis, 20 of the participants' images were presented twice in random order. A second blinded investigator with more than 10 years of experience confirmed the final segmentations' quality.

The cross-sectional area was calculated by summating all pixels within the manually segmented mask multiplied with the image resolution. The fat infiltration was estimated using fat fraction, in which the amount of fat signal within the manually segmented mask was divided by the sum of the water and fat signal within the mask: fat fraction = fat/(fat + water).

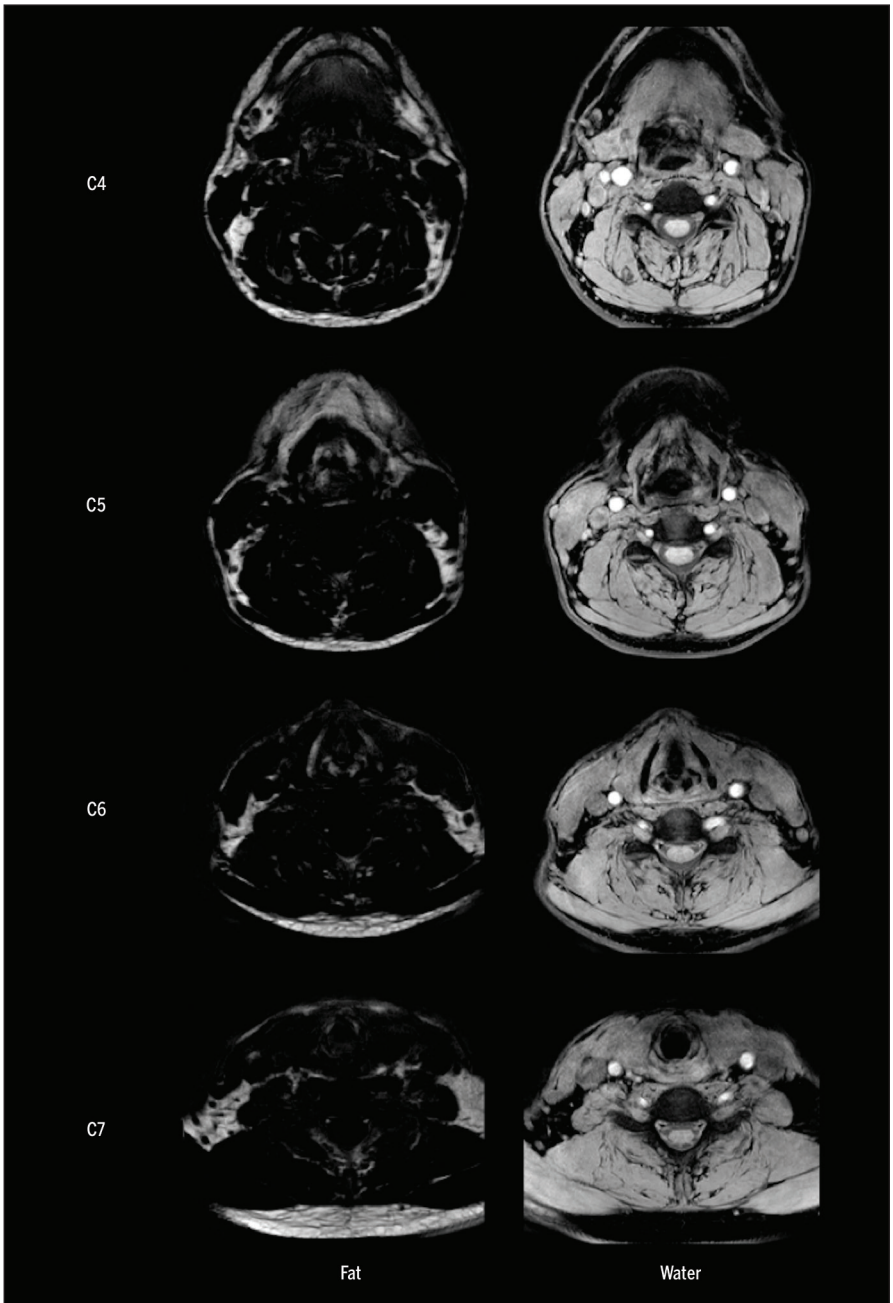

FIGURE 1. Cross-sections at segmental levels C4 through C7, using fat- and water-separated images with an in-plane resolution of 0.75 × 0.75 mm^2.

Statistical Analysis

The intrarater reliability was measured using a 2-way, random-effects, single-measure intraclass correlation coefficient (ICC) with absolute agreement. For investigation of the normal distribution, the Shapiro-Wilk test was used. A 3-way, 2-repeated-measures analysis of variance (ANOVA) was chosen as the model for investigation of the cross-sectional area and fat infiltration. The model was built using the segmental levels and the lateral sides as within-participant variables and

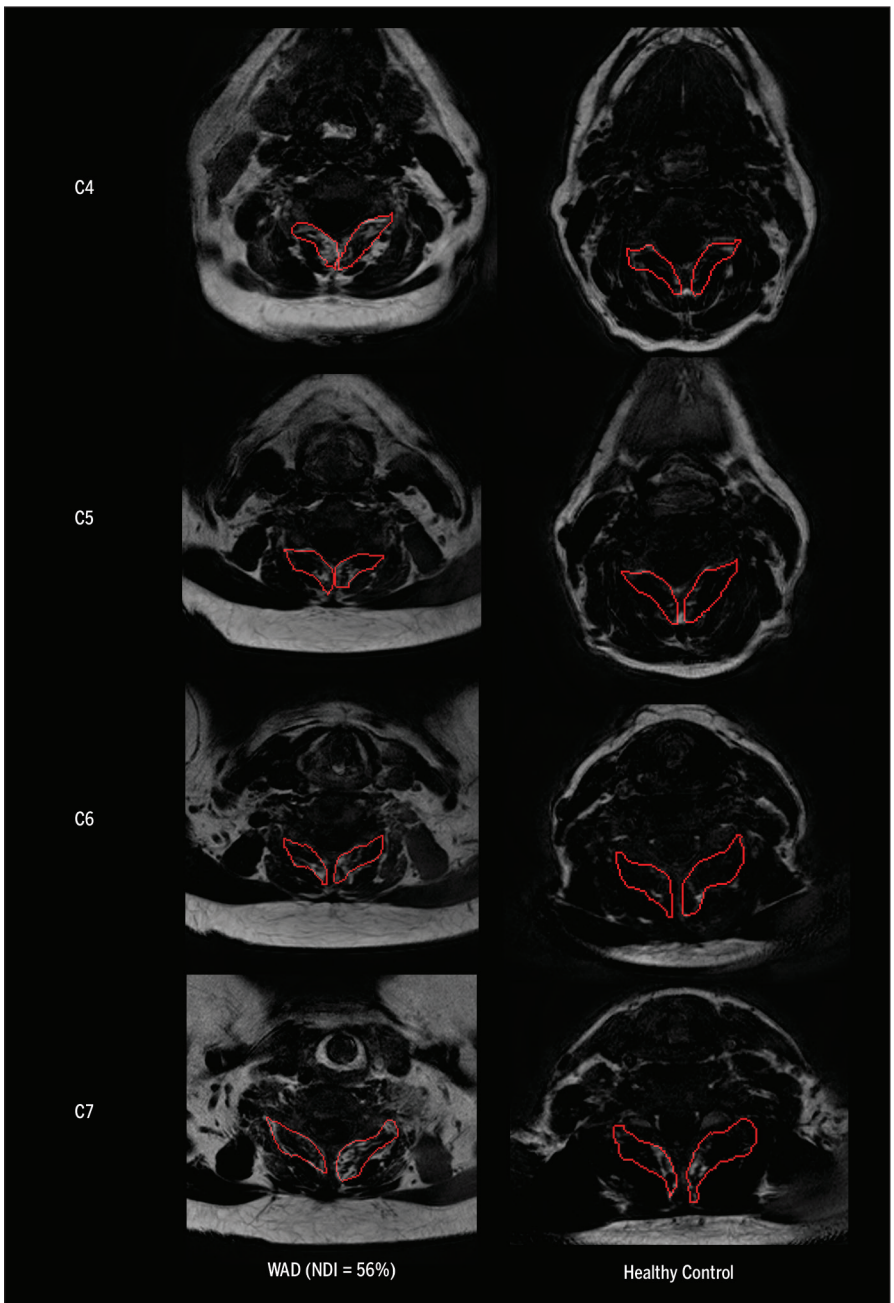

FIGURE 2. Cross-sections at vertebral levels C4 through C7 of the multifidus muscle, marked on the fat images of (left) a participant with severe disability secondary to WAD and (right) an age- and sex-matched control. Abbreviations: NDI, Neck Disability Index; WAD, whiplash-associated disorder.

the group as the between-participant variable. In total, 4 separate ANOVAs were performed to analyze the following variables/groups: (1) cross-sectional area and (2) fat infiltration in individuals with WAD compared to healthy controls; and (3) cross-sectional area and (4) fat infiltration, comparing those with WAD and NDI scores of 40% or greater, those with WAD and NDI scores less than 40%, and healthy controls. Post hoc tests with Bonferroni corrections for multiple comparisons were performed to investigate significant differences from the ANOVAs. All statistical tests were performed using SPSS Version 23 (IBM Corporation, Armonk, NY).

RESULTS

The ICCs for intrarater reliability for measurements of cross-sectional area at the 4 different segmental levels for both right and left sides ranged from 0.81 to 0.93 (95% confidence interval: 0.57, 0.98). The ICCs for the measurements of fat infiltration ranged from 0.82 to 0.97 (95% confidence interval: 0.60, 0.99). **FIGURE 2** shows a representative example of the segmentation of the multifidus muscle in a participant with severe WAD compared to a sex- and age-matched control. The Shapiro-Wilk test indicated normal data distribution for the different groups. Descriptive data for cross-sectional area of the multifidus muscle for the healthy controls and both groups with WAD are presented in **TABLE 2**.

TABLE 3 provides the *P* values from the initial ANOVAs. No significant differences were identified for any of the interaction terms for any of the ANOVAs: WAD versus controls ($P = .08$-$.45$); mild/moderate WAD versus severe WAD versus controls ($P = .06$-$.45$). The multifidus cross-sectional areas on the left side were significantly larger than those on the right side (WAD versus controls, $P = .02$; severe WAD versus mild/moderate WAD versus controls, $P = .007$). With only 2 exceptions, the cross-sectional areas were significantly different ($P<.001$) between segmental levels (**TABLE 4**). No significant difference was found for cross-sectional area when comparing healthy controls to the pooled WAD group ($P = .75$) (**TABLE 3**). No significant difference was found for cross-sectional area when comparing the 3 groups of participants ($P = .41$) (**TABLE 3**).

Descriptive data (mean ± SD) for fat fraction [fat/(fat + water)] for all 3 groups are presented in **TABLE 5**. There were no significant differences in multifidus fat infiltration between left and right sides (2-group model, $P = .71$; 3-group

TABLE 2 Multifidus Cross-sectional Area at Vertebral Levels C4 Through C7, Comparing Healthy Controls With Participants With Mild (NDI<40%) and Severe (NDI≥40%) Disability Related to WAD*

	Healthy Controls	Mild WAD	Severe WAD
C4			
Left	272 ± 64	248 ± 56	261 ± 62
Right	261 ± 71	238 ± 48	277 ± 128
Average	267 ± 64	243 ± 47	269 ± 91
C5			
Left	272 ± 69	280 ± 70	305 ± 93
Right	263 ± 62	260 ± 64	275 ± 88
Average	268 ± 62	270 ± 61	290 ± 87
C6			
Left	296 ± 79	297 ± 74	363 ± 130
Right	300 ± 79	287 ± 91	309 ± 91
Average	298 ± 76	292 ± 78	336 ± 105
C7			
Left	339 ± 108	331 ± 79	390 ± 119
Right	332 ± 90	347 ± 99	370 ± 115
Average	335 ± 95	339 ± 85	380 ± 112
Average, C4-C7			
Left	295 ± 69	289 ± 55	329 ± 83
Right	289 ± 67	283 ± 64	308 ± 89
Average	292 ± 67	286 ± 58	319 ± 85

Abbreviations: NDI, Neck Disability Index; WAD, whiplash-associated disorder.
**Values are mean ± SD square millimeters. No significant (P>.05) differences were observed between the groups.*

TABLE 3 *P* Values for the 3-Way ANOVAs for Multifidus Cross-sectional Area and Muscular Fat Infiltration*

	Controls Versus WAD†		Controls Versus Mild/Moderate WAD Versus Severe WAD‡	
Multivariate Test	Area	Fat Infiltration	Area	Fat Infiltration
Level	<.001	<.001	<.001	<.001
Level by group	.08	.36	.45	.18
Side	.02	.71	.01	.53
Side by group	.45	.46	.27	.74
Level by side	.41	.60	.14	.60
Level by side by group	.08	.31	.06	.48
Group	.75	.32	.41	.02

Abbreviations: ANOVA, analysis of variance; NDI, Neck Disability Index; WAD, whiplash-associated disorder.
**Significance level was set at P<.05.*
†Comparisons between healthy controls and all those with WAD.
‡Comparisons between healthy controls, those with mild/moderate disability (NDI<40%) related to WAD, and those with severe disability (NDI≥40 %) related to WAD.

model, $P = .53$) (**TABLE 3**). There were, however, significant differences ($P<.001$) among segmental levels. Follow-up post hoc tests with Bonferroni correction for multiple comparisons indicated that segmental levels C4 and C7 had significantly greater ($P<.001$) fat infiltration than levels C5 and C6 (**TABLE 4**).

No significant difference in fat infiltration was found when comparing the pooled WAD group to healthy controls ($P = .32$), but significant differences were found when the analysis was performed after dividing those with WAD into severe (NDI of 40% or greater) and mild/moderate (NDI less than 40%) levels of disability (**TABLE 3**). The participants with severe WAD had 38% greater ($P = .03$) fat infiltration compared to healthy controls and 45% greater fat infiltration compared to participants with mild/moderate WAD ($P = .02$) (**TABLE 3**). There were no significant differences between healthy controls and participants with mild/moderate disability.

DISCUSSION

Based on the average of segmental levels C4 to C7 and both sides, the present study demonstrated significantly greater levels of multifidus fat infiltration in the participants with persistent severe pain-related disability after a whiplash injury compared to those with mild/moderate disability and healthy controls. No significant statistical interactions were observed between segmental levels and groups or between sides and groups. However, the result showed significant difference in multifidus cross-sectional areas and fat infiltration between segmental levels, indicating a high level of anatomical variability among cross-sectional slices. In future studies or clinically, acquiring images of the entire multifidus muscle and subsequently segmenting a high percentage of muscle may help to obtain valid measurements of cross-sectional areas and fat infiltration. A future solution may be to apply a more

automated segmentation method capable of segmenting the entire muscle in 3 dimensions.

In this study, we used dual-echo Dixon water and fat imaging instead of the earlier-used T1-weighted imaging[6,7] for analyzing cross-sectional area and fat infiltration in the multifidus muscles. By using later echoes (second out of phase and third in phase) and a robust reconstruction method, with phase-sensitive reconstruction,[24,25] we were able to acquire the very high resolution needed to accurately detect the complete structures of the multifidus muscle, with the possibility of acquiring the total volume of the muscle. Imaging with water and fat separation produces 2 perfectly matched images, one containing only water and the other containing only fat, which is beneficial for analyzing fat contents inside muscles.

The participants with Quebec Task Force grade II and III WAD included in this study were also participating in an ongoing clinical trial with strict inclusion/exclusion criteria comparing 3 different exercise programs. While the participants may not be representative of all individuals with WAD, the findings are in agreement with other investigations performed on Australian[6] and American[5,10] cohorts, suggesting that the presence of muscle fat infiltration provides an objective marker for chronic WAD.

The findings from the present study also support the findings previously reported by Elliott et al,[5-7] showing increased fat infiltration for those with more severe pain-related disability from whiplash compared to those with mild pain-related disability or healthy controls. These findings highlight that morphological changes exist in individuals with severe pain-related disability, suggesting the importance of investigating the structure of muscle and not only size (cross-sectional area).[9]

The mechanism behind the expression of muscle fat infiltration is somewhat unclear, given a number of explanatory models, such as disuse, segmental nerve irritation or injury, and damage to segmental structures such as the facet joint, disc, or the muscle itself provoking an inflammatory reaction.[20,28] Preliminary evidence also exists to suggest that central mechanisms could drive muscle changes secondary to reductions in alpha-motoneuron drive.[8]

The etiology of chronic WAD and especially the cause and effect are still unclear. An improved knowledge of how a whiplash injury affects the structure of the neck muscles (or vice versa) will allow clinicians to improve their diagnostic/prognostic/treatment decisions and thereby target improved outcomes for patients. Increased fat infiltration seems to be specific for a whiplash injury[4,6,7] and potentially related to more severe pain-related disability and signs of posttraumatic stress.[6,7] While we did not collect data related to posttraumatic stress, our study does suggest a relationship between greater muscle fat infiltration and pain-related disability. This is suggested to be the result of a more severe injury, but other robust predictive factors, such as posttraumatic stress, should be included in replication efforts.[6]

Structural[6,7,9] and functional alteration in the neck[1,26] and low back multifidus[13] has been reported to be a factor related to abnormal neuromuscular control, and thus a cause for recurrent spinal symptoms.[3,13] To further understand the pathophysiological mechanism and to develop more informed clinical practice for patients with traumatic neck disorders, future research should investigate the specific distribution of muscle fat within these deep extensor muscles across patients with varying levels of pain-related disability. Quantifying the magnitude and distribution of muscle fat may improve our knowledge of the mechanisms underlying disturbed neuromuscular control of posture and dynamic stability of the head and neck following whiplash. Such knowledge may provide a foundation for exploring and developing more informed treatment regimens targeting specific muscle groups to improve functional recovery.

One inclusion criterion for this study was that participants had to be right handed and have dominant pain on the right side or bilateral pain. The purpose of this criterion was to reduce the risk of hand dominance or side of more severe pain as confounding factors. One limita-

TABLE 4 *P* Values for Post Hoc Tests of Segmental-Level Comparisons, Using the Bonferroni Correction for Multiple Comparisons for Multifidus Cross-sectional Area and Muscular Fat Infiltration*

	Controls Versus WAD†		Controls Versus Mild/Moderate WAD Versus Severe WAD‡	
Post Hoc Test: Segmental Level	**Area**	**Fat Infiltration**	**Area**	**Fat Infiltration**
C4 versus C5	.13	<.001	.06	<.001
C4 versus C6	<.001	<.001	<.001	.001
C4 versus C7	<.001	1.0	<.001	1.0
C5 versus C6	<.001	1.0	<.001	1.0
C5 versus C7	<.001	<.001	<.001	<.001
C6 versus C7	<.001	<.001	.001	<.001

Abbreviations: NDI, Neck Disability Index; WAD, whiplash-associated disorder.
**Significance level was set at P<.05.*
†*Comparisons between healthy controls and all those with WAD.*
‡*Comparisons between healthy controls, those with mild/moderate disability (NDI<40%) related to WAD, and those with severe disability (NDI≥40%) related to WAD.*

TABLE 5 Descriptive Data for Fat Fraction at Segmental Levels C4 Through C7 for Healthy Controls and Those With Mild/Moderate (NDI<40%) and Severe (NDI≥40%) Disability Related to WAD

	Healthy Controls	Mild WAD	Severe WAD
C4			
Left	0.184 ± 0.077	0.161 ± 0.105	0.259 ± 0.139
Right	0.193 ± 0.074	0.162 ± 0.090	0.272 ± 0.127
Average	0.189 ± 0.071	0.161 ± 0.094	0.265 ± 0.130
C5			
Left	0.141 ± 0.091	0.130 ± 0.050	0.176 ± 0.075
Right	0.146 ± 0.080	0.137 ± 0.054	0.163 ± 0.089
Average	0.143 ± 0.080	0.133 ± 0.049	0.170 ± 0.079
C6			
Left	0.147 ± 0.061	0.131 ± 0.072	0.186 ± 0.085
Right	0.134 ± 0.060	0.138 ± 0.089	0.211 ± 0.114
Average	0.141 ± 0.053	0.135 ± 0.077	0.199 ± 0.085
C7			
Left	0.181 ± 0.101	0.194 ± 0.089	0.264 ± 0.105
Right	0.173 ± 0.089	0.188 ± 0.098	0.263 ± 0.080
Average	0.177 ± 0.088	0.191 ± 0.087	0.263 ± 0.084
Average, C4-C7			
Left	0.163 ± 0.063	0.154 ± 0.062	0.221 ± 0.090
Right	0.162 ± 0.061	0.156 ± 0.068	0.227 ± 0.078
Average	0.162 ± 0.058	0.155 ± 0.063	0.224 ± 0.082

Abbreviations: NDI, Neck Disability Index; WAD, whiplash-associated disorder.
**Values are mean ± SD fat ratio [fat/(water + fat)].*

tion could therefore be that the results are biased to right-handed individuals. Another limitation of this study was that only the individuals in the original WAD group (n = 31) were age and sex matched to those in the control group. When the individuals in the WAD group were stratified by NDI measurement, no such matching to those in the control group could be performed.

This study included 62 participants, using a cross-sectional design. The number of participants is not small for including a new MRI technology on an earlier uninvestigated patient cohort. However, to investigate the multifidus fat infiltration and cross-sectional area between severe and mild/moderate WAD using fat/water MRI, more studies with a larger number of participants would increase the statistical power of the results. Another limitation was the use of a single-peak lipid resonance model, which could not measure T2, resulting in a possible T1 bias. Due to the use of a relatively high flip angle to ensure a sufficient signal-to-noise ratio, a bias in the fat measurement might have occurred.

CONCLUSION

Participants with severe pain-related disability after a whiplash injury had larger amounts of fat infiltration in the cervical multifidus muscles when compared to healthy controls and those with mild/moderate disability following a whiplash injury. The findings of this study, using a different cohort and refined imaging technology, are in agreement with previously reported findings of increased morphometric changes in the multifidus muscle for those with severe persistent pain-related disability following whiplash injury. Assessment of fat infiltration in affected muscle is an important step toward developing better objective diagnostic tools for those with chronic WAD. ◉

KEY POINTS

FINDINGS: Participants with more severe self-reported WAD symptoms (NDI greater than or equal to 40%) had greater fat infiltration in the cervical multifidus muscles compared to healthy controls and to participants with more moderate WAD-related symptoms (NDI less than 40%). These were the findings of a new technique for high-resolution imaging of the neck that enabled the acquisition of water- and fat-separated images.

IMPLICATIONS: Another research group, using a traditional T1-weighted imaging technique in an earlier study, reported similar findings. The verification of such findings indicates that fat infiltration could be a step toward the development of objective evaluation and monitoring tools for those with chronic WAD.

CAUTION: The original WAD group (n = 31) was age and sex matched to the controls. When stratification was performed using the NDI measurement, no such matching to the controls was performed.

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