Opinion

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When *might* isn't right: the impact of muscle weakness on physical function in systemic lupus erythematosus

"Differences in body composition, and in particular differences in muscle strength, represent an important etiology of reduced physical functioning among individuals with systemic lupus erythematosus."

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James Andrews
University of California, 500 Parnassus Ave, San Francisco, CA 94143, USA
james.andrews@ucsf.edu

"What surprises me most is that everyone is not surprised by weakness."
–Blaise Pascal (*Les Pensées*)

Pascal, the renowned 17th century French philosopher and mathematician, was admittedly concerned less with physical weakness, than with spiritual or moral weakness when he penned this statement of surprise. Nevertheless, the sense of astonishment underlying his words remains apropos to our discussion of physical weakness among individuals with systemic lupus erythematosus (SLE). Reduced physical functioning is common among individuals with SLE and is frequently associated with significantly reduced health-related quality of life [1,2]. Differences in body composition, and in particular differences in muscle strength, represent an important etiology of reduced physical functioning among individuals with SLE. What is truly surprising is that despite the considerable burden of physical disability and muscle weakness in SLE, published data addressing these relationships remain limited.

There exists, however, a body of literature examining relationships between body composition, muscle strength and physical disability among other chronic conditions, both rheumatic and nonrheumatic. Among elders and individuals with osteoarthritis (OA), muscle strength and muscle mass (both regional and total body muscle mass) are inversely related to physical disability [3,4]. However, muscle strength is more closely related to the degree of disability than is muscle mass among the elderly [5]. Among individuals with rheumatoid arthritis (RA), similar relationships exist between muscle mass, muscle strength and physical disability [6]; and, similar to in OA, in RA measures related to muscle function are more strongly associated with differences in physical functioning than are measures of muscle mass [7]. Taken together, these observations suggest that muscle strength makes an important contribution to an individual's physical functioning in various populations.

Until recently it was not known whether similar relationships exist among individuals with SLE. Our group recently demonstrated that among women with SLE muscle strength is directly associated with differences in physical functioning even when adjusting for differences in muscle mass; and differences in muscle strength at baseline predict changes in physical functioning 2 years later [8,9]. In this cohort of adult women with SLE, reduced lower extremity muscle strength (measured by knee strength and chair stand time) but not reduced muscle mass was associated with reduced self-reported physical functioning on the SF-36 Physical Functioning subscale and on the Valued Life Activities assessment, when adjusting for covariates such as disease activity, medication use and depression. Reduced knee strength also predicted significant decreases in physical functioning approximately 2 years later, as measured by the Short Physical Performance Battery

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(SPPB), in similarly adjusted models. Moreover, the effect of baseline muscle strength on future SPPB scores was greatest among women with lowest baseline muscle strength. These observations demonstrate that muscle strength makes important and independent contributions to physical functioning among women with SLE, and they suggest that interventions focusing on muscle strength may be beneficial in improving physical functioning and health-related quality of life for these individuals.

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Despite this recent evidence that differences in muscle strength account for changes in physical functioning over time among women with SLE, several questions remain regarding these relationships. For example, how weak does an individual need to be before his or her weakness becomes clinically relevant? Answers to questions such as this are emerging, thanks in large part due to research done by the Foundation for the National Institutes of Health Sarcopenia Project, which aims to advance understanding of aging-related changes in body composition, muscle strength and physical functioning. The Sarcopenia Project investigators recently published recommended definitions of clinically meaningful muscle weakness and low muscle mass for geriatric populations. These recommended cutpoints of weakness and reduced muscle mass predicted significant changes in a clinically relevant measure of physical functioning, walking speed [10,11]. For example, a hand grip strength less than 16 kg, compared with grip strength more than 16 kg, was associated with approximately twice the odds of developing incident mobility impairment or death over 10 years among elderly women [11]. While a similar cutpoint of grip strength, approximately 14 kg, emerged in our group's study of women with SLE; this definition of weakness did not predict significant changes in a similar measure of physical functioning. Instead, lower extremity weakness was a better predictor of changes in physical functioning over time [8]. Further work is needed to determine among individuals with SLE, and other rheumatic illness, the most appropriate definitions of clinically relevant muscle weakness.

It is also not known what causes muscle weakness in SLE; and how muscle weakness, independent from effects of muscle loss, contributes to physical disability. Exciting insights into these questions have come from the study of weakness in nonrheumatic chronic inflammatory conditions, including congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD). Mounting evidence suggests that chronic inflammation can directly impede muscle fiber contractility and cause weakness that is not simply a function of muscle atrophy [12,13]. Various biomarkers of inflammation, including TNF-α, IL-6 and c-reactive protein (CRP), inversely correlate with muscle strength among individuals with CHF and COPD [12]. Of these biomarkers, TNF is perhaps the best studied. Serum levels of TNF correlate with diaphragm and limb muscle strength in CHF patients [14]. In mouse models of CHF, TNF upregulation leads to increased oxidative stress in muscle fibers, and this increased oxidative stress reduces the force generated by muscle fibers when they contract [15]. Last, the ability of increased oxidative stress to impede muscle fiber contractility is abrogated by antioxidant therapy, such as N-acetyl-cysteine [16]. These findings, taken together, suggest a compelling potential mechanism by which chronic inflammatory conditions, including SLE, may lead to reduced skeletal muscle function and reduced muscle strength.

Despite its potentially great relevance to mechanisms of reduced physical functioning, understanding of relationships between chronic systemic inflammation and muscle weakness among individuals with rheumatic illness remains limited. Among individuals with RA, IL-6 serum levels correlate with measures of muscle quality and some measures of physical functioning [7]; and DAS28-CRP values are associated with differences in calf muscle quality [17]. These relationships have not been directly characterized among individuals with SLE.

Recent exciting discoveries of the secretory functions of skeletal muscle may further unify these inter-related observations on chronic inflammation, muscle strength and physical function. Whereas skeletal muscle has historically been viewed as a 'workhorse' that received a stimulus, contracts and generates movement; growing evidence reveals that when skeletal muscle contracts it may also secret a whole host of cytokines that have pleiotropic effects throughout the body [18]. As a result, we now speak of 'myokine' pathways to describe the effects that these muscle-secreted cytokines have on processes ranging from lipid metabolism, to insulin sensitivity, to bone turnover [19]. These myokine pathways hold great promise for both advancing understanding of the pathogenesis of physical disability and developing new treatment modalities.

With these recent advances, we find ourselves at an exciting crossroads with respect to research on muscle strength and physical functioning among individuals with SLE and other rheumatic illnesses. There are

many important areas that require further investigation. One important next step is to determine how best to identify individuals at greatest risk for muscle weakness and reduced physical functioning. Do certain clinical features identify which individuals are at particular risk for going on to become weak and disabled? By identifying those at greatest risk, we can then work to develop focused interventions aimed at increasing muscle strength, improving physical functioning and optimizing health-related quality of life for these individuals. After all, one of the greatest potential impacts of learning how muscle weakness contributes to reduced physical functioning among individuals with SLE is to develop ways of preventing this physical disability from occurring in the first place. Ideally the day will come where what is most surprising about muscle weakness, is in fact the array of modalities used to treat it.

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References

1 Katz P, Julian L, Tonner MC *et al.* Physical activity, obesity, and cognitive impairment among women with systemic lupus erythematosus. *Arth. Care Res. (Hoboken)* 64(4), 502–510 (2012).

2 Katz P, Morris A, Trupin L, Yazdany J, Yelin E. Disability in valued life activities among individuals with systemic lupus erythematosus. *Arthritis Rheum.* 59(4), 465–473 (2008).

3 Santos ML, Gomes WF, Pereira DS *et al.* Muscle strength, muscle balance, physical function and plasma interleukin-6 (IL-6) levels in elderly women with knee osteoarthritis (OA). *Arch. Gerontol. Geriatr.* 52(3), 322–326 (2011).

4 Goodpaster BH, Park SW, Harris TB *et al.* The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J. Gerontol. A. Biol. Sci. Med. Sci.* 61(10), 1059–1064 (2006).

5 Cawthon PM, Fox KM, Gandra SR *et al.* Do muscle mass, muscle density, strength, and physical function similarly influence risk of hospitalization in older adults? *J. Am. Geriatr. Soc.* 57(8), 1411–1419 (2009).

6 Giles JT, Bartlett SJ, Andersen RE, Fontaine KR, Bathon JM. Association of body composition with disability in rheumatoid arthritis: impact of appendicular fat and lean tissue mass. *Arthritis Rheum.* 59(10), 1407–1415 (2008).

7 Kramer HR, Fontaine KR, Bathon JM, Giles JT. Muscle density in rheumatoid arthritis: associations with disease features and functional outcomes. *Arthritis Rheum.* 64(8), 2438–2450 (2012).

8 Andrews JS, Trupin L, Schmajuk G *et al.* Muscle strength predicts changes in physical function in women with systemic lupus erythematosus. *Arth. Care Res. (Hoboken)* doi:1002/acr22560 (2015) (Epub ahead of print).

9 Andrews JS, Trupin L, Schmajuk G *et al.* Muscle strength, muscle mass, and physical disability in women with systemic lupus erythematosus. *Arth. Care Res. (Hoboken)* 67(1), 120–127 (2015).

10 Mclean RR. The "weakness" link: can muscle impairment be identified as a cause of disability in rheumatology patients? *Arth. Care Res. (Hoboken)* 67(1), 1–3 (2015).

11 Mclean RR, Shardell MD, Alley DE *et al.* Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the foundation for the national institutes of health (FNIH) sarcopenia project. *J. Gerontol. A. Biol. Sci. Med. Sci.* 69(5), 576–583 (2014).

12 Reid MB, Moylan JS. Beyond atrophy: redox mechanisms of muscle dysfunction in chronic inflammatory disease. *J. Physiol.* 589(Pt 9), 2171–2179 (2011).

13 Roubenoff R. Rheumatoid cachexia: a complication of rheumatoid arthritis moves into the 21st century. *Arthritis Res. Ther.* 11(2), 108 (2009).

14 Toth MJ, Ades PA, Tischler MD, Tracy RP, Lewinter MM. Immune activation is associated with reduced skeletal muscle mass and physical function in chronic heart failure. *Int. J. Cardiol.* 109(2), 179–187 (2006).

15 Doehner W, Bunck AC, Rauchhaus M *et al.* Secretory sphingomyelinase is upregulated in chronic heart failure: a second messenger system of immune activation relates to body composition, muscular functional capacity, and peripheral blood flow. *Eur. Heart J.* 28(7), 821–828 (2007).

16 Empinado HM, Deevska GM, Nikolova-Karakashian M, Yoo JK, Christou DD, Ferreira LF. Diaphragm dysfunction in heart failure is accompanied by increases in neutral sphingomyelinase activity and ceramide content. *Eur. J. Heart Fail.* 16(5), 519–525 (2014).

17 Baker JF, Von Feldt J, Mostoufi-Moab S *et al.* Deficits in muscle mass, muscle density, and modified associations with fat in rheumatoid arthritis. *Arth. Care Res. (Hoboken)* 66(11), 1612–1618 (2014).

18 Benatti FB, Pedersen BK. Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. *Nat. Rev. Rheumatol.* 11(2), 86–97 (2015).

19 Pal M, Febbraio MA, Whitham M. From cytokine to myokine: the emerging role of interleukin-6 in metabolic regulation. *Immunol. Cell Biol.* 92(4), 331–339 (2014).