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Association of phenotypic frailty and hand grip strength with telomere length in SLE

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ABSTRACT

Objective Frailty and objective hand grip strength (one of the components of the frailty phenotype) are both risk factors for worse health outcomes in SLE. Whether telomere length, an established cellular senescence marker, is a biologic correlate of the frailty phenotype and hand grip strength in patients with SLE is not clear. First, we aimed to evaluate differences in telomere length between frail and non-frail women with SLE and then assessed whether frailty or hand grip strength is differentially associated with telomere length after adjusting for relevant confounders.

Methods Women ≥18 years of age with validated SLE enrolled at a single medical centre. Fried frailty status (which includes hand grip strength), clinical characteristics and telomere length were assessed cross-sectionally. Differences between frail and non-frail participants were evaluated using Fisher's exact or Wilcoxon rank-sum tests. The associations between frailty and hand grip strength and telomere length were determined using linear regression.

Results Of the 150 enrolled participants, 131 had sufficient data for determination of frailty classification; 26% were frail with a median age of 45 years. There was a non-significant trend towards shorter telomere length in frail versus non-frail participants (p=0.07). Hand grip strength was significantly associated with telomere length (beta coefficient 0.02, 95% CI 0.004, 0.04), including after adjustment for age, SLE disease activity and organ damage, and comorbidity (beta coefficient 0.02, 95% CI 0.002, 0.04).

Conclusions Decreased hand grip strength, but not frailty, was independently associated with shortened telomere length in a cohort of non-elderly women with SLE. Frailty in this middle-aged cohort may be multifactorial rather than strictly a manifestation of accelerated ageing.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Physical frailty and hand grip strength, a component of the frailty construct, are risk factors for worse health outcomes in SLE.

WHAT THIS STUDY ADDS

⇒ Decreased hand grip strength, but not frailty, was associated with shortened telomere length in women with SLE independent of standard disease severity metrics.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Frailty in non-elderly women with SLE may be multifactorial rather than strictly a manifestation of accelerated ageing.

INTRODUCTION

Frailty is a marker of vulnerability to adverse health.[1] While multiple approaches to frailty measurement exist, physical (also known as phenotypic) frailty according to Fried's definition is widely recognised.[1] The Fried phenotype is found in up to 20% of adults with SLE and associated with worse health-related quality of life, disability and mortality.[2 3]

Hand grip strength, a component of the Fried phenotype, has been proposed as a proxy for health status in the general population.[4] Weaker hand grip strength has been observed in adults with SLE relative to non-SLE comparators,[5] and weaker hand grip is associated with higher cardiometabolic risk when adjusted for body mass index (BMI).[6]

Telomeres consist of repetitive DNA sequences and protein complexes that protect chromosomes from damage and rearrangement.[7] Telomere shortening occurs in the context of somatic cell division, with telomere length widely considered a biomarker of cellular senescence.[7] Shortened telomere length has been associated with higher overall mortality in the general population of adults, as well as cardiovascular, respiratory, gastrointestinal and musculoskeletal mortality.[8]

There has been some study of telomere length in adults with SLE.[9] Adults with SLE have been found to have shorter telomere lengths relative to healthy comparators, including in whole blood and peripheral

mononuclear cells.[9] In adults with SLE, longer telomere length has been associated with factors such as Ro positivity, glucocorticoid treatment, higher BMI and tobacco use.[10] Telomere length has been variably associated with disease activity in SLE.[10 11] In Mendelian randomisation analyses, longer telomere length has been associated with higher risk of developing SLE.[12 13]

While it is hypothesised that shortened telomere length may reflect increased physiologic stress associated with frailty, evidence of an association between physical frailty and hand grip strength and shortened telomere length in the general population has been inconsistent.[14–16] If physical frailty or hand grip strength is associated with shortened telomere length in adults with SLE, then this would provide intriguing data linking cellular biology with clinical phenotypes. We aimed to evaluate differences in telomere length between frail and non-frail women with SLE and to assess whether the Fried phenotype or hand grip strength is associated cross-sectionally with telomere length after adjusting for confounders.

MATERIALS AND METHODS

Participants

Women ≥18 years of age seen at Hospital for Special Surgery (HSS) from August 2020 to October 2021 were eligible. SLE diagnosis was validated through medical record review.[17] Exclusions included dialysis, pregnancy, active malignancy (apart from non-melanomatous skin cancer), overlap autoimmune inflammatory disease (apart from Sjogren's or antiphospholipid syndrome), impairment due to recent surgery or injury, or inability to complete surveys in English. Written informed consent was received from participants.

Frailty and hand grip strength

Frailty was assessed using Fried's definition as operationalised in SLE.[1–3] This included (1) unintentional weight loss: self-report loss ≥10 pounds in the preceding year or BMI <18.5 kg/m^2; (2) weakness: below the set threshold of hand grip strength via dynamometer adjusted for BMI; (3) fatigue: positive response to ≥1/2 questions on the Center for Epidemiologic Studies Depression scale[18]; (4) slow gait: below the set threshold of time to walk 4 m adjusted for height; and (5) low activity: <600 MET-min/week using the International Physical Activity Questionnaire.[19] Frailty was present when ≥3 criteria were met. Fried frailty status has been associated with multiple adverse health outcomes, including higher mortality, in general population studies.[1]

Sociodemographic and clinical characteristics

Date of birth and Charlson Comorbidity Index[20] were derived from medical record review. Race, ethnicity, cigarette smoking, SLE duration and fibromyalgia were self-reported.

Disease activity and damage

SLE disease activity and organ damage were assessed using the Safety of Estrogens in Lupus National Assessment (SELENA)-SLE Disease Activity Index (SLEDAI)[21] and the Systemic Lupus International Collaborating Clinics/ACR Damage Index for SLE (SDI), respectively.[22]

Telomere length

Telomere length was determined from whole blood using Southern analysis of terminal restriction fragments.[23] Chromosomal DNAs were isolated from whole blood, digested with *Hinf*I and *Rsa*I, and fractionated in 0.6% agarose gels. After transfer to nylon membranes, the terminal restriction fragments were detected via hybridisation to a telomere repeat probe ($(TTAGGG)_{82}$). Average telomere lengths were determined from PhosphorImager scans of the blots as previously described.[23]

Sample size

Sample size was based on an a priori calculation. Given a standardised mean difference (SMD) in telomere length of 0.835 (95% CI −1.291, −0.380) between adults with SLE and healthy comparators,[9] 29 adults with SLE and 29 healthy comparators would be needed to detect a difference in telomere length between adults with SLE and healthy comparators at α of 0.1. From these estimates, we assumed that 29 frail participants with SLE and 29 non-frail participants with SLE would be needed to detect a similar difference in telomere length. Given Fried frailty prevalence of 21% in an interim analysis of a pilot study of women with SLE conducted at our centre,[3] we planned to recruit at least 144 participants with SLE to identify 30 frail participants and conservatively anticipated enrolment of a total of 150 participants with SLE.

Analysis

Differences in clinical characteristics and telomere length between frail and non-frail participants were evaluated using Fisher's exact or Wilcoxon rank-sum tests. Associations of frailty and frailty components, both expressed as categorical variables, with telomere length expressed as a continuous variable were assessed using linear regression. In addition, the association of hand grip strength with telomere length, both expressed as continuous variables, was modelled using linear regression. Each regression model was adjusted for age, SLE disease activity and organ damage, and Charlson Comorbidity Index. A sensitivity analysis in which each regression model was further adjusted for cigarette smoking status also was performed. All model results were reported after conducting multiple imputation using chained equations to account for missing values. We performed 15 imputations for the components of frailty, and the parameter estimates were aggregated using Rubin's rules.

RESULTS

Sample characteristics

Of the 150 total participants, 131 provided sufficient data to assess frailty status: 17.3% were Black or African American; 20.7% were Hispanic or Latino. Participants had median age of 45 years (IQR 32–57 years), SLE disease

Table 1 Characteristics of participants with SLE by physical frailty classification

Median (IQR) unless otherwise specified	All (n=131)	Non-frail (n=97)	Frail (n=34)	P value
Age (years)	45 (32, 57)	44 (30, 56)	48 (38. 62)	0.05
Race and ethnicity, N (%)				0.67
Black or African American	26 (17.3)	14 (14.4)	7 (20.6)	
Hispanic or Latino	31 (20.7)	18 (18.6)	7 (20.6)	
White	20 (13.3)	14 (14.4)	2 (5.9)	
Other	15 (10.0)	11 (11.3)	3 (8.8)	
Declined	58 (38.7)	40 (41.2)	15 (44.1)	
Ever smoking, N (%)	17 (13.7)	8 (8.8)	9 (27.3)	0.01
SLE disease duration (years)	15 (8, 24)	15 (8, 25)	15 (8, 20)	0.40
SELENA-SLEDAI score	2 (0, 4)	2 (0, 4)	2 (0, 5)	0.57
SLICC/ACR Damage Index score	1 (0, 2)	0 (0, 2)	2 (1, 4)	<0.01
Charlson Comorbidity Index	2 (0, 3)	1 (0, 3)	2 (1, 4)	0.02
Self-report fibromyalgia, N (%)	23 (17.6)	12 (13.2)	11 (33.3)	0.02
Self-report current steroid use	41 (31.3)	35 (41.2)	6 (23.1)	0.25
Telomere length (kilobases)	6.49 (6.03, 7.13)	6.56 (6.08, 7.29)	6.41 (5.81, 6.90)	0.07

SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index; SLICC/ACR Damage Index, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index.

duration of 15 years (IQR 8–24), SELENA-SLEDAI score of 2 (IQR 0–4) and SDI score of 1 (IQR 0–2) (table 1). The 19 participants whose frailty status could not be determined did not differ significantly in terms of age, race, ethnicity or organ damage from those with classifiable frailty status. Of the 131 participants with known frailty status, 34 (26.0%) were frail (table 2). In the multiply imputed data, 27.0% of the sample was frail.

Frail participants were similar in age to non-frail participants (median 48 years (IQR 38–62) vs 44 years (IQR 30–56), p=0.05), with higher prevalence of lifetime cigarette smoking (27.3% vs 8.8%, p=0.01) (table 1). Compared with non-frail participants, frail participants had greater organ damage (median SDI score: 2 (IQR 1–4) vs 0 (IQR 0–2), p<0.01) and comorbidity (median Charlson Comorbidity Index: 2 (IQR 1–4) vs 1 (IQR 0–3), p=0.02) and more prevalent fibromyalgia (33.3% vs 13.2%, p=0.02). Among all participants, 41 (31.3%) used steroids daily. However, among those with frailty, this proportion was smaller (23.1%) compared with those who were not frail (41.2%), although this difference did not reach statistical significance (p=0.25).

Table 2 Prevalence of individual components in adults with SLE by physical frailty classification

Component N (%)	All (N=131)	Non-frail (n=97)	Frail (n=34)
Weight loss	28 (21.4)	14 (14.4)	14 (41.2)
Fatigue	51 (38.9)	23 (23.7)	28 (82.4)
Slow gait	25 (19.1)	7 (7.2)	18 (52.9)
Weakness	82 (62.6)	51 (52.6)	31 (91.2)
Inactivity	26 (19.8)	7 (7.2)	19 (55.9)

Association of frailty status and and hand grip strength with telomere length

There was a non-significant trend towards shorter telomere length in frail versus non-frail participants (p=0.07) (table 1). Hand grip strength was significantly associated with telomere length (beta coefficient 0.02, 95% CI 0.004, 0.04) (table 3). This relationship remained significant after adjustment for age, disease activity, organ damage, and Charlson Comorbidity Index (beta coefficient 0.02, 95% CI 0.002, 0.04) and further adjustment for smoking status (beta coefficient 0.02, 95% CI 0.002, 0.04).

DISCUSSION

Among women with SLE, phenotypic frailty was present in 26.0% of participants despite median age of 45 years. A non-significant trend towards shorter telomere length was observed in frail versus non-frail individuals with SLE. Hand grip strength was associated with telomere

Table 3 Cross-sectional association of physical frailty and individual frailty components with telomere length (kilobases) in adults with SLE

	Unadjusted		Adjusted*	
Models	Beta coefficient	95% CI	Beta coefficient	95% CI
Frailty	−0.22	−0.51, 0.07	−0.18	−0.50, 0.15
Weight loss	0.26	−0.05, 0.57	0.19	−0.11, 0.49
Fatigue	−0.002	−0.28, 0.28	−0.04	−0.31, to 0.23
Slow gait	−0.30	−0.59, 0.004	−0.18	−0.49, 0.14
Weakness	−0.30	−0.57, −0.03	−0.17	−0.45, 0.10
Inactivity	−0.15	−0.51, 0.21	−0.09	−0.40, 0.23
	Beta coefficient	**95% CI**	**Beta coefficient**	**95% CI**
Grip strength	0.02	0.004 to 0.04	0.02	0.002 to 0.04

*Adjusted for age, disease activity, organ damage and Charlson Comorbidity Index.

length, even after adjustment for confounders, including standard disease severity metrics.

Prior studies examining the association between physical frailty and telomere length in older adults have generated inconsistent results.[14 15] In a recent meta-analysis (frail: n=355; non-frail: n=1894), physically frail individuals had significantly shorter telomeres versus non-frail comparators (SMD −0.41; 95% CI −0.73, −0.09; p=0.01; I^2=82%).[15] In contrast, a second recent meta-analysis with partially overlapping study samples (frail: n=639 frail; non-frail: n=1199) did not demonstrate a significant difference in telomere length between physically frail and non-frail participants (mean difference=0.07; 95% CI −0.03, 0.16; p=0.17; I^2=76%).[14]

It is known that adults with SLE have shorter telomere lengths relative to healthy comparators.[9] A recent meta-analysis demonstrated significantly shorter telomere length in adults with SLE (n=472) compared with age-matched healthy comparators (n=365) (SMD −0.835; 95% CI=−1.291,−0.380; p=3.3×10^{-4}).[9] In a cross-sectional sample of 164 adults with SLE, longer telomere length was associated with multiple factors, including glucocorticoid therapy, BMI, tobacco use and carotid plaque.[10] In contrast, we did not find an association between weight loss and telomere length. Further study of the relationship between telomere length and physical frailty is needed in larger SLE cohorts as shortened telomere length is an appealing candidate biomarker of frailty. Whether the combination of telomere length and physical frailty classification is more predictive of adverse health outcomes in adults with SLE than either factor alone is also a future direction.

We found that hand grip strength was independently associated with telomere length. As with frailty, the association of hand grip strength with telomere length in the general population has been mixed.[16] In the general population, greater hand grip strength is associated with reduction in mortality, cardiovascular death risk and incidence of disability.[4] Hand grip strength normalised for BMI has been associated with proxy measures for cardiovascular health in individuals with SLE.[6] Longitudinal studies are needed to evaluate whether telomere length predicts worse health outcomes, including mortality, in women with SLE.

Our study has limitations. We might have been underpowered to identify a small, but clinically significant difference in telomere length between frail and non-frail participants; it is possible that those who were most frail were not enrolled due to the ongoing COVID-19 pandemic. Evaluating other frailty definitions besides the Fried phenotype and menopausal status were beyond the scope of our study. We did not consider individuals with other autoimmune inflammatory conditions or healthy comparators.

To our knowledge, this is the first study to evaluate relationships between physical frailty status and hand grip strength and telomere length among women with SLE. We found an independent significant association between hand grip strength and telomere length, but not frailty and telomere length in this cohort of middle-aged women with SLE. Frailty in non-elderly women with SLE may be multifactorial rather than a manifestation of accelerated biologic ageing.

Our data suggest that hand grip strength, an easily available metric, may be particularly informative in studies of SLE and frailty across the lifespan and potentially clinically relevant for assessment by physical therapists or exercise physiologists if the association with telomere length is confirmed in future studies. Further investigation is needed in larger SLE cohorts to clarify the relationship between frailty, hand grip strength and telomere length.

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