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Quantitative ultrasound of muscle can detect corticosteroid effects

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HIGHLIGHTS

- Quantitative ultrasound techniques detect the impact of corticosteroids on muscle.
- Corticosteroids has the greatest impact on echointensity in tibialis anterior.
- Quantitative ultrasound values correlated with overall exposure to corticosteroid therapy.

ABSTRACT

Objectives: In this study, we sought to determine whether quantitative ultrasound (QUS) could detect the impact of corticosteroids on muscle in the absence of frank weakness.
Methods: QUS was performed on selected limb muscles of 20 brain tumor patients treated with dexamethasone and 30 healthy controls. Echointensity was quantified using gray scale level (GSL) analysis and compared between groups; correlation to corticosteroid exposure was also performed.
Results: Average 4-muscle GSL (±standard deviation) was greater in patients compared to controls (35.5 ± 5.61 arbitrary units (AU) versus 30.4 ± 4.17 AU, p = 0.001), with the greatest differences in tibialis anterior. Average muscle GSL also correlated to length of corticosteroid therapy (rho = 0.52, p = 0.01).
Conclusions: These findings suggest that QUS may be able to quantify skeletal muscle alterations associated with chronic corticosteroid use. Further study of this approach is warranted.
Significance: The findings of this study may provide a tool to evaluate corticosteroid myopathy.

1. Introduction

Corticosteroid myopathy (CM) is the most common drug-induced myopathy (Pereira and Freire de Carvalho, 2011) and is characterized by weakness most prominent in proximal muscles (Batchelor et al., 1997). Cachectic individuals, older adults, and patients with cancer are at higher risk (Afifi et al., 1968) for this condition. Further, a myopathy is more likely to develop with use of fluorinated preparations of these drugs, (e.g., dexamethasone), than non-fluorinated preparations (e.g., prednisone, prednisolone) (Anagnos et al., 1997). However, all forms of these medications cause preferential atrophy of fast-twitch glycolytic muscle fibers (Schakman et al., 2008), as well as thickening of sarcolemmal and capillary basement membranes (Djaldetti et al., 2009), intramuscular fat deposition (Prineas et al., 1968), mitochondrial dysfunction and oxidative damage (Kelly et al., 1986; Djaldetti et al., 2009).

No definitive diagnostic test or set of clinical criteria for CM has been developed (Bowyer et al., 1985). The diagnosis is typically made in the setting of proximal muscle weakness and a history of treatment with corticosteroids. Importantly, clinical manifestations can be varied, ranging from very mild proximal weakness to severe weakness that impacts distal muscles. Creatinine kinase (CK) and other muscle enzymes, as well as other serologic studies, are usually normal in CM (Askari et al., 1976). Needle electromyography (EMG) is not especially sensitive to the changes produced by corticosteroids, in part because there are no associated fibrillation potentials. Moreover, alterations in motor unit potential

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morphology can be modest, and quantification of these alterations is difficult, since EMG mostly measures the action of type 1 muscle fibers (Preston, 2012) which are relatively spared in CM (Minetto et al., 2011).

Quantitative ultrasound (QUS) is a convenient, sensitive, and non-invasive method that provides objective data on muscle condition. In QUS, the gray scale (GSL) image is converted into numerical data using an image-processing program in a uniform way across muscles and subjects; increasing echointensity generally suggests increasingly abnormal muscle. The approach has been used to identify the presence and severity of many disorders. For instance, echointenisty is increased in Duchenne muscular dystrophy (Zaidman et al., 2010; Jansen et al., 2012; Rutkove et al., 2014), spinal muscular atrophy (Pillen et al., 2011), non-dystrophic myotonias (Trip et al., 2009) and late-onset acid maltase deficiency (Zaidman et al., 2011). It has also been shown to have high reproducibility (Zaidman et al., 2014). Despite the growing number of studies evaluating the use of QUS in neuromuscular disease, to our knowledge it has not been used to evaluate the presence of CM in a cohort of predisposed patients.

A near-ideal approach for studying the potential value of QUS is to evaluate a group of brain tumor patients being treated with corticosteroids, since most will not have systemic disease and generally they will have a readily identifiable corticosteroid initiation date. Moreover, because these individuals are given high-potency corticosteroids to reduce peritumoral edema and accompanying symptoms, (El Kamar and Posner, 2004) they are at particular risk of developing CM. In fact, previous work has shown that in as few as two weeks of use, dexamethasone use can produce clinical alterations, including mild weakness (El Kamar and Posner, 2004). Thus, in this study, we evaluate whether the exposure to corticosteroids alters muscle QUS values in the absence of frank clinical CM.

2. Methods

2.1. Participants and recruitment

Beth Israel Deaconess Medical Center (BIDMC) institutional review board approved the protocol and all participants or family members provided written consent. Healthy participants were recruited via online advertising. Patients were recruited from the BIDMC brain tumor clinic. The inclusion criteria for patients were: (a) ages between 21 and 90 years, (b) daily exposure to dexamethasone for at least one month and (c) diagnosis of a central nervous system (CNS) tumor, and (d) Karnofsky Performance Score (KPS) (Mor et al., 1984) of 50 or above. Exclusion criteria for all participants were: (a) age less than 21 years, (b) presence of a generalized neuromuscular disease, (c) presence of an additional chronic medical condition (i.e., widespread metastatic disease, heart failure) or drug therapy that could negatively impact muscle health. Potential healthy controls were excluded if they were taking steroids for any reason (e.g. asthma).

2.2. Corticosteroid exposure and functional status of patients

Total cumulative dose of corticosteroids was calculated by multiplying average daily dose of dexamethasone by duration of therapy in days. Karnofsky Performance Score was also calculated.

2.3. Ultrasound image acquisition and analysis

All ultrasound images were obtained using a Terason t3000 system (Teracorp, Inc, Burlington, MA) with a 10 MHz transducer with all ultrasound parameters kept constant across all patients. Ultrasound measurements were performed on deltoid, biceps brachii, rectus femoris, and tibialis anterior since these muscles were easily accessible and representative of both proximal and distal limb segments. Unilateral measurements were generally performed on the dominant side. If a patient had asymmetric weakness attributable to the CNS lesion, then the contralateral limbs were studied. For each measurement, the transducer was placed transversely on the belly of the muscle; participants were positioned consistently (Table 1). Measurements were taken at a single time point by one of three raters trained in the technique. We note that measurements were only taken once, rather than as an average of multiple measurements, (Wallwork et al., 2007; Wong et al., 2012) so as to be as minimally intrusive in data collection as possible in this group of debilitated individuals.

All obtained images were imported into an image-processing program and then converted to .jpg files for analysis using Matlab® (MathWorks, Inc, Natick, MA). A region of interest (ROI) was selected using the most superficial one-third of the muscle (Jansen et al., 2012) and the relative luminosity of therein pixels measured to calculate a GSL (Jansen et al., 2012) (Fig. 1). We did not assess additional QUS parameters, such as muscle thickness, in this study because it was not possible to capture the entire muscle accurately in some cases.

2.4. Data analysis

Statistical analysis was performed using Matlab® (MathWorks, Inc, Natick, MA) and GraphPad Prism® (GraphPad Software, La Jolla, CA). A Shapiro-Wilk test was performed before any comparison to determine the data distribution and appropriately apply either an independent t-test or Wilcoxon signed rank test as well as Pearson's correlation (r) or a Spearman's rank correlation (rs). Chi-square analysis was used to evaluate differences in categorical demographic values. A p value of < 0.05, two-tailed was considered significant for all tests.

3. Results:

3.1. Participant characteristics

Table 2 summarizes participant demographics. No significant differences were present in weight, height, BMI or age between groups. Gender distribution was also similar.

Twenty (11 men, 9 women) brain tumor patients were included in the study (Table 3). Of these patients, 15 had primary CNS tumors and 5 had metastatic lesions to the brain; the latter group had only known isolated metastatic brain lesions at the time of study. All of the assessed muscles were full strength on clinical examination (i.e., 5/5, on the Medical Research Council grading scale).

Table 1
Ultrasound Probe Location and Subject's Position for each muscle.

Muscles	Location of US Transducer	Participant's Position
Deltoid	One fifth distance from acromion to lateral epicondyle.	Seated, arm at side, forearm supinated and supported with a pillow.
Biceps	Two thirds distance from acromion to antecubital fossa.	
Rectus Femoris	Two thirds distance from inguinal crease to superior aspect of patella.	Seated, knee bent at 90 degrees.
Tibialis Anterior	One forth distance from fibula head to lateral malleolus midpoint.	Seated, ankle in neutral position.

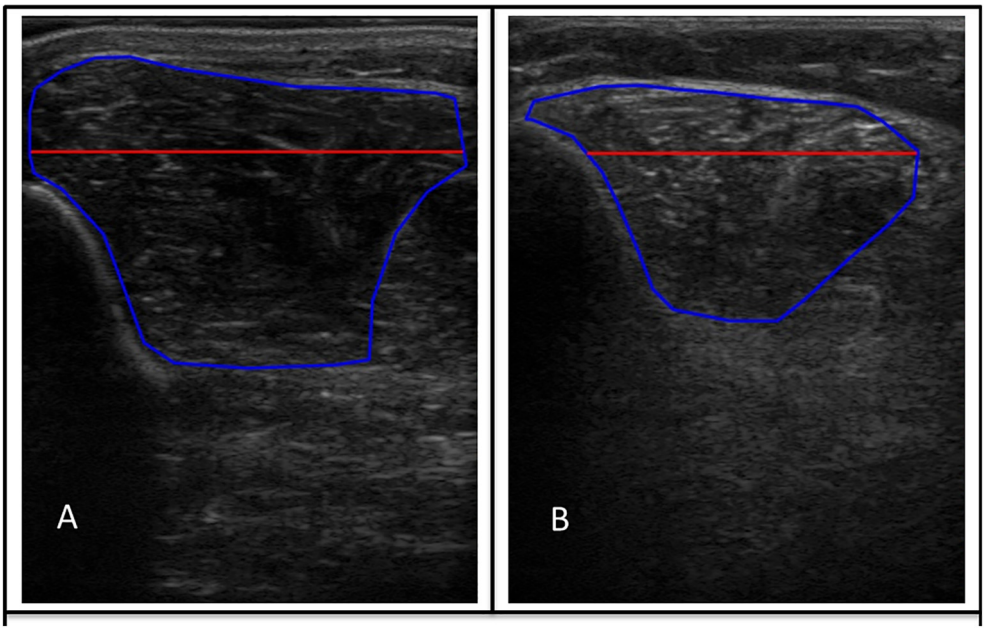

Fig. 1. Comparison of TA in 71-year-old healthy woman (A) and a 66-year-old woman exposed to corticosteroids (B). The GSL for image A is 24, while for B was 56. The region of interest is encompassed by the blue line and the upper 1/3 of the image is the section above the red line from which the GSL is derived. GSL: gray scale level.

Table 2
Patient and healthy participant characteristics.

Variables	Patients	Healthy Participants	P-value
Sample Size	20	30	-
Mean Age (range)	60 (30–81) years	57.57 (36–72) years	0.37
Mean Weight (±SD)	195 (46.8) lbs.	184.2 (43.7) lbs.	0.42
Mean Height (±SD)	66.7 (3.9) in	66.9 (4.14) in	0.8
Mean BMI (±SD)	31 (7.2)	28.73 (5.25)	0.2
Gender			
Men	11	18	0.73
Women	9	12	-

3.2. Differences in the echointensity of corticosteroid-exposed and healthy muscle

The average (±standard deviation) GSL across all four muscles was higher in the patients than in the control group (35.5 ± 5.61 arbitrary units (AU) versus 30.4 ± 4.17 AU, $p = 0.001$) (Table 4). Most of this effect was related to the GSL of tibialis anterior which was significantly higher in patients taking corticosteroids than in healthy controls (47.3 ± 7.98, AU versus 34.0 ± 8.02 AU, $p < 0.001$). While the differences were not significant, the GSLs of deltoid, biceps brachii, and rectus femoris were also uniformly higher in the patient group.

Table 3
Tumor types amongst patients and Karnofsky Performance Score.

Diagnosis		Karnofsky Performance Score	
Primary CNS:	**15**	**KPS:**	**Number of Patients:**
• **GBM**	10		
• **AA**	2		
• **Lymphoma**	1	50	1
• **Pineal Tumor**	1	60	11
• **AM**	1	70	7
Metastatic Tumors:	**5**	80	1
• **Breast Ca**	2		
• **RCC**	2		
• **DLBCL**	1		

KPS, Karnofsky Performance Score, GBM: Glioblastoma Multiforme, AA: Anaplastic, AM: Atypical Meningioma, RCC: Renal Cell Carcinoma, DLBCL: Diffuse Large B Cell Lymphoma.

Table 4
GSL (gray scale level) values per muscles including average of muscles and p-value.

Muscles	Unexposed GSL (SD)	Exposed GSL (SD)	Percentage of increased GSL between exposed and unexposed	p-value
Deltoid	27.2 (±7.3)	31.5 (±8.9)	15.8	0.07
Biceps	23.7 (±5.02)	26.2 (±5.6)	10.5	0.11
Rectus Femoris	37.5 (±10.7)	37.9 (±10.5)	1.3	0.7
Tibialis Anterior	34.05 (±8.02)	47.3 (±7.98)	39	<0.001
Average	30.4 (±4.17)	35.5 (±5.61)	16.8	0.001

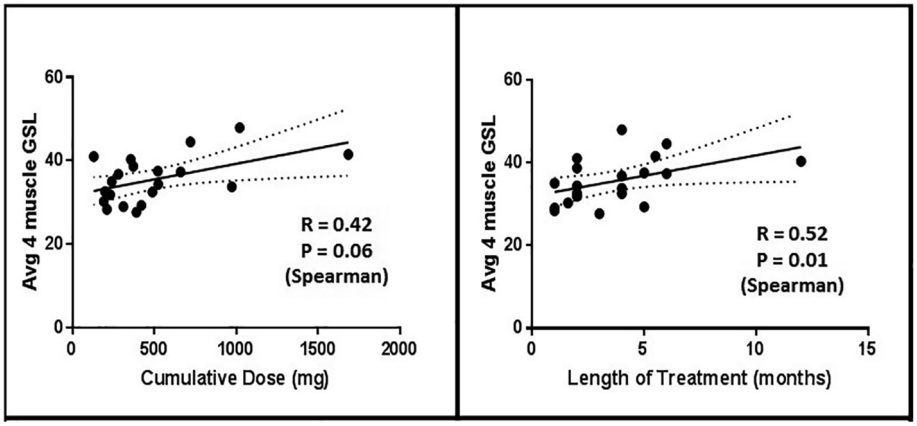

Fig. 2. Spearman correlations of cumulative dose vs. average GSL (left) and length of treatment vs. average GSL (right). Dashed lines represent the 95% confidence interval. Both show a positive correlation but only the length of treatment vs. average GSL relationship is significant (p = 0.01). GSL: gray scale level.

3.3. Relationship between echointensity and corticosteroid exposure

At the time of QUS data acquisition, brain tumor patients had been receiving dexamethasone for a mean of 3.3 (±1.7) months at an average dose of 10.25 (±5.5) mg per day. The degree of corticosteroid exposure appeared to be moderately associated with average GSL across all 4 muscles assessed. A greater cumulative dose showed a trend toward higher average GSL (rho = 0.42, p = 0.06). Length of corticosteroid treatment was positively correlated with average GSL (rho = 0.52, p = 0.01) (Fig. 2).

3.4. Relationship between echointensity and patient characteristics

No significant difference in GSL was detected based on participant gender. Further, there was no meaningful difference in GSL based on patient tumor type (metastatic versus primary CNS), although given the small number of subjects, the power to identify such a difference was low. There was also no relationship between GSL and Karnovsky performance Score.

4. Discussion

The main objective of this study was to determine if QUS could distinguish between healthy participants and brain tumor patients exposed to long-term corticosteroids. The results suggest that QUS can identify differences. Moreover, increased duration of corticosteroid therapy correlated to the degree of increased muscle echointensity, supporting that the relationship was not merely due to the brain tumor or associated disability itself.

The specific pathophysiology underlying the noted GSL differences is uncertain. GSL increases with deposition of endomysial fat, development of connective tissue, and myofiber atrophy. It is probable that one, or a combination, of these mechanisms is playing a role in the elevated GSL in the participants exposed to dexamethasone.

Given the classic distribution of weakness in steroid myopathy and the systemic exposure to dexamethasone, we expected the highest GSL to be found in the proximal muscles assessed – or in all of muscles – in patients on corticosteroids. Therefore, we were surprised to find that the GSL difference between healthy and corticosteroid-exposed muscle was most pronounced in tibialis anterior (TA). There is no specific reason as to why this muscle should be more impacted than any other. For example, it is not especially rich in type II fibers, which are most vulnerable to corticosteroid effects. In fact, studies have shown that this muscle in humans has a lower percentage of type II fibers than the other muscles we evaluated (Johnson et al., 1973; Dahmane et al., 2005). One potential explanation for this finding may be that, of all the muscles we evaluated, tibialis anterior usually has the thinnest layer of overlying subcutaneous fat. This could reduce the amount of QUS variation across subjects since there would be minimal attenuation of the acoustic energy and perhaps the greatest sensitivity to corticosteroid-related change.

Of note, the patients included in this study did not have clinical weakness on bedside neurological examination. This is compelling because it suggests that QUS may detect associated sub-clinical change. If future work can build on this proof-of-concept study to confirm that QUS can detect corticosteroid-related change in advance of a loss of power, it could be of considerable utility in clinical and research settings. For example, QUS could be used to monitor muscle condition in patients undergoing high-dose or prolonged corticosteroid therapy for a variety of reasons and facilitate a transition off of corticosteroids prior to a meaningful decline in strength. It could also serve as a valuable tool in research evaluating the ability of novel therapies (such as myostatin inhibitors or a synthetic peptide analog of the human corticotropin releasing factor, corticorelin acetate), to reduce the impact of corticosteroids on muscle (Recht et al. 2013).

Several limitations warrant consideration. First, the sample size was small. Second it is not possible to know whether cachexia and/or disuse were also playing a role in findings; broadening similar

studies to healthy individuals taking high dose steroids for other reasons (e.g. asthma) could potentially help elucidate this matter. Third, the patients in this study were all brain tumor patients taking dexamethasone so it is not clear if these results would be generalizable to patients with other disorders taking other forms of corticosteroids. Fourth, none of the patients included here had clinical weakness; it would be very helpful to learn if the GSL of weak muscles is even higher. Fifth, this was a cross-sectional study so we can only comment on the association between corticosteroid use and muscle changes. A longitudinal study evaluating GSL values before, during, and after treatment to determine if there is a clear temporal relationship between drug exposure and muscle alteration would be a worthwhile next step. Such a longitudinal study could help better characterize the time it takes for changes to develop and if there is a "threshold" GSL value above which clinical weakness becomes apparent. Finally, we did not correlate the QUS findings with other measures such as EMG or tissue samples. Biopsies of muscles displaying high GSL could provide information on the associated histological changes.

In conclusion, this study suggests potential value to using QUS for the assessment of corticosteroid-induced muscle change. If proven out with subsequent work across larger populations of individuals, this relatively simple and painless approach to muscle assessment could find wider utility in clinical trials and in day-to-day patient care.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

We confirmed that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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