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Fatty Infiltration in the Cervical Extensor Muscles in Persistent Whiplash-Associated Disorders

A Magnetic Resonance Imaging Analysis

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Study Design. Cross-sectional investigation of muscle changes in patients suffering from persistent whiplash-associated disorders (WAD).

Objectives. To quantitatively compare the presence of fatty infiltrate in the cervical extensor musculature in a cohort of chronic whiplash patients (WAD II) and healthy control subjects across muscle and cervical segmental level.

Summary of Background Data. Magnetic resonance imaging (MRI) can be regarded as the gold standard for muscle imaging; however, there is little knowledge about *in vivo* features of neck extensor muscles in patients suffering from persistent WAD and how fat content alters across the factors of muscle, vertebral segments, age, self-reported pain and disability, compensation status, body mass index, and duration of symptoms.

Methods. A reliable MRI measure for fatty infiltrate was performed of the cervical extensor muscles bilaterally in 113 female subjects (79 WAD, 34 healthy control; 18–45 years, 3 months to 3 years post injury). The measure was performed on all subjects for the rectus capitis posterior minor and major, multifidus, semispinalis cervicis and capitis, splenius capitis, and upper trapezius.

Results. The WAD subjects had significantly larger amounts of fatty infiltrate for all of the cervical extensor muscles compared with healthy control subjects (all $P < 0.0001$). In addition, the amount of fatty infiltrate varied by both cervical level and muscle, with the rectus capitis minor/major and multifidi at C3 having the largest amount of fatty infiltrate ($P < 0.0001$). Intramuscular fat was independent of age, self-reported pain/disability, compensation status, body mass index, and duration of symptoms.

Conclusion. There is significantly greater fatty infiltration in the neck extensor muscles, especially in the deeper muscles in the upper cervical spine, in subjects with persistent WAD when compared with healthy controls. Future studies are required to investigate the relationships between muscular alterations and symptoms in patients suffering from persistent WAD.

Key words: MRI, cervical, muscle, fat, whiplash. **Spine 2006;31:E847–E855**

Studies indicate that up to 40% of people who have had a whiplash injury will continue to have pain for 6 months and between 10% and 30% of patients will continue to report symptoms for 2 years or longer.[1–3] While the cause for such chronicity is not well understood, it is clear that if symptoms persist for 6 months following injury, the status of a whiplash patient is unlikely to change significantly. One of the focal problems confounding the appropriate early management of acute whiplash-injured patients is the inability to make a pathoanatomic diagnosis.[4–7] Arguably, an early diagnosis could lend itself to the development of prognostic indicators, which might identify those patients who are most susceptible to chronicity.

The value of diagnostic magnetic resonance imaging (MRI) for acute whiplash-associated disorders (WAD) from a pathoanatomic perspective is reported to be poor with MRI usually failing to identify any structural lesion(s) related to symptoms.[4–7] However, these studies have focused on changes in the intervertebral disc, facets, and ligaments with little focus on muscular tissue. MRI has been and continues to be widely used as a diagnostic modality in the evaluation of muscles, for example, to demonstrate atrophy and fatty infiltrate in the deep extensor musculature in patients with lumbar spine syndromes.[8–11] MRI signal change in the cervical extensor muscles has been reported in two studies of cervical root avulsion.[12,13] Hayashi *et al*[13] found a pattern of signal change in the ipsilateral multifidus muscle extending from one level superior to two levels inferior to the injured segmental nerve. Hallgren *et al*[14] and McPartland *et al*,[15] in 2 case series of patients with chronic neck pain, qualitatively observed atrophy and fatty infiltrate in the suboccipital muscles that they thought could be associated with a nerve injury. Nevertheless, muscle degeneration, including fatty infiltration, could also be associated with other mechanisms such as generalized disuse atrophy,[16] chronic denervation,[17–19] motoneuron lesions,[20,21] meta-

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bolic disorders,[22,23] aging,[24–26] and other direct muscle disorders.[27]

The purpose of this cross-sectional study was to: 1) assess for the presence of MRI signal intensity changes (SI) in the cervical extensor musculature in a cohort of chronic whiplash patients (WAD II); 2) evaluate and quantify muscular tissue SI changes (indicative of fatty infiltration) across muscle and segmental level; 3) determine whether there was a difference in fatty infiltration between WAD and healthy control subjects within a defined age range (18–45 years); and 4) determine if age, Neck Disability Index (NDI) scores, compensation status, body mass index (BMI), and duration of symptoms had an influence on fatty infiltrate. It was hypothesized that fatty infiltration in the cervical extensor musculature would be present to a larger extent in patients with persistent WAD than healthy control subjects.

■ Materials and Methods

Subjects. Volunteer subjects with persistent WAD were gained through referral from physical therapists and general medical practitioners in both the Denver and Brisbane metropolitan areas. Healthy control subjects were recruited through advertising in the local press, and within the local university fraternity.

Participants with whiplash were included if they had persistent neck pain and disability (between 3 months and 3 years status postinjury) resulting from a motor vehicle crash (MVC) and classifiable as WAD II as per Quebec Task Force classification.[28] All subjects were females within the age range of 18 to 45 years. The cohort was restricted to females, as they have a higher incidence of persistent pain following whiplash.[29] Volunteers were excluded when classified as WAD III or IV, if they had lost consciousness as a result of their MVC, had a previous history of a MVC, or had previous neck pain in the absence of a MVC in the past 10 years, which required treatment. In addition, subjects were excluded if they had previously been diagnosed with a neurologic disorder (*e.g.*, multiple sclerosis); inflammatory conditions (*e.g.*, rheumatoid arthritis); metabolic disorders (*e.g.*, diabetes); were pregnant; were claustrophobic; or did not meet inclusion/exclusion criteria to have an MRI.

A total of 136 (101 WAD and 35 healthy controls) volunteers were initially recruited. Twenty-two WAD subjects were excluded for the following reasons: over the age limit (1), pregnancy (1), more than one MVC (16), claustrophobia (2), and lost consciousness as a result of MVC (2). The remaining 79 WAD subjects were included in the study. One healthy control subject was excluded because of complaints of neck pain and dizziness resulting from a previous neck injury 5 years before the study. Thus, 34 healthy control subjects were included. The total population consisted of 94 American subjects (78 WAD and 16 controls) and 19 Australian subjects (1 WAD and 18 controls). This project was granted approval by Institutional Medical Research Ethical Committees. All subjects (79 WAD and 34 controls) provided written informed consent before inclusion in the study.

MRI Acquisition: United States. Sagittal and axial slices were obtained of the cervical spine from the midpoint of the cerebellum through the T1 segmental level to ensure proper capture of the entire extensor musculature. The suboccipital muscles (rectus capitis posterior minor and major) and the cervical extensor muscles (multifidus, semispinalis cervicis and capitis, splenius capitis and upper trapezius) were measured at each segment (C0–C7). MR images were obtained using a Horizon LX General Electric 1.5T scanner (Milwaukee, WI). A conventional spin-echo pulse sequence of 656 milliseconds TR and 14 ms TE was used. All images were acquired on 256 × 256 pixel matrix with a 20 × 20 mm field of view. These image parameters were chosen to acquire MR images that were T1-weighted in order to obtain reasonable tissue contrast of fat and muscle.[30] Slice thickness was 4 mm.

MRI Acquisition: Australia. Sagittal and axial slices were obtained using a SONATA 1.5T magnet (Siemens, Erlangen, Germany). Parameters for the T1-weighted axial conventional spin echo sequence consisted of 448 ms TR and 14 ms TE. All images were acquired on a 256 × 256 pixel matrix with a 200 mm FOV. Slice thickness was 4 mm. A dedicated neck coil of the manufacturers (GE and Siemens) was used as a receiver coil.

Image Analysis. The images were analyzed post hoc with MRIcro software (www.mricro.com)[31] and stored on a secured laptop computer. There was no systematic difference found between images acquired in the United States and those acquired in Australia. Analysis consisted of manually tracing defined regions of interest (ROI) over each of the bilateral cervical extensor muscles on the axial T1-weighted images at each vertebral segment (C0–C7). Histograms were then created from the summated user-defined ROI, displaying each particular muscular pixel intensity profile. The numerical representation for each muscle profile was created and exported to a Microsoft Excel spreadsheet. Measures for the suboccipital muscles (rectus capitis posterior minor and rectus capitis posterior major) were taken at C0–C1 for the rectus capitis posterior minor muscle after identifying the dens and occipital condyles and at the most cephalad portion of the C2 vertebral level for the rectus capitis posterior major muscle on the axial MR slices. Measures for the extensor muscles at C3 were taken from the most inferior line on the axial MR slice at C3. The measures for the C4–C7 extensor muscles were taken from the most superior line on the axial MR slices for each vertebral level. No extensor muscles (deep or superficial) were measured at C2 due to the large amount of peri-articular fatty tissue and lack of identifiable deep muscle fibers (multifidus and semispinalis cervicis).

One user-identified ROI consisting of an area of intermuscular fat was also created from an axial slice at the C2 vertebral level for each subject on the right side. Careful attention was taken to ensure the fat ROI consisted only of an area of high-signal intensity, which invariably produced a population of voxels with higher pixel intensities on the fat histogram.

An index of fat within the muscle was then created from the pixel intensity summary with MRIcro software.[31] The measure, which was developed, consisted of the pixel intensities for each muscle ratioed to the standardized region of intermuscular fat allowing comparisons between individuals. The measure, based on the contrasting pixel intensities of fat and soft-aqueous tissue on T1-weighted imaging, allows for the straightforward, reproducible process of quantifying intramuscular fat relative to an acknowledged area of intermuscular fat.[32]

The repeatability of the MRI measure was performed on 5 randomly selected images (total of 35 muscles) for the right-sided cervical extensor muscles. The intratester reliability measures were performed on 2 separate days (24 hours apart). The

Table 1. Demographic Details of Subjects

Group	Age (yr)	BMI (kg/m^2)	NDI	Duration (mo)	Compensation Status (% yes)
WAD (n = 79)	29.7 (7.7)	25.1 (5.73)	45.5 (15.9)	20.3 (9.55)	51/79 = 65%
Control (n = 34)	27.0 (5.6)	23.0 (4.44)	—	—	—

NDI indicates Neck Disability Index.[33]
Data are mean ± SD.

ICC values for intratester and intertester reliability were 0.93 and 0.94, respectively, indicating a high level of repeatability.

Statistical Analysis. Data were analyzed with the procedures implemented by using SPSS 13.0. Analysis was performed through several steps. The values for all muscles were plotted for cervical level and side and a linear regression analysis was used to determine any trends in the cervical segments at which all muscles were measured (C3–C7). A linear mixed model multifactorial analysis of variance (MANOVA) was applied to investigate the group means of whiplash and control subjects for fat indexes in the cervical extensor muscles across muscle, side and level (C3–C7). A linear mixed model with unequal variances allowed for the WAD and control subject variation. Bonferroni post hoc comparisons were used to compare any group by muscle interactions at each cervical level. One-way ANOVA was used to determine if there were group differences between WAD and control subjects for fat indexes in the right and left suboccipital, rectus capitis posterior minor, and rectus capitis posterior major muscles. Multiple regression analyses were also performed to determine if the score on the Neck Disability Index (NDI)[33] age, BMI, compensation status, and length of history from date of injury had an influence on fatty infiltrate. Significance was set conservatively at $P < 0.0005$.

■ Results

Table 1 presents the demographic characteristics for the two groups. Figure 1 presents the values (averaged between sides) for the fat:muscle ratio for the whiplash and control groups. The graphs show a primarily linear decrease in the fat:muscle ratio from C3–C7 levels for each of the five muscles measured in the two groups. As can be observed, the regression trends are very different between normal and WAD subjects. This reflects a generally higher level of fat within all extensor muscles in the WAD group. Notably, the multifidus muscle in the WAD group had a higher index of fat within muscle at all cervical levels but particularly at C3. Semispinalis cervicis also had a high index at C3 in the WAD group. When muscles were plotted by left and right sides, there was very little difference in the regression lines (trends) between sides in either the normal or WAD groups. Analysis of the slopes in fat indexes of the five muscles across segments revealed positive differences in the average linear trends across levels for each of the five muscles between the normal and the WAD subjects (all $P <$ 0.0001). The positive values confirm the observation that the decline in the fat index within muscle across levels is less for the normal group than for the WAD group for all muscles. There was little difference in this linear trend between muscles in either group with the exception of multifidus in the WAD group where the fat:muscle index varied at the lower cervical levels.

Preliminary analysis of the data revealed that there were some heterogeneity issues such that the within-subjects variance was larger for the WAD than the control subjects. An analysis of variance with weighted variances based on group strata revealed little change in the inference for fixed effects. The results of the MANOVA revealed significant main effects for group, muscle, segmental level, and side (all $P < 0.0001$), and significant interactions between group:muscle, group:level, muscle:level, and group:side (all $P < 0.0001$). Inspection of the raw data revealed that the difference between sides was of a mean magnitude of 3.92% ± 0.09%, which although consistent and reaching statistical significance, is unlikely to be of clinical relevance. Consequently, the sides were averaged for each muscle and level for Bonferroni *post hoc* analysis.

As was observed (Figure 1), there was a primarily linear decrease in the fat:muscle ratio from C3–C7 levels for each of the five muscles measured in the two groups. For the control group, there were no significant differ-

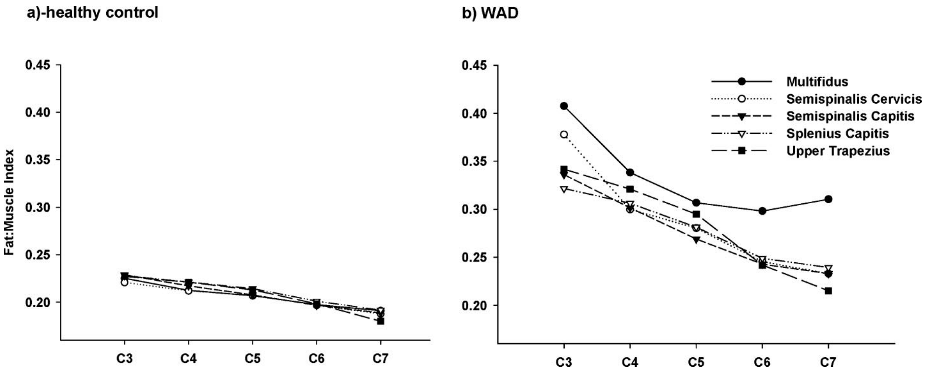
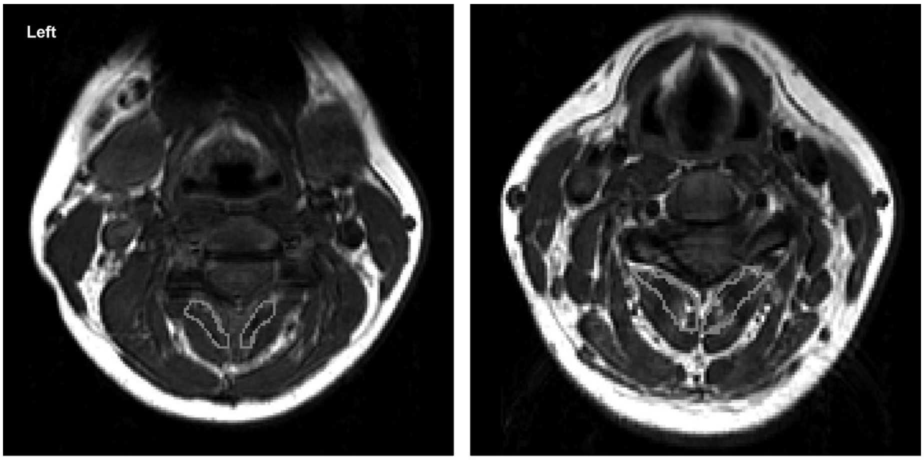
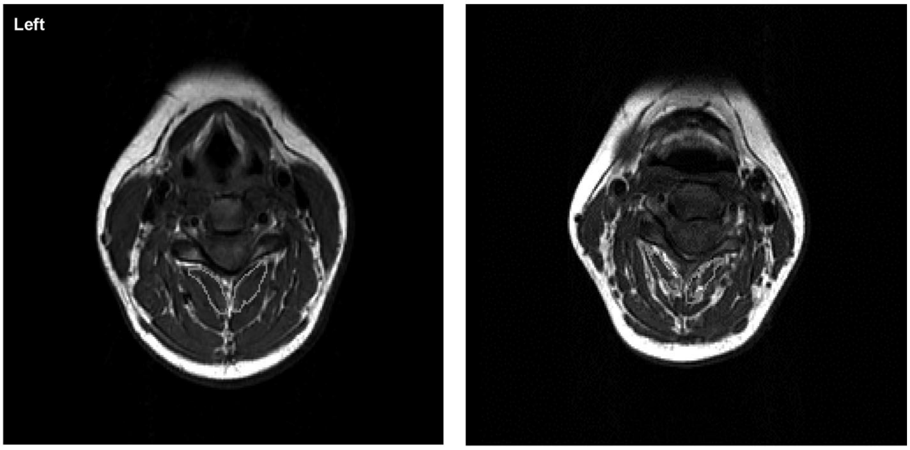


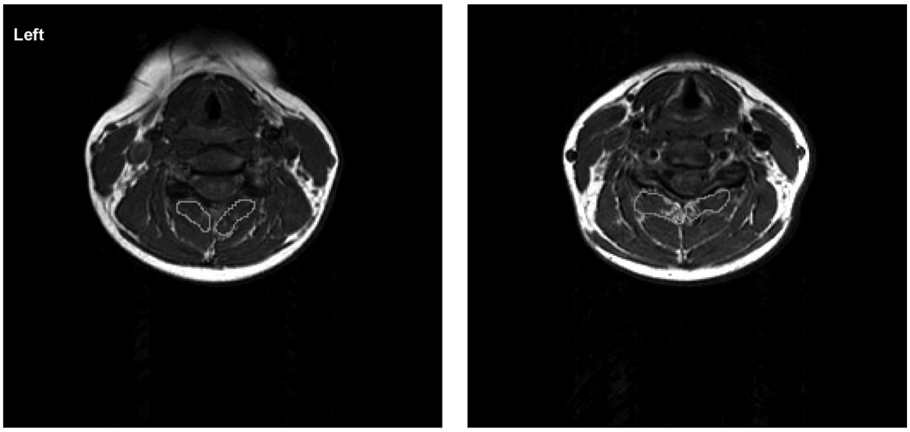
Figure 1. Mean differences for the fat indexes in the cervical segmental muscles across segmental vertebral levels (C3–C7) in the healthy control (a) and WAD (b) groups.



a) C3 Healthy control WAD



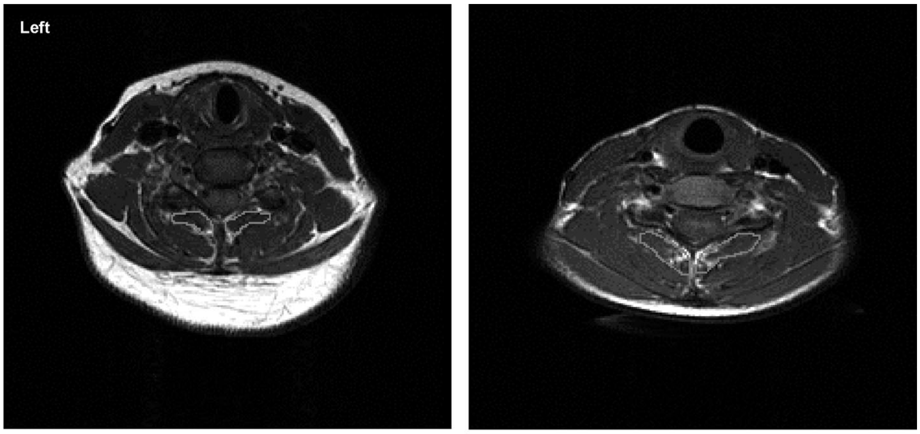
b) C4 Healthy control WAD



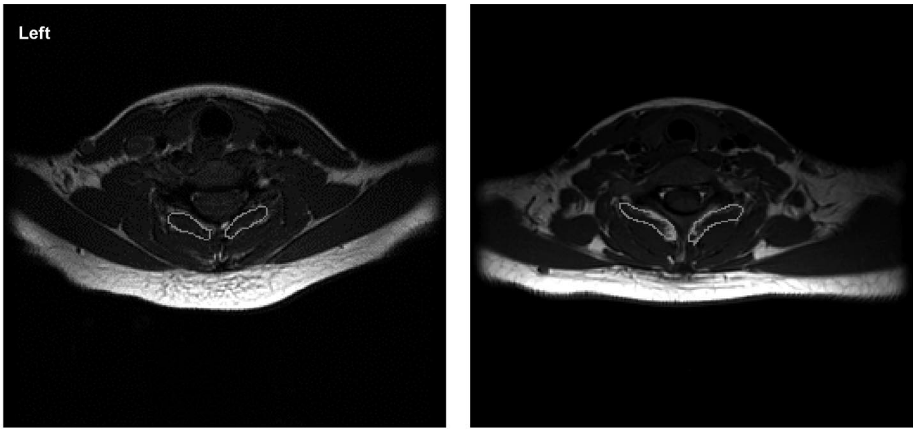
c) C5 Healthy control WAD

Figure 2. a–e, Bilateral axial MR images of the segmental cervical multifidus muscles, C3–C7 (healthy control *vs.* WAD subjects).

ences in the fat indexes across muscle, levels and side ($P = 0.09$), nor were there any significant interactions for the control group. For the WAD subjects (Figure 1b), the multifidus muscle had significantly higher fat content at each level compared with the corresponding levels for all other muscles ($P < 0.0001$) with the exception of the comparison between multifidus and upper trapezius at C5, which was not significant ($P = 0.010$). In addition, multifidus muscle had significantly larger fat content at C3 when compared with the caudal multifidi at C4, C5, C6, and C7 ($P < 0.0001$) and the C4 multifidi fat index was significantly higher when compared with C5, C6, and C7 ($P < 0.0001$). Bilateral multifidus axial MR images are shown in Figure 2.



d) C6



e) C7

Figure 2. Continued

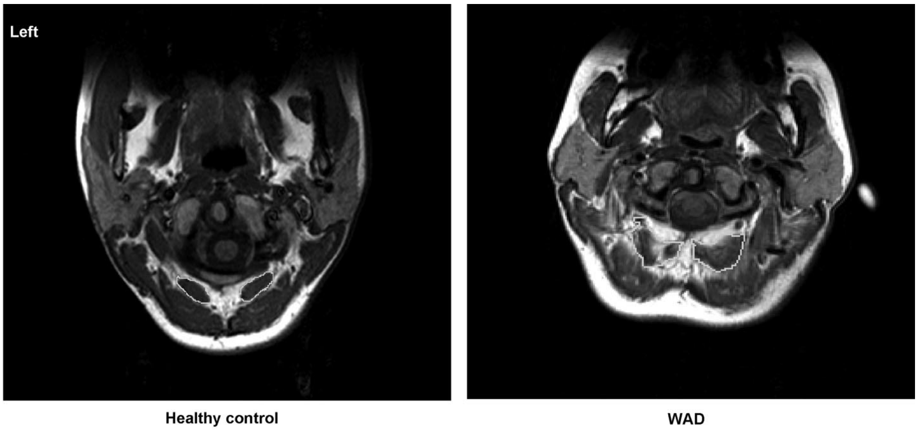
The one-way ANOVA revealed that there were higher fat:muscle indexes in the whiplash group compared with the control group in the rectus capitis posterior minor and rectus capitis posterior major muscles ($P < 0.0001$). Bilateral rectus capitis posterior minor and rectus capitis posterior major axial MR images are shown in Figure 3. Mean group differences for the fat indexes in the rectus capitis posterior minor and rectus capitis posterior major muscles are shown in Figure 4.

There was no association between the fat:muscle indexes in all of the whiplash extensor muscles and NDI scores ($P = 0.81$), age ($P = 0.14$), duration of symptoms ($P = 0.99$), compensation status ($P = 0.37$), or BMI ($P = 0.74$).

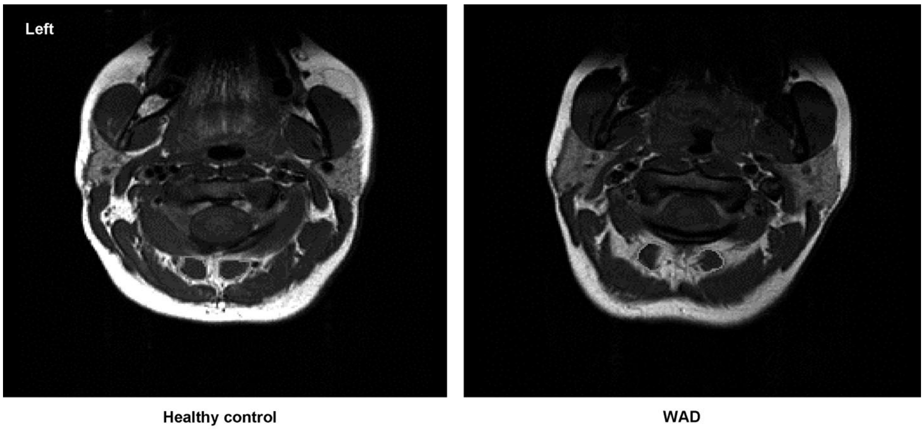
Discussion

The data in this study indicate that the MRI measure for fatty infiltrate[32] identified changes in the cervical extensor muscles in patients with persistent WAD. Specific patterns of muscle fatty infiltrate were identified throughout the entire cervical extensor muscles in both normal and WAD subjects, although significantly larger amounts of fatty infiltrate occurred throughout the extensor muscles in the WAD group. The largest amounts of intramuscular fat were found in the rectus capitis posterior minor, major, and deep cervical multifidii muscles in the WAD group. These changes were independent of age (both healthy and WAD subjects), duration of symptoms (changes established at 3 months), compensation status, BMI, and self-reported levels of pain and disability (NDI) in the WAD subjects. NDI scores (mean, 45.5 ± 15.9; range, 16–82) indicate that WAD subjects were reporting symptoms and functional disability ranging from milder to severe levels. The finding that the overall fatty indexes in this WAD group were not influenced by the self-reported NDI scores was unexpected as higher levels of pain and disability have previously been related to more severe injuries.[34]

There was a cephalad to caudad decline in fat content in all muscles in both the WAD and control groups, albeit significantly higher levels of fatty infiltrate in all muscles and at all cervical segments in the WAD subjects. This pattern was observed in the deep suboccipital and multifidus muscles as well as the intermediate and superficial muscles, the semispinalis cervicis and capitis, splenius capitis, and upper trapezius. The higher levels of fatty infiltrate in the suboccipital (rectus capitis posterior minor and major) and multifidus muscles, particularly at the C3 segment in the WAD group, could lead to the contention that there was a greater injury with consequent change in the



a) rcpmin (C0)



b) rcpmaj (C2)

Figure 3. a, b, Bilateral axial MR images of the rectus capitis posterior minor and rectus capitis posterior major muscles, C0–C2 (healthy control *vs.* WAD subjects).

muscles at these segments. Although it is known that a whiplash injury can damage any number of structures at any segment in the cervical spine,[35–38] it is possible that those with upper cervical injuries may be more prone to chronicity. Certainly headache[39,40] and the symptoms of lightheadedness and unsteadiness,[41] which are consistent with impairments in the upper cervical structures, are common in those with chronic WAD.

The exact cause of the nonuniform changes in the muscle layers and at certain cervical segments cannot be determined from this study, but it is reasonable to speculate on the possible underlying mechanisms for the fatty

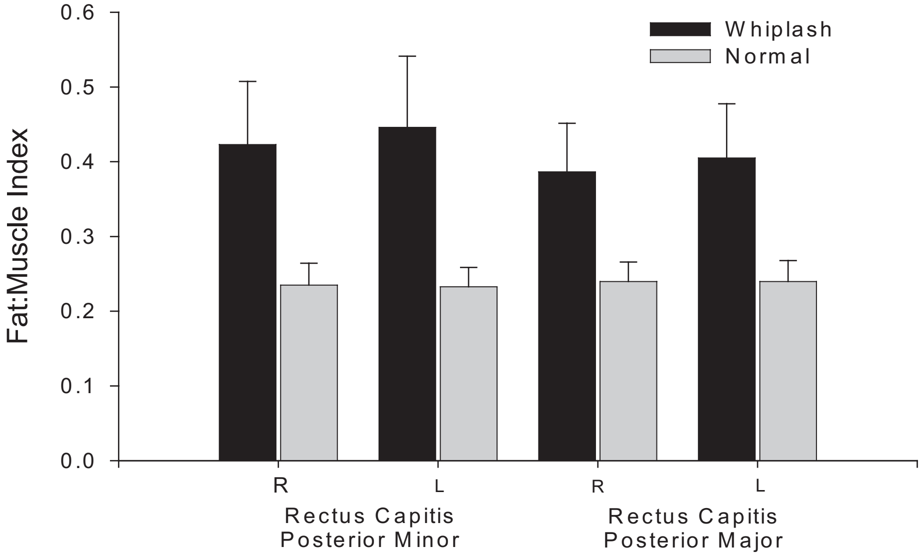


Figure 4. Mean group differences for the fat indexes in the right and left rectus capitis posterior minor and rectus capitis posterior major muscles (mean ± SD).

infiltration found in the whiplash group. Fatty infiltration in the muscles could be associated with mechanisms, such as generalized disuse,[16] chronic denervation,[17–19] motoneuron lesions,[20,21] metabolic disorders,[22,23] aging,[24–26] or other muscle disorders.[27] In the first instance, the mechanism of muscle degeneration is not likely to result from direct trauma to the paraspinal muscles, as the findings are too widespread. Aging is also unlikely to be the cause of our findings of fatty infiltration, as we determined no association between age and fatty infiltrate. This is not surprising as an age-related reduction in fat-free muscle mass is reported not to commence until much later in life[24–26] and our age group closely resembles "young to middle-age" adults. BMI did not impact on the amount of fatty infiltrate in any of the cervical extensor muscles in the either the control or WAD subjects.

The fact that fatty infiltrate was widespread and not isolated to one level in this whiplash group suggests that the degeneration may be a consequence of generalized disuse. Numerous authors argue that atrophic changes in muscle are not uniform and there are greater changes in slow-twitch muscles (*e.g.*, more Type I fibers).[42–45] Data from human cadavers provide evidence for greater density of Type I fibers in the deep cervical multifidus[46] and fiber type distribution is associated with the number of muscle spindles, *e.g.*, Type I fiber distribution is linked with the larger distribution of spindles.[47–49] The broader contention may then be that our findings of larger fat infiltration in the deep suboccipitals, which feature high spindle density,[50–52] and the deep multifidus, which are primarily comprised of Type I fibers,[46] are the consequence of generalized disuse. Conversely, the smaller amounts of fatty infiltrate in the more superficial muscles may be a consequence of larger proportion of Type II fibers,[53] which have been shown to be more resistant to fiber transformation in patients with cervical spine dysfunction.[54] What is currently unknown is how soon following injury these changes occur.

Alternatively, a greater presence of fatty infiltration in the deep cervical WAD muscles may be the consequence of either a minor nerve injury or irritated and subsequently demyelinated nerve tissue resulting from an acute inflammatory process[55] with the other variable disuse adding to the changes over time. Previous studies have shown that damage to nearby structures including the zygapophysial joint and intervertebral discs can cause inflammation and thus irritate the mechanosensitive nerve tissue.[56,57] Others have demonstrated ipsilateral, multisegmental muscle changes with MR following a segmental preganglionic nerve injury.[13] If it were that our findings of larger amounts of fatty infiltrate in the deeper musculature of the upper cervical spine were the result of a minor nerve injury, then there would be indications, based on the higher distribution of fat within the suboccipital and multifidus at C3, that the C1–C4 nerves would be involved.[58] The bilateral changes in the muscles in this region could be consistent with an inflammatory mechanism and attendant changes in the central nervous system[59–61] from either a minor nerve injury or damage to somatic structures. Further research is required to determine if chronic muscle changes on MRI indirectly reflect either acute ipsilateral nerve pathology or possible secondary effects of inflammation on bilateral nerve tissues in the upper cervical region.

Regardless of the mechanisms governing the muscle changes observed in this study, these changes may provide insight into the various functional impairments commonly observed in patients suffering from persistent WAD. From a proprioceptive standpoint, it is the smaller, non-torque-producing muscles that possess large spindle densities and are largely required for fine motor control. Muscles recruited for gross movement are comprised of comparatively smaller spindle densities.[51,62] Animal studies have demonstrated regional differences with regards to the central connections of lumbosacral as compared with cervical muscle afferents with terminal branches from the upper cervical region projecting to the inferior olivary nucleus and cerebellum.[63] It is currently unknown if similar differences in central connections exist between cervical muscles and muscle segmental levels in the cervical region. That information could help draw conclusions from the inferences regarding the potential association between the muscular changes observed in this study and functional impairments commonly observed in these patients, *e.g.*, kinesthetic deficits.

■ Conclusion

This is the first study to demonstrate that female patients (18–45 years) with persistent WAD (II) show quantifiable MRI changes in the fat content of the cervical extensor musculature, and these changes are not present in subjects with no history of neck pain. In particular, this study demonstrates larger signal change in the deep extensor musculature at higher cervical segments. It is currently unclear whether the patterns of fatty infiltration are the result of local structural damage, a nerve injury, or a generalized disuse phenomenon. Further work is warranted to investigate the potential mechanisms involved and to whether the findings of fatty infiltrate in the cervical extensor musculature are related to the clinical signs and symptoms of persistent WAD. Ultimately, this information would provide the basis for assessment and possibly provide some prognostic information.

■ Key Points

- MRI muscular fatty infiltration was found in the suboccipital and segmental extensor muscles in the cervical spine in healthy controls and those subjects suffering from persistent WAD.

- Subjects with WAD had significantly more fatty infiltrate in all of the suboccipital and segmental extensor muscles compared with the healthy control group. Fatty infiltration occurred to a larger extent in the rectus capitis posterior minor and major muscles and the multifidi at the C3 segmental level in those subjects suffering from persistent WAD.
- Fatty infiltrate was independent of age, symptom severity or duration, BMI, and compensation status.
- These data may reflect a myriad of mechanisms, including disuse and/or chronic denervation.

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