Commentary

Resistance Training as Treatment for Sarcopenia: Examining Sex-Related Differences in Physiology and Response

Ryan Cheng, BS[1]; Aidan Maloney[2]; Jay Moran, BS[1]; Thomas H. Newman, BA[3]; and Elizabeth C. Gardner, MD[1]

[1]Yale University School of Medicine, Department of Orthopaedic Surgery and Rehabilitation, New Haven, CT, USA; [2]Yale College, Yale University, New Haven, CT, USA; and [3]Hawkin Dynamics, Portland, ME, USA

ABSTRACT

Sarcopenia or muscle mass atrophy reportedly occurs in up to 50% of those aged >80 years and is a significant risk factor for functional disability and poor physical performance. Over time, the deterioration in both skeletal muscle quality and composition may compromise functional independence and has been shown to independently increase the risk for falls, fractures, and overall poor health in the elderly population. These are seen most obviously in older women. Given these serious consequences, much effort has been directed toward promoting increased activity and resistance training for muscle maintenance or even muscle regeneration in older adults. The Centers for Disease Control and Prevention states that for all adults ≥65 years of age, weekly aerobic and strength training are vital to healthy aging. Older patients who have not previously participated in strength training may be hesitant about starting a resistance training program and resort to simple and familiar aerobic exercise options such as walking, jogging, or cycling. However, the benefits of strength training are too important to miss: it can improve skeletal muscle metabolic capacity, mitigate effects of aging on functional capacity, maintain bone density, and, most importantly, help individuals maintain a higher quality of life and independence. Due to their increased risk of disability and injury, this opportunity for "exercise as medicine" is particularly important to women and must be encouraged by clinicians. As such, the purpose of this commentary was to highlight known sex-related differences in muscle metabolism and potential benefits of resistance training for elderly patients. A comprehensive understanding of the issues and prevention measures presented here may allow clinicians to better serve their patients, especially older female patients, and, ultimately, alleviate the burden placed on our society by our rapidly aging population. (*Clin Ther.* 2022;44:33–40.) Published by Elsevier Inc.

Keywords: elderly, resistance training, sarcopenia, skeletal muscle.

INTRODUCTION

The world's population is aging rapidly. Increased longevity and the aging of the large "baby boomer" cohort have shifted global demographics such that elderly adults constitute a larger proportion of the world's population than ever before.[8] By 2050, more than one quarter of the United States' population will be aged ≥60 years. Aging has been associated with higher rates of chronic health conditions and increased prevalence of impairment and disability.[9] As such, the increasing number of people in older age groups is expected to place an overwhelming burden on our health care system.[8]

Although the gender gap in life longevity has been widely recognized for decades,[3] statistically, elderly women do not possess advantages over their male counterparts in their physical health and injury risk.[3,6] According to the US Census Bureau's study on Americans with Disabilities, between the ages of 15 and

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24 years, women have a lower prevalence of disability (9.8%) compared with men (11.6%). This relationship is reversed in older age groups, however. Women in the 55- to 64-year-old age group are more likely to have disabilities (37.2%) compared with men (34.0%) in the same group.[6] Although falls are considered a major risk factor for both elderly men and women,[10] older women are 50% more likely to fall[1,2] and are at a greater risk of sustaining serious injuries, such as hip fractures, after a fall because of the higher rates of osteoporosis within this group.[1–7]

Sarcopenia, otherwise known as the age-related loss of skeletal mass and function, has gradually become recognized as a geriatric syndrome and a key contributor to disability, especially for women.[11,12] Women with sarcopenia and sarcopenic obesity also reportedly have a higher mortality risk than their male counterparts.[12] Due to these potentially devastating consequences, the treatment or prevention of sarcopenia with resistance training, particularly in elderly women, has become a growing area of interest.[4,5] The 2018 *Physical Activity Guidelines for Americans, 2nd Edition*, from the US Department of Health and Human Service recommends that in addition to moderate to vigorous aerobic activity, "adults should also do muscle-strengthening activities of moderate or greater intensity that involve all major muscle groups for 2 or more days a week."[13]

However, despite compelling evidence and public health recommendations, few older women consistently engage in muscle-strengthening exercises. Among women 45 to 64 years of age, only 18% strength train 2 or more days per week; among women aged 65 to 74 years, this number drops to 11%.[14] As such, it is incumbent upon clinicians to educate their patients on the complementary benefits of strength training to traditional aerobic exercise and encourage participation, especially among novices, by sharing the simple and safe available guidelines for resistance training in elderly adults.

The goal of the present commentary was to highlight the known sex-related differences in sarcopenia, both in its physiology and consequences, as has been reported in the available literature. By doing so, clinicians will be better armed to work with their elderly female patients to initiate a strength training program that best fits their individual needs and social circumstances.

DISCUSSION

Physiology

Skeletal muscle is the largest metabolic organ system in the body, accounting for ~40% of the body's fat-free mass.[15] Human skeletal muscle fibers consist of 2 types: slow twitch (type I) and fast twitch (type II).[16] Muscle fiber types are generally distinguished by the myosin heavy chain isoforms they express. As their names suggest, slow-twitch fibers have slower contraction speeds and lower force production compared with fast-twitch fibers. However, the slow-twitch fibers fatigue much slower than fast-twitch fibers. The neural excitation of these motor units allows for voluntary contraction of skeletal muscle and, ultimately, conscious locomotion and functional independence.[17] However, as the human body ages, this organ begins to deteriorate, with changes seen in the quality and composition of skeletal muscle, mitochondrial function, autophagy, and inflammation.[18,19] This ultimately results in a decrease in an individual's functional capability.[18]

Sarcopenia has been defined as the age-related loss of muscle mass and strength, and is strongly correlated with physical disability, quality of life, and death.[12,20,21] Risk factors for sarcopenia include sex, age, and physical activity levels.[20] Sarcopenic individuals are also at risk of developing sarcopenic obesity, which occurs when an individual experiences an increase in fat mass along with the decrease in lean mass.[20] Although this change in body composition may be disguised by a steady body weight, individuals with sarcopenic obesity also experience a measurable loss of muscle strength.

Although sarcopenia has become a commonly studied health concern in our rapidly aging population, studies examining differences in the occurrence of sarcopenia between female and male subjects are limited.[22,23] Batsis et al,[12] who studied 4652 subjects aged ≥60 years, reported that the prevalence of sarcopenia was greater in men (75.5%) than in women (35.4%). Sarcopenic obesity was 4 times more prevalent in male subjects compared with female subjects; however, women with either sarcopenia or sarcopenic obesity had a higher mortality risk compared with men with sarcopenia or sarcopenic obesity. Even after adjusting for mobility limitations, sarcopenia was still associated with higher mortality risk in women. Interestingly, sarcopenia and sarcopenic obesity were not significant predictors of risk of death

for men. This is likely related to the difference in typical body composition between the sexes throughout life. A study conducted on men and women between the ages of 18 and 88 years showed that men, on average, have more skeletal muscle mass in both absolute terms (33.0 kg vs 21.0 kg) and relative to body mass (38.4% vs. 30.6%) compared with women.[24] This lower initial muscle mass level places older women at a higher risk of dropping below a critical threshold of muscle, and thus losing functional independence[24] and becoming disabled.[3]

The physiology of sarcopenia is thought to be multifactorial, with many proposed explanations, including neurodegenerative processes, reduction in anabolic hormone production or sensitivity, dysregulation of cytokine secretions, and a modification in the inflammatory state.[25] An understanding of the underlying muscle physiology can help to explain both phenomena and may be the basis for its treatment and prevention.

As skeletal muscle ages, muscle tissue quality and composition deteriorate as a result of lipid, adipose, and fibrotic tissue infiltration.[26] Deterioration of muscle quality due to fat infiltration may be predictive of losses in skeletal muscle function with age.[27] In addition to adipose tissue infiltration, aging is associated with infiltration of intramyocellular lipids.[26] Intramyocellular lipid infiltration is known to be associated with decreased functionality in lower extremities.[28] It has been proposed that one mechanism by which fat tissue decreases skeletal muscle force is through increased tumor necrosis factor alpha production,[9] as shown in cardiac myocytes.[29]

Sarcopenia is also thought to be partly a result of altered autophagy, which is the recycling of cellular components that is critical for cellular homeostasis.[19] With age, this process is reduced.[26] As a result, misfolded proteins and dysfunctional organelles are able to accumulate within skeletal muscle, causing losses in muscle strength and function, as well as a disruption in metabolic homeostasis.[30] This decline in muscle mass and strength is associated with an increased risk of physical sequelae such as falls[31] and hip fractures[32] and with metabolic conditions such as glucose intolerance[33] and loss of bone mineral density.[34]

Aging also affects the muscle fibers themselves, with a decrease in the overall skeletal muscle content as well as atrophy of specific muscle fibers.[18] Sarcopenia may be due to a decrease in the number of satellite cells, which are responsible for the maintenance of skeletal muscle homeostasis and regeneration. The loss of satellite cells supporting type II myosin heavy chains predominates,[35] contributing to the disproportionate loss of these fast-twitch myofibers with age. However, potential sex-related differences in satellite cells have not been well studied and may provide further insight for disability prevention and muscle regeneration.

On a molecular level, there may be some sex-related difference in the pathophysiology of sarcopenia, attributed to differences in various inflammatory markers. Payette et al[36] assessed the role of inflammatory cytokine interleukin 6 (IL-6) and insulin-like growth factor-1 (IGF-1) in predicting 2-year changes in fat-free mass. The study, which included 326 women and 232 men between the ages of 72 and 92 years, determined the relationship between inflammatory cytokine IL-6 and IGF-1 production with sarcopenia. Higher cellular IL-6 levels proved to be a significant predictor of sarcopenia in women, but similar catabolic effects of IL-6 were not observed in men. Furthermore, IGF-1 levels had a protective effect on sarcopenia in men but in women. The authors concluded that sarcopenia predictors include sex-specific metabolic predictors as well as body composition characteristics specific to men and women. These results support the general idea that sarcopenia is due in part to an increase in catabolic stimuli (eg, IL-6) and a decrease in anabolic stimuli (eg, IGF-1). However, more research is needed to better understand the underlying role of inflammatory cytokines on sarcopenia in both sexes.

Finally, hormonal differences between men and women may also provide insight into the increased morbidity of sarcopenia in elderly women. The effects of estrogen loss, particularly during menopause, on skeletal muscle metabolism have been studied.[37] It is postulated that estrogen influences skeletal muscle via the ubiquitin-proteasome system, but this evidence is scant and at times conflicting.[37] Estrogen seems to support skeletal muscle mass by protecting against apoptosis, but further research is required to better understand and confirm these effects on sarcopenia in women.

Altogether, the deterioration of skeletal muscle due to fat infiltration, mitochondrial quality, autophagy, and increased inflammation creates a physically frail population with compromised balance, decreased functional capability, and lower quality of life.[26–28,38–40]

Frailty has been associated with increased risk of falls, higher incidence of death, and potential long-term disabilities.[38] With elderly women more at risk for frailty, future studies understanding the underlying pathophysiology of sarcopenia, and highlighting any potential differences between men and women, may aid in combating sarcopenia, thus decreasing disability and with it societal health care costs.

Resistance Training for Healthy and Sarcopenic Elderly Women

Prescribed physical exercise as a form of modern medicine is a widely accepted but complex concept, especially in elderly populations. Countless studies have shown that resistance training provides various benefits for older adults, ranging from increased muscle mass and bone density to improved overall health.[38,41–44] Given the known physiological differences between older men and women, several studies have focused on resistance training interventions in elderly women to show its efficacy.

One recent randomized controlled trial by Seo et al[45] studied the effects of a 16-week resistance training program on muscle quality and muscle growth factors in older women with sarcopenia. The study group was assigned to three 1-hour sessions per week for the 16-week trial, whereas the control group maintained their typical daily activities. Each training session consisted of a 5-minute warm-up, 50 minutes of resistance training, and 5 minutes of cool-down. Larger and smaller muscle groups were targeted with weight-bearing and elastic band exercises, respectively. Both types of exercises were managed with a progressive-overload approach with 60 seconds of rest between sets. The study aimed to simulate easy-to-perform exercises that could be reproduced without the use of a traditional gym. Ultimately, the resistance training group had improved functional fitness and lower age-related increases in intramuscular fat compared with the control group. Resistance training participants also benefited from improvements in their gait speed, isometric muscle strength, and grip strength. These findings suggest that resistance exercises may be adequate to treat and prevent the age-related adverse effects on muscle quality and function in sarcopenic elderly women.

While Seo et al[45] studied the impact of resistance training in sarcopenic older women, Liao et al[46] conducted a similar randomized controlled trial but studied the effects of elastic resistance exercise on body composition and physical capacity in older women with sarcopenic obesity. The 55-minute exercise sessions were conducted 3 times a week for 12 weeks under the supervision of a licensed physical therapist. Each session began with 10 minutes of warm-up, followed by 40 minutes of elastic resistance exercises and 5 minutes of cool-down. Concentric and eccentric exercises were completed in 3 sets of 10 repetitions and with a progressive loading scheme. The outcome measures were measured at the end of the 12-week intervention and at 6 months' postintervention and were compared versus preintervention values. The results showed that participation in elastic band resistance training increased total skeletal mass and improved muscle quality and physical capacity at both time intervals, including 6 months' postintervention. This offers a safe and effective treatment option for sarcopenic obesity in older women.

Although the previous studies examined the effects of long-term resistance training, few studies have reported on the short-term outcomes of resistance training in these patient populations. However, Herda et al[47] conducted a randomized controlled trial and showed that short-term resistance training in older adults improves muscle quality. The study divided participants into 1 of 3 groups: control, dumbbell resistance training, or elastic band resistance training. Both dumbbell and elastic band resistance training participants completed 2 training sessions per week for 6 weeks. Each functional movement exercise (chest press, squats, overhead press, deadlift, bent-over row, and upright row) was performed in 3 sets of 8 to 12 repetitions under the supervision of a designated trainer. During the first 2 weeks, participants had 120 seconds of rest between sets. Rest periods were decreased to 90 and 60 seconds during weeks 3 to 4 and 5 to 6, respectively. As with previous studies, resistance training difficulty was increased progressively by decreasing rest time, increasing the number of repetitions completed, or increasing the exercise intensity. The results of this study showed that dumbbell resistance training provided greater bench press strength improvements (27%) than elastic band resistance training (15%) and the control group (13%). Leg press strength gains in the dumbbell group were significant compared with the control group but not when comparing dumbbell with elastic band resistance training and elastic band training with the

control group. Differences in strength improvement between the 2 training programs were thought to be due to the nature of the training exercises. Although dumbbells produce a constant load at all points during the repetition, elastic bands produce a variable load depending on the distance pulled. These findings suggest that elastic band resistance training provides benefits in terms of affordability and portability, but dumbbell resistance training may produce superior improvements in strength metrics. The results of the study by Herda et al also show that resistance training regimens, even when performed for a short period of time, can increase muscle mass and potentially motivate patients, especially those who are initially hesitant about a long-term commitment, to participate.

Guidance to the Clinician

Although clinicians are not expected to manage the daily exercise regimen of their elderly patients, the ability to confidently recommend physical exercise, and to encourage an effective program, is certainly within the treatment scope. When determining frequency, intensity, and the duration of exercise programs for sarcopenic older women, clinicians are encouraged to systematically recommend a training regimen to limit injury risk and optimize effectiveness.

Multiple studies have shown that resistance training can safely and effectively produce improvements in muscle mass, functional capacity, and quality of life for both healthy and frail elderly individuals.[48,49] In accordance with national public health recommendations by the Centers for Disease Control and Prevention and the US Department of Health and Human Service guidelines, our institution suggests at least 2 sessions of resistance training per week for elderly individuals to maximize health and functional benefits while also allowing for adequate rest between training days. Each session should incorporate 1 to 2 multi-joint exercises per major muscle group as resistance training improves both upper- and lower-body strength.[43] During the initial phase of resistance training, a slow progression up from 1 to 3 sets per exercise is generally recommended for greatest improvements in muscle growth, with each set consisting of 8 to 10 repetitions.[43,50,51] If 3 sets of 8 to 10 repetitions can be completed with proper form, then progressively more difficult resistances/weights can be attempted. A 120-second rest period is recommended between sets. However, rest periods should be adjusted to accommodate each individual's workout tolerance and ensure a symptom-free progression (ie, no nausea or dizziness). It is important to note that these repetitions do not need to be performed until failure. Studies have shown that repetitions to failure are not necessary for strength and power adaptive responses for the elderly.[52] Furthermore, muscle fatigue associated with repetitions to failure may place sarcopenic older women at an unnecessary risk of sustaining serious injuries. Thus, our institution suggests adopting a more conservative approach and completing as many repetitions as possible without compromising form.

When suggesting training programs for patients, as with all behavioral interventions, clinicians should take into consideration variables that may affect participation rates and thus treatment efficacy. Seguin et al[53] surveyed older women participating in the StrongWomen Program, a nationally disseminated community strength-training program. Personal factors associated with adherence to strength training were older age, higher lifetime physical activity levels, and better perceived health. Aside from increasing age, these findings suggest that the very women who most likely need strength training are less likely to be adherent to it. Interestingly, socioeconomic factors such as race, educational attainment, and income were not significant predictors of adherence to the program.

Visek et al[54] conducted a randomized controlled trial examining factors affecting adherence to resistance training in older women. Their primary finding was that prescribed exercise time was the strongest determinant of duration of participation. More specifically, longer workout times decreased the likelihood of completion. Surprisingly, increased intensity of a training program was positively correlated with both attendance and duration of participation, possibly because higher intensity programs tend to be shorter in duration. In a similar study, Hong et al[55] found that group-based and resistance exercise programs predicted higher attendance rates compared with individually based and aerobic exercise programs, and facility-based exercise was associated with higher completion rates than home-based exercise.

Other barriers to implementation may include willingness to participate, access to gyms and exercise equipment, and intimidation when using an unfamiliar space or doing an unfamiliar activity. Fortunately, the aforementioned studies have attested to safe and

easy methods of resistance training methods at home, without the use of a traditional gym. Beyond home training, gyms could provide designated spaces where trainers are readily available to ensure that beginners can maintain proper form and gain confidence in a safe learning environment. These recommendations may ease the concerns of this patient population, such that they may reap the many benefits of this training.

It must be said, of course, that the medical comorbidities of the individual patient will be one of the primary factors affecting the specifics of any recommended resistance training program. Concurrent physical ailments, such as osteoarthritis, should not be considered as contraindications to training, because with appropriate accommodation of the specific exercises, great benefit can be achieved.[56] Similarly, the cardiovascular safety of an appropriate strength training program has been shown as well.[57]

CONCLUSIONS

The effect of sarcopenia on the functional independence and health of aging women is clear and profound. Because interventions at the cellular and molecular levels are not yet possible, prevention, or at least treatment, in the form of exercise remains our best option. National guidelines have clearly recommended a combination of both aerobic and strength training as critical elements to this prescription. Unfortunately, most older women do not regularly participate in strength training, even though they are most in need of its benefits. With an improved understanding of the underlying pathophysiology of sarcopenia, as well as the robust evidence supporting the safety and efficacy of resistance training, clinicians may reassure and encourage their patients to view exercise as medicine.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Address correspondence to: Elizabeth C. Gardner, MD.E-mail: elizabeth.gardner@yale.edu.