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Reduction in stiffness of proximal leg muscles during the first six months of glucocorticoid therapy for giant cell arteritis: A pilot study using shear wave elastography.

Short title: Muscle stiffness after glucocorticoid therapy.

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Abstract

Aim

To investigate muscle stiffness changes in patients treated for giant cell arteritis (GCA) with high-dose oral glucocorticoids.

Methods

Using ultrasound elastography, shear wave velocity (SWV) was measured in the quadriceps, hamstrings and biceps brachii muscles of 14 patients with GCA (4 males, mean age(\pm SD) 68.2 \pm 4.3 years) within the first 2 weeks of initiating glucocorticoid treatment (baseline) and repeated after 3 and 6 months treatment. Muscle strength and performance tests were performed at each visit. Baseline measures were compared with those from 14 healthy controls. Linear mixed models were used to test for change in patient measures over time.

Results

At baseline, muscle SWV in patients was not significantly different to controls. With glucocorticoid treatment, there was a reduction in SWV in the leg but not the arm muscles. SWV decreased by a mean of 14% (range 8.3%–17.3%; $p=0.001$) after 3 months and 18% (range 10.2%–25.3%; $p<0.001$) after 6-months in the quadriceps and hamstrings during the resting position. The baseline, 3-months and 6-months mean SWV(\pm SD) for the vastus lateralis were 1.62 \pm 0.16m/s, 1.40 \pm 0.10m/s and 1.31 \pm 0.06m/s respectively ($p<0.001$). In the patient group as a whole, there was no significant change in muscle strength. However, there were moderate correlations ($r=0.54$ – 0.69) between exhibiting weaker muscle strength at follow-up visits and a greater reduction in SWV.

Conclusion

Glucocorticoid therapy in patients with GCA was associated with a significant reduction in proximal leg muscle stiffness during the first 6 months. Future research should study a larger sample of patients for a longer duration to investigate if diminished muscle stiffness precedes signs of glucocorticoid-induced myopathy.

Key words: Elasticity Imaging Techniques; Diagnostic Imaging; Muscles; Glucocorticoids; Giant Cell Arteritis, Muscular Diseases.

Introduction

Glucocorticoid therapy is commonly used for a range of medical conditions due to its powerful anti-inflammatory and immunosuppressive effects. However, despite their efficacy, they are linked to numerous adverse events, which have been estimated to cost the UK at least £165 per patient annually to manage ¹. This [paper study](#) focuses on glucocorticoid induced myopathy (GIM), a non-inflammatory condition affecting largely the proximal muscles and associated with muscle weakness, wasting and fatigability. Glucocorticoids, irrespective of the route administered (inhaled, oral or intra-venous), have shown to be associated with myopathy ²⁻⁷. The mechanisms of GIM have been linked to the decline in protein synthesis (anti-anabolic action) and the rise in the catabolic rate of protein breakdown (catabolic action) ⁸. These mechanisms can consequently lead to the loss of muscle strength and mass ⁷.

In rheumatology, glucocorticoids are the backbone of the management for a number of inflammatory-mediated disorders. In many cases, they are used only for short periods and at a relatively low dose. However, more serious conditions such as giant cell arteritis (GCA) require much higher doses and for longer periods of more than six months. Proven et al.⁹ prospectively assessed 125 GCA patients for muscle weakness (based on the physician's diagnosis supported by physical examination of proximal muscles) and reported that "most patients" developed muscle weakness (exact incidence and severity were not mentioned). Currently, the identification of muscle involvement is largely based on patient reported symptoms and physical evidence of weakness in the hip girdle and proximal thigh muscles using manual muscle testing methods ^{10,11}. However, the diagnosis and monitoring of GIM may be challenging as these features may be non-specific and poorly sensitive to change.

A recent review by Minetto et al. ¹⁰ has highlighted the importance of quantitative tests and the lack of predictive and prognostic tools for the steroid myopathic process. The available tests are either invasive or lack feasibility at the bedside with respect to time and availability. Imaging studies employing ultrasound, CT or MRI are limited but generally focus on morphological changes and muscle mass ⁴. In contrast, shear wave elastography (SWE), a relatively new ultrasound technology, offers the opportunity to evaluate a different method of evaluating muscle through its ability to objectively measure tissue stiffness ¹². A role for SWE has previously been established for the management of various liver, thyroid and breast pathologies ¹². Muscle stiffness increases proportionally with muscle force, and SWE have demonstrated reliable readings for determining this proportionality ¹³. It was also a sensitive biomarker in identifying patients with peripheral muscle weakness ¹⁴.

Histological evidence supports a hypothesis of altered muscle stiffness in GIM ^{15,16}. However, relatively little research has been conducted on muscle SWE and to our knowledge, there have been none in GIM. Moreover, limited research has evaluated a combined assessment of muscle mass, strength and performance as recommended in the diagnostic workup of GIM ¹⁰. Investigating the combination of these muscle aspects in patients taking high steroid doses could provide new insights into the mechanism of GIM development. Therefore, the main aim of this study was to investigate the responsiveness of muscle stiffness as measured by SWE and physical strength tests in patients exposed to high doses of glucocorticoid treatment.

Patients and Methods

Study design

This study was conducted as a longitudinal cohort study at Leeds Teaching Hospitals in the UK between May 2017 to October 2018. Patients with giant cell arteritis were first seen up to 14 days post-treatment initiation (baseline (visit 1)) then followed up after three (visit 2) and six months (visit 3), with deviations of up to 15 days allowed. These follow-up time points were selected based on the expected onset of early signs of myopathy⁶. Patients were compared at baseline to age and gender frequency-matched healthy controls to evaluate their muscle characteristics.

The study had been approved by the Nottingham UK research ethics committee (Reference: 17/EM/0079; approved April 2017) and written informed consent was obtained from all participants. No formal sample size/power calculations have been carried out due to a lack of available data. However, to estimate parameters for powering future research on GIM, published rules of thumb recommend a minimum of 12 subjects per group of interest to provide a reasonable effect size estimate^{17, 18}.

Patients

The inclusion criteria for the patients were: 1- 50 years or older; 2- suspected or diagnosed with GCA as determined by the clinician, and fulfilling the American College of Rheumatology (ACR) classification criteria for GCA¹⁹; 3- due to start or started (≤ 14 days) on prednisolone (≥ 40 mg/day). Exclusion criteria were: 1- presence or history of any muscle condition; 2- glucocorticoid treatment > 5 mg/day for more than three months in the past five years; 3- Taking glucocorticoids for a chronic obstructive pulmonary disease for more than six months in the past five years. Healthy controls were eligible if they were asymptomatic, not been treated with glucocorticoid at any dose in the past five years and did not have a history of any muscle condition.

Patients were commenced on prednisolone 40–60 mg/day according to the established guidelines²⁰. The glucocorticoids were rapidly tapered to stop the treatment if the subsequent temporal biopsy results were negative and the clinical suspicion was not high. Otherwise, the patient continued on the glucocorticoid regimen and gradually tapered (unless relapse occurred) according to the management guidelines²⁰ as follows:

1. Initial prednisolone dose (40–60 mg/day) continued for four weeks until resolution of symptoms and laboratory abnormalities.
2. Dose reduced by 10 mg every two weeks to 20 mg.
3. Then reduced by 2.5 mg every 2–4 weeks to 10 mg.
4. Then reduced by 1 mg every 1–2 months provided there is no relapse.

Clinical characteristics

Relevant patient characteristics were collected including age, sex, body mass index (BMI). Additionally, muscle mass and fat mass were analyzed using a bioelectrical impedance analyzer [Tanita DC-430 MA (Tanita Europe B.V., Manchester, UK)]. Moreover, cumulative dose of glucocorticoids and mean daily dosage were noted. The previous and following variables were assessed at each visit.

Shear wave elastography

The operated SWE system was the two-dimensional Aixplorer (Supersonic Imagine, Aix-en-Provence, France) system using the SuperLinear™ SL10--2MHz probe, which has demonstrated a substantial reliability in muscle SWE in our previous work²¹. The principle of SWE is available elsewhere¹². Briefly, the ultrasound machine sends a strong acoustic pulse that deforms the tissue and induce the propagation of

relatively slow-travelling shear waves. The machine then sends tracking waves to detect the velocity of the shear waves in meters/seconds (m/s), which can be used as a surrogate for tissue stiffness¹². The muscle SWE acquisition technique was adapted from our previous work²¹⁻²³. The probe was oriented along the muscle fibers and placed with minimal load on skin to avoid causing tissue deformation.

The scanned muscles included the quadriceps [vastus lateralis (VL), rectus femoris (RF), vastus medialis (VM) and vastus intermedius (VI)], the hamstrings [biceps femoris (BF), semitendinosus (ST) and semimembranosus (SM)] and the biceps brachii (BB). Selecting these muscles was based on the evidence indicating GIM prevalence in the proximal thigh muscles¹¹. However, we also scanned the BB to test the involvement in upper body muscles. The muscles were scanned in a relaxed resting position with no active contraction. The quadriceps were also scanned with the knee flexed at 90° in a sitting position to assess the muscles' passive elastic property. Only the dominant side was assessed due to time constraints and the previous evidence reporting pronounced muscle atrophy at the dominant leg in patients with GIM²⁴.

Muscle strength measurements

Isometric handgrip strength was measured while sitting using the handheld Jamar Plus+ electronic dynamometer (Lafayette Instrument Company, Lafayette, USA) by calculating the average of three measurements of the dominant hand in units of kilogram-force (kg_F)²⁵. Next, the expanded timed get-up-and-go (ETGUG) test was conducted, which involves recording the time to stand from a chair, walk 10 meters, turn around, walk back and sit down²⁶. The participants then performed the 30-second chair stand test (maximum number of chair stands in 30 seconds)²⁷.

Lastly, isokinetic concentric knee extension/flexion in the sitting position was tested using the Biodex system 4 (IRPS Mediquipe, UK). Previous evidence showed that this test demonstrated diminished strength in GIM²⁸. We chose to investigate concentric strength based on evidence showing that eccentric muscle strength can be preserved in diseases associated with sarcopenia and weakness²⁹. After warm-up of three sets at 50% effort, the participants performed three sets of three knee extension and flexion repetitions at 100% effort separated by a 30 sec rest period between the sets at 60°/sec angular velocity³⁰. The isokinetic strength outcomes of interest were the weight-normalised peak torque [Newton-meters (Nm)] to represent muscle strength (maximum force generated) and weight-normalised average power (Watts) to represent muscle power (work done per unit of time). The trial runs before the final tests provided sufficient test familiarization. The participants were encouraged to perform their best during testing.

Statistical analysis

Descriptive statistics are expressed as frequencies for categorical data and as means (standard deviations) or medians for continuous data depending on the distribution. Independent sample t-test was employed to test for difference between healthy controls and patients at the baseline.

The difference in SWV between the timepoints was correlated with the differences in muscle strength and functional tests using the Pearson's correlation coefficients. This analyzed whether the longitudinal changes in SWV are associated with changes in muscle strength and function. The effect of cumulative glucocorticoid dose at 3 and 6 months on SWV changes of each patient was plotted in a line chart.

The longitudinal data for the GCA patients were analyzed using linear mixed models to test if SWV significantly changes after three and six months of glucocorticoid treatment following previously described methods³¹. The model was initially conducted as an unconditional base growth model then repeated in a second model after adding the time variable to determine if adding the follow-up visits will result in a significantly better model fit by comparing their -2 log likelihood (-2LL).

~~The tests were conducted and reported on each muscle separately.~~ Considering the small sample size, the data was also re-analysed using non-parametric methods and reported as supplementary material. The results showed the same findings as the parametric methods. We report the parametric results in the main text as our data satisfied the related assumptions and the fact that the same variables collected on a larger group were normally distributed³². ~~The tests were conducted and reported on each muscle separately.~~ A ~~n~~ alpha level (p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25 (Armonk, NY: IBM Corp).

Results

Seventy-nine patients with GCA were invited to take part in the study; 20 patients met the criteria and agreed to take part in the study; 6 were lost before the 3-month follow-up. Therefore, a total of 14 patients formed the basis of this study and were followed-up. The flowchart in Figure 1 highlights the recruitment timeline including the 7 patients dropped out before the 6-months visit.

The mean \pm SD age \pm SD of the GCA cohort was 68.2 ± 4.3 years (range 61.3–76.5) with ten (71%) of the cohort being female. The patient characteristics and glucocorticoid information are listed in [Table 1](#)~~Table 1~~. They were recruited on average seven days (range -1 to 12 days) after commencing glucocorticoid treatment. The mean (SD, range) cumulative prednisolone dose was 2701 mg (619, 2280–4190) and 4233 (926, 2962–5632) at 3 and 6 months respectively.

Half of the patients had a positive temporal artery biopsy, one refused the procedure and the remaining six had a negative biopsy but were clinically diagnosed as GCA (strong clinical symptoms and rapid response to prednisolone). None of the patients complained of limb claudication. Two patients presented with symptoms of polymyalgia rheumatica (both had positive temporal biopsies). Two patients had hypertension, one had prostate hypertrophy and one had hypothyroidism. Additional prescribed medications included alendronic acid (n=7), omeprazole (n=3), Calceos (n=3), vitamin D (n=1), lansoprazole (n=1), aspirin (n=1), co-codamol (n=1) and levothyroxine (n=1).

The patients and controls were frequency matched for age, sex, BMI and other body characteristics. In the muscle assessments, the GCA patients performed generally less well than controls; however, for most variables this difference did not reach statistical significance (supplementary table 1).

Shear wave elastography

The baseline SWE readings for the GCA patients were not significantly different from the healthy control group across all muscles (supplementary table 2). For the patients, the mean and differences in SWV between the visits are listed in [Table 2](#)~~Table 2~~ ([see supplementary table 3 for the non-parametric analysis](#)). These results are graphically illustrated in the line charts for the muscles in the resting position in Figure 2-a and during passive stretching in Figure-2-b. In general, significant and consistent reductions were noted in the resting SWV measurements (Figure 2-a); the quadriceps readings under passive stretching showed greater variability (Figure 2-b).

From baseline to 3 months, and to 6 months, there was a general reduction in SWV in all the leg muscles, but not in the arm muscle (biceps brachii). During the resting position in the quadriceps and hamstrings, SWV decreased by a mean of 14% (range 8.3% – 17.3%) after 3 months and 18% (range 10.2% – 25.3%) after 6 months ([Table 2](#)~~Table 2~~). SWE image examples from the quadriceps, hamstrings and BB are displayed in Figure 3. The two patients with PMR symptoms did not exhibit any different patterns compared to others.

In the mixed linear models, adding the fixed effect of glucocorticoid consumption timepoints (baseline, 3-months and 6-months) had significant p-values for explaining longitudinal variations in SWV: $p < 0.005$ in VL, $p < 0.001$ in RF, $p = 0.005$ in VM, $p < 0.001$ in VI, $p < 0.001$ in BF, $p < 0.001$ in ST, $p = 0.001$ in SM and $p = 0.028$ in stretched VI. However, it did not explain a significant linear change in the BB ($p = 0.98$), stretched VL ($p = 0.51$), stretched RF ($p = 0.18$) and stretched VM ($p = 0.18$). The full list of the models

with the model fits (-2LL) and estimates for all muscles are provided in supplementary table [34](#).

The cumulative steroid dose did not affect the magnitude of change in SWV. In other words, receiving a high cumulative glucocorticoid dose did not result in a greater change in SWV and vice versa. Profiles of relative change plotted as a function of cumulative glucocorticoid dose received for each patient can be reviewed in supplementary figure 1.

Muscle assessments

The longitudinal data for the muscle assessments are described in [Table 3](#)~~Table-3~~ [\(see supplementary table 5 for the non-parametric analysis\)](#). The results show unremarkable fluctuations in body composition. Functional and strength performances remained generally similar to baseline. Pearson's correlation coefficients were used to evaluate the association between SWV and muscle performance differences at the 3 months follow-up visit. The difference at 3-months for the isokinetic knee extension strength correlated significantly with SWV differences in VL, VI and SM with coefficients (p-value) of 0.54 (0.048), 0.69 (0.006) and 0.60 (0.022) respectively. For the isokinetic knee extension power, the correlation coefficients (p-value) for the same muscles were 0.55 (0.041), 0.68 (0.007) and 0.50 (0.049) respectively. Weaker grip strength after 3-months correlated with lower SWV for ST ($r=0.56$; $p=0.009$). The correlation coefficients for changes between the other muscles and tests were generally weak ($r < 0.30$) or insignificant ($p > 0.05$). The full correlation results can be referred to in supplementary table [46 and 7](#). The small number of patients followed-up after 6 months ($n=7$) did not permit a meaningful correlation analysis as the coefficients can be easily influenced by outliers.

Discussion

The aim of this study was to investigate muscle stiffness changes in patients receiving high doses of glucocorticoids after 3 and 6-months. To our knowledge, this is the first study to conduct this type of quantitative analysis. Half of the 14 recruited patients were lost in the last 6 months follow-up visit, where little subsequent drop in muscle stiffness was observed. The main result indicates that the proximal lower limb muscles of GCA patients can lose on average 15% and up to one-quarter of its stiffness after being exposed to high glucocorticoid dose therapy for 3 and 6-months. Additionally, this loss correlated with changes in muscle strength. However, the cumulative dose of glucocorticoids received either at 3 or 6 months was not related to the magnitude of the detected stiffness changes. The observed change in muscle stiffness might be explained by the microscopic morphological alterations induced by the catabolic and anti-anabolic effects of glucocorticoids on skeletal muscle ^{15, 16}.

~~No studies thus far have been conducted to~~ [There is a lack of studies](#) investigating the usefulness of SWE or similar imaging modalities for diagnosis or monitoring of GIM on humans. Nonetheless, the findings are in line with a recent preclinical study on rats, which demonstrated a significant reduction in muscle stiffness after glucocorticoid treatment ³³. Their reported reduction of 10% is close to the mean change of 15% in this study regardless of the relatively different follow-up durations. They also stated that dosage (100ug/100g vs 50ug/100g) did not influence muscle stiffness which is in agreement with the presented results.

A recent case study of Cushing's syndrome myopathy suggested the usefulness of muscle echo intensity as a recovery sign after resolution of the hypercortisolemic state ³⁴. Moreover, Nawata et al. ⁴ recently used computed tomography and showed a significant reduction in muscle mass ($p=0.039$) in a mixed group of patients taking glucocorticoids (>30 mg/day) for an average of three months. The usefulness of computed tomography, however, is complicated by the cost and exposure to ionizing radiation.

For prolonged high-dose glucocorticoid exposure, the reported prevalence of GIM is remarkably variable in the literature ranging from 2% to 60% ^{2, 3, 24}. In these studies, there was no significant muscle weakness observed in the follow-up visits suggestive of GIM. To the contrary, patients performed on average better after 3 and 6 months, except for the number of chair stands that decreased gradually at follow-up visits. Nawata et al. ⁴ also reported an improvement in muscle strength after 3-months of glucocorticoid treatment despite a significant reduction in muscle volume.

In the present study, the changes in muscle strength were significantly associated with changes in muscle stiffness whereby patients who performed worse in the follow-ups lost more muscle stiffness. At baseline, the patients presented with headache and pain due to the GCA symptoms and were generally feeling lethargic. This may have diminished their actual physical performance in the muscle assessments. Indeed, the self-reported general state of health rating (VAS scores in [Table 3](#)) improved gradually at the follow-ups. Furthermore, they performed on average worse than the healthy controls at baseline. It is possible that if the patients' baseline muscle performance was normal, the correlations between SWV and muscle assessment differences would have been stronger and more consistent. It is worth noting that despite the age of the participants, it is unlikely that any of them has sarcopenia that could have affected the measurements, as the muscle strength and stiffness

measurements are appropriate for age when compared to a non-sarcopenic population ³².

Steroid-induced atrophy seems to affect glycolytic fast-twitch fibers (i.e. type IIb) ¹⁶. The BB has a high proportion (>60%) of type II fibers ³⁵ compared to a balanced ratio in the quadriceps and hamstrings. This knowledge does not support the current results of preserved muscle stiffness in BB and diminished stiffness in quadriceps and hamstrings. The reason behind the differences is therefore not clear. Overall, the VL and BF demonstrated the least variability and most consistent significant changes between all time points. Moreover, the muscle stiffness changes were observed during resting and passive stretched positions. However, the readings variation during passive stretching was large, and the changes were less consistent compared to the resting position.

Clinically, the tools to monitor or diagnose GIM are extremely limited and inadequate. EMG does not offer positive findings until late chronic stages of GIM ¹⁰. Muscle enzymes such as CK and aldolase usually appear within normal limits. Muscle biopsy can show signs of type IIb myofibre atrophy but is not feasible as a monitoring tool. No evidence has previously demonstrated the clinical usefulness for quantitative or qualitative MRI imaging in GIM.

The clinical goal in GIM is to detect any myopathic changes prior to their manifestation to help taper the glucocorticoid dose promptly. This focuses on the prevention of GIM rather than identifying it at later stages when atrophy has occurred. The presented results highlight that the muscle strength loss was marginal compared to the SWV observed differences. This may suggest that muscle stiffness alterations may precede GIM symptoms of muscle weakness.

The small sample size is acknowledged as a major limitation of the results. Additionally, half of the patients dropped out between 3 and 6 months. An attempt to improve the overall statistical power was made by employing multilevel modelling statistics ³⁶. It was not feasible to study the patients before commencing treatment as the management guidelines recommend immediate start of glucocorticoids ²⁰. Our aim was to follow-up the GCA cohort; hence the control group was only tested at the baseline to confirm the normal state of GCA muscles. We did not evaluate inter-operator reproducibility. However, the decreasing trend observed on most muscles suggests that the changes were not merely due to day-to-day reading variability.

Notwithstanding the above limitations, the promising findings call for future cohort studies to follow-up a larger sample of patients for a longer duration to assess if decreased muscle elasticity is a valid and reliable early sign for steroid-myopathy. To detect a 15% difference in the stiffness of VL after 3 months with 90% power and 0.05 alpha level, a future study should aim to recruit a minimum of 63 GCA patients. Assuming the preliminary results are validated by other studies, SWE had the potential of being a non-invasive clinic-based tool for monitoring and detecting early signs of the glucocorticoid-induced myopathic process. Additionally, it may aid a physician's decision to taper glucocorticoids more promptly.

In conclusion, our results show that muscle stiffness measured by SWE may become significantly reduced in GCA patients receiving high doses of glucocorticoid after 3 and 6-months of treatment. Furthermore, higher reduction in muscle stiffness correlated with worse physical performance at the follow-up visits. Future research should study the results in a larger sample of patients for a longer duration to investigate if diminished muscle stiffness precedes GIM signs of muscle weakness.

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Conflict of interest

Authors declare no conflict of interest.

Contributions

AMA, ALT, POC, PE, SM RJW: contributed to the conceptualisation and design of the study. AMA: acquired, analysed and interpreted the data then drafted the manuscript. AMA, ALT, POC, PE, SM, RJW: revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1 Clinical and glucocorticoid dose information of the patients treated with prednisolone for giant cell arteritis.

| Case No | Sex | Age, years | Starting dose, mg | Daily dose at 3m, mg | Cumulative dose at 3m, mg | Daily dose at 6m, mg | Cumulative dose at 6m, mg |
|---------|--------|------------|-------------------|----------------------|---------------------------|----------------------|---------------------------|
| 1 | Female | 76.5 | 60 | 30 | 3935 | 7.5 | 5632 |
| 2 | Male | 63.0 | 40 | 10 | 2280 | 1 | 2962 |
| 3 | Female | 66.5 | 40 | 8 | 2723 | 10 | 4422 |
| 4 | Female | 69.2 | 40 | 12.5 | 2415 | - | - |
| 5 | Female | 74.3 | 40 | 15 | 2543 | 7 | 3474 |
| 6 | Female | 61.3 | 50 | 17.5 | 4190 | - | - |
| 7 | Female | 70.4 | 40 | 15 | 2690 | 10 | 3606 |
| 8 | Female | 67.8 | 60 | 15 | 3850 | 9 | 4767 |
| 9 | Male | 65.7 | 40 | 15 | 2990 | - | - |
| 10 | Male | 65.3 | 40 | 5 | 2375 | - | - |
| 11 | Female | 70.5 | 40 | 10 | 2712 | - | - |
| 12 | Female | 71.2 | 40 | 12.5 | 2528 | 17.5 | 4770 |
| 13 | Female | 69.5 | 40 | 15 | 2680 | - | - |
| 14 | Male | 63.7 | 60 | 60 | 3080 | - | - |

3m= three months. 6m= six months. The dashes indicate data unavailability.

Table 2 Mean muscle shear wave velocity at each visit in the patients treated with glucocorticoids for giant cell arteritis.

| Muscle | Baseline | | 3 Months (n=14) | | | 6 Months (n=7) | | | Difference to baseline |
|---------------------|-------------|------------|-----------------|------------|-------------------------------------|----------------|------------|----------------------------------|-------------------------------------|
| | Mean (SD) | 95% CI | Mean (SD) | 95% CI | Difference to baseline | Mean (SD) | 95% CI | Difference to 3 months | |
| Vastus lateralis | 1.62 (0.16) | 1.52, 1.71 | 1.40 (0.10) | 1.35, 1.46 | -0.22 (-13.6%) p<0.001 | 1.31 (0.06) | 1.26, 1.36 | -0.09 (-6.4%) p=0.037 | -0.31 (-19.1%) p<0.001 |
| passively stretched | 2.67 (0.33) | 2.46, 2.88 | 2.66 (0.33) | 2.46, 2.86 | -0.01 (-0.4%) p=0.96 | 2.50 (0.34) | 2.19, 2.81 | -0.16 (-6%) p=0.91 | -0.17 (-6.4%) p=0.30 |
| Rectus femoris | 1.68 (0.11) | 1.62, 1.74 | 1.54 (0.13) | 1.47, 1.62 | -0.14 (-8.3%) p=0.010 | 1.41 (0.15) | 1.28, 1.55 | -0.13 (-8.4%) p=0.25 | -0.27 (-16.1%) p=0.002 |
| passively stretched | 2.28 (0.63) | 1.87, 2.68 | 1.99 (0.28) | 1.82, 2.16 | -0.29 (-12.7%) p=0.08 | 2.05 (0.11) | 1.95, 2.15 | 0.06 (3%) p=0.99 | -0.23 (-10.1%) p=0.16 |
| Vastus Medialis | 1.70 (0.33) | 1.51, 1.88 | 1.36 (0.12) | 1.29, 1.43 | -0.34 (-20%) p=0.001 | 1.41 (0.15) | 1.27, 1.55 | 0.05 (3.7%) p=0.99 | -0.29 (-17.1%) p=0.012 |
| passively stretched | 2.41 (0.28) | 2.23, 2.59 | 2.30 (0.22) | 2.17, 2.43 | -0.11 (-4.6%) p=0.07 | 2.30 (0.15) | 2.16, 2.43 | 0 (0%) p=1.00 | -0.11 (-4.6%) p=0.18 |
| Vastus Intermedius | 1.96 (0.33) | 1.77, 2.15 | 1.62 (0.19) | 1.51, 1.73 | -0.34 (-17.3%) p<0.001 | 1.76 (0.22) | 1.56, 1.96 | 0.14 (8.6%) p=0.030 | -0.20 (-10.2%) p=0.26 |
| passively stretched | 2.42 (0.22) | 2.28, 2.56 | 2.37 (0.34) | 2.16, 2.58 | -0.05 (-2.1%) p=0.39 | 2.08 (0.34) | 1.77, 2.39 | -0.29 (-12.2%) p=0.08 | -0.34 (-14%) p=0.013 |
| Biceps Brachii | 1.83 (0.30) | 1.66, 2.01 | 1.82 (0.18) | 1.72, 1.93 | -0.01 (-0.5%) p=0.94 | 1.84 (0.28) | 1.58, 2.10 | 0.02 (1.1%) p=0.99 | 0.01 (0.5%) p=0.92 |
| Biceps Femoris | 1.62 (0.17) | 1.52, 1.72 | 1.37 (0.09) | 1.31, 1.42 | -0.25 (-15.4%) p<0.001 | 1.21 (0.10) | 1.12, 1.31 | -0.16 (-11.7%) p=0.022 | -0.41 (-25.3%) p<0.001 |
| Semitendinosus | 1.58 (0.15) | 1.49, 1.66 | 1.36 (0.08) | 1.31, 1.41 | -0.22 (-13.9%) p<0.001 | 1.26 (0.08) | 1.18, 1.33 | -0.10 (-7.4%) p=0.043 | -0.32 (-20.3%) p<0.001 |
| Semimembranosus | 1.59 (0.15) | 1.51, 1.68 | 1.41 (0.11) | 1.34, 1.47 | -0.18 (-11.3%) p<0.001 | 1.35 (0.10) | 1.26, 1.44 | -0.06 (-4.3%) p=0.66 | -0.24 (-15.1%) p<0.001 |

p-values computed using linear mixed models from the significance of difference estimates at 3 and 6-months. p-values significant at 95% are in bold

Table 3 Clinical and muscle assessment results at each visit for the patients treated with glucocorticoids for giant cell arteritis.

| Variable | Baseline | 3 Months (n=14) | | 6 Months (n=7) | | |
|-------------------------------|--------------|-----------------|------------------------|----------------|------------------------|------------------------|
| | Mean (SD) | Mean (SD) | Difference to baseline | Mean (SD) | Difference to 3 months | Difference to baseline |
| Weight (kg) | 75.5 (16.8) | 77.6 (16.4) | 2.1 (2.8%) | 75.2 (15.1) | -2.4 (-3.1%) | -0.3 (-0.4%) |
| Body mass index (BMI) | 27.1 (4.0) | 27.9 (4.2) | 0.8 (2.9%) | 28.0 (4.3) | 0.1 (0.3%) | 0.9 (3.3%) |
| Fat mass (kg) † | 29.0 (13–31) | 28.5 (21–31) | -0.5 (-1.7%) | 27.1 (22–32) | -1.4 (-4.9%) | -1.9 (-6.5%) |
| Muscle mass (kg) † | 45.0 (38–52) | 46.6 (42–55) | 1.6 (3.6%) | 45.5 (41–47) | -1.1 (-2.4%) | 0.5 (1.1%) |
| Muscle mass index | 16.8 (1.8) | 17.5 (2.1) | 0.7 (4.2%) | 17.3 (2.1) | -0.2 (-1.1%) | 0.5 (3.0%) |
| Visual score of health (mm) † | 25 (10–40) | 19 (8–46) | -6 (-24%) | 15 (4–21) | -4 (-21.0%) | -10 (-40%) |
| ETGUGT, Total time (sec) * | 21.0 (5.7) | 21.2 (6.3) | 0.2 (0.9%) | 19.3 (5.4) | -1.9 (-9.0%) | -1.7 (-8.1%) |
| 30 sec chair sit-to-stands | 12.2 (6.5) | 11.0 (4.5) | -1.2 (-9.8%) | 10.7 (2.4) | -0.3 (-2.7%) | -1.5 (-12.3%) |
| Handgrip strength (kg) | 25.9 (13.2) | 26.7 (12.7) | 0.8 (3.10%) | 28.8 (11.3) | 2.1 (7.9%) | 2.9 (11.2%) |
| Knee extension torque (Nm/kg) | 1.03 (0.34) | 1.04 (0.33) | 0.01 (1.0%) | 1.07 (0.40) | 0.03 (2.9%) | 0.04 (3.9%) |
| Knee flexion torque (Nm/kg) | 0.53 (0.22) | 0.60 (0.25) | 0.07 (13.2%) | 0.63 (0.16) | 0.03 (5.0%) | 0.1 (18.9%) |
| Knee extension power (W/kg) | 0.57 (0.24) | 0.56 (0.26) | -0.01 (1.8%) | 0.57 (0.24) | 0.01 (1.8%) | 0 (0%) |
| Knee flexion power (W/kg) | 0.29 (0.15) | 0.34 (0.17) | 0.05 (17.2%) | 0.34 (0.09) | 0 (0%) | 0.05 (17.2%) |

† Median and interquartile range. * Other ETGUG test components had similar trends and were therefore omitted.

Figure legends

Fig 1 A flowchart of participant screening, recruitment and follow-up

Fig 2 Muscle stiffness changes in the GCA patients during the resting position (a) and for the quadriceps during passive stretching (b)

Fig 3 Longitudinal shear wave elastography examples with velocity readings highlighting a significant reduction with time in the VL and VF compared to the insignificant change in BB

Supplementary material

Supplementary Table 1. Demographics and baseline characteristics of the GCA patients and healthy controls.

| Characteristic | GCA patients* | Healthy controls* | p-value‡ |
|---|---------------------------|----------------------------|--------------|
| Sex | 10 Females (71%) | 10 Females (71%) | 1.00 |
| Age (years) | 68.2 (4.3) | 68.0 (6.0) | 0.91 |
| Height (cm) | 166.3 (11.9) | 163.8 (8.7) | 0.53 |
| Weight (kg) | 75.4 (16.8) | 72.1 (9.7) | 0.52 |
| Body mass index (BMI) | 26.6 (4.3) | 27.0 (4.5) | 0.79 |
| Waist-hip ratio | 0.90 (0.09) | 0.90 (0.10) | 0.95 |
| Fat mass † | 28.9 (13.8–31.8) | 27.3 (24.4–29.3) | 0.66 |
| Muscle mass † | 44.9 (37.7–52.0) | 42.7 (38.6–44.2) | 0.53 |
| Muscle mass index | 16.8 (1.8) | 17.0 (2.5) | 0.83 |
| Ever smoked (yes) | 7 (50%) | 9 (64%) | 0.44 |
| Smoking pack-years † | 12.0 (7.5–45.0) | 8.8 (2.0–33.0) | 0.63 |
| Drinking alcohol consumption (units/week) † | 5 (35%) 2.0 (1.0–13.0) | 5 (35%) 10.0 (1.5–38.0) | 1.00 0.07 |
| Visual analogue score of health (mm) † | 25 (10–40) | 4.5 (1–18) | 0.07 |
| ETGUGT, sit to stand (sec) | 1.4 (0.4) | 1.2 (0.4) | 0.24 |
| ETGUGT, Gait initiation (sec) | 1.1 (0.5) | 0.9 (0.3) | 0.37 |
| ETGUGT, Walk 1 (sec) | 5.4 (1.6) | 4.2 (1.0) | 0.027 |
| ETGUGT, Turn around (sec) | 3.8 (1.1) | 3.4 (1.4) | 0.44 |
| ETGUGT, Walk 2 (sec) | 5.4 (1.6) | 4.5 (1.0) | 0.09 |
| ETGUGT, Slow, stop (sec) | 3.2 (0.9) | 2.8 (0.8) | 0.16 |
| ETGUGT, Total time (sec) | 21.0 (5.7) | 17.0 (3.3) | 0.038 |
| 30 sec chair sit-to-stands | 12.2 (6.5) | 16.1 (3.9) | 0.06 |
| Handgrip strength (kg) | 25.9 (13.2) | 29.7 (11.0) | 0.42 |
| Knee extension torque (Nm/kg) | 1.03 (0.33) | 1.18 (0.33) | 0.23 |
| Knee flexion torque (Nm/kg) | 0.53 (0.21) | 0.68 (0.22) | 0.07 |
| Knee extension power (W/kg) | 0.57 (0.24) | 0.71 (0.18) | 0.09 |
| Knee flexion power (W/kg) | 0.29 (0.15) | 0.40 (0.12) | 0.032 |

* Data presented as mean and standard deviation unless otherwise stated.

† Median and interquartile range.

‡ p-values significant at 95% are highlighted in bold. Continuous variables tested via independent t-test or Mann-Whitney, and categorical data tested using Chi-square test.

Supplementary table 2. Shear wave elastography readings at the baseline for the GCA patients compared to healthy.

| Muscle | GCA patients | | Healthy controls | | Difference | 95% CI of the difference | p-value [‡] |
|-------------------------|--------------|------------|------------------|------------|------------|--------------------------|----------------------|
| | Mean* | 95% CI | Mean* | 95% CI | | | |
| Vastus lateralis (VL) | 1.62 (0.16) | 1.52, 1.71 | 1.68 (0.20) | 1.56, 1.79 | 0.06 | -0.08, 0.20 | 0.39 |
| passively stretched | 2.67 (0.33) | 2.46, 2.88 | 2.80 (0.33) | 2.60, 3.00 | 0.13 | -0.14, 0.41 | 0.33 |
| Rectus femoris (RF) | 1.68 (0.11) | 1.62, 1.74 | 1.74 (0.15) | 1.65, 1.83 | 0.06 | -0.05, 0.16 | 0.28 |
| passively stretched | 2.28 (0.63) | 1.87, 2.68 | 2.19 (0.26) | 2.03, 2.35 | -0.09 | -0.48, 0.31 | 0.66 |
| Vastus Medialis (VM) | 1.70 (0.33) | 1.51, 1.88 | 1.60 (0.18) | 1.48, 1.71 | -0.10 | -0.31, 0.11 | 0.34 |
| passively stretched | 2.41 (0.28) | 2.23, 2.59 | 2.36 (0.21) | 2.23, 2.49 | -0.05 | -0.25, 0.16 | 0.63 |
| Vastus Intermedius (VI) | 1.96 (0.33) | 1.77, 2.15 | 1.85 (0.11) | 1.79, 1.92 | -0.11 | -0.30, 0.09 | 0.26 |
| passively stretched | 2.42 (0.22) | 2.28, 2.56 | 2.40 (0.28) | 2.23, 2.57 | -0.02 | -0.23, 0.19 | 0.85 |
| Biceps Brachii (BB) | 1.83 (0.3) | 1.66, 2.01 | 1.87 (0.23) | 1.74, 2.00 | 0.04 | -0.17, 0.25 | 0.71 |
| Biceps Femoris (BF) | 1.62 (0.17) | 1.52, 1.72 | 1.65 (0.22) | 1.52, 1.78 | 0.03 | -0.12, 0.18 | 0.69 |
| Semitendinosus (ST) | 1.58 (0.15) | 1.49, 1.66 | 1.65 (0.24) | 1.51, 1.78 | 0.07 | -0.09, 0.22 | 0.37 |
| Semimembranosus (SM) | 1.59 (0.15) | 1.51, 1.68 | 1.58 (0.13) | 1.51, 1.66 | -0.01 | -0.12, 0.10 | 0.81 |

* Data in m/s with standard deviation. † Results are based on independent sample t-test.

Supplementary table 3. Median muscle shear wave velocity at each visit in the patients treated with glucocorticoids for giant cell arteritis.

| Muscle | Baseline | | 3 Months (n=14) | | | 6 Months (n=7) | | | Difference to baseline |
|--------|----------|---------------------|-----------------|---------------------|------------------------|----------------|---------------------|------------------------|------------------------|
| | Median | interquartile range | Median | interquartile range | Difference to baseline | Median | interquartile range | Difference to 3 months | |

| | | | | | | | | | |
|----------------------------|-------------|--------------------|-------------|--------------------|-----------------------|-------------|--------------------|-----------------------|-----------------------|
| <u>Vastus lateralis</u> | <u>1.60</u> | <u>[1.52–1.73]</u> | <u>1.37</u> | <u>[1.33–1.43]</u> | <u>-0.23 (-14.4%)</u> | <u>1.31</u> | <u>[1.29–1.35]</u> | <u>-0.06 (-4.4%)</u> | <u>-0.29 (-18.1%)</u> |
| <u>passively stretched</u> | <u>2.65</u> | <u>[2.37–2.91]</u> | <u>2.67</u> | <u>[2.47–2.90]</u> | <u>0.02 (0.8%)</u> | <u>2.58</u> | <u>[2.44–2.69]</u> | <u>-0.09 (-3.4%)</u> | <u>-0.07 (-2.6%)</u> |
| <u>Rectus femoris</u> | <u>1.68</u> | <u>[1.63–1.72]</u> | <u>1.49</u> | <u>[1.44–1.60]</u> | <u>-0.19 (-11.3%)</u> | <u>1.42</u> | <u>[1.36–1.46]</u> | <u>-0.07 (-4.7%)</u> | <u>-0.26 (-15.5%)</u> |
| <u>passively stretched</u> | <u>2.10</u> | <u>[1.90–2.22]</u> | <u>1.91</u> | <u>[1.82–2.09]</u> | <u>-0.19 (-9%)</u> | <u>2.06</u> | <u>[2.05–2.12]</u> | <u>0.15 (7.9%)</u> | <u>-0.04 (-1.9%)</u> |
| <u>Vastus Medialis</u> | <u>1.70</u> | <u>[1.59–1.82]</u> | <u>1.37</u> | <u>[1.31–1.44]</u> | <u>-0.28 (-17%)</u> | <u>1.37</u> | <u>[1.27–1.50]</u> | <u>0 (0%)</u> | <u>-0.28 (-17%)</u> |
| <u>passively stretched</u> | <u>2.41</u> | <u>[2.30–2.48]</u> | <u>2.24</u> | <u>[2.17–2.39]</u> | <u>-0.17 (-7.1%)</u> | <u>2.28</u> | <u>[2.15–2.47]</u> | <u>0.04 (1.8%)</u> | <u>-0.13 (-5.4%)</u> |
| <u>Vastus Intermedius</u> | <u>1.98</u> | <u>[1.74–2.16]</u> | <u>1.62</u> | <u>[1.51–1.73]</u> | <u>-0.36 (-18.2%)</u> | <u>1.79</u> | <u>[1.64–1.99]</u> | <u>0.17 (10.5%)</u> | <u>-0.19 (-9.6%)</u> |
| <u>passively stretched</u> | <u>2.38</u> | <u>[2.21–2.65]</u> | <u>2.34</u> | <u>[2.16–2.54]</u> | <u>-0.04 (-1.7%)</u> | <u>2.10</u> | <u>[1.78–2.37]</u> | <u>-0.24 (-10.3%)</u> | <u>-0.28 (-11.8%)</u> |
| <u>Biceps Brachii</u> | <u>1.77</u> | <u>[1.65–1.92]</u> | <u>1.76</u> | <u>[1.70–1.86]</u> | <u>-0.01 (-0.6%)</u> | <u>1.76</u> | <u>[1.63–1.97]</u> | <u>0 (0%)</u> | <u>-0.01 (-0.6%)</u> |
| <u>Biceps Femoris</u> | <u>1.60</u> | <u>[1.49–1.75]</u> | <u>1.37</u> | <u>[1.30–1.42]</u> | <u>-0.23 (-14.4%)</u> | <u>1.27</u> | <u>[1.20–1.35]</u> | <u>-0.1 (-7.3%)</u> | <u>-0.33 (-20.6%)</u> |
| <u>Semitendinosus</u> | <u>1.54</u> | <u>[1.42–1.69]</u> | <u>1.35</u> | <u>[1.31–1.38]</u> | <u>-0.19 (-12.3%)</u> | <u>1.27</u> | <u>[1.24–1.30]</u> | <u>-0.08 (-5.9%)</u> | <u>-0.27 (-17.5%)</u> |
| <u>Semimembranosus</u> | <u>1.58</u> | <u>[1.47–1.73]</u> | <u>1.37</u> | <u>[1.32–1.43]</u> | <u>-0.21 (-13.3%)</u> | <u>1.34</u> | <u>[1.27–1.42]</u> | <u>-0.03 (-2.2%)</u> | <u>-0.24 (-15.2%)</u> |

Supplementary Table 34. Mixed linear models and fixed effect estimates for shear wave velocity on the various tested muscles.

| Vastus lateralis | | | |
|---|---------------|--------------|---------|
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= -18.938 | | | |
| Intercept | 1.47 (0.03) | 1.41, 1.53 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= -43.958 | | | |
| Δ fit= 25.02 p-value= <0.001 | | | |
| Intercept | 1.62 (0.04) | 1.52, 1.71 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.21 (0.05) | -0.31, -0.11 | <0.001 |
| Time=6 months | -0.30 (0.05) | -0.41, -0.20 | <0.001 |
| Time (type III test of fixed effect*) | - | - | <0.001 |
| Rectus femoris | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= -25.294 | | | |
| Intercept | 1.57 (0.03) | 1.52, 1.63 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= -36.027 | | | |
| Δ fit= 10.73 p-value= <0.05 | | | |
| Intercept | 1.68 (0.03) | 1.62, 1.74 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.14 (0.05) | -0.24, -0.04 | 0.010 |
| Time=6 months | -0.27 (0.06) | -0.41, -0.12 | 0.002 |
| Time (type III test of fixed effect) | - | - | 0.002 |
| Vastus medialis | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 12.248 | | | |
| Intercept | 1.50 (0.05) | 1.41, 1.60 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= -11.718 | | | |
| Δ fit= 23.97 p-value= <0.001 | | | |
| Intercept | 1.70 (0.09) | 1.51, 1.88 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.34 (0.08) | -0.51, -0.16 | 0.001 |
| Time=6 months | -0.28 (0.10) | -0.49, -0.07 | 0.012 |
| Time (type III test of fixed effect) | - | - | 0.005 |
| Vastus intermedius | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 17.310 | | | |
| Intercept | 1.78 (0.05) | 1.68, 1.89 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= -0.594 | | | |
| Δ fit=17.9 p-value= <0.001 | | | |
| Intercept | 1.96 (0.09) | 1.76, 2.16 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.34 (0.07) | -0.49, -0.18 | <0.001 |
| Time=6 months | -0.12 (0.10) | -0.32, 0.09 | 0.26 |

| | | | |
|--|---------------|--------------|---------|
| Time (type III test of fixed effect) | - | - | <0.001 |
| Biceps brachii | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. Fit (-2LL)= 5.630 | | | |
| Intercept | 1.83 (0.04) | 1.74, 1.92 | <0.001 |
| Model 2: (time) Fit (-2LL)= 7.819 Δ fit=2.19 p-value= >0.05 | | | |
| Intercept | 1.83 (0.08) | 1.65, 2.01 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.01 (0.09) | -0.2, 0.19 | 0.94 |
| Time=6 months | 0.01 (0.13) | -0.27, 0.30 | 0.92 |
| Time (type III test of fixed effect) | - | - | 0.98 |
| Biceps femoris | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. Fit (-2LL)= -7.065 | | | |
| Intercept | 1.44 (0.03) | 1.37, 1.51 | <0.001 |
| Model 2: (time) Fit (-2LL)= -37.098 Δ fit=30.03 p-value= <0.001 | | | |
| Intercept | 1.62 (0.05) | 1.52, 1.72 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.26 (0.05) | -0.37, -0.14 | <0.001 |
| Time=6 months | -0.41 (0.06) | -0.53, -0.29 | <0.001 |
| Time (type III test of fixed effect) | - | - | <0.001 |
| Semitendinosus | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. Fit (-2LL)= -19.407 | | | |
| Intercept | 1.42 (0.03) | 1.37, 1.48 | <0.001 |
| Model 2: (time) Fit (-2LL)= -48.795 Δ fit=29.39 p-value= <0.001 | | | |
| Intercept | 1.58 (0.04) | 1.50, 1.66 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.22 (0.03) | -0.30, -0.15 | <0.001 |
| Time=6 months | -0.34 (0.05) | -0.44, -0.23 | <0.001 |
| Time (type III test of fixed effect) | - | - | <0.001 |
| Semimembranosus | | | |
| | Estimate (SE) | 95% CI | p-value |
| Model 1: unconditional growth. Fit (-2LL)= -24.429 | | | |
| Intercept | 1.47 (0.03) | 1.42, 1.53 | <0.001 |
| Model 2: (time) Fit (-2LL)= -37.704 Δ fit=13.28 p-value= <0.025 | | | |
| Intercept | 1.59 (0.04) | 1.51, 1.68 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.19 (0.04) | -0.28, -0.09 | 0.001 |
| Time=6 months | -0.24 (0.05) | -0.35, -0.13 | <0.001 |
| Time (type III test of fixed effect) | - | - | 0.001 |
| Vastus lateralis (stretched) | | | |
| | Estimate (SE) | 95% CI | p-value |

| | | | |
|--|---------------|--------------|------------|
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 21.913 | | | |
| Intercept | 2.63 (0.06) | 2.51, 2.74 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= 24.783 | | | |
| Δ fit=2.87 p -value= >0.05 | | | |
| Intercept | 2.67 (0.09) | 2.46, 2.88 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.01 (0.13) | -0.28, 0.27 | 0.96 |
| Time=6 months | -0.17 (0.16) | -0.52, 0.17 | 0.30 |
| Time (type III test of fixed effect) | - | - | 0.51 |
| Rectus femoris (stretched) | | | |
| | Estimate (SE) | 95% CI | p -value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 40.455 | | | |
| Intercept | 2.11 (0.08) | 1.95, 2.27 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= 17.862 | | | |
| Δ fit= 22.59 p -value= <0.001 | | | |
| Intercept | 2.30 (0.17) | 1.93, 2.67 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.29 (0.15) | -0.63, 0.04 | 0.08 |
| Time=6 months | -0.25 (0.17) | -0.62, 0.11 | 0.16 |
| Time (type III test of fixed effect) | - | - | 0.18 |
| Vastus medialis (stretched) | | | |
| | Estimate (SE) | 95% CI | p -value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 0.698 | | | |
| Intercept | 2.34 (0.04) | 2.26, 2.42 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= -3.832 | | | |
| Δ fit=4.53 p -value= >0.05 | | | |
| Intercept | 2.43 (0.08) | 2.26, 2.59 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.13 (0.07) | -0.27, 0.01 | 0.07 |
| Time=6 months | -0.12 (0.09) | -0.3, 0.06 | 0.18 |
| Time (type III test of fixed effect) | - | - | 0.18 |
| Vastus intermedius (stretched) | | | |
| | Estimate (SE) | 95% CI | p -value |
| Model 1: unconditional growth. | | | |
| Fit (-2LL)= 20.815 | | | |
| Intercept | 2.33 (0.06) | 2.21, 2.44 | <0.001 |
| Model 2: (time) | | | |
| Fit (-2LL)= 8.673 | | | |
| Δ fit=12.14 p -value= <0.05 | | | |
| Intercept | 2.42 (0.06) | 2.29, 2.55 | <0.001 |
| Time=baseline | ref | ref | ref |
| Time=3 months | -0.07 (0.08) | -0.23, 0.09 | 0.39 |
| Time=6 months | -0.34 (0.11) | -0.60, -0.09 | 0.013 |
| Time (type III test of fixed effect) | - | - | 0.028 |

-2LL= -2 restricted log-likelihood (estimate of the model fit displayed in smaller-is-better form). SE= standard error. * Omnibus test of significance for the time variable. Δ fit= change in model fit [significance determined comparing the Δ fit value to the chi-square statistic critical values for 0.001 (99%), 0.025 (97.5%) and 0.05 (95%)].

Supplementary table 5. Clinical and muscle assessment results at each visit for the patients treated with glucocorticoids for giant cell arteritis (presented as medians).

| Variable | Baseline | 3 Months (n=14) | | 6 Months (n=7) | | |
|--------------------------------------|------------------|------------------|------------------------|------------------|------------------------|------------------------|
| | Median [IQR] | Median [IQR] | Difference to baseline | Median [IQR] | Difference to 3 months | Difference to baseline |
| Weight (kg) | 75.1 [63.0–88.5] | 75.3 [63.8–92.4] | 0.2 (0.27%) | 75.2 [60.7–82.3] | -0.1 (-0.13%) | 0.1 (0.13%) |
| Body mass index (BMI) | 27.9 [24.0–30.2] | 27.4 [23.4–30.7] | -0.5 (-1.79%) | 29.0 [25.3–31.9] | 1.6 (5.84%) | 1.1 (3.94%) |
| Fat mass (kg) | 28.9 [13.7–31.9] | 28.5 [19.5–31.4] | -0.4 (-1.38%) | 27.1 [21.0–33.1] | -1.4 (-4.91%) | -1.8 (-6.23%) |
| Muscle mass index | 29.0 [13–31] | 28.5 [21–31] | -0.5 (-1.7%) | 27.1 [22–32] | -1.4 (-4.9%) | -1.9 (-6.5%) |
| Muscle mass (kg) | 45.0 [38–52] | 46.6 [42–55] | 1.6 (3.6%) | 45.5 [41–47] | -1.1 (-2.4%) | 0.5 (1.1%) |
| Visual score of health (mm) | 25 [10–40] | 19 [8–46] | -6 (-24%) | 15 [4–21] | -4 (-21.0%) | -10 (-40%) |
| ETGUGT, Total time (sec)* | 21.3 [17.5–25.5] | 20.7 [18.1–24.2] | -0.6 (-2.82%) | 19 [13.4–24.0] | -1.7 (-8.21%) | -2.3 (-10.8%) |
| 30 sec chair sit-to-stands | 12 [8.7–14.5] | 11 [8.7–14.2] | -1 (-8.33%) | 11 [8.5–12.5] | 0 (0%) | -1 (-8.33%) |
| Handgrip strength (kg) | 24.0 [18.2–35.5] | 24.0 [18.4–34.6] | 0 (0%) | 27.1 [22.0–34.0] | 3.1 (12.92%) | 3.1 (12.92%) |
| Knee extension torque (Nm/kg) | 0.95 [0.81–1.29] | 0.98 [0.80–1.27] | 0.03 (3.16%) | 1.00 [0.80–1.54] | 0.02 (2.04%) | 0.05 (5.26%) |
| Knee flexion torque (Nm/kg) | 0.51 [0.35–0.75] | 0.60 [0.40–0.74] | 0.09 (17.65%) | 0.61 [0.53–0.73] | 0.01 (1.67%) | 0.1 (19.61%) |
| Knee extension power (W/kg) | 0.55 [0.35–0.75] | 0.53 [0.40–0.74] | -0.02 (-3.64%) | 0.53 [0.53–0.73] | 0 (0%) | -0.02 (-3.64%) |
| Knee flexion power (W/kg) | 0.30 [0.20–0.39] | 0.35 [0.27–0.43] | 0.05 (16.67%) | 0.35 [0.28–0.40] | 0 (0%) | 0.05 (16.67%) |

Supplementary Table 46. Correlation coefficients for the associations between SWV and muscle performance differences at the 3 months follow-up visit.

| | | VL | RF | VM | VI | BF | ST | SM |
|---|-------------|--------|-------|-------|--------|-------|--------|--------|
| ETGUGT Total time | Coefficient | -.280 | -.121 | -.008 | -.076 | .100 | -.207 | -.037 |
| | p-value | .332 | .681 | .979 | .796 | .734 | .478 | .901 |
| Number of chair sit to stands in 30 sec | Coefficient | .307* | .346* | -.039 | .092 | -.107 | .172 | .447* |
| | p-value | .286 | .225 | .895 | .755 | .715 | .556 | .109 |
| Handgrip strength | Coefficient | .429* | .417* | .184 | .112 | .206 | .559* | .111 |
| | p-value | .126 | .138 | .529 | .703 | .479 | .038 | .706 |
| Isokinetic peak torque extension | Coefficient | .535** | .293 | .452* | .692** | .38 | .450* | .606* |
| | p-value | .048 | .309 | .105 | .006 | .180 | .106 | .022 |
| Isokinetic peak torque flexion | Coefficient | -.043 | .135 | .149 | .383* | .382* | .372* | .193 |
| | p-value | .884 | .645 | .61 | .177 | .178 | .191 | .508 |
| Isokinetic mean power extension | Coefficient | .552** | .284 | .394* | .682** | .411* | .26 | .501** |
| | p-value | .041 | .326 | .164 | .007 | .144 | .369 | .049 |
| Isokinetic mean power flexion | Coefficient | .059 | .384* | .297 | .584** | .594* | .504** | .329* |
| | p-value | .842 | .175 | .302 | .028 | .025 | .066 | .250 |

* low correlation (r=0.30–0.49)

** moderate correlation (r=0.50–0.70)

Supplementary table 7. Spearman's rho correlation coefficients for the associations between SWV and muscle performance differences at the 3 months follow-up visit.

| | | <u>VL</u> | <u>RF</u> | <u>VM</u> | <u>VI</u> | <u>BF</u> | <u>ST</u> | <u>SM</u> |
|--|--------------------|--------------|--------------|-------------|---------------|--------------|--------------|--------------|
| <u>ETGUGT</u> <u>Total time</u> | <u>Coefficient</u> | <u>-.22</u> | <u>.059</u> | <u>.068</u> | <u>-.02</u> | <u>.002</u> | <u>-.349</u> | <u>-.086</u> |
| | <u>p-value</u> | <u>.45</u> | <u>.84</u> | <u>.817</u> | <u>.946</u> | <u>.994</u> | <u>.221</u> | <u>.771</u> |
| <u>Number of</u> <u>chair sit to</u> <u>stands in 30</u> <u>sec</u> | <u>Coefficient</u> | <u>.334</u> | <u>.169</u> | <u>.062</u> | <u>.073</u> | <u>.071</u> | <u>.364</u> | <u>.389</u> |
| | <u>p-value</u> | <u>.244</u> | <u>.564</u> | <u>.833</u> | <u>.803</u> | <u>.809</u> | <u>.20</u> | <u>.169</u> |
| <u>Handgrip</u> <u>strength</u> | <u>Coefficient</u> | <u>.095</u> | <u>-.033</u> | <u>.015</u> | <u>-.143</u> | <u>.064</u> | <u>.523*</u> | <u>.108</u> |
| | <u>p-value</u> | <u>.748</u> | <u>.911</u> | <u>.958</u> | <u>.626</u> | <u>.829</u> | <u>.41</u> | <u>.714</u> |
| <u>Isokinetic</u> <u>peak torque</u> <u>extension</u> | <u>Coefficient</u> | <u>.455</u> | <u>.196</u> | <u>.433</u> | <u>.723**</u> | <u>.354</u> | <u>.376</u> | <u>.582*</u> |
| | <u>p-value</u> | <u>.102</u> | <u>.503</u> | <u>.122</u> | <u>.003</u> | <u>.215</u> | <u>.185</u> | <u>.029</u> |
| <u>Isokinetic</u> <u>peak torque</u> <u>flexion</u> | <u>Coefficient</u> | <u>-.018</u> | <u>.174</u> | <u>.051</u> | <u>.323</u> | <u>.349</u> | <u>.279</u> | <u>.187</u> |
| | <u>p-value</u> | <u>.952</u> | <u>.553</u> | <u>.864</u> | <u>.26</u> | <u>.221</u> | <u>.334</u> | <u>.523</u> |
| <u>Isokinetic</u> <u>mean power</u> <u>extension</u> | <u>Coefficient</u> | <u>.601*</u> | <u>.305</u> | <u>.516</u> | <u>.705**</u> | <u>.31</u> | <u>.196</u> | <u>.459</u> |
| | <u>p-value</u> | <u>.023</u> | <u>.288</u> | <u>.059</u> | <u>.005</u> | <u>.281</u> | <u>.503</u> | <u>.098</u> |
| <u>Isokinetic</u> <u>mean power</u> <u>flexion</u> | <u>Coefficient</u> | <u>.152</u> | <u>.451</u> | <u>.262</u> | <u>.622*</u> | <u>.520*</u> | <u>.433</u> | <u>.512</u> |
| | <u>p-value</u> | <u>.604</u> | <u>.106</u> | <u>.366</u> | <u>.018</u> | <u>.49</u> | <u>.122</u> | <u>.061</u> |

* low correlation (r=0.30–0.49)

** moderate correlation (r=0.50–0.70)

Supplementary Figure 1. Change in shear wave velocity relative to the total cumulative dose received (grams) for each patient at 3 (a) and 6 (b) months.

The SWV value at the follow-up visits was subtracted from the baseline visit to give the relative change in SWV relative to baseline. These SWV difference values were then subtracted from the total cumulative dose (divided by 1000 to be in grams). This allows us to see the profile of the changes in SWV, and compare these according to how much total steroid the patient had; they start from their cumulative steroid dose and change by the amount their SWV changed over time.

|