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Serum Biomarkers of Inflammation and Muscle Strength among Women with Systemic Lupus Erythematosus

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Abstract

Objectives—Muscle strength is an important determinant of physical function in women with systemic lupus erythematosus (SLE). Serum biomarkers of inflammation, including interleukin-6 (IL-6) and C-Reactive Protein (CRP), are associated with differences in muscle strength among individuals without rheumatologic disease. We examined whether serum levels of IL-6 and CRP are associated with upper and lower extremity muscle strength among adult women with SLE.

Methods—One hundred thirty-six women with SLE participated in this crosssectional study. High-sensitivity CRP was analyzed by nephelometry. IL-6 serum levels were analyzed by high sensitivity enzyme-linked immunosorbent assay. Upper and lower extremity muscle strength were assessed by grip strength and peak torque of knee extension and flexion, respectively. Regression analyses modeled associations of CRP and IL-6 with upper and lower extremity muscle strength controlling for age, SLE duration, physical activity, prednisone use, BMI, plaquenil use, and pain.

Results—Higher serum levels of IL-6 and CRP were associated with significantly weaker upper and lower extremity muscle strength even when controlling for covariates.

Conclusions—Increased serum IL-6 and CRP are associated with clinically significant differences in upper and lower extremity muscle strength and may be useful in identifying those at risk for weakness and decreased physical function.

Keywords

Systemic lupus erythematosus; Inflammation; Cytokines; Outcomes Research

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Introduction

Reduced muscle strength is strongly related to decreased physical function among women with systemic lupus erythematosus (SLE) (1, 2). Interleukin-6 (IL-6) mediates immune signaling pathways that influence skeletal muscle protein homeostasis and myogenesis (3). In addition, serum levels of C-reactive protein (CRP) and IL-6 are inversely associated with measures of muscle strength in the general population and in individuals with chronic inflammatory conditions, such as chronic obstructive pulmonary disease and congestive heart failure (4, 5). Rheumatologic illnesses, such as rheumatoid arthritis (RA) and SLE, are characterized by chronic, increased inflammation and frequently lead to decreased physical function. However, only limited data exist that examine whether IL-6 and CRP are associated with differences in muscle strength in this population (6); and to our knowledge, no data have been published examining the association of IL-6 and CRP with muscle strength among individuals with SLE.

Given the important role of muscle weakness as a determinant of physical function in SLE, the goal of the present study was to address this gap in the literature by testing whether serum levels of IL-6 and CRP are cross-sectionally associated with differences in upper and lower extremity muscle strength.

Subjects and Methods

Subjects

Participants were drawn from the University of California, San Francisco (UCSF) Lupus Outcomes Study (LOS) (7). SLE diagnoses by the American College of Rheumatology (ACR) criteria were verified by medical record review. LOS participants living in the greater San Francisco Bay area were recruited for an inperson assessment that included measurement of upper and lower extremity muscle strength. Exclusion criteria were non-English speaking, age <18 years, current daily oral prednisone dose >50 mg, current pregnancy, uncorrected vision problems that would interfere with reading, and joint replacement within 12 months. The final sample for the present cross-sectional study is comprised of the 136 women for whom complete CRP and IL-6 data were available. This study was approved by the UCSF Committee on Human Research.

Biomarkers of Inflammation

Blood samples were collected during study visits and frozen at −80°C. Biomarker levels were assessed from frozen-stored serum. High-sensitivity CRP was analyzed by nephelometry at a regional clinical laboratory. High-sensitivity IL-6 was analyzed by ELISA (R&D Systems) using a MRX Revelation spectrophotometer/luminometer (LaJolla Tech, La Jolla CA).

Muscle strength

Lower extremity muscle strength was assessed by peak isokinetic torques of knee extension and flexion as previously described (1). Maximum grip strength was measured using a hand-

held dynamometer (1). Three trials, separated by rest intervals, were conducted for each hand. The maximum grip on the dominant hand was used in analysis.

Other Variables

Age and SLE disease duration were obtained from the baseline LOS telephone interview. Systemic Lupus Activity Questionnaire (SLAQ), a validated, self-report measure of disease activity in SLE, measured disease activity (8). The SLAQ was assessed at the LOS interview prior to the in-person visit (mean time to visit = 54.4 days). The following measures were all assessed at the time of the inperson visit. Glucocorticoid and hydroxychloroquine use were assessed by selfreport. Physical activity was measured by self-report using the long form of the International Physical Activity Questionnaire (IPAQ) (9). Participants who expended fewer than 600 metabolic equivalent (MET) minutes per week were classified as inactive (9). Body mass index (BMI) was measured as weight/height^2 (kg/m^2). Pain severity was assessed by the Short Form 36 (SF-36) bodily pain assessment, in which participants were asked, “How much bodily pain have you had in the last 4 weeks?” Scores are standardized to range from 0–100 (mean ± SD = 50 ± 10), and higher scores reflect less pain (10).

Statistical Analysis

Due to skewedness, levels of IL-6 and CRP were logarithmically transformed to the normal distribution prior to inclusion in regression analyses. Linear regression analyses then modeled the associations between the log of the inflammation biomarkers and muscle strength with and without adjusting for covariates (age, disease duration, prednisone and plaquenil use, low physical activity, and pain). Statistical analyses were performed using Stata, version 13.1 (StataCorp, College Station, TX).

Results

Subject characteristics

Participant characteristics are shown in Table 1. The overall median (interquartile range) serum level of IL-6 and CRP was 1.6 pg/mL (1.1, 2.7, reference range 0–5) and 1.3 mg/L (0.6, 4.5, reference range 0–10), respectively. The observed values of IL-6 and CRP in this cohort are comparable to those observed in other SLE cohorts (11, 12). The mean ± SD peak torques of knee extension and flexion were 44.2 ± 16.0 and 29.8 ± 11.5 N-m, respectively; and of grip strength was 22.4 ± 6.8 kg.

Association of serum inflammation with physical function

In unadjusted models, both IL-6 and CRP were significantly associated with differences in all strength measures, such that greater inflammation was linked to greater weakness. In adjusted models, IL-6 was significantly associated with differences in knee flexion and grip strength and trended towards an association with knee extension. By contrast, the adjusted models for CRP showed a significant association with differences in knee extension and trended towards an association with knee flexion and grip strength (Table 2).

Missing Muscle Strength Data

Of the 136 women, 112 (82%) completed the knee torque assessment, 115 (85%) completed the grip strength assessment; 97 (71%) completed both assessments. The most common reasons for non-completion were pain or health-related contraindications to the procedures (e.g., high or low blood pressure). Compared to women with complete strength data, women missing either knee torque or grip strength data or both, had greater mean age (51.5 ± 10.1 vs 46.3 ± 12.6 years), BMI (31.1 ± 7.9 vs 25.9 ± 5.8 kg/m^2), pain (37.4 ± 8.4 vs 44.0 ± 11.4), SLAQ score (17.1 ± 6.4 vs 11.3 ± 7.4); and lower peak torque of knee extension (33.0 ± 13.8 vs 45.9 ± 15.7 N-m) (all $p<0.05$). These women also trended towards greater disease duration (17.9 ± 8.7 vs 15.1 ± 9.4 years; $p=0.1$), decreased physical activity (38% vs 25%; $p=0.1$), and lower peak torque of knee flexion (26.1 ± 11.9 vs 30.3 ± 11.4 N-m; $p=0.2$). Mean daily prednisone dose, plaquenil use, inflammation biomarkers levels, and grip strength did not significantly differ ($p>0.05$) between women with complete versus partial strength data (data not shown).

Discussion

We observed that among adult women with SLE increased serum levels of IL-6 and CRP were associated with reduced upper and lower extremity muscle strength, even when controlling for differences in body composition, physical inactivity, medication use, and pain. To our knowledge, ours is the first study to demonstrate this relationship in SLE.

This study builds upon our prior observation that muscle weakness is a major determinant of physical function in women with SLE (1, 2) by identifying an important relationship between systemic inflammation and muscle strength in these individuals. In addition, the present study addresses the question of whether relationships between chronic inflammation and muscle strength that have been observed in the elderly and individuals without rheumatologic illness may also exist among a relatively younger cohort of women with SLE. These findings suggest that biomarkers of increased systemic inflammation may have utility in identifying increased risk of reduced muscle strength in SLE as well. Additional clinical and basic science studies are needed to directly evaluate hypothesized mechanisms of inflammation-mediated muscle weakness in SLE as well as longitudinal relationships between these biomarkers of inflammation, muscle strength, and physical function outcomes.

The observed effects of IL-6 and CRP on differences in muscle strength are clinically meaningful. The minimum clinically important difference (MCID) for a health-related quality of life measure is often estimated as a one-half standard deviation (SD) difference (13). For example, we observed that a 1-unit increase in the natural logarithm of IL-6 is associated with approximately 4 N-m decrease in peak torque of knee flexion and 3 kg decrease in grip strength (Table 2). Therefore, a 1-logarithm increase in IL-6 from 1 pg/mL to 2.7 pg/mL (from the 25th to 75th percentile) is associated with decreases in knee flexion and grip strength that approach the MCID, even when controlling for covariates.

We observed more consistent associations of muscle strength with IL-6 than with CRP in this cohort of women with SLE. Several possible explanations may contribute to this

observation. As an acute phase reactant produced by various inflammatory pathways, CRP has been noted to correlate less closely with SLE disease activity than do other measures of inflammation, such as the sedimentation rate (ESR) (14). In addition, IL-6, a specific pro-inflammatory cytokine and an anti-inflammatory myokine, has been noted to correlate with SLE disease activity and is directly implicated in pathways affecting muscle strength and physical function in various populations (15). These hypotheses need to be directly evaluated. Lastly, while the statistical significance of the associations of IL-6 and CRP with muscle strength varied between different strength measures, the overall trend was consistent: increased serum levels of IL-6 and CRP were associated with reduced muscle strength. In adjusted models, all point estimates of the effect were negative and all confidence intervals included mainly negative values. We hypothesize that the observed differences in statistical significance between models are likely driven by inadequate power.

Our study has potential limitations. This is a cross-sectional study, and there are no data available from a control comparison group of women without SLE. The study's power may be limited by missing data and the tendency of more physically impaired women not to complete the strength assessments.

There are also strengths of our study. This is to our knowledge the first study of SLE to utilize objective measures of muscle strength in evaluating the association of serum biomarkers of inflammation with muscle strength. We used standardized, objective methods to quantify upper and lower extremity muscle strength and their relationship to IL-6 and CRP.

In summary, we observed that in women with SLE, increased serum levels of IL-6 and CRP are associated with clinically meaningful decreases in upper and lower extremity muscle strength even when controlling for differences in obesity, physical activity, and pain. Further studies are needed to examine the longitudinal relationships between systemic inflammation, muscle strength, and physical function outcomes in SLE.

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Highlights

- This study is the first to examine relationships of specific inflammation biomarkers to muscle strength in SLE.
- Greater systemic inflammation, measured as higher serum IL-6 and CRP, is associated with clinically significant declines in upper and lower extremity muscle strength among adult women with SLE.
- There may be a role for IL-6 and CRP in identifying those women at greatest risk for being or becoming weaker and more physically disabled.

Tablel 1

Participant Characteristics (n=136)[#]

Age, years	47.8 ± 12.1
Disease Duration, years	15.9 ± 9.3
SLAQ Score Prednisone use, mg/day % (n)	13.0 ± 7.6
0	51.4 (70)
1–4.5	6.6 (9)
5–9.5	20.6 (28)
10–14.5	13.2 (18)
15–19.5	3.7 (5)
≥ 20	2.2 (3)
Low Activity[+], % (n)	28.7 (39)
BMI, kg/m^2	27.4 ± 6.9
Plaquenil User, % (n)	65.4 (89)
Pain Score[++]	42.1 ± 11.0
IL-6, pg/mL	1.6 (1.1, 2.7)
hsCRP, mg/L	1.3 (0.6, 4.5)
Biodex®, N-m	
Knee Extension	44.2 ± 16.0 (n=112)
Knee Flexion	29.8 ± 11.5 (n=112)
Grip Strength, kg	22.4 ± 6.8 (n=115)

[#]Values are mean ± standard deviation or median (interquartile range) unless otherwise indicated. Inflammation biomarker reference ranges: hsCRP (0–10), IL-6 (0–5).

[+]Based on International Physical Activity Questionnaire (IPAQ)

[++]Based on SF36 Overall Pain Assessment

Table 2

Models of Muscle Strength as a Function of the Natural Log of Interleukin-6 or C-Reactive Protein among Women with SLE [#]

		IL-6		CRP	
Model	**Outcome**	**Unadjusted**	**Adjusted[##]**	**Unadjusted**	**Adjusted[##]**
1	Knee Extension, N-m	−4.36 (−8.15, −0.59) *	−2.37 (−5.69, 0.96)	−4.34 (−6.47, −2.20) ***	−3.03 (−5.22, −0.84) **
2	Knee Flexion, N-m	−4.98 (−7.60,−2.36) ***	−3.77 (−6.21, −1.34) **	−2.13 (−3.72, −0.53) **	−0.71 (−2.42, 1.01)
3	Grip Strength, kg	−2.56 (−4.07, −1.05) **	−2.74 (−4.36, −1.11) **	−1.11 (−2.01, −0.20) *	−0.97 (−2.01, 0.07)

[#] Values are the regression beta coefficient (95% confidence interval) for the mean change in outcome measure associated with a 1 -unit change in the natural log of IL-6 or CRP. The minimum clinically important difference (MCID), calculated as one-half standard deviation change, for knee extension, knee flexion, and grip strength are 8 N-m, 5.75 N-m, and 3.4 kg, respectively.

[##] Model is adjusted for covariates: age, disease duration, prednisone use, low physical activity level (active vs inactive), BMI, plaquenil use, and pain.

* p<0.05

** p<0.01

*** p<0.001