



UNIVERSITY OF LEEDS

This is a repository copy of *Muscle stiffness in rheumatoid arthritis is not altered or associated with muscle weakness: a shear wave elastography study*.

White Rose Research Online URL for this paper:
<http://eprints.whiterose.ac.uk/149040/>

Version: Accepted Version

Article:

Alfuraih, AM orcid.org/0000-0002-4655-7248, Tan, AL orcid.org/0000-0002-9158-7243, O'Connor, P et al. (2 more authors) (2019) Muscle stiffness in rheumatoid arthritis is not altered or associated with muscle weakness: a shear wave elastography study. *Modern Rheumatology*. ISSN 1439-7595

<https://doi.org/10.1080/14397595.2019.1645374>

This article is protected by copyright. All rights reserved. This is an author produced version of a paper published in *Modern Rheumatology*. Uploaded in accordance with the publisher's self-archiving policy.

Reuse

Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

MORH-D-19-00166 Received: 15-May-2019; Accepted: 12-Jul-2019

Original Article

Muscle stiffness in rheumatoid arthritis is not altered or associated with muscle weakness: a shear wave elastography study.

Abdulrahman M. Alfuraih^{1,2,3}, Ai Lyn Tan^{2,3}, Philip O'Connor³, Paul Emery^{2,3}, Richard J. Wakefield^{2,3},

¹Radiology and Medical Imaging Department, College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University, Kharj, Saudi Arabia.

²Leeds Institute of Rheumatic and Musculoskeletal Medicine, Chapel Allerton Hospital, University of Leeds, United Kingdom.

³NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom.

Corresponding author: Abdulrahman M. Alfuraih

LIRMM, 2nd Floor, Chapel Allerton Hospital, Chapeltown Road, Leeds, LS7 4SA, UK.

Phone: +44 113 392 4854, E-mail: a.alfuraih@psau.edu.sa

Abstract

Objective

To investigate muscle stiffness and strength in rheumatoid arthritis patients compared to healthy controls.

Methods

A sample of 80 RA patients from three discrete groups: 1-newly diagnosed treatment-naïve RA (n=29), 2-active RA for at least 1 year (n=18) and 3-in remission RA for at least 1 year (n=33), was compared to 40 healthy controls. Shear wave velocity (SWV) was measured using shear wave elastography as a surrogate for tissue stiffness in multiple muscles. All participants performed isometric grip strength, timed get-up-and-go test, 30-sec chair stand test and isokinetic knee extension/flexion(60°/sec). The difference in SWV amongst the groups was tested using one-way ANOVA, and the correlation between SWV and muscle strength results were calculated using Pearson's coefficients.

Results

The mean age \pm SD was 61.2 \pm 12.8 for RA patients and 61.5 \pm 10.5 years for controls. SWV was not significantly different amongst the groups on all muscles ($p>0.05$). In comparison to controls, the new and active RA groups showed a significantly lower isokinetic strength by -29%($p=0.013$) and -28%($p=0.040$), fewer chair stands by -28%($p=0.001$) and -44%($p<0.001$), longer walking times by -25% ($p=0.025$) and -30% ($p=0.001$) respectively, and weaker grip strength by -45% for both ($p<0.001$). The muscle strength in the remission RA groups was not significantly lower, except in the isokinetic knee strength (-21%; $p=0.027$). The correlations between SWE and the muscle assessment results were weak and insignificant ($r<0.30$; $p>0.05$).

Conclusions

Significant muscle weakness was demonstrated in patients with RA disease. However, muscle stiffness was normal and not associated with muscle strength.

Keywords

Elasticity Imaging Techniques; Diagnostic Imaging; Muscles, Arthritis, Rheumatoid, Muscle Weakness; Muscle Strength.

Introduction

Myopathy is a recognised but less investigated clinical feature of rheumatoid arthritis (RA) compared to other extra-articular manifestations. Its aetiology is thought to be multi factorial including joint inflammation, myositis, vasculitis and drug-induced myopathies [1, 2]. Few studies have investigated the frequency of myopathy occurring in RA [1-8]. Most have estimated the prevalence between 6% and 19% [4-6] whereas others reported it higher at 50%–70% [2, 7, 8]. All studies utilised invasive muscle biopsy to investigate the histological and immunohistochemical characteristics. They reported the presence of inflammatory cell infiltrates [1-5], muscle fibre atrophy [1-4] and fibre size variability [2, 4]. Muscle weakness is a commonly reported complaint in RA patients, which has been associated with a reduction in quality of life and increased burden on society due to impaired work capacity [9]. Moreover, recent studies have highlighted the association between muscle weakness in RA and increased risk of falls [10] and physical disability [11]. Reports show that RA patients have 25%–70% weaker muscles compared to healthy matched controls [2, 9].

To date, the outline and extent of myopathic features in RA are poorly detailed. There are no established criteria for diagnosing or managing myopathy in RA. No studies yet have utilised a non-invasive quantitative method to define and investigate myopathic features in RA. Novel biomarkers such as muscle stiffness can now be assessed non-invasively using ultrasound shear wave elastography (SWE), which may offer new insight into the biomechanical state of RA muscles. The usefulness of SWE has been demonstrated for evaluating peripheral muscle deficits [12] and detecting active idiopathic inflammatory myopathies [13, 14]. The combination of inflammation, atrophy, muscle weakness and lower muscle density [9, 15] may hypothesise an impaired elastic property of RA muscles. Understanding muscle involvement in RA via SWE can help in developing prevention and therapeutic strategies. Additionally, it can emphasise the breadth of extra-articular manifestations of RA as a systemic inflammatory disease.

We hypothesised that: 1-SWE can detect an altered muscle stiffness in RA muscles compared to healthy controls, 2-muscle strength varies depending on disease duration and activity, and correlates with muscle stiffness. We thus aimed to define muscle stiffness in three cohorts of RA patients: newly diagnosed untreated, those in disease remission and those who have an ongoing active disease and compare them to a group of healthy controls. The second aim was to investigate the participants' muscle strength and evaluate its association with muscle stiffness.

Materials and methods

Study design

This study was conducted in a cross-sectional design. Patients were prospectively recruited from a single centre (Chapel Allerton Hospital, part of Leeds Teaching Hospitals NHS Trust) between May 2017 and August 2018. The investigations took place in the research facility based at the same centre (Leeds Biomedical Research Centre). Healthy controls were enrolled to compare the RA patients' muscle characteristics against. Ethical approval for was granted by the Nottingham UK research ethics committee (Ref: 17/EM/0079) prior to commencing recruitment. All participants provided a written informed consent.

Patients

To test muscle characteristics in RA patients, three main groups of varying disease activities were specified: a- newly diagnosed and untreated (new RA), b- diagnosed over 1 year and in remission (remission RA), and c- diagnosed over 1 year and is active (active RA). These distinct groups were defined to study the muscles in active RA but not affected by treatment (new RA), effect of continuing inflammation and medication (active RA) and no inflammation in RA (remission RA). The eligibility criteria are detailed below for each group.

Inclusion/exclusion criteria

The inclusion criteria for the RA patients were as follows:

1. ≥ 18 years old.
2. Have an established diagnosis of RA based on the adopted criteria [16].
3. For new RA:
 - 3.1. Newly diagnosed with RA.
 - 3.2. Disease-modifying antirheumatic drugs (DMARD)-naïve.
4. For active RA:
 - 4.1. Diagnosed with RA for at least 12 months.
 - 4.2. Disease activity score-28 (DAS28) ≥ 3.2 at the time of recruitment [17].
 - 4.3. At least two of the following markers of active disease within the past 12 months:
 - 4.3.1. DAS28 ≥ 3.2 in at least one additional clinic visit prior to recruitment.

- 4.3.2. Raised inflammatory markers [(raised C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)].
 - 4.3.3. Required corticosteroid therapy (intra-muscular or oral) to control the disease.
 - 4.3.4. Ultrasound evidence of active disease. Active disease was determined by the presence of B-mode (grey scale) synovial hypertrophy with increased power Doppler signal. The scans were performed as directed by the clinician using a GE LOGIQ E9 machine employing 6–15 MHz linear transducer.
 - 4.3.5. A physician's determined long-standing active disease for more than one year (based on clinical RA symptoms, early morning stiffness, joint pain and swelling).
 - 4.3.6. Escalation to, or recent changes in biologic medication.
5. For remission RA:
 - 5.1. Diagnosed with RA for at least 12 months.
 - 5.2. Achieved remission for the past 12 months with a DAS28 <2.6 [18].
 - 5.3. No disease flares during the past 12 months.

The exclusion criteria were a history of any primary muscle disease (e.g. myositis, muscular dystrophy, etc.) or neuropathy. The eligibility conditions described above were adapted from the established definitions of RA disease activity [16, 18-20]. The eligibility for the active RA group was set to ensure the inclusion of a prolonged active disease. As for healthy controls, eligibility was based on: 1) being asymptomatic; 2) no previous history of muscle, neurological or joint disorder; 3) not currently taking or previously taken a corticosteroid treatment for the past three years with doses >5mg/day; 4) not currently taking or previously taken a HMG-CoA reductase inhibitors (statins) for the past three years.

Shear wave elastography

SWE was performed using the Aixplorer system (Supersonic Imagine, Aix-en-Provence, France) operating the SuperLinear™ SL10–2MHz probe. The system estimates tissue stiffness by measuring the propagation velocity of shear waves (in meters per second, m/s) induced by acoustic radiation force impulses. Shear wave velocity (SWV) increases proportionally with the elasticity modulus and can be used as a surrogate for tissue stiffness [21].

The investigated muscles were the quadriceps [vastus lateralis (VL), rectus femoris (RF), vastus medialis (VM), vastus intermedius (VI)], hamstrings [biceps femoris (BF), semitendinosus (ST), semimembranosus (SM)] and biceps brachii (BB) of the dominant side. All muscles were tested in the most relaxed resting position. For the quadriceps, the participants were supine on a flat bed. For the hamstrings, they were prone on a flat bed with the knees flexed at 90° and rested on a wall. For the BB, they were supine and elbow was flexed at 90° with the forearm rested on the body and hand in supination.

Three repeated measurements of shear wave velocity (SWV) were acquired per muscle and the mean was reported. The probe was oriented along muscle fibres and rested with minimal load on the skin to avoid tissue deformation. The region of interest size was set at 10mm. These technical acquisition methods were validated before [22, 23].

Clinical and muscle assessments

Age, sex, body mass index (BMI), global visual analogue scale (VAS) 100mm score of general health, smoking status (pack-years) and alcohol intake (units/week) were documented. To evaluate the relationship between muscle stiffness and the patients' disease status, the DAS28 score, swollen joint count and tender joint count were reviewed by board-certified rheumatologists. In addition, the main inflammatory blood markers (CRP and ESR) were recorded.

As muscle weakness is a common symptom in RA, muscle strength and function were assessed by a series of four tests. Isometric handgrip strength was measured 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) [24]. 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 down [25]. The participants then performed the 30-second chair stand test (maximum number of chair stands in 30 seconds) [26].

Lastly, isokinetic knee extension/flexion (for quadriceps and hamstrings) was tested using the Biodex system 4 (IRPS Mediquipe, UK). After warm-up, 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 velocity [27]. 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). This test provides an accurate assessment of muscle strength in RA and correlates with disease activity [28].

Statistical analysis

Due to the lack of prior information and similar studies, no power calculations were carried out to determine a sample size. However, sample between 12 – 30 per group of interest has been recommended as a general rule of thumb to provide an acceptable precision around the estimates [29, 30].

Descriptive analyses were employed to present patient characteristics and the main findings. The data distribution was checked using histogram plots and Shapiro–Wilk test to verify normality. One-way analysis of variance (ANOVA) followed by Tukey-Kramer corrected post-hoc multiple comparisons to test the hypothesis of differences in muscle stiffness (i.e. SWV) and strength assessments amongst the various groups. Further analyses using two-way analysis of covariance (ANCOVA) were employed to adjust for the independent effects of age (covariate) and sex (moderator variable). The hypothesised correlations of SWV with the disease activity variables (i.e. DAS-28 and CRP) and muscle strength tests were analysed using Pearson's correlation coefficients.

Intra-operator reliability for the three repeated measurements were evaluated using intraclass correlation coefficients (ICC), and were interpreted as follows: .00–.20 'poor agreement', .21–.40 'fair agreement', .41–.60 'moderate agreement', .61–.80 'substantial agreement' and >.80 'almost perfect agreement' [31]. The tests mentioned above were repeated for each muscle evaluated by SWE. *P* values <0.05 were regarded as statistically significant. All statistical analyses were performed on SPSS version 25 (Armonk, NY: IBM Corp).

Results

Clinical characteristics

A total of 80 RA patients have been recruited, of whom 29 were new RA, 18 active RA and 33 remission RA. Additionally, 40 healthy controls were recruited with a similar age distribution to the RA groups. The demographic and clinical characteristics of all participants are listed in Table 1. The age of the control group (61.5 ± 10.5 years) was not significantly different from the new RA (56.7 ± 10.6

years; $p=0.85$), active RA (60.8 ± 15.9 years; $p=0.94$) or remission RA (65.9 ± 11.6 years; $p=0.07$).

However, the new RA group was younger (-9.2 years; $p=0.011$) than the remission RA group. None of the participants had any deformities or disabilities.

Median duration since RA diagnosis and range was 88 month (12–347 month) for active RA and 59 month (12–212 month) for remission RA. Early morning stiffness median (interquartile range) was 60 minute (29–60 minute) and 45 minute (30–60) for the active and new RA groups respectively. No patients in the remission RA group complained of early morning stiffness. Regarding treatment, the active RA group were on methotrexate ($n=8$), prednisolone ($n=4$), rituximab ($n=3$), etanercept ($n=2$), tocilizumab ($n=2$), hydroxychloroquine ($n=2$), sulfasalazine ($n=1$), tofacitinib ($n=1$), adalimumab ($n=1$) and abatacept ($n=1$). As for the remission RA group, they were on methotrexate ($n=26$), hydroxychloroquine ($n=8$), sulfasalazine ($n=5$), etanercept ($n=4$), adalimumab ($n=2$), infliximab ($n=2$) and prednisolone ($n=1$).

Table 1 Demographic and clinical characteristics of the rheumatoid arthritis patients and healthy controls.

Characteristic	Healthy controls (a) (n=40)	New RA (b) (n=29)	Active RA (c) (n=18)	Remission RA (d) (n=33)	p-value [†]	Post hoc [‡]
Sex	12 Males (30%)	8 Males (28%)	4 Males (22%)	19 Males (58%)	0.026	d>a,b,c
Age (years)	61.5 (10.5)	56.8 (10.6)	60.9 (15.9)	65.9 (11.6)	0.030	d>b
Height (cm)	166.4 (9.6)	163.9 (12.0)	164.1 (9.6)	167.8 (9.5)	0.41	-
Weight (kg)	75.2 (14.1)	80.4 (17.7)	74.3 (18.6)	76.8 (16.0)	0.53	-
BMI	27.2 (4.6)	30.2 (7.6)	27.4 (5.7)	27.1 (4.2)	0.10	-
Waist-hip ratio	0.88 (0.09)	0.88 (0.08)	0.88 (0.10)	0.92 (0.07)	0.24	-
Ever smoked	17 (42%)	16 (55%)	10 (55%)	22 (67%)	0.27	-
pack-years *	2.5 (1.8–4.0)	18.8 (9.3–30.2)	19.7 (6.4–39.0)	10.2 (3.7–28.1)	0.037	a<b,c,d
Drinking alcohol (units/week) *	23 (57%) 8 (6–15)	15 (52%) 6 (1–15)	9 (50%) 13 (3–20)	25 (75%) 10 (4–18)	0.17 0.80	- -
VAS health (mm) *	10 (3–22)	27 (15–50)	47 (31–58)	9 (3–18)	<0.001	a,d<b,c
Months since diagnosis *	-	0	88 (45–163)	59 (38–77)	<0.001	b<d<c
DAS-28	-	4.7 (1.2)	4.6 (1.0)	1.8 (0.3)	<0.001	d<b,c
Swollen joints	-	8.0 (5.9)	4.4 (3.5)	0	<0.001	d<c<b
Tender joints	-	9.7 (7.0)	10.2 (5.9)	0	<0.001	d<b,c
CRP (mg/l) *	-	10 (5–23)	6 (5–25)	<5.0	0.003	b>d
ESR (mm/hr) *	-	26 (13–48)	13 (5–32)	11 (8–17)	0.018	b>d

Data in brackets represent standards deviation for means, or percentages for ratio.

* Median (interquartile range).

† p-values significant at 95% are highlighted in bold. Continuous variables tested via one-way ANOVA, and categorical data tested using Chi-square test.

‡ The signs > or < indicate that the group(s) are significantly higher or lower at 0.05 significance level compared to others.

VAS=Visual analogue scale of health; DAS=Disease activity score; CRP= C-reactive protein; ESR=Erythrocyte sedimentation rate.

Shear wave elastography

The SWE for the healthy controls and RA groups are presented in Table 2 and Figure 1 to investigate the first hypothesis of altered RA muscle stiffness compared to healthy controls. The results of the one-way ANOVA in the last column of the table showed no significant differences between the groups ($p>0.05$). The tendency observed in the VM muscle ($p=0.052$) was further analysed after adjusting for age using the ANCOVA test, which confirmed the lack of SWV statistical difference ($p=0.149$) amongst the participants. Age, however, had a significant effect on SWV measurements in VM ($p<0.001$). This significant effect of age was also observed after further analysis on VL ($p=0.011$), RF ($p<0.001$), VI ($p=0.014$), BB ($p<0.001$), BF ($p=0.003$), ST ($p<0.001$) and SM ($p=0.029$), but not in BB ($p=0.86$). In contrast, sex had no significant impact on SWV measurements (all $p>0.10$).

Despite the lack of statistically significant differences, the descriptive statistics in Table 2 showed that the active group had on average 5% difference in the quadriceps and hamstrings SWV compared to healthy controls. The difference was highest over the SM muscle at 7.5% (1.60 versus 1.48 m/s), though it was not statistically significant in post hoc multiple comparisons ($p=0.34$). A higher difference at 8.6% ($p=0.21$) in the same muscle was noted between the active RA (1.48 m/s) and remission RA (1.62 m/s).

Comparing the healthy controls to a pooled group of all RA patients also showed no significant differences between their mean SWV measurements [VL ($p=0.24$), RF ($p=0.86$), VM ($p=0.08$), VI ($p=0.97$), BB ($p=0.35$), BF ($p=0.27$), ST ($p=0.23$) and SM ($p=0.47$)]. A lack of significant difference was also observed when comparing RA groups amongst each other [VL ($p=0.41$), RF ($p=0.87$), VM ($p=0.14$), VI ($p=0.14$), BB ($p=0.50$), BF ($p=0.34$), ST ($p=0.37$) and SM ($p=0.22$)].

Intra-operator reliability for the repeated measurements were all above 0.80 indicating 'almost perfect' reliability [31]. The ICC (95% CI) were 0.97 (0.95–0.98) for VL, 0.95 (0.93–0.96) for RF, 0.99 (0.98–1.0) for VM, 0.93 (0.90–0.95) for VI, 0.94 (0.91–0.96) for BB, 0.97 (0.96–0.98) for BF, 0.95 (0.94–0.97) for ST and 0.96 (0.95–0.97) for SM.

Correlation with clinical variables

Correlation analysis showed no significant associations between SWV and DAS-28 across all muscles. The correlation coefficient (p -value) were 0.06 ($p=0.59$) for VL, 0.09 ($p=0.45$) for RF, 0.12 ($p=0.32$) for VM, -0.01 ($p=0.91$) for VI, 0.15 ($p=0.18$) for BB, -0.07 ($p=0.53$) for BF, 0.02 ($p=0.85$) for ST and -0.15 ($p=0.19$) for SM. Similar results of poor ($r<0.3$) and insignificant ($p>0.05$) coefficients were observed between SWV and CRP as well as ESR.

Table 2 Shear wave velocity measurements for all participants.

Muscle	Healthy controls (n=40)		New RA (n=29)		Active RA (n=18)		Remission RA (n=33)		p-value [†]
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	
Vastus lateralis	1.64 (0.15)	1.59– 1.69	1.63 (0.26)	1.54– 1.73	1.55 (0.17)	1.47– 1.64	1.58 (0.21)	1.5– 1.65	0.32
Rectus femoris	1.69 (0.15)	1.64– 1.74	1.68 (0.18)	1.61– 1.75	1.70 (0.16)	1.62– 1.78	1.68 (0.14)	1.63– 1.73	0.96
Vastus medialis	1.62 (0.17)	1.57– 1.68	1.62 (0.32)	1.49– 1.76	1.52 (0.20)	1.42– 1.62	1.50 (0.18)	1.44– 1.57	0.052
Vastus intermedius	1.84 (0.19)	1.78– 1.91	1.78 (0.22)	1.70– 1.87	1.93 (0.25)	1.80– 2.06	1.85 (0.25)	1.76– 1.94	0.21
Biceps brachii	1.83 (0.18)	1.78– 1.89	1.92 (0.36)	1.78– 2.06	1.81 (0.14)	1.74– 1.88	1.89 (0.35)	1.77– 2.01	0.45
Biceps femoris	1.57 (0.18)	1.52– 1.63	1.56 (0.23)	1.47– 1.64	1.46 (0.21)	1.36– 1.57	1.54 (0.21)	1.47– 1.62	0.30
Semitendinosus	1.56 (0.17)	1.51– 1.62	1.53 (0.16)	1.47– 1.59	1.45 (0.17)	1.37– 1.54	1.54 (0.25)	1.45– 1.63	0.30
Semimembranosus	1.60 (0.16)	1.55– 1.65	1.54 (0.15)	1.48– 1.60	1.48 (0.18)	1.38– 1.57	1.62 (0.41)	1.48– 1.77	0.21

Mean values represent shear wave velocity in units of m/s.

Muscle assessments

The participants' performance in the muscle assessment tests are described and compared in Table 3 to investigate the second hypothesis of muscle strength variability depending on disease duration and activity. The results are also graphically represented in Figure 2 and Figure 3. A summary of the mean difference percentages for the RA groups compared to the healthy control group are displayed in Figure 4.

Overall, the RA patients' performance was worse than healthy controls across all tests. Though, the remission RA patients performance was not significantly different to the healthy control group except in the isokinetic knee flexion strength (-21%, $p=0.027$). In contrast, the new and active RA groups exhibited significant muscle weakness.

Correlation with muscle stiffness and clinical variables

The correlations in Table 4 indicates that the SWV measurements were not associated with significant positive or negative changes in any of the muscle test results in RA patients. Evaluating the association between disease activity (i.e. DAS-28) and the muscle assessment outcomes showed that it moderately correlated with ETGUG total walking time ($r=0.473$; $p<0.001$), number of chair stands ($r=-0.369$; $p=0.001$), handgrip strength ($r=-0.609$; $p<0.001$), knee extension torque ($r=-0.356$; $p<0.001$) and knee flexion torque ($r=-0.249$; $p=0.001$).

Table 3 Muscle assessment results for all participants.

Test	Healthy controls (a)		New RA (b)		Active RA (c)		Remission RA (d)		p-value	Post hoc*
	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI	Mean (SD)	95% CI		
ETGUGT, Total time (sec)	16.6 (4.3)	15.3–18.0	20.7 (5.7)	18.7–22.9	21.5 (6.3)	18.7–24.5	18.2 (4.5)	16.6–19.7	0.002	a>b,c
Number of chair stands in 30 sec	17.0 (5.8)	15.2–18.8	12.3 (6.0)	10.1–14.5	9.5 (6.3)	6.6–12.4	14.0 (5.4)	12.1–15.8	<0.001	a>b,c
Handgrip strength (kg _F)	31.5 (13.7)	27.4–35.9	17.3 (8.1)	14.6–20.5	17.3 (8.4)	13.7–21.5	26.6 (10.9)	23.1–30.6	<0.001	a,d>b,c
Knee extension torque (Nm/kg)	1.29 (0.42)	1.16–1.42	1.06 (0.45)	0.89–1.22	0.93 (0.47)	0.72–1.15	1.20 (0.40)	1.06–1.33	0.026	a>c
Knee flexion torque (Nm/kg)	0.75 (0.27)	0.66–0.83	0.53 (0.27)	0.43–0.63	0.60 (0.29)	0.46–0.73	0.59 (0.25)	0.50–0.67	0.006	a>b,d
Knee extension power (W/kg)	0.75 (0.29)	0.66–0.84	0.58 (0.30)	0.47–0.69	0.52 (0.32)	0.37–0.67	0.68 (0.28)	0.59–0.78	0.029	a>c
Knee flexion power (W/kg)	0.47 (0.18)	0.41–0.52	0.32 (0.19)	0.25–0.39	0.34 (0.21)	0.25–0.44	0.34 (0.18)	0.28–0.40	0.005	a>b,d

Mean results are presented as unweighted marginal means adjusted by sex and age in two-way ANCOVA.

* The signs > or < indicate that the group(s) are significantly higher or lower at 0.05 significance level compared to others.

Table 4 Correlation coefficients showing no significant association between shear wave velocity and results of the muscle assessment tests in RA patients.

	VL	RF	VM	VI	BB	BF	ST	SM
ETGUGT, Total time (sec)	-0.02 (p=0.83)	-0.12 (p=0.3)	0.02 (p=0.87)	-0.17 (p=0.13)	-0.18 (p=0.11)	0.13 (p=0.26)	0.05 (p=0.63)	-0.01 (p=0.91)
30-sec Chair stand test	-0.18 (p=0.12)	-0.08 (p=0.46)	-0.05 (p=0.66)	-0.09 (p=0.43)	-0.04 (p=0.71)	0.1 (p=0.38)	0.02 (p=0.89)	0.12 (p=0.31)
Handgrip Strength (kg _F)	0.02 (p=0.86)	-0.07 (p=0.56)	-0.02 (p=0.88)	0.02 (p=0.88)	-0.22 (p=0.05)	0.11 (p=0.35)	0.08 (p=0.51)	0.01 (p=0.93)
Knee extension torque (Nm/kg)	-0.03 (p=0.78)	-0.04 (p=0.75)	-0.17 (p=0.14)	-0.01 (p=0.9)	-0.17 (p=0.14)	0.1 (p=0.39)	0.18 (p=0.13)	0.14 (p=0.22)
Knee flexion torque (Nm/kg)	0.01 (p=0.96)	0.01 (p=0.94)	-0.01 (p=0.9)	0.01 (p=0.99)	-0.2 (p=0.08)	0.12 (p=0.28)	0.08 (p=0.49)	-0.02 (p=0.85)
Knee flexion power (W/kg)	-0.05 (p=0.68)	-0.02 (p=0.89)	-0.11 (p=0.36)	-0.04 (p=0.71)	-0.17 (p=0.15)	0.09 (p=0.42)	0.09 (p=0.43)	0.03 (p=0.78)
Knee extension power (W/kg)	-0.02 (p=0.83)	-0.12 (p=0.3)	0.02 (p=0.87)	-0.17 (p=0.13)	-0.18 (p=0.11)	0.13 (p=0.26)	0.05 (p=0.63)	-0.01 (p=0.91)

Data presented as correlation coefficients (p-value) based on Pearson's test.

Discussion

Our main aim was to explore muscle stiffness in RA patients compared to a healthy population.

Despite the tendency for RA patients to have a lower muscle stiffness (i.e. lower SWV) compared to healthy controls, especially those with active disease, the differences were not statistically significant.

This main finding does not substantiate our proposed hypothesis of altered muscle stiffness in RA, although, it confirms the effect of ageing on muscle stiffness [32].

The normal muscle stiffness in RA, as indirectly measured by SWE, may indicate that the degree of reported muscle fibre atrophy and inflammatory cell infiltrates in RA subjects might not be profound

enough to detrimentally affect the biomechanical properties of skeletal muscles. This argument can be supported by the studies on myositis patients [14, 33], where significant structural changes (i.e. fibre atrophy) and inflammation (i.e. oedema) were associated with abnormal elastography results.

Additionally, the prevalence of such myopathic features in RA was also low as reported previously [4, 5].

The second main finding was that all RA patients exhibited a significantly lower strength and functional performance based on the objective muscle assessment tests employed. The positive muscle weakness, but lack of abnormal SWV, may suggest other primary intrinsic (intracellular) muscular dysfunction factors rather than an altered biomechanical property in skeletal muscle. For example, impairment in the metabolic process of reactive nitrogen species in RA muscles can attack the proteins responsible for force production (actin and myosin) [34]. Similarly, a molecular imbalance in the Ca^{2+} release can cause myofibrillar dysfunction [9].

By contrast, other researchers support the theory that secondary factors promote muscle weakness in RA. For instance, the disuse due to a sedentary lifestyle, joint deformity, pain and stiffness, and the increase in energy expenditure during rest are factors attributable to muscle deconditioning and subsequent weakness in RA [15, 35, 36]. These factors might lead to secondary muscle wasting [35]. Indeed, Baker et al. [15] showed that RA patients have a significant skeletal muscle mass deficit compared to healthy controls ($p < 0.001$). However, Helliwell and Jackson argued that the reduction in strength is often greater and precedes what could be explained by muscle mass decline in RA [36]. Their argument was later supported by others [37, 38].

It is important to highlight the difficulty of directly assessing the influence of inflammation on the results of strength assessments due to the secondary factors mentioned above. Our results revealed that the weakness might vary depending on disease activity. The presented percentages of muscle weakness deficits match those observed in previous studies. In isokinetic knee strength testing, Madsen et al. [39] reported a -32% reduction in extension strength (-28% in this study) and -28% reduction in flexion strength (-20% in this study) over a group of active RA. A lesser reduction of -22% in extension strength and -28% in flexion strength was reported by Meireles et al. [40]. In remission RA, another study found comparable differences in flexion strength of -29% (-21% in this study) and extension strength of -9% (-7% in this study) [41].

As for grip strength weakness, the presented difference of -45% in the new and active RA is in agreement with the -43% average reduction calculated in a large meta-analysis of more than ten thousand RA patients [42]. Using another variation of the chair stand test, one study found a slightly worse performance of -23% in remission RA compared to -18% in this study [41]. Similar to our observations, Bohler et al. [43] used the chair stand test and a shorter version of the ETGUG, and demonstrated that RA patients in higher disease activity categories generally performed worse than patients in remission. They reported a significant correlation for DAS-28 with chair standing and walking time of -0.314 ($p < 0.05$) and 0.437 ($p < 0.001$) respectively, which are close to what we reported (-0.369 for chair stand; 0.473 for ETGUG).

Although the remission patients had better results in most of the tests compared to the new and active RA patients, they performed worse than controls in all strength and function assessments. This suggests that although modern therapies may be effective in counteracting disease activity, there may be other aspects such as RA-induced weakness that require further investigations [9]. Thus, future RA therapies could trial the use of conventional effective treatments coupled with resistance exercises to control disease activity and improve muscular strength respectively, and perhaps even consider muscle protein stabilising compounds [9]. Generally, the higher muscle strength in the remission RA patients reinforces the importance of achieving this disease state.

As the biomechanical properties of skeletal muscles do not appear to be compromised in RA, the focus of future SWE research might be better directed at pathologies of primary muscle disease, such as idiopathic inflammatory myopathies [13, 14], Duchenne muscular dystrophy [44] and muscle spasticity [45]. Besides, the scale of observed muscle weakness calls for researchers to develop assessment methods that can readily assist healthcare professionals in identifying patients at risk. Also, a better understanding of the various aspects associated with muscle quality in RA is vital for developing novel muscle-related interventions. Stanmore [46] has published useful recommendations for assessing and preventing falls in RA, which could be a helpful resource for RA-associated muscle impairment.

Our study has some limitations. There were unequal numbers of patients in each patient group. It has been previously been recognised that achieving an equal number of participants in each category is challenging in observational studies in contrast to experimental studies [47]. In our study, it was particularly difficult to recruit the active RA patients (smallest group, $n=18$) since cases seldom persist

with such prolonged and uncontrolled disease activity, as a result of close disease monitoring. To mitigate the effect of this limitation on the results, type III sums of squares and unweighted marginal means were used in the statistical analysis when possible. This also addressed the larger ratio of male patients in the remission group. A second limitation reflects the investigation of only large upper and lower limb muscles. Smaller muscles, such as the hand muscles, were not evaluated. Finally, we did not perform inter-reader reliability due to the unavailability of a second reader.

In conclusion, muscle stiffness, as evaluated using SWE, did not appear to be affected in RA patients from various cases of disease activity compared to healthy controls. However, muscle strength and physical performance were significantly reduced in RA patients. This reduction did not correlate with SWE measurements of muscle stiffness. Rather, the weakness is believed to be a result of a complicated mixture of primary (e.g. intracellular molecular imbalance) and secondary (e.g. myofibre deconditioning due to disuse) factors. Doubts remain regarding muscle quality in RA considering the lack of clinically meaningful criteria to define RA-associated muscle impairment. The muscle weakness results call for interventions focused on improving muscle strength and physical function in RA to prevent consequent disability.

Acknowledgements

The research is supported by the National Institute for Health Research (NIHR) Leeds Biomedical Research Centre. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Authors' contributions

AMA, ALT, POC, PE, RJW: conceptualised and designed the study. AMA: collected, analysed and interpreted the data then wrote the manuscript. AMA, ALT, POC, PE, RJW: revised the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Conflict of interest

None.

References

1. Miró Ó, Pedrol E, Casademont J, García-Carrasco M, Sanmarti R, Cebrián M, et al. Muscle involvement in rheumatoid arthritis: clinicopathological study of 21 symptomatic cases. *Seminars in arthritis and rheumatism*. 1996;25;421-8.
2. Agrawal V, Husain N, Das SK, Bagchi M. Muscle involvement in rheumatoid arthritis: clinical and histological characteristics and review of literature. *J Indian Rheumatol Assoc*. 2003;11;98-103.
3. De Palma L, Chillemi C, Albanelli S, Rapali S, Bertoni-Freddari C. Muscle involvement in rheumatoid arthritis: an ultrastructural study. *Ultrastructural pathology*. 2000;24;151-6.
4. Ancuța C, Ancuța E, Iordache C, Ceaușu M, Chirieac R. Immunohistochemical study of skeletal muscle in rheumatoid myositis. *Romanian Journal of Morphology and Embryology*. 2009;50;223-7.
5. Ancuta C, Pomirleanu DC, Anton C-R, Moraru E, Anton E, Chirieac RM, et al. Rheumatoid myositis, myth or reality? A clinical, imaging and histological study. *Romanian journal of morphology and embryology= Revue roumaine de morphologie et embryologie*. 2014;55;781.
6. Nakajima A, Yoshino K, Soejima M, Kawaguchi Y, Satoh T, Kuwana M, et al. High frequencies and co-existing of myositis-specific autoantibodies in patients with idiopathic inflammatory myopathies overlapped to rheumatoid arthritis. *Rheumatology international*. 2012;32;2057-61.
7. Halla JT, Koopman WJ, Fallahi S, Oh SJ, Gay RE, Schrohenloher RE. Rheumatoid myositis. *Arthritis & Rheumatism*. 1984;27;737-43.
8. Schlaeger JM, Roach K, Golas M, Takayama M, Wilkie DJ. Treatment-Seeking Behaviors of Persons With Rheumatoid Arthritis. *Journal of holistic nursing : official journal of the American Holistic Nurses' Association*. 2018;36;179-91.
9. Yamada T, Steinz MM, Kenne E, Lanner JT. Muscle Weakness in Rheumatoid Arthritis: The Role of Ca(2+) and Free Radical Signaling. *EBioMedicine*. 2017;23;12-9.
10. Lourenco MA, Carli F, de Assis MR. Characterization of falls in adults with established rheumatoid arthritis and associated factors. *Advances in rheumatology (London, England)*. 2018;58;16.
11. Sferra da Silva G, de Almeida Lourenco M, de Assis MR. Hand strength in patients with RA correlates strongly with function but not with activity of disease. *Advances in rheumatology (London, England)*. 2018;58;20.

12. Maslarska M, Weis C, Bode C, Hehrlein C. Shear Wave Elastography of Peripheral Muscle Weakness in Patients with Chronic Congestive Heart Failure. *Ultrasound in medicine & biology*. 2018,44;2531-9.
13. Alfuraih AM, O'Connor P, Tan AL, Hensor EMA, Ladas A, Emery P, et al. Muscle shear wave elastography in idiopathic inflammatory myopathies: a case–control study with MRI correlation. *Skeletal Radiology*. 2019,48;1209-19.
14. Berko NS, Hay A, Sterba Y, Wahezi D, Levin TL. Efficacy of ultrasound elastography in detecting active myositis in children: can it replace MRI? *Pediatric radiology*. 2015,45;1522-8.
15. Baker JF, Von Feldt J, Mostoufi-Moab S, Noaiseh G, Taratuta E, Kim W, et al. Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. *Arthritis care & research*. 2014,66;1612-8.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid arthritis classification criteria: An American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis & Rheumatism*. 2010,62;2569-81.
17. Fransen J, van Riel PL. The Disease Activity Score and the EULAR response criteria. *Rheumatic diseases clinics of North America*. 2009,35;745-57, vii-viii.
18. Fransen J, Creemers M, Van Riel P. Remission in rheumatoid arthritis: agreement of the disease activity score (DAS28) with the ARA preliminary remission criteria. *Rheumatology*. 2004,43;1252-5.
19. Aletaha D, Ward MM, Machold KP, Nell VPK, Stamm T, Smolen JS. Remission and active disease in rheumatoid arthritis: Defining criteria for disease activity states. *Arthritis & Rheumatism*. 2005,52;2625-36.
20. Felson DT, Smolen JS, Wells G, Zhang B, Tuyl LHDv, Funovits J, et al. American College of Rheumatology/European League Against Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. *Arthritis & Rheumatism*. 2011,63;573-86.
21. Sigrist RMS, Liao J, Kaffas AE, Chammas MC, Willmann JK. Ultrasound Elastography: Review of Techniques and Clinical Applications. *Theranostics*. 2017,7;1303-29.
22. Alfuraih AM, O'Connor P, Hensor E, Tan AL, Emery P, Wakefield RJ. The effect of unit, depth, and probe load on the reliability of muscle shear wave elastography: Variables affecting reliability of SWE. *Journal of Clinical Ultrasound*. 2018,46;108-15.

23. Alfuraih AM, O'Connor P, Tan AL, Hensor E, Emery P, Wakefield RJ. An investigation into the variability between different shear wave elastography systems in muscle. *Medical ultrasonography*. 2017,19;392-400.
24. Fees E. *Grip Strength* (2nd ed). Chicago: American Society of Hand Therapists. 1992.
25. Wall JC, Bell C, Campbell S, Davis J. The Timed Get-up-and-Go test revisited: measurement of the component tasks. *Journal of rehabilitation research and development*. 2000,37;109.
26. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Research quarterly for exercise and sport*. 1999,70;113-9.
27. J. SJ, Ali G, Yanyan Z, C. ZA, Douglas GK, Margaret C, et al. Quadriceps weakness, patella alta, and structural features of patellofemoral osteoarthritis. *Arthritis Care & Research*. 2011,63;1391-7.
28. Schiottz-Christensen B, Lyngberg K, Keiding N, Ebling A, Danneskiold-Samsøe B, Bartels E. Use of isokinetic muscle strength as a measure of severity of rheumatoid arthritis: a comparison of this assessment method for RA with other assessment methods for the disease. *Clinical rheumatology*. 2001,20;423-7.
29. Browne RH. On the use of a pilot sample for sample size determination. *Stat Med*. 1995,14;1933-40.
30. Julious SA. Sample size of 12 per group rule of thumb for a pilot study. *Pharmaceutical Statistics*. 2005,4;287-91.
31. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;159-74.
32. Akagi R, Yamashita Y, Ueyasu Y. Age-Related Differences in Muscle Shear Moduli in the Lower Extremity. *Ultrasound Med Biol*. 2015,41;2906-12.
33. McCullough MB, Domire ZJ, Reed AM, Amin S, Ytterberg SR, Chen Q, et al. Evaluation of muscles affected by myositis using magnetic resonance elastography. *Muscle & nerve*. 2011,43;585-90.
34. Yamada T, Fedotovskaya O, Cheng AJ, Cornachione AS, Minozzo FC, Aulin C, et al. Nitrosative modifications of the Ca²⁺ release complex and actin underlie arthritis-induced muscle weakness. *Annals of the Rheumatic Diseases*. 2015,74;1907-14.
35. Targowski T. Sarcopaenia and rheumatoid arthritis. *Reumatologia*. 2017,55;84-7.

36. Helliwell PS, Jackson S. Relationship between weakness and muscle wasting in rheumatoid arthritis. *Annals of the Rheumatic Diseases*. 1994;53;726-8.
37. Fraser A, Vallow J, Preston A, Cooper RG. Predicting 'normal' grip strength for rheumatoid arthritis patients. *Rheumatology*. 1999;38;521-8.
38. Lemmey AB, Wilkinson TJ, Clayton RJ, Sheikh F, Whale J, Jones HSJ, et al. Tight control of disease activity fails to improve body composition or physical function in rheumatoid arthritis patients. *Rheumatology*. 2016;55;1736-45.
39. Madsen OR, Egsmose C. Associations of isokinetic knee extensor and flexor strength with steroid use and walking ability in women with rheumatoid arthritis. *Clin Rheumatol*. 2001;20;207-12.
40. Meireles S, Oliveira L, Andrade M, Silva A, Natour J. Isokinetic evaluation of the knee in patients with rheumatoid arthritis. *Joint Bone Spine*. 2002;69;566-73.
41. Fridén C, Thoors U, Glenmark B, Kosek E, Nordmark B, Lundberg IE, et al. Higher pain sensitivity and lower muscle strength in postmenopausal women with early rheumatoid arthritis compared with age-matched healthy women—a pilot study. *Disability and rehabilitation*. 2013;35;1350-6.
42. Beenakker KG, Ling CH, Meskers CG, de Craen AJ, Stijnen T, Westendorp RG, et al. Patterns of muscle strength loss with age in the general population and patients with a chronic inflammatory state. *Ageing research reviews*. 2010;9;431-6.
43. Böhler C, Radner H, Ernst M, Binder A, Stamm T, Aletaha D, et al. Rheumatoid arthritis and falls: the influence of disease activity. *Rheumatology*. 2012;kes198.
44. Lacourpaille L, Gross R, Hug F, Guével A, Péréon Y, Magot A, et al. Effects of Duchenne muscular dystrophy on muscle stiffness and response to electrically-induced muscle contraction: A 12-month follow-up. *Neuromuscular Disorders*. 2017;27;214-20.
45. Mathevon L, Michel F, Aubry S, Testa R, Lapole T, Arnaudeau LF, et al. Two-dimensional and shear wave elastography ultrasound: A reliable method to analyse spastic muscles? *Muscle Nerve*. 2018;57;222-8.
46. Stanmore EK. Recommendations for assessing and preventing falls in adults of all ages with rheumatoid arthritis. *British Journal of Community Nursing*. 2015;20;529-33.
47. Iversen GR, Wildt AR, Norpoth H, Norpoth HP. *Analysis of variance*: Sage;1987.

Figure legends

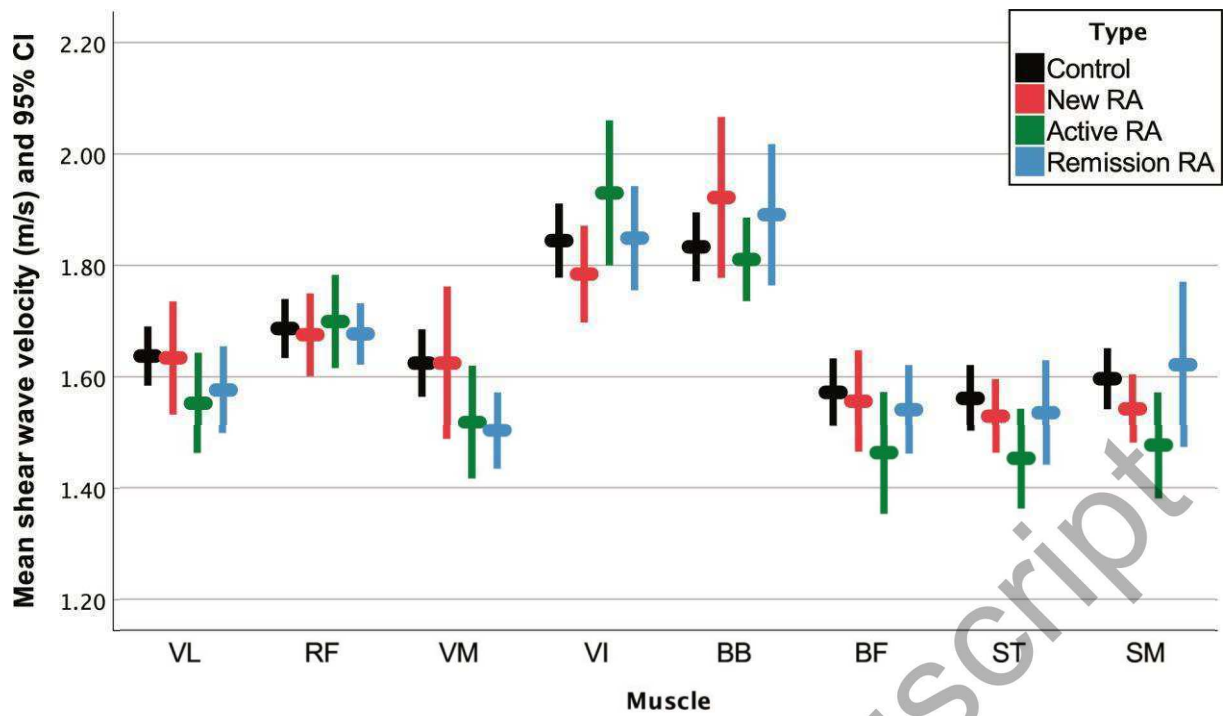


Fig.1 Shear wave velocity means and 95% CI for each participant group.

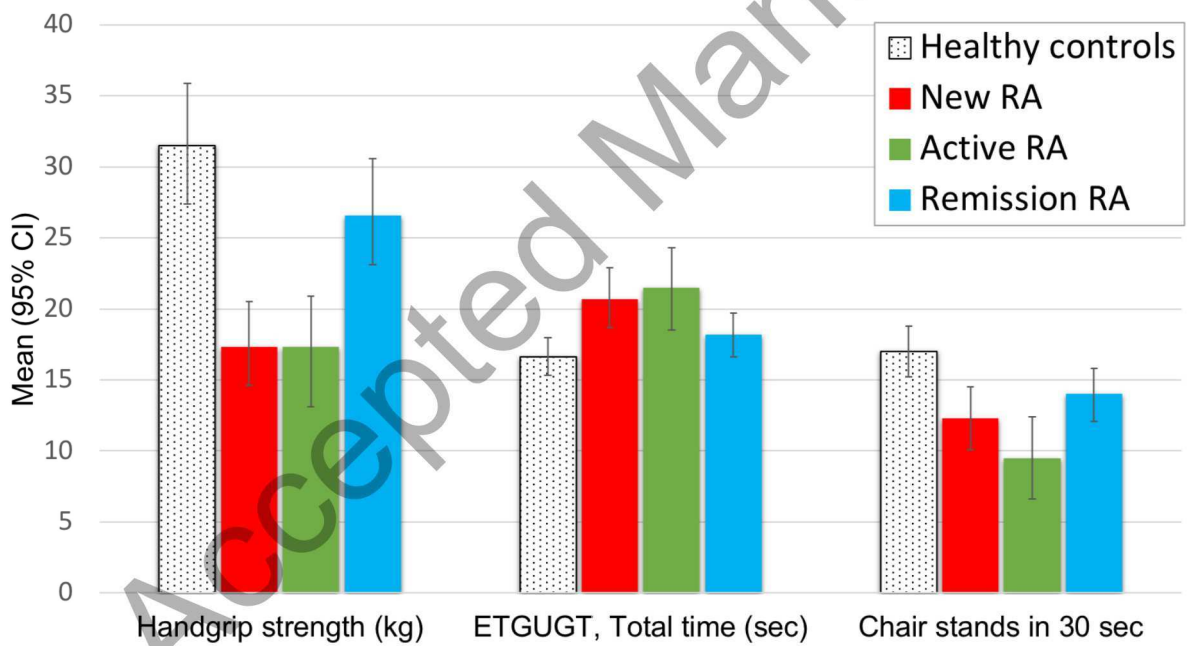


Fig.2 Participants' performance in handgrip strength, walking time and number of chair stands in 30 seconds.

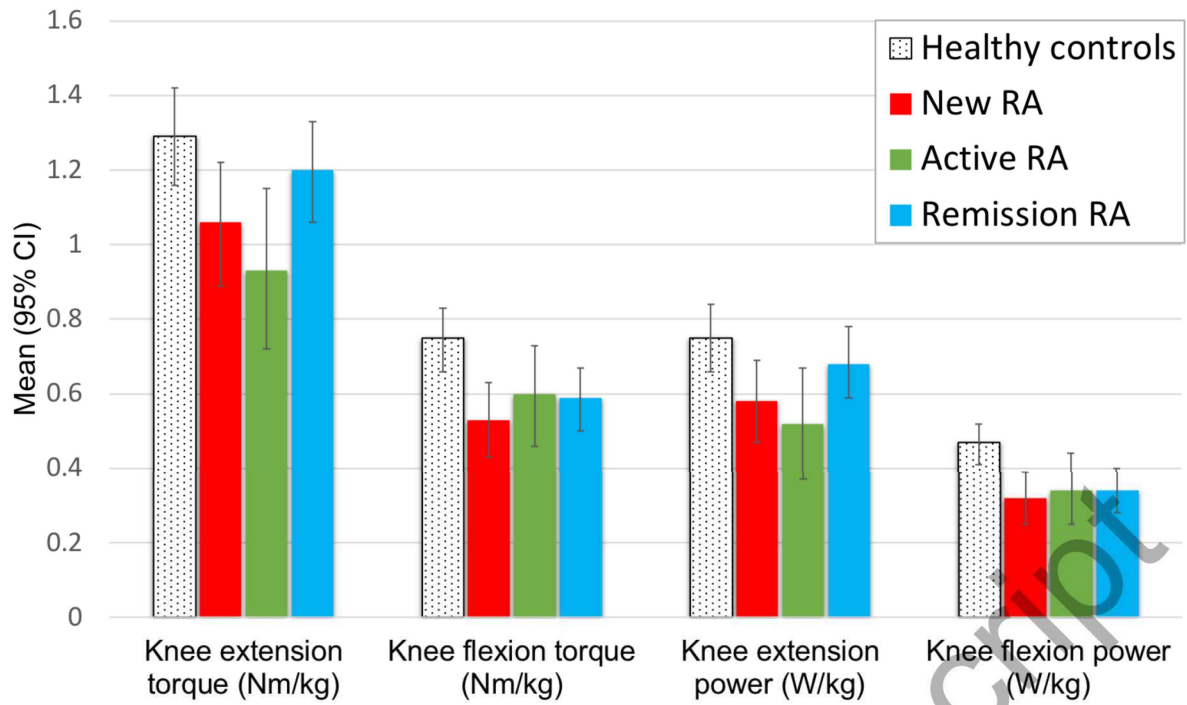


Fig.3 Isokinetic knee strength during flexion and extension for the healthy controls and RA patients.

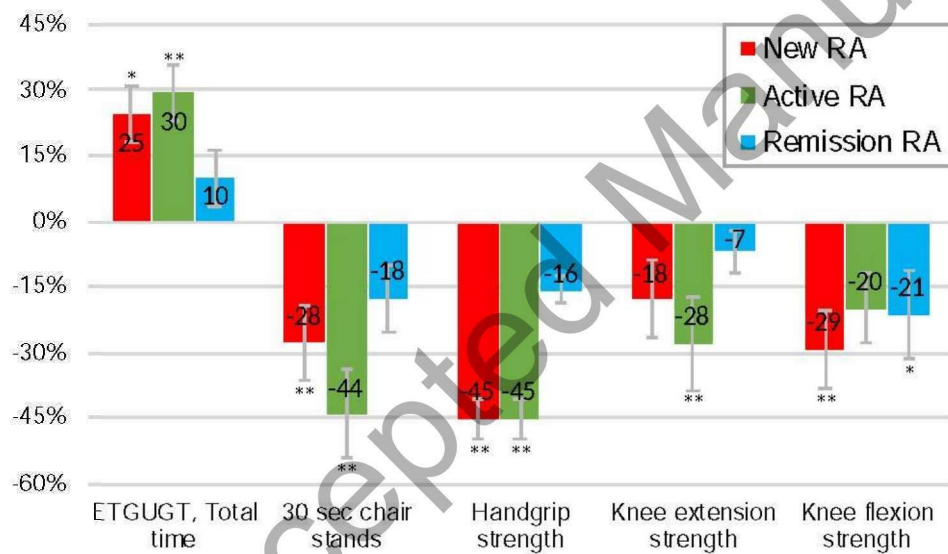


Fig.4 Difference percentages in muscle assessment results for the RA patients relative to the healthy controls. (*) significant at $p < 0.05$, (**) significant at $p < 0.001$.