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Skeletal Muscle Function in The Oldest-Old: The Role of Intrinsic and Extrinsic Factors

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Abstract

Although skeletal muscle function is diminished with advanced age, single muscle fiber function appears to be preserved. Therefore, this review examines the hypothesis that the skeletal muscle fiber, per se, is not the predominant factor responsible for the reduction in force generating capacity in the oldest-old, but, rather, is attributable to a combination of factors external to the muscle fibers.

SUMMARY for table of contents

Greatly diminished skeletal muscle function with advanced age may be a consequence of factors external to the muscle fibers.

Keywords

Aging; force; sarcopenia; neuromuscular control; fiber type; cross-sectional area

Introduction

In developed countries one of the fastest growing segments of the population is comprised of people who are beyond 85 years of age and are currently considered the oldest-old. Unfortunately, the majority of people who reach this advanced age experience a significant loss of locomotor function, with very few people still able to move independently. This loss

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of mobility results in a significant decline in quality of life, and a high risk of falls which often represents the terminal event in life. These factors can lower the frailty threshold for the oldest-old, with the consequent loss of adaptability, which is an essential feature of successful aging. This process of deteriorating mobility, although multifactorial, including the decline of cognitive function, increased bone fragility, and reduced joint flexibility, is heavily dependent on impaired muscle performance. However, understanding the changes in muscle function with advancing age is complicated not only by the interplay between reduction in muscle mass, altered architecture, and disrupted innervation, but also by the observation that the decline in muscle function occurs to differing extents and at non-uniform rates between individual muscles. Furthermore, aging is also accompanied by greater variability of motor performance than in young adults (1). This inter-individual variability increases with advancing age and may appear even greater in oldest-old (2). Of note, numerous factors also interact with the aging process and perhaps exacerbate the age-related variability in motor performance, including genetic background, physical activity level, nutritional status, hormonal, and inflammatory levels (2). In this complicated and multifaceted scenario, the impact of lifestyle and more specifically the level of physical activity on the preservation of muscle function is debated. Indeed, the effective contribution of lifelong physical exercise to the preservation of neuromuscular structure and function (3–5) and, more generally, to successful aging (6) is still controversial.

Initially, the oldest-old may appear to represent a human model of successful aging. However, several physiological characteristics associated with the age-related loss of skeletal muscle mass and force seem further compromised in this population, suggesting a nonlinear age-related decline in the skeletal muscle function. The contribution of intrinsic factors, such as the progressive atrophy of skeletal muscle fibers, or systemic factors such as modifications of hormonal, metabolic, inflammatory status, and nervous system changes in response to the rapid drop of skeletal muscle loss after this “tipping-point” in the aging process (80–85 years) is still a matter of debate. Moreover, it is not completely clear if and how exercise training can mitigate or reverse this phenomenon. Our novel hypothesis is that, if we consider the population of the oldest-old (above 85 years of age), intrinsic factors associated with the skeletal muscle fiber, per se, are not responsible for the reduction in force generating capacity but, rather, muscle dysfunction is attributable to a combination of factors external to the muscle fibers.

Characteristics of the oldest-old

Aging is a biological process, which is manifest from the cellular to the systemic level, and is generally characterized by numerous functional changes which become apparent across the lifespan (7). Some components of this process are often considered programmed regressive phenomena. However, other age-related factors such as cardiovascular and metabolic disease, orthopaedic issues, and cognitive deterioration, although not present to the same extent in all individuals, can significantly affect physical function and, therefore, play a role in determining health and longevity in the oldest-old. In Western societies, the significant increase in quality of life and advances in medicine in the last 50 years have positively influenced life expectancy and, therefore, the growth of the oldest-old population. However, it is important to also note that the majority of the oldest-old, due to chronic co-

morbidities, still experience a progressive fall in their quality of life, even if considered relatively healthy. Therefore, it is not surprising that most epidemiological studies highlight that only a minimal number of the oldest-old are totally independent in terms of performing activities of daily living, while the majority are partially or totally dependent. Therefore, there is a clear and present need to better understand the physiological consequences of advanced age to facilitate the development of countermeasures to combat the declining physical function in the oldest-old. In this review, we focus, in particular, on the decline of muscle function with advanced age, an aspect extremely relevant to the preservation of independent life.

Chronological and biological aging of skeletal muscle

Unlike chronologic aging, which merely documents the passage of time, cellular aging, from a biological point of view, is an overall decline in cellular homeostasis and a reduced capacity to respond to physiological stressors. Telomeres, terminal sequences of TTAGGG repeats, form the natural end of chromosomes and provide a useful marker of cellular aging. Telomere length is reduced by successive cell divisions and therefore differs across somatic tissue in proportion to that tissue's replicative activity. Interestingly, in skeletal muscle, a relatively quiescent tissue, genotoxic stressors, such as free radicals, rather than replicative activity, play a pivotal role in telomere shortening and functional decline. It is also important to note that the age-related loss of muscle mass is associated with a reduction in the capacity of myosatellite cells to proliferate and differentiate, resulting in attenuated muscle function in the oldest-old. In this complicated scenario, we have recently documented the relation between arm and leg muscle telomere length shortening and physical inactivity (8) (Figure 1, adapted from Venturelli et al. (8)), suggesting that skeletal muscle biological aging is exacerbated by increasing muscle inactivity and not by chronological age, per se. In the same study, the mechanism responsible for this apparent inactivity-related asynchrony in human skeletal muscle telomere shortening was associated with the accumulation of free radicals (8). In combination, these data suggest that in skeletal muscle, a tissue with a low proliferative rate, the genotoxic stress of an increased free radical concentration triggers the erosion of telomeres and this marker of cellular aging is clearly linked to physical inactivity and not simply chronological age. Recognition that the cellular aging of skeletal muscle is not simply age-dependent but is the consequence of inactivity and the subsequent increase in free radicals, highlights the importance of maintaining physical activity across the lifespan. This dramatic accumulation of free radicals that we have detected in the skeletal muscle of the inactive oldest-old likely have a plethora of negative effects also beyond the myonuclei. For example, as reported by Hepple and coworkers (9, 10), age-related denervation is associated with an increased reactive oxygen species (ROS) production and, thus, represents an additional major source of free radicals in senescent muscles.

Discordant effect of aging on skeletal muscle mass and force

The loss of muscle mass, or muscle atrophy, is likely the most conspicuous hallmark of skeletal muscle aging. Starting from the beginning of the 4th decade, muscle mass decreases by approximately 0.5% every year (see (11) for a comprehensive review), and this is the result of a multifactorial process which, among its causative factors, includes reduced levels

of anabolic hormones, chronic inflammation, degradation of the muscle contractile proteins, loss of regenerative capacity, altered neural activation, and mitochondrial dysfunction. The loss of muscle mass necessarily involves a loss of contractile performance, measured as either force or power (12). Several studies, however, document a dissociation between the fall in muscle mass and the related decrease in voluntary force in older adults so that the torque developed with a maximal voluntary contraction (MVC) normalized to muscle volume or, better to muscle PCSA (physiological cross sectional area), is reduced in the elderly compared to young, (see, for example, (12)). Cross sectional studies, however, tend to underestimate the rates of decline of muscle mass and force, because of possible selection bias, with only the most fit individuals surviving and being present in the older groups. Thus, more robust data are provided by longitudinal studies. Delmonico et al (13) followed a population of more than 3000 elderly, in their 8th decade, for 5 years and reported an annualized rate of loss of knee extensor torque normalized to quadriceps area of 2% and attributed part of this to the accumulation of intramuscular fat. Hughes et al (14) followed 120 people for approximately 10 years with a starting age between 46 and 78 years and reported an annual rate of force loss between 1 and 2 percent, depending on muscle group and gender, and 60% greater than the loss expected from the reduction in muscle mass. Frontera et al (15) documented, in a longitudinal study, performed on 12 men in their 8th decade, annual rates of decline of isokinetic torque on the order of 2–3% per year in the knee extensors and 0.5–1% per year in the knee flexors.

Both cross-sectional and longitudinal studies have consistently documented an acceleration in the decline of muscle mass and force during the eighth decade. Indeed, the relationship between age and muscle mass (kg) and force or torque (N or Nm), for a given large muscle group (for example, the leg extensors), across the lifespan can be better interpolated by a quadratic rather than a linear function (16). Of note, the decline in the number of muscle fibers (17, 18) and spinal motor neurons (17) also exhibits an acceleration somewhat earlier in life, evident in the seventh decade (9, 10) (see below and Figure 2). The enhanced skeletal muscle atrophy and the more pronounced reduction in muscle voluntary force with advancing age strongly suggests that additional physiological mechanisms combine to yield this functional impairment. Alterations of neural control, the deterioration of muscle architecture with increased fat and connective tissue accumulation, and changes in the contractile units, i.e. single muscle fibers, can all be identified as possible determinants and will be discussed here below.

It is important, however, to note that these age-related changes in skeletal muscle mass and function appear to be muscle and limb specific. The muscle volume of the upper limbs is less affected by aging (19, 20) and, therefore, the loss of muscle fibers, with advancing age, is very limited in arm muscles (21). Moreover, in the lower limbs, flexor muscles are less affected than the extensors (15). In agreement with this, comparative analyses have documented that the tibialis anterior, an ankle flexor, is more resistant to atrophy than the quadriceps (22). Interestingly, a greater resistance to the age-dependent loss of muscle mass has also been observed in rodent forelimbs compared to hindlimbs (22, 23). Currently, it is still uncertain at the exact mechanism responsible for this disparity between legs and arms as well as forelimbs and hindlimbs, but structural differences, such as the axon length or the volume of activity may play a role (23).

However, at least in humans, with advancing age and especially in the oldest-old, there is, typically, a clear reduction of physical activity, with significant periods of lower limb inactivity (24). This reduced movement may accelerate the loss of skeletal muscle mass and subsequently lower-limb force generating capacity (20). Conversely, the muscle volume of the upper-limbs is less affected by the reduction in physical activity across the lifespan (8), likely because the arms are constantly utilized for the activities of daily living, even in those with mobility-limitations. Recently, utilizing a human-model of the oldest-old and varying levels of limb disuse, we demonstrated that the progressive fall in skeletal muscle use, as seen in the legs, likely plays a significant role in exacerbating the loss of muscle mass (8). Moreover, with the data from a subsequent study (20) we observed that, despite the maintenance of muscle mass in the arms in the oldest-old, there was still a significant decrement in voluntary force production in these limbs in both the mobile and the immobile oldest-old compared to the young. Although complicated somewhat by clear evidence of sarcopenia in the legs, the equivalent findings of diminished force regardless of muscle mass, achieved by calculating muscle specific force, was also apparent in the lower-limbs of the oldest-old, in this case, as a consequence of both advanced age and disuse. These first, very simplistic, observations, supported later by several more complex assessments, imply that the predominant factor responsible for the reduction in force generating capacity in the oldest-old, is likely a combination of factors external to the muscle fibers.

Neuromuscular factors in the oldest-old

Voluntary force represents the integration of cortical inputs to motor neurons, motor neuron discharge, neuromuscular junction transmission, and the muscle response (2). Several studies have indicated that potential candidates for the recognized age-related decline in voluntary force include the reduction in the number of motor neurons, alterations in motor unit structure and function, and diminished motoneuron firing rate, altogether, leading to an attenuated performance of skeletal muscle contraction (25–28).

Cortical inputs to motor neurons

Significant age-associated changes in the structure and function of the cortical neurons contribute to the neuromuscular system dysfunction associated with aging. Specifically, during advanced aging, neuronal atrophy is evident in the central nervous system (29), with a 40% reduction in the number motor cortex cells, coupled with a general reductions in gray and white matter volume (30). Indeed, the importance of the age-related reduction in cerebral cortex thickness is indicated by its correlation with specific motor-task performance. With advanced age, cortical function is characterized by a significant decrease in inhibition and increased activity in many areas of the cerebral cortex. Specifically, utilizing the transcranial magnetic stimulation approach, it has been recognized that there is a decreased inter-hemispheric inhibition (29, 31), shorter silent period after fatiguing exercise (32), and a reduced intra-cortical inhibition. It is also important to note that both contralateral and ipsilateral hemispheres are heavily activated during motor tasks in the elderly (31). This failure to not inhibit crucial cortical areas during motor tasks may lead to hyper activation of additional motor units. Whether these age-related changes in cortical

inputs are the result of a neural dysfunction or are compensatory mechanisms, is still a matter of debate (29).

Motor neurons

Motor neurons represent the final pathway through which central command is translated to the musculoskeletal system. Aging is accompanied by changes in motor unit morphology and properties, coupled with altered inputs from peripheral, spinal, and supraspinal centers (26, 33–35). The age-related apoptosis of spinal motor neurons accelerates after the age of 60 yrs, while in contrast, a rapid decline in human muscle mass and function seem to be evident relatively later in life (approximately 75 – 80 yrs of age, Figure 2) (17, 26, 33–35). Recent evidence suggests that these age-related morphological changes in motor neurons are, at least in part, due to the accumulation of oxidative stress and inflammation (26, 36). Another factor important to recognize is the lack of reinnervation of the fibers of these damaged motor units by adjacent axons through collateral sprouting (26), resulting in fewer and larger surviving motor units with advancing age, ultimately resulting in lasting functional consequences in oldest-old (18). Aging is associated with remodeling of the neuromuscular junction and impaired neuromuscular transmission (36) that may decrease motor unit activation among oldest-old. It is important to underline that, while the decline of muscle mass and contractile parameters can be clearly demonstrated by comparing people around 70 years to young people in the 3rd decade of life (see reference above), the loss of motor units becomes already relevant during the 7th decade of life. This was initially observed by autopsy studies of Tomlison and Irving (37) and confirmed by motor unit number estimates (33). Thus, the accelerated decay of muscle mass and function in the oldest-old likely represents the interplay of different mechanisms with differing time courses and probably an overwhelming impact of the deterioration in neural control.

Voluntary activation in the oldest-old

The effectiveness of voluntary activation of motor units can be measured by stimulating the motor cortex, peripheral nerves or muscle, during maximal isometric contractions. The literature on this matter with respect to aging is disparate, some studies reports lower activation levels in the elderly, whereas others indicate that older adults can activate the skeletal muscle to similar extent as young people (38). Furthermore, less physical activity among the elderly may exacerbate apparent age-related differences in voluntary activation. In a recent study by our group (20), we documented the contribution of voluntary activation as a modulator of the decline in voluntary force production with advancing age. Specifically, despite a progressive reduction in voluntary force generation, the locomotor limbs of the oldest-old (more than 85 y old) exhibited a similar fall in muscle voluntary activation regardless of their loss or preservation of independent locomotion. This reduction in muscle voluntary activation was also apparent in non-locomotor limbs. Additional evidence of the potential neuromuscular contribution to the reduction in voluntary force is the electrically-evoked resting twitch specific force. This variable is an indicator of contractile force, divorced from neural drive and physiological cross-sectional area as potentially limiting factors, and our data (20) suggest a preservation of resting twitch specific force in the locomotor and non-locomotor limbs of the oldest-old. Therefore, with recognition of the

reduction in muscle voluntary activation with advanced aging, it seems reasonable to assume that a deficit in neural drive plays a significant role in the attenuated voluntary force production in the oldest-old. Taken together, these results support the concept that voluntary force development is largely dependent upon neural activity and this is likely impaired in the oldest-old.

Single muscle fiber contractile function in elderly and oldest-old

When considered at cellular level, skeletal muscle can be viewed as a complex organ comprising of several diverse cellular populations. Specifically, the muscle fibers or myofibers are embedded in connective tissue layers which host blood vessels, motor and sensory nerve endings, inflammatory cells, and adipocytes. Muscle fibers, however, represent the determinants of contractile performance in terms of force and power generation. In regard to the contribution of myofibers to muscle atrophy, available evidence supports the view that the loss of muscle mass is a consequence of a decrease in size of the single myofibers and a decrease in fiber number (39). On the other hand, it is currently unknown to what degree the functional decline in whole muscle is a consequence of the decrease in the single myofibers ability to develop force and power.

Since the seminal work of Lexell (40), 30 years ago, it has been generally accepted that aging involves a loss of muscle fibers, which parallels the loss of motor neurons and the related denervation process, for which anatomical and electromyographic (see above) evidence is available (33, 34). Small angular fibers and fiber clustering, signs of denervation and re-innervation, have been consistently reported in skeletal muscle with healthy aging (41, 42). The fate of many or, possibly, most denervated fibers is death and, ultimately, disappearance. The open question of whether with advanced age, muscle fiber size is preserved or whether they all undergo a decrease in transverse area (CSA) is, thus, restricted to the surviving fibers.

Most studies are based on cross sectional comparisons, that is comparisons among subjects of different ages, generally taking into account health conditions, physical activity, and gender. The limitations inherent to such cross sectional studies are the same as for the assessments of muscle mass and function discussed above. The sampling is typically performed by percutaneous biopsy which allows the analysis of just several hundred fibers, in most cases collected from the vastus lateralis. In a few studies (40, 43), however, the whole muscle has been analyzed from post mortem sampling. The comparison with animal models, particularly rats, has been proposed (44), but it is uncertain whether the observations of fiber atrophy in aged rats can be directly applied to human aging. For mice, a specific strain, called sarco-mice, overexpressing neurotrypsin and characterized by sporadic denervation has been studied as a model of age-dependent denervation and mitochondria dysfunction (41, 42). Although some studies (45, 46) did not identify any age-dependent atrophy, most studies agree that fast fibers do undergo significant atrophy (39–41, 43, 47) with some studies also observing atrophy of the slow fibers (48) although less pronounced than in fast fibers. It is worth recalling that, possibly in relation to the denervation-re-innervation process or due to a change in functional demand to muscles, the proportion of hybrid fibers (fibers expressing a protein complement intermediate between fast and slow

fibers and, in particular, two or more myosin isoforms), becomes particularly abundant with aging (48–50). As clearly demonstrated by Purves-Smith and coworkers (51), this makes it far more difficult to attribute muscle fibers of the elderly to a given, slow or fast, type and, thus, identify atrophy of a specific fiber type and possible fiber type transitions (51).

The changes in contractile performance of individual myofibers with advancing age are even more complex to define. Actually, functional experiments on single fibers dissected from a biopsy samples face two main drawbacks: first, the limited number of fibers analyzed, even when several hundreds of fibers are tested *ex vivo*, represent much less than 1% of the whole muscle. Second, is the high risk of biased selection during the manual dissection procedure which tends to overlook the tiniest or the most fragile fibers. Taking into account such limitations, different, and, to some extent, opposite, results can be found in a survey of the relevant literature. Data in favor of a complete preservation of major contractile parameters, isometric tension (P_o , i.e. isometric force normalized to cross sectional area), unloaded shortening velocity (V_o), and peak power (W_{max}), have been provided by Trappe et al. (52). In this work, they (46) compared men and women in their third and eighth decades and reported only some minor decreases in cross sectional area in elderly women. Data in favor of functional preservation also comes from the longitudinal studies published by Frontera and coworkers (15) who could not detect any change in CSA or contractile parameters through the eighth decade (from 71 to 80 yrs). In contrast, D'antona et al (53) have documented a decrease in CSA, P_o and V_o in slow and fast 2A fibers when comparing men in their 30s with men in their eighth decade of life. Korhonen et al. (54) investigated a special group of subjects, men who maintained lifelong exercise training as sprinters, and observed not only a marked atrophy of fast fibers, but also a reduction in V_o of slow fibers and a decreased W_{max} . In partial agreement, a recent paper by Power et al. (3) documented a decrease in CSA, P_o , V_o and K_{TR} (the rate constant of tension redevelopment) in slow fibers of men at the end of their eighth decade compared to young men in their twenties, regardless of their physical activity. Of note, there was actually a subgroup of master athletes, among the elderly group, but this did not change the interpretation.

It is worth underlining that the functional parameters determined in single permeabilized fibers are obtained at low temperature, in optimal conditions from the metabolic point of view, as full ATP availability is guaranteed, and with full calcium activation. There are reliable data indicating that calcium activation is not well preserved in elderly muscle due to impaired excitation-contraction coupling (55, 56). Moreover, the impairment of mitochondrial aerobic metabolism in the elderly has been demonstrated *in vivo* and *in vitro* (57) and more recent data also point to an impairment of glycolytic pathway (47). All these data sets highlight the limitations of data obtained from single fibers *in vitro* and concerns regarding the translation of such findings to the contractile behavior of fibers assessed *in situ*. However, our recent data (20) lend support to the relevance of data obtained *in vitro*, by showing a high direct correlation between the average isometric tension generated by single fibers during maximal activation and the isometric tension generated during electrical stimulation of the whole muscle. Specifically, when electrical stimulation activates, all functioning fibers, even for a single maximal twitch, the tension output is proportional to that measurable in activated single fibers *in vitro*.

In view of the evidence of the accelerated muscle deterioration with aging in the eighth decade (13), the question about changes occurring in the ninth and tenth decades, the oldest-old, becomes very important. However, very few studies have investigated the properties of individual muscle fibers of people in that range of age. Raue et al. (58) have documented, in vastus lateralis of subjects of both sexes well above 80 years of age, the presence of slow and fast fibers with size (CSA) and contractile parameters (Po, Vo) similar or even higher than those measured in young people of the same sex in their third decade. These results are consistent with our recent work in this area (20) that compared single muscle fibers from both the arms and legs in a small cohort of oldest-old women (≈ 88 y) and their young (≈ 20 y) counterparts and documented the preservation of fiber size, expressed as cross-sectional area, as well as the preservation of isometric tension (Figure 3). Furthermore, a recent study by Grosicki et al. (59) revealed that the peak power developed by single muscle fibers from healthy octogenarians (≈ 89 y), maximally activated *in vitro*, was not different from that of young subjects. It is important to recall that both Raue et al. (58) and Venturelli et al. (20) determined that there was an extremely large heterogeneity of fiber size in the vastus lateralis of subjects aged 90 yrs or more. Interestingly, whereas the presence of thin and atrophic fibers may be linked to the denervation process, the survival of thick and strong fibers is not only a clear sign of preserved innervation, but also an indication of the capacity of these fibers to preserve or even increase their size. To explain the preservation of muscle fiber size, two main hypotheses have been proposed: First, a mechanism based on compensatory hypertrophy has been suggested by Frontera et al. (15). Specifically, it is proposed that, as consequence of the discrepancy between functional demands and the progressive decrease in the number of muscle fibers and motor units, the surviving fibers respond with a compensatory hypertrophy. Second, as an alternative explanation, Grosicki and coworkers (59) have proposed that the preservation of fiber size is the result of a selection process, such that only the largest and strongest fibers survive. The partial failure to achieve muscle loading-induced hypertrophy with resistance training in the oldest-old (58), lends support to the concept of a selective mechanism. However, the real nature of such a mechanism still needs to be fully understood in order to better exploit these processes with countermeasures aimed to improve muscle structure and function in the oldest-old.

Conclusion

Skeletal muscle function is greatly diminished with advanced aging, however, a population of single muscle fibers is able to preserve structure and function. Indeed, there is now significant evidence supporting the concept that the skeletal muscle fibers, per se, are not the predominant factor responsible for the reduction in force generating capacity in the oldest-old (Figure 3). Instead, the loss of muscle function with advanced age, is likely attributable to a combination of factors external to the muscle fibers, among them impaired neural control and changes in muscle composition. This observation should prompt future studies to put an emphasis on the control of such factors and their role in aging and loss of mobility.

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References

1. Degens H, Korhonen MT. Factors contributing to the variability in muscle ageing. *Maturitas*. 2012; 73(3):197–201. [PubMed: 22902240]
2. Hunter SK, Pereira HM, Keenan KG. The aging neuromuscular system and motor performance. *J Appl Physiol*. 2016; 121(4):982–95. [PubMed: 27516536]
3. Power GA, Allen MD, Gilmore KJ, et al. Motor unit number and transmission stability in octogenarian world class athletes: Can age-related deficits be outrun? *J Appl Physiol*. 2016; 121(4):1013–20. [PubMed: 27013605]
4. Piasecki M, Ireland A, Stashuk D, Hamilton-Wright A, Jones DA, McPhee JS. Age-related neuromuscular changes affecting human vastus lateralis. *J Physiol*. 2016; 594(16):4525–36. [PubMed: 26486316]
5. Power GA, Dalton BH, Behm DG, Vandervoort AA, Doherty TJ, Rice CL. Motor unit number estimates in masters runners: use it or lose it? *Med Sci Sports Exerc*. 2010; 42(9):1644–50. [PubMed: 20142771]
6. Jones DA, McPhee JS, Degens H. Is ageing ‘highly individualistic’? *J Physiol*. 2015; 593(14):3219. [PubMed: 26173828]
7. Venturelli M, Schena F, Richardson RS. The role of exercise capacity in the health and longevity of centenarians. *Maturitas*. 2012; 73(2):115–20. [PubMed: 22883374]
8. Venturelli M, Morgan GR, Donato AJ, et al. Cellular aging of skeletal muscle: telomeric and free radical evidence that physical inactivity is responsible and not age. *Clinical science*. 2014; 127(6):415–21. [PubMed: 24708050]
9. Hepple RT. When motor unit expansion in aging muscle fails, atrophy ensues. *J Physiol*. 2018; Epub 2018/03/14. doi: 10.1113/JP275981
10. Piasecki M, Ireland A, Piasecki J, et al. Failure to expand the motor unit size to compensate for declining motor unit numbers distinguishes sarcopenic from non-sarcopenic older men. *J Physiol*. 2018; Epub 2018/03/13. doi: 10.1113/JP275520
11. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. *Front Physiol*. 2012; 3:260. [PubMed: 22934016]
12. Petrella JK, Kim JS, Tuggle SC, Hall SR, Bamman MM. Age differences in knee extension power, contractile velocity, and fatigability. *J Appl Physiol*. 2005; 98(1):211–20. [PubMed: 15347625]
13. Delmonico MJ, Harris TB, Visser M, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *Am J Clin Nutr*. 2009; 90(6):1579–85. [PubMed: 19864405]
14. Hughes VA, Frontera WR, Wood M, et al. Longitudinal muscle strength changes in older adults: influence of muscle mass, physical activity, and health. *J Gerontol A Biol Sci Med Sci*. 2001; 56(5):B209–17. [PubMed: 11320101]
15. Frontera WR, Reid KF, Phillips EM, et al. Muscle fiber size and function in elderly humans: a longitudinal study. *J Appl Physiol*. 2008; 105(2):637–42. [PubMed: 18556434]
16. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20–93 yr. *J Appl Physiol*. 1997; 83(5):1581–7. [PubMed: 9375323]
17. McNeil CJ, Doherty TJ, Stashuk DW, Rice CL. Motor unit number estimates in the tibialis anterior muscle of young, old, and very old men. *Muscle Nerve*. 2005; 31(4):461–7. [PubMed: 15685623]
18. Reid KF, Fielding RA. Skeletal muscle power: a critical determinant of physical functioning in older adults. *Exerc Sport Sci Rev*. 2012; 40(1):4–12. [PubMed: 22016147]
19. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol*. 2000; 89(1):81–8. [PubMed: 10904038]
20. Venturelli M, Saggin P, Muti E, et al. In vivo and in vitro evidence that intrinsic upper- and lower-limb skeletal muscle function is unaffected by ageing and disuse in oldest-old humans. *Acta Physiol*. 2015; 215(1):58–71.

21. Klein CS, Marsh GD, Petrella RJ, Rice CL. Muscle fiber number in the biceps brachii muscle of young and old men. *Muscle Nerve*. 2003; 28(1):62–8. [PubMed: 12811774]
22. Pannérec A, Springer M, Migliavacca E, et al. A robust neuromuscular system protects rat and human skeletal muscle from sarcopenia. *Aging (Albany NY)*. 2016; 8(4):712–28. [PubMed: 27019136]
23. Hashizume K, Kanda K. Differential effects of aging on motoneurons and peripheral nerves innervating the hindlimb and forelimb muscles of rats. *Neurosci Res*. 1995; 22(2):189–96. [PubMed: 7566699]
24. Dufour AB, Hannan MT, Murabito JM, Kiel DP, McLean RR. Sarcopenia definitions considering body size and fat mass are associated with mobility limitations: the Framingham Study. *J Gerontol A Biol Sci Med Sci*. 2013; 68(2):168–74. [PubMed: 22503991]
25. Doherty TJ, Vandervoort AA, Taylor AW, Brown WF. Effects of motor unit losses on strength in older men and women. *J Appl Physiol*. 1993; 74(2):868–74. [PubMed: 8458808]
26. Hepple RT, Rice CL. Innervation and neuromuscular control in ageing skeletal muscle. *J Physiol*. 2016; 594(8):1965–78. [PubMed: 26437581]
27. Lexell J. Evidence for nervous system degeneration with advancing age. *The Journal of nutrition*. 1997; 127(5 Suppl):1011S–3S. [PubMed: 9164286]
28. Piasecki M, Ireland A, Coulson J, et al. Motor unit number estimates and neuromuscular transmission in the tibialis anterior of master athletes: evidence that athletic older people are not spared from age-related motor unit remodeling. *Physiol Rep*. 2016; 4(19)
29. Ward NS. Compensatory mechanisms in the aging motor system. *Ageing Res Rev*. 2006; 5(3):239–54. [PubMed: 16905372]
30. McGinnis SM, Brickhouse M, Pascual B, Dickerson BC. Age-related changes in the thickness of cortical zones in humans. *Brain Topogr*. 2011; 24(3–4):279–91. [PubMed: 21842406]
31. Mattay VS, Fera F, Tessitore A, et al. Neurophysiological correlates of age-related changes in human motor function. *Neurology*. 2002; 58(4):630–5. [PubMed: 11865144]
32. Oliviero A, Profice P, Tonali PA, et al. Effects of aging on motor cortex excitability. *Neurosci Res*. 2006; 55(1):74–7. [PubMed: 16584795]
33. Campbell MJ, McComas AJ, Petito F. Physiological changes in ageing muscles. *J Neurol Neurosurg Psychiatry*. 1973; 36(2):174–82. [PubMed: 4708452]
34. Tomlinson BE, Irving D. The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J Neurol Sci*. 1977; 34(2):213–9. [PubMed: 925710]
35. Tracy BL, Maluf KS, Stephenson JL, Hunter SK, Enoka RM. Variability of motor unit discharge and force fluctuations across a range of muscle forces in older adults. *Muscle Nerve*. 2005; 32(4):533–40. [PubMed: 15986419]
36. Deschenes MR. Motor unit and neuromuscular junction remodeling with aging. *Current aging science*. 2011; 4(3):209–20. [PubMed: 21529328]
37. Tomlinson BE, Irving D. The numbers of limb motor neurons in the human lumbosacral cord throughout life. *Journal of the Neurological Sciences*. 34(2):213–9. DOI: 10.1016/0022-510X(77)90069-7
38. De Serres SJ, Enoka RM. Older adults can maximally activate the biceps brachii muscle by voluntary command. *J Appl Physiol*. 1998; 84(1):284–91. [PubMed: 9451648]
39. McPhee JS, Cameron J, Maden-Wilkinson T, et al. The contributions of fibre atrophy, fibre loss, in situ specific force and voluntary activation to weakness in sarcopenia. *J Gerontol A Biol Sci Med Sci*. 2018; Epub 2018/03/13. doi: 10.1093/gerona/gly040
40. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci*. 1988; 84(2–3):275–94. [PubMed: 3379447]
41. Scelsi R, Marchetti C, Poggi P. Histochemical and ultrastructural aspects of m. vastus lateralis in sedentary old people (age 65–89 years). *Acta Neuropathol*. 1980; 51(2):99–105. [PubMed: 7435151]
42. Spendiff S, Vuda M, Gouspillou G, et al. Denervation drives mitochondrial dysfunction in skeletal muscle of octogenarians. *J Physiol*. 2016; 594(24):7361–79. [PubMed: 27619626]

43. Lexell J, Taylor CC. Variability in muscle fibre areas in whole human quadriceps muscle: effects of increasing age. *J Anat.* 1991; 174:239–49. [PubMed: 2032938]
44. Rowan SL, Rygiel K, Purves-Smith FM, Solbak NM, Turnbull DM, Hepple RT. Denervation Causes Fiber Atrophy and Myosin Heavy Chain Co-Expression in Senescent Skeletal Muscle. *PLOS ONE.* 2012; 7(1):e29082.doi: 10.1371/journal.pone.0029082 [PubMed: 22235261]
45. Monemi M, Kadi F, Liu JX, Thornell LE, Eriksson PO. Adverse changes in fibre type and myosin heavy chain compositions of human jaw muscle vs. limb muscle during ageing. *Acta Physiol Scand.* 1999; 167(4):339–45. [PubMed: 10632637]
46. Frontera WR, Suh D, Krivickas LS, Hughes VA, Goldstein R, Roubenoff R. Skeletal muscle fiber quality in older men and women. *Am J Physiol Cell Physiol.* 2000; 279(3):C611–8. [PubMed: 10942711]
47. Murgia M, Toniolo L, Nagaraj N, et al. Single Muscle Fiber Proteomics Reveals Fiber-Type-Specific Features of Human Muscle Aging. *Cell Reports.* 2017; 19(11):2396–409. [PubMed: 28614723]
48. Andersen JL. Muscle fibre type adaptation in the elderly human muscle. *Scand J Med Sci Sports.* 2003; 13(1):40–7. [PubMed: 12535316]
49. Klitgaard H, Bergman O, Betto R, et al. Co-existence of myosin heavy chain I and IIa isoforms in human skeletal muscle fibres with endurance training. *Pflugers Arch.* 1990; 416(4):470–2. [PubMed: 2399119]
50. Hepple RT. Mitochondrial involvement and impact in aging skeletal muscle. *Front Aging Neurosci.* 2014; 6:211. [PubMed: 25309422]
51. Purves-Smith FM, Solbak NM, Rowan SL, Hepple RT. Severe atrophy of slow myofibers in aging muscle is concealed by myosin heavy chain co-expression. *Exp Gerontol.* 2012; 47(12):913–8. [PubMed: 22884852]
52. Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J, Trappe T. Single muscle fibre contractile properties in young and old men and women. *J Physiol.* 2003; 552(Pt 1):47–58. [PubMed: 12837929]
53. D'Antona G, Pellegrino MA, Adami R, et al. The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J Physiol.* 2003; 552(Pt 2):499–511. [PubMed: 14561832]
54. Korhonen MT, Cristea A, Alen M, et al. Aging, muscle fiber type, and contractile function in sprint-trained athletes. *J Appl Physiol.* 2006; 101(3):906–17. [PubMed: 16690791]
55. Delbono O, O'Rourke KS, Ettinger WH. Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. *J Membr Biol.* 1995; 148(3):211–22. [PubMed: 8747553]
56. Lamboley CR, Wyckelsma VL, Dutka TL, McKenna MJ, Murphy RM, Lamb GD. Contractile properties and sarcoplasmic reticulum calcium content in type I and type II skeletal muscle fibres in active aged humans. *J Physiol.* 2015; 593(11):2499–514. [PubMed: 25809942]
57. Lanza IR, Nair KS. Muscle mitochondrial changes with aging and exercise. *Am J Clin Nutr.* 2009; 89(1):467S–71S. [PubMed: 19056588]
58. Raue U, Slivka D, Minchev K, Trappe S. Improvements in whole muscle and myocellular function are limited with high-intensity resistance training in octogenarian women. *J Appl Physiol.* 2009; 106(5):1611–7. [PubMed: 19246651]
59. Grosicki GJ, Standley RA, Murach KA, et al. Improved single muscle fiber quality in the oldest-old. *J Appl Physiol.* 2016; 121(4):878–84. [PubMed: 27516537]
60. Faulkner JA, Larkin LM, Claflin DR, Brooks SV. Age-related changes in the structure and function of skeletal muscles. *Clinical and Experimental Pharmacology and Physiology.* 2007; 34:1091–1096. [PubMed: 17880359]

KEY POINTS

- Skeletal muscle mass and voluntary force generation are greatly diminished with advanced age.
- Single muscle fiber function appears to be well preserved.
- The predominant factor responsible for the reduction in force generating capacity in the oldest-old, is likely a combination of factors external to the muscle fibers.

Figure 1.

Conceptual schematic of telomere shortening in somatic tissues with differing proliferative activity and intracellular stress. During childhood, a period of rapid growth, it is likely that all somatic tissues experiences telomeric shortening. During adulthood, leg skeletal muscles (dark gray line), characterized by low proliferative activity, undergo greater inactivity with increasing age. This inactivity promotes accumulation of intramuscular free radicals, which erode telomeres. With a severe increase in leg skeletal muscle inactivity in wheelchair bound people (dark gray dotted line), intramuscular free radical levels are further augmented resulting in greater genotoxic stress and exacerbated telomere erosion. Due to the bi-pedal nature of human locomotion, arm skeletal muscles (light gray line), also characterized by

low proliferative activity, does not experience an increase in inactivity across the human lifespan. Thus, intramuscular free radicals are not increased and telomere shortening across adulthood is avoided. In contrast, the highly proliferative leucocytes (black line) are not influenced by physical activity, but experience rapid telomere shortening as a consequence of time and replicative activity, with leukocyte telomeres becoming shorter quicker than in minimally proliferative somatic tissue such skeletal muscles. [Adapted from (8). Copyright © 2014 Portland Press Ltd. Used with permission.]

Figure 2.

Decline of skeletal muscle fibers and motor units across the human life span. Panel A represents the relationship between total number of fibers in the vastus lateralis muscle and the age of men between 18 to 82 years of age. Panel B represents the relationship between the number of motor units in the extensor digitorum brevis muscles and the age of men between the 5 and 88 years of age (Reprinted from (60). Copyright © 2007 John Wiley and Sons. Used with permission.)

Figure 3.

An illustration of the novel hypothesis that skeletal muscle fibers, per se, are not the predominant factor responsible for the reduction in force generating capacity in the oldest-old, but, rather, is attributable to a combination of factors external to the muscle fibers, such as a reduction in cortical inputs, increased cerebral cortex atrophy, increased motor-neurons apoptosis and neuromuscular junction impairments associated with increased levels of reactive oxygen species derived from mitochondrial dysfunction.