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First pilot study of extracellular volume MRI measurement in peripheral muscle of systemic sclerosis patients suggests diffuse fibrosis

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Abstract

Objectives

Peripheral muscle involvement in systemic sclerosis (SSc) may comprise myositis or a non-inflammatory myopathy. There is little understanding on the nature of SSc myopathy. This pilot study aimed to evaluate for the presence of diffuse fibrosis in the peripheral muscle of patients with SSc by determining extracellular volume (ECV) MRI measurement.

Methods

SSc patients, with suspected myopathy or no muscle involvement, and healthy volunteers (HV) had native T1 and ECV MRI quantification of the thigh and creatine-kinase (CK) measured. Suspected myopathy was defined as current/history of minimally raised CK (<600 IU/l) +/- presence of clinical signs-symptoms (proximal muscle weakness and/or myalgia) +/- a Manual Muscle Testing score <5 in the thighs.

Results

12 SSc patients and 10 HV were recruited. 9/12 patients had limited cutaneous SSc, 4/12 interstitial lung disease, 7/12 suspected myopathy. Higher skeletal muscle ECV was recorded in SSc patients compared to HV [mean (SD) 23(11)%, vs 11(4)% p=0.04].

Peripheral muscle ECV associated with CK (rho=0.554, p=0.061) and was higher in SSc patients with myopathy compared to those with no myopathy [mean (SD) 28 (10) vs 15 (5), p=0.023]. An ECV of 22% was determined to best identify myopathy with a sensitivity of 71% and a specificity of 80%.

Conclusion

This hypothesis-generating study showed higher ECV in SSc patients compared to HV as well as association of ECV with suspected myopathy, suggesting the presence of diffuse fibrosis in the peripheral muscle of SSc patients. Further studies are needed to understand the nature of SSc myopathy.

Keywords: systemic sclerosis myopathy, extracellular volume magnetic resonance, diffuse fibrosis

Key messages:

- A first study to implement extracellular volume (ECV) MRI measurement in the peripheral muscle of SSc patients
- Higher ECV, suggesting diffuse fibrosis in SSc patients compared to controls, and in SSc patients with suspected myopathy was observed
- ECV MRI may be useful in identifying and understanding the nature of SSc peripheral muscle involvement

Introduction

Peripheral muscle involvement in systemic sclerosis (SSc; SSc myopathy) represents a significant cause of disability and is associated with increased mortality (1, 2). The prevalence of SSc myopathy ranges widely, depending on the definition and diagnostic modalities used, with estimates of between 10% to 90% (3-5). Its pathogenesis is complex and in line with SSc pathology, stigmata of microangiopathy, fibrosis and inflammation have been described at the histopathological level (3, 6).

There is no formal definition or classification criteria for SSc peripheral muscle involvement, which is partly attributable to the heterogenous nature of muscle involvement as well as the lack of new evidence investigating SSc myopathy. The majority of studies focus on the inflammatory pattern, which resembles that of dermatomyositis/polymyositis and typically subsides with immunosuppressive treatment (4, 7, 8). A non-inflammatory pattern is also recognised, being characterised by modest proximal weakness, poor endurance and mildly elevated creatine kinase (CK) levels (4, 8).

T1 mapping with extracellular volume (ECV) quantification is now widely used in cardiovascular magnetic resonance (CMR) to assess interstitial and diffuse processes, particularly diffuse fibrosis, in various cardiac pathologies. Multiple studies show good association of CMR mapping measurements with histological findings of myocardial interstitial fibrosis and increasing data demonstrate elevated CMR ECV, including in SSc (9-11) . More recently, T1 mapping and ECV measurement has been successfully applied in other pathologies and organs including the liver, spleen, kidney and brain (12-14). Higher ECV has also been demonstrated in the thoracic muscle visible at the edge of the CMR field in amyloidosis, idiopathic inflammatory myopathy as well as SSc (11, 12, 15). No studies to date have *a priori* measured ECV in the peripheral muscle of SSc patients using s dedicated protocol.

The current study aimed to assess the feasibility of ECV measurement for evaluating the presence of diffuse fibrosis in the peripheral muscle of SSc patients. The feasibility of measuring ECV in the peripheral muscle of healthy volunteers was previously undertaken and has been reported (16).

Methods

Participants

Participants were recruited from The Leeds Teaching Hospital and consented to the 'MUSCLE II study: Contrast-Enhanced MRI scan', that allowed contrast administration. The study was conducted according to the Declaration of Helsinki with approval from the Yorkshire & The Humber - Leeds East Research Ethics Committee (RR17/92933, REC ref:17/EM/0079). All participants provided written informed consent.

All patients fulfilled the 2013 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for SSc (17). Two SSc groups were included in the study: participants with no muscle involvement and participants with suspected myopathy. Suspected myopathy was defined as current/history of minimally raised CK (>320; <600 IU/l) +/- presence of clinical signs-symptoms (including proximal lower limb muscle weakness and/or myalgia) +/- a Manual Muscle Testing (MMT) 8 score <5 in the thighs. Participants with no muscle involvement were defined as SSc patients with a MMT score >5 in the thighs, with no history of raised CK or clinical features including muscle weakness or myalgia. Patients were excluded if they had a confirmed diagnosis of myositis or any known degenerative muscle disease, an immune mediated inflammatory disease (IMID) other than SSc, if they were receiving treatment with and/or equivalent of more than 5 mg of prednisolone and/or lipid lowering treatment with statins.

Ten healthy volunteers (HV) with no muscle pathology and no statin or steroid use were also recruited and had a peripheral muscle MRI with T1 measurements and ECV quantification.

Data collection

All patients had demographic and clinical data collected, including SSc subtype, disease duration, treatment, organ involvement. Patients were questioned for proximal lower limb muscle weakness and/or myalgia and muscle strength was tested by the same assessor (RBD), using the standardised

MMT 8 score (18). Routine blood tests including full blood count C-reactive protein (CRP) and creatine kinase (CK) were measured at the visit/within 4 weeks from the study visit. Any history of repeatedly minimal CK elevation (<600 IU/l) was also recorded. As part of standard care, all patients had ANA screen (multiplex flow immunoassay, Bioplex 2200) and myositis-associated antibody panel was performed upon specific clinical request. These were tested at the Leeds Teaching Hospital NHS Trust and the results retrospectively collected.

MRI protocol

Both SSc patients and HV underwent MRI imaging of the dominant thigh on a Siemens Verio 3 T scanner (Siemens Healthineers, Erlangen, Germany). The MRI protocol and image analysis has been fully described (16). T1 measurements were performed using an inversion recovery steady-state free precession sequence. Pre and 20 minutes post contrast acquisitions were acquired for the thigh and the abdominal aorta. Regions of Interest (ROI)s within the vastus intermedius and the abdominal aorta were drawn for each participant. ECV was calculated as previously reported (16).

MATLAB (MATLAB R2015a, The MathWorks Inc., Natick, MA, 2015) and ImageJ (ImageJ 1.51k, National Institute of Health, Maryland, USA) were used for image analysis.

Statistical analysis

The statistical analysis was performed using SPSS (IBM SPSS Statistics 22) and GraphPad Prism V8. Descriptive summary statistics are provided for all variables. Continuous variables are reported as mean (SD) or median (IQR) and categorical data reported as percentage. Student's t-test, chi square test, Fischer exact test or Mann-Whitney U test when appropriate were used to assess for differences between groups. Correlation of clinical and serum biomarkers and MRI measures were assessed by Spearman's or Pearson rho test. For exploratory purposes, Receiver-operating characteristic (ROC) curves and Youden test were used to assess the ability of muscle ECV for identifying myopathy.

As this was a small pilot study, p-values are reported to only ascribe strength of descriptive differences rather than assign definitive significance, in line with good practice (19).

Results

Twelve SSc patients participated in the study with a median (IQR) age and disease duration of 52 (41, 65) and 7 (2, 17) years respectively. The cohort included ten (83%) females, and nine limited cutaneous SSc (lcSSc) (Table 1). The median (IQR) modified Rodnan skin score (mRSS) was 3 (1,4), one patient had arthritis and four had a history of digital ulcers (DU) and interstitial lung disease (ILD). None of the patients had a confirmed diagnosis of pulmonary hypertension or cardiac involvement. All patients had positive antinuclear antibodies (ANA): five anti-topoisomerase antibody (Scl70), four anticentromere antibody (ACA) and three had myositis associated antibodies (MSA): two Pm/Scl70 positive and one Anti Ro antibody. Seven SSc patients were receiving treatment with disease modifying anti-rheumatic drugs (DMARD), five on mycophenolate mofetil and two on methotrexate. Two patients were on minimal corticosteroid treatment, one patient receiving 5 mg daily and the other patient receiving 2.5 mg of prednisolone.

Ten HV (six females) were included in the study, with a median (IQR) age of 36 (33-40). None had muscle pathology, and none were receiving any medication.

Muscle MRI finding in HV compared to SSc patients

Higher skeletal muscle ECV was noted in SSc patients compared to HV [mean (SD) 23 (11)% vs 11(4)%, mean diff (95%CI) -12 (-19, -40)%, p=0.04]. Skeletal muscle native T1 values were comparable between the 2 groups although modestly higher in SSc patients compared to HV [mean (SD) 1396 (56) ms vs 1387 (42) ms, mean diff (95%CI) -8 (-53, 37) ms] (Figure 1).

Peripheral muscle MRI and association with disease phenotype

Except for a positive association between peripheral muscle T1 native and a lcSSc subset (rho=0.641, p=0.025), no other association with disease characteristic, including a diagnosis of ILD, history of DU, disease duration, arthritis, mRSS, or antibodies was found. All 3 patients with MSA had a suspected myopathy: 1 patient (Anti Ro) had muscle weakness and a MMT score of 4/5 involving the hip adductors, one patient had increased CK levels at the time of the visit, and one had a history of repeatedly raised CK levels.

Muscle MRI findings in SSc patients with myopathy

Seven of the twelve SSc patients had a diagnosis of suspected myopathy. Four patients reported proximal muscle weakness and had a MMT score of 4/5 involving the hip adductors, of whom three also had a history of CK elevation, one patient had a history of proximal lower limb muscle weakness, and another two patients had a history of CK elevation of whom one had increased CK levels at the time of the visit (400 IU/l).

Peripheral muscle ECV associated with CK (R^2 =0.307, rho=0.554, p=0.062) and higher ECV values were found in those with myopathy compared to those with no muscle involvement [mean (SD) 28 (10)% vs 15 (5)%, mean diff (95%CI)-13 (-24, -3)%, p=0.023]. There was no difference in T1 native between those with and without myopathy [mean (SD) of 1395 (73) ms vs 1395 (26) ms, mean diff (95%CI) 0.08 (-77, 77) ms, p=0.998] (Figure 2).

For exploratory purposes, a ROC curve was performed to find potential cut-off values of muscle ECV for identifying myopathy. AUC (95%CI) was strongest at 0.886 (-0.690, 1)%, p=0.028. Using Youden test, an ECV value of 22% was found to best identify myopathy with a sensitivity of 71% and a specificity of 80%.

Discussion

This hypothesis testing pilot study demonstrated the feasibility of using ECV to evaluate the presence of diffuse fibrosis in the peripheral muscle of SSc patients. Higher ECV was noted in SSc patients compared to HV and in SSc patients with a myopathy compared to those without, suggesting the presence of diffuse fibrosis in the peripheral muscle of SSc patients, which may represent the substrate for the non-inflammatory myopathy. These data can inform larger studies to explore the significance of interstitial fibrosis in the peripheral muscle.

The study was a first to use ECV as a marker of diffuse fibrosis in the peripheral muscle, employing a dedicated skeletal muscle protocol. Higher ECV was observed in the peripheral muscle of SSc patients compared to HV. Previous studies have measured skeletal muscle ECV in patients with amyloidosis, idiopathic inflammatory myopathy as well as SSc, although using the thoracic muscle visible at the edge of the CMR field (11, 12, 15), which may be more susceptible to errors than a dedicated skeletal muscle protocol. Our study measured ECV in the peripheral muscle (vastus intermedius) the main muscle group affected in SSc and other IMID, as opposed to axial muscle, minimising cardiac and breathing artefacts and providing larger muscle volume for T1 measurement.

Muscle ECV values of HV were comparable to those reported in the literature, however, there were significant discrepancies between the muscle T1 native values of HV and ECV values of SSc patients compared to other studies (11, 20). These discrepancies are likely due to the limitations of the cardiac T1 measurement sequences, which have to contend with cardiac gating, rather than errors in our skeletal muscle sequences, which used a pure, single readout per inversion method.

Patients presenting with suspected myopathy had greater ECV compared to the non-myopathy group, demonstrating the potential value of ECV in detecting low-grade muscle pathology. A muscle ECV of 22% was found to best identify myopathy in this cohort. CK was also associated with ECV, albeit only one patient had a CK above the normal value and three more had intermittently

minimally raised CK, suggesting the potential clinical importance of low level CK in detecting muscle abnormalities. Other studies have documented the association of low level CK with impaired muscle strength, abnormalities on EMG as well as biopsy findings of fibrosis (1, 4).

Except for a positive association of lcSSc and ECV, likely reflecting the small sample size, with the majority of patients (9/12) having lcSSc, no other association with clinical characteristics was found. This is in accordance with other studies that reported no association between disease characteristics, in particular poor prognostic factors of SSc and myopathy (4).

The main limitation of the study is the sample size. However, this is a novel, pilot, hypothesis-generating study, which sought to assess the feasibility of ECV measurement in the peripheral muscle of SSc patients. To avoid confounding, an age and gender matched HV cohort would have been desirable. ECV can increase in the setting of both fibrosis and oedema. Muscle biopsy evaluation would have been ideal to explore the MRI findings of increased ECV although not feasible in healthy and asymptomatic patient populations. The same contrast equilibrium that was determined in HV was applied in SSc patients. A longer time for reaching equilibrium would imply higher ECV values in SSc patients.

In conclusion, this study demonstrated increased skeletal muscle ECV, suggestive of interstitial fibrosis in the peripheral muscle of SSc patients, providing pathophysiological insights into non-inflammatory myopathy in SSc. T1 measurement with ECV quantification may therefore be a valuable imaging tool to characterise peripheral muscle in SSc. Further research is needed to validate the findings of this pilot study and identifying the prognostic value of interstitial fibrosis in the peripheral muscle of SSc patients.

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Competing interests: The authors have declared no conflicts of interest.

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Data availability statement: The data underlying this article are available in the article.

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Figure legends

Figure 1. Peripheral muscle T1 mapping in healthy volunteers and SSc patients. A. ECV in HV and SSc patients. B. Native T1 in HV and SSc patients

ECV, extracellular volume; HV, healthy volunteer, SSc, systemic sclerosis

Figure 2. Muscle extracellular volume in SSc patients with myopathy. A. Mean (SD) peripheral muscle ECV in those with and without myopathy B. Mean (SD) peripheral muscle native T1 in those with and without myopathy C. Correlation between peripheral muscle ECV and CK.

CK, creatine kinase; ECV, extracellular volume

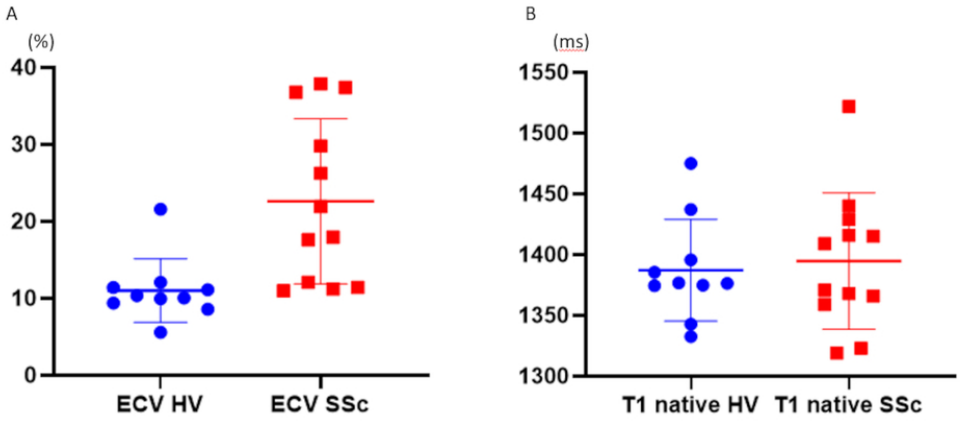
Table 1. Disease characteristics of SSc patients.

SSc phenotype	SSc patients, n=12
Demographics and disease history	
Age (years), median (IQR)	52 (41, 65)
Female, n (%)	10 (83%)
LcSSc	9 (75%)
DcSSc	3 (25%)
Disease duration (years), median (IQR)	7 (2,17)
Raynaud's duration	14 (3, 29)
History of, n (%)	
Digital ulceration	4 (33%)
Calcinosis	2 (17%)
GORD	10 (83%)
Interstitial lung disease	4 (33%)
PAH	0
Cardiac involvement	0
Clinical profile	
Total modified Rodnan skin score, median (IQR)	3 (1,4)

Presence of, n (%)	
Digital ulceration	4 (33%)
Tendon friction rubs	0
Calcinosis	3 (25%)
Joint contractures	2 (17%)
Any TJC	3 (25%)
Any SJC	1 (8%)
NFC vasculopathy pattern, n (%)	
Non-specific	3 (25%)
Early	3 (25%)
Active	4 (33%)
Late	2 (17%)
Antibody profile and serology	
Antibody positive, n (%)	
ANA	12 (100%)
ACA	4 (33%)
Scl70	5 (42%)

Pm-Scl70	2 (17%)
Ro antibodies	1 (8%)
CRP (mg/L) (normal range <5), median (IQR)	5 (5, 6)
CK (IU/l), median (IQR)	83 (53, 190)
Pulmonary function tests	
FVC%, mean (SD)	107 (20)
TLC%, mean (SD)	95 (16)
DLCO%, mean (SD)	63 (19)
DLCO/VA%, mean (SD)	82 (21)

ACA, anti-centromere antibody; ANA, antinuclear antibodies; CK, creatine kinase; DcSSc, diffuse cutaneous systemic sclerosis; DLCO, diffusing capacity of the lungs for carbon monoxide; DLCO/VA, DLCO adjusted for volume; FVC, forced vital capacity; GORD, gastro-oesophageal reflux disease; IQR, interquartile range; lcSSc, limited cutaneous systemic sclerosis; NFC, nailfold capillaroscopy; NSIP, non-specific interstitial pneumonia; Scl70, anti-topoisomerase antibody; SD, standard deviation; SJC, swollen joint count; TJC, total joint count; TLC, total lung capacity.



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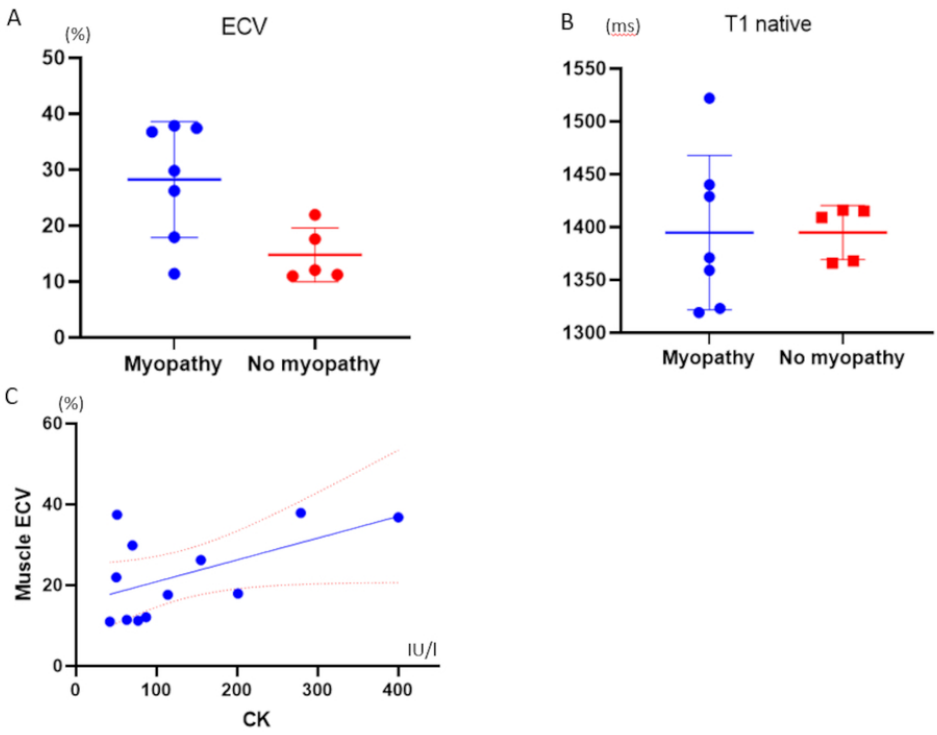

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