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Review Article

Therapeutic potential of eccentric exercises for age-related muscle atrophy

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Recent studies have focused on evidence-based interventions to prevent mobility decline and enhance physical performance in older adults. Several modalities, in addition to traditional strengthening programs, have been designed to manage age-related functional decline more effectively. In this study, we reviewed the current relevant literatures to assess the therapeutic potential of eccentric exercises for age-related muscle atrophy (sarcopenia). Age-related changes in human skeletal muscle, and their relationship with physical performance, are discussed with reference to *in vitro* physiologic and human biomechanics studies. An overview of issues relevant to sarcopenia is provided in the context of the recent consensus on the diagnosis and management of the condition. A decline in mobility among the aging population is closely linked with changes in the muscle force–velocity relationship. Interventions based specifically on increasing velocity and eccentric strength can improve function more effectively compared with traditional strengthening programs. Eccentric strengthening programs are introduced as a specific method for improving both muscle force and velocity. To be more effective, exercise interventions for older adults should focus on enhancing the muscle force–velocity relationship. Exercises that can be performed easily, and that utilize eccentric strength (which is relatively spared during the aging process), are needed to improve both muscle force and velocity.

1. Introduction

By the age of 80 years, humans generally lose ∼30–40% of their skeletal muscle fibers, particularly Type II fibers.[1] The decline in muscle mass and strength with age is well documented.[2,3] In general, the muscle mass of 60–70-year-olds decreases to 70–80% of that of younger people (<60 years old).[4,5] The main features associated with aging skeletal muscles are muscle weakness, decreased flexibility, vulnerability to certain types of injury, and impaired functional restoration, which result in the deterioration of physical performance and function.[6] Lower extremity strength decreases linearly with

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age in both men and women, as shown by numerous cohort studies.[7–9] Physical performance, with respect to balance and gait speed, for example, is closely linked with muscle mass and strength.[10] Therefore, age-related changes in muscle mass and strength should be carefully monitored for signs of decline. Although functional decline with increased age is typical, the mechanisms underlying this decline, and the features that characterize it, are complex and variable. Therefore, it is important to develop specific interventions that will prevent or delay functional decline based on understanding age-related changes in the muscular systems of older adults.

Concerning exercise interventions that have therapeutic potential specifically for age-related muscle atrophy, recent studies have focused on evidence-based interventions aimed at preventing mobility decline or enhancing physical performance in older adults.[11–13] Several different treatment modalities, other than traditional strengthening programs, have been designed to manage age-related functional decline more effectively.[12,14] In this study, we reviewed the literature to delineate the role of physical function in disability and falls in older adults, and to assess the therapeutic potential of eccentric exercises for age-related muscle atrophy.

2. Sarcopenia: Definition and diagnosis

Sarcopenia is defined as the loss of skeletal muscle mass and strength with increased age.[15–17] This results in weakness, limited mobility, and increased susceptibility to injury. Several operational definitions have been used to diagnose sarcopenia, of which the most prevalent is an appendicular skeletal muscle mass (ASM) value ≥ 2 standard deviations below the ASM of young adults, divided by height squared (kg/m^2) or weight. As a rule, the relationship between mass and strength is linear, as is that between muscle strength and performance. However, there is no linear correlation between muscle mass and function. We found that muscle mass was not associated with physical performance in weak older adults, suggesting that measures of muscle strength may be of greater clinical importance in this population than muscle mass per se. The correlation between muscle mass and functional performance was significant in the higher strength group, but not in the weaker group.[18] This is because fatty or connective tissue infiltration into muscle tissues are included in muscle mass in those patients such that we cannot distinguish abnormal intramuscular changes by evaluating muscle mass alone, particularly in patients with mobility impairments. Therefore, the functional status of intramuscular tissues should be included in any assessment of sarcopenia.[8,18]

Mobility decline among the aging population is closely linked with changes in the muscle force–velocity relationship.[19] Such changes have functional implications, e.g., slower walking speeds. In recent studies, gait speed, or walking velocity, was highlighted as a major indicator of mobility decline or sarcopenia in geriatric populations.[20–22] Predicted years of remaining life, for both sexes, increases commensurate with gait speed regardless of age, according to a pooled analysis of nine cohort studies on walking speed and survival.[23] Gait speeds of 1.0 m/s or higher were consistently associated with longer survival than would be expected based on age and sex alone. According to the consensus in European group for determining sarcopenia, gait speed should be measured initially, and mass profiles should be evaluated when gait speed is abnormal. Sarcopenia should be diagnosed when gait speed is normal only if strength is abnormal.[22]

3. Changes in skeletal muscle structure and function with advancing age

The mechanical properties of muscles can be assessed according to their active, contractile characteristics, and passive tension or stiffness. Intrinsic contractile characteristics related to the cross-bridge mechanics of single fibers change with aging.[24] Some studies have reported that both a decrease in contractile materials and a reduced force-generating capacity per cross-bridge affect the contractile properties of aging muscles. A selective loss of Type II (fast twitch) muscle fibers is associated with the age-related decline in strength.[25] Cross-sectional dissections of whole thigh muscles of older cadavers have also shown an 18% decline in total muscle area and a 25% decrease in the total number of muscle fibers, with a particular decrease in the number of Type II muscle fibers.[26] These results are also supported by other cross-sectional studies that have shown that the area of Type I mean fibers is preserved with aging, whereas Type II fibers show atrophy.[27] In addition to changes in muscle fiber size and number with advancing age, specific changes in the intrinsic ability of aged muscles to generate force have also been observed. In humans, decreased specific force (i.e., force normalized by cross-sectional area [CSA]) and unloaded shortening velocity in the Type I and IIa fibers of older sedentary males have been reported relative to young sedentary controls.[28,29] These changes are also consistent with those observed in rat skeletal muscle throughout life. Thompson et al [30] reported decreases in the specific force and unloaded shortening velocity of the soleus muscles of aging rats. They further noted a dissociation between loss of muscle CSA and a decline in maximal force. These human and rat data provide evidence that intrinsic changes in muscle quality may also be important for understanding age-related changes in the function of skeletal muscle. Future studies should evaluate the relationship between the intrinsic force and shortening velocity of aging skeletal muscle, and the relationship between these factors and age-related declines in whole muscle strength and peak power.

Changes in both the fiber elasticity and contractility of Type I and Type IIa fibers have been assessed in terms of instantaneous stiffness, that is, according to the ratio between force changes and corresponding length changes.[24] As an active component of elasticity, instantaneous stiffness reflects the elastic characteristics of muscle fibers but has some limitations with respect to indexing passive components. Passive elastic properties are instead assessed in terms of passive stiffness, or tension, which is thought to be related to sarcolemma, connective tissues, and titin filaments.[31] Passive stiffness is measured by the tensile force associated with displacement during stretching of the skeletal muscles.[32] Increased stiffness, or decreased extensibility, of the muscle or muscle-tendon unit has been reported in aging skeletal muscles.[33]

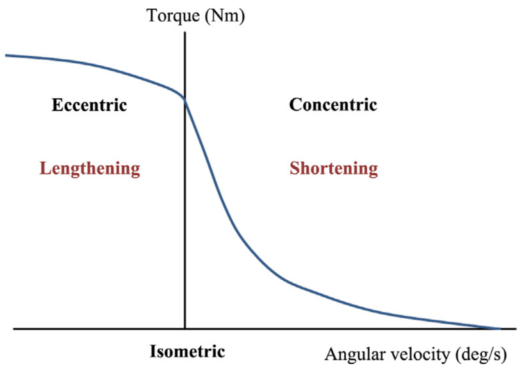

Fig. 1 – Force–velocity relationship shows eccentric muscle contraction involves a lengthening contraction that has greater force than shortening contraction.

Increased stiffness, along with decreased size and contractility, could lead to impaired muscle function and an increased vulnerability to injury.[32] Stiff collagen tissue, fatty changes, and changes in muscle cells are major determinants of passive stiffness in aging muscles. At a cellular level, sarcomere proteins such as titin, nebulin, and intermediate filaments control elastic muscle functions.[34] There has been some controversy regarding the increase in muscle stiffness due to aging: in a previous study, muscle stiffness remained unchanged with older age; however, it accounted for a greater proportion of total tension because of significant declines in muscle mass and contractile tension with age.[32]

4. Relative preservation of eccentric strength in aging

Due to physiological and structural changes, the force–velocity relationship of human muscles changes with age, and muscular strength and power are reduced at all contraction speeds.[35–38] However, older adults show a relatively preserved capacity for eccentric strength. The preservation of eccentric strength in older adults is a well-established phenomenon.[39] Compared with concentric force, eccentric force shows relatively less decline with age (2–48%). Thus, preservation of eccentric strength in elders underpins the therapeutic potential of eccentric exercises in this population.[37,39,40] Eccentric muscle contraction involves a lengthening contraction that has greater force than shortening contraction with less energy expended per unit of muscle force (Fig. 1). Eccentric muscle contraction is very useful when a high degree of muscle strength is required. Many functional activities require eccentric contraction, although delayed-onset muscle soreness can be problematic.[39] Although the mechanisms underlying eccentric contraction remain unclear, they appear to originate in the muscle itself, where both passive and active elements may regulate muscle stiffness. Increased passive stiffness due to age-related accumulation of noncontractile material confers a mechanical advantage during eccentric contraction.[33,39] Ochala et al[24] reported greater instantaneous stiffness per force unit, indicating greater active stiffness in the cross-bridge, in the fibers of older versus younger men; this may represent a compensatory mechanism against less efficient muscle contraction with aging. In older muscle, a relative increase in active stiffness in the cross-bridge may be a mechanism underlying reduced muscle contraction efficiency. In a study on skeletal muscle fiber, we measured residual force enhancement (RFE) after lengthening contraction in aged rats. RFE is a well-known phenomenon that the isometric steady-state force at the stretched length after lengthening contraction is greater than the steady-state isometric force at that same length for a purely isometric contraction.[39] We found that RFE was greater in older versus younger muscle fibers (unpublished data). We concluded that preservation of eccentric strength likely contributed to the observed increase in RFE in aged skeletal muscle fibers. However, further studies are required to elucidate the mechanism underlying the preservation of eccentric strength. Although the mechanisms remain unclear, an understanding of why older adults show this relative maintenance of eccentric strength could be relevant for practical applications, such as training and rehabilitation of elderly people.[39]

5. Specific interventions for the prevention of mobility decline

Many trials have aimed to understand how to prevent or delay functional decline, as well as the development of disability, in older adults. It is clear that exercise can play a key role in this respect, but issues remain regarding the specific interventions that are most effective and practically useful for functionally impaired individuals. Many types of exercise can be used to enhance the physical function of older adults. The exercise recommendations of the American Geriatric Society have been widely accepted as being applicable to older adults.[41] However, although the guidelines may be effective and safe for the healthy aging population, they may be too general for the mobility-impaired aging population.

Exercise training for elderly persons involves special considerations. Aging is associated with a decrease in the proportion of Type II muscle fibers, a decrease in fiber CSA, and a change in contractile properties such as P_0, P_0/CSA, and V_0.[29,42] Type II fibers seem to be more affected by aging than other fibers, because they show greater decreases in CSA, which in turn leads to increases in the relative muscle area occupied by Type I fibers. Several recent studies have suggested that, when the training stimulus is of an appropriate intensity (i.e., 70–90% of the one-repetition maximum [1RM]), gains in muscle strength and size in older healthy and frail individuals are comparable to the gains observed in young individuals.[43] The difference in strength gains (28–227%) reported by various studies may be related to several factors, such as the participants' initial strength, age, comorbidities, and differences in the muscles trained. Effects of resistance training on the single muscle fibers of older individuals were detected in both Type I and IIa fibers in males, but not in females.[43,44] Moreover, the contractility of single-fibers might be sensitive to changes in physical activity levels, rather than aging per se. In several studies, progressive resistance training was associated with minimal improvements in peak

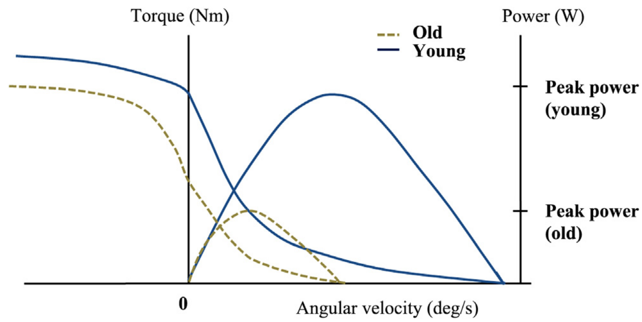

Fig. 2 – Power output derived from the force–velocity curve using Hill's Equation indicates a greater decrease in power output than in force in old group compared with young group.

power; therefore, training interventions need to be designed to maximize peak power in older individuals.[11,14,44]

Regarding the muscle force–velocity relationship, power output is derived from the force–velocity curve using Hill's Equation (Fig. 2). In an assessment of decline in older versus younger adults, there was a greater decrease in power output than in force in the former group. Power output, which is the maximum capacity to perform muscular work per unit time, is a critical variable in muscle impairment, functional limitation, and subsequent disability.[44–46] Bean et al[47,48] reported that peak power in lower extremities was closely associated with functional limitations and self-reported disability in community-dwelling men and women. It was also more closely associated with gait speed than strength. Strength (i.e., force) and muscle power are both closely linked to functional performance; power output has a strong correlation with performance in a number of functional tasks, such as climbing stairs, rising from a chair, and walking, which shows that power is a better indicator of poor mobility compared with hand grip, knee extensor torque, and muscle mass. Therefore, interventions capable of enhancing or maintaining power output in older adults will be more effective. Regarding ways to improve the force–velocity relationship in old age, Raj et al[19] reviewed studies on the effects of different exercises on the force–velocity relationship. Traditional resistance training (TRT), such as the slow lifting and lowering of heavy loads according to the 1RM, had a significant positive effect on strength, but only modest effects on functional measures such as gait speed; furthermore, changes in the force–velocity curve were not significant.[49] In other studies, power training (PT) was more effective for improving muscular power and functional capacity in older adults, and was also associated with significant improvements in isometric and concentric strength, as well as power, compared with TRT.[11,46] Concerning power-oriented exercises, high velocity, low-resistance exercise can be used for PT. When using an exercise machine, around 40% 1RM represents a suitable external force for an effective increase in exercise velocity. Reid et al[12] reported several positive effects of power-specific exercise interventions in community-dwelling older women. However, a study that compared TRT with PT found that they were equally effective for improving muscular strength.[50] Another study reported changes in peak leg extensor power in response to 12 weeks of resistance training in older women; increases in strength of 22–27% were observed, in addition to a nonsignificant increase in leg extensor power.[51]

6. Therapeutic potential of eccentric contraction and eccentrically biased training

One potential intervention to enhance force and function in aging muscles is eccentric muscle exercise. Eccentric exercise has several important therapeutic advantages for aging populations, including low metabolic cost and minimal cardiorespiratory burden. Why is the metabolic cost lower during eccentric contractions? Elastic strain energy is used to resist the external force during eccentric contractions, such that muscle exertion requires minimal energy from adenosine 5′-triphosphate (ATP) breakdown; although some ATP is used during eccentric contractions, more is used during concentric and static contractions.[52] Therefore, chronic eccentric exercises can be easily applied to elderly and functionally limited patients, because these exercises do not require high energy consumption. Furthermore, such individuals may be so limited in their ability to perform exercises that walking may represent the limit of, or even exceed, their aerobic capacity, thereby precluding exercises performed at intensities sufficient to prevent muscle wasting (sarcopenia).

Eccentric exercise can cause substantial biologic changes in intramuscular structure and functional capability (e.g., increased muscle fascicle length).[19] Muscle fascicle length is known to decrease following immobilization, as well as with aging,[53] but it can be increased by lengthening contractions.[19,54] Eccentric resistance training alone has been reported to increase vastus lateralis fascicle length in elderly people to a greater extent than TRT.[54] Carlsson et al[55] reported that myotilin, which plays a key role in the dynamic molecular events that mediate myofibrillar assembly, may also be involved in the development of new sarcomere structures after stretching stimulation.

Another reason for the usefulness of eccentric exercise is a less delayed onset of muscle soreness in older populations.[56,57] Age-related muscle atrophy tends to occur predominantly in Type II fibers. Choi et al[58] found that resistance of the myofilament lattice to mechanical strain was reduced in Type IIa and Type IIa/IIx, but not in Type I, fibers, which indicates that aging muscle may be less vulnerable to eccentric exercise-induced muscle injury. As mentioned above, compared with the decline in concentric force that occurs with age, eccentric force is relatively unimpaired. This preservation of eccentric strength in elders underlies the therapeutic potential of eccentric exercises, which could be used to specifically target this facet of strength.

The potential advantages of eccentric resistance training might be particularly important during the initial stages of resistance training interventions for older adults with poor muscle strength.[59] Eccentric resistance training is generally conducted using specialized equipment, such as an isokinetic dynamometer. In a recent study, resistance exercises involving negative, eccentrically induced work were applied to older cancer survivors using a specially designed, motor-driven ergometer.[60] At only low levels of exertion, these exercises can produce a relatively high muscle workload via the motor-driven eccentric exercise machine. In addition, reverse cycling of electric-powered pedals can induce biological overload through progressive increases in eccentric power. During this exercise, the patient must try to slow down the moving pedals. To date, consistent with the evidence presented above, a number of studies have reported advantages of eccentric versus concentric resistance training. However, other studies have reported little or no additional benefit of eccentric resistance training over conventional training. In addition, the traditional negative standpoint on damage induction by eccentric contraction still remains an academic barrier to its clinical application. Accordingly, further research is needed to optimize eccentric resistance training for older adults, particularly by improving the physical function domain.

7. Conclusion

To be more effective, exercise interventions for older adults should focus on enhancing the muscle force–velocity relationship. Physiological and biomechanical evidence for an effect of lengthening contraction, as well as eccentrically biased training, on skeletal muscle properties and function has accumulated. There is a need to develop exercises that can be performed easily and utilize eccentric strength, which is relatively spared during the aging process, to improve both force and velocity in people with age-related muscle atrophy.

Conflicts of interest

The author has no conflicts of interest to declare.

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