

Evolving concepts on the age-related changes in “muscle quality”

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Received: 9 September 2011 / Accepted: 26 December 2011 / Published online: 3 February 2012
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Abstract The deterioration of skeletal muscle with advancing age has long been anecdotally recognized and has been of scientific interest for more than 150 years. Over the past several decades, the scientific and medical communities have recognized that skeletal muscle dysfunction (e.g., muscle weakness, poor muscle coordination, etc.) is a debilitating and life-threatening condition in the elderly. For example, the age-associated loss of muscle strength is highly associated with both mortality and physical disability. It is well-accepted that voluntary muscle force production is not solely dependent upon muscle size, but rather results from a combination of neurologic and skeletal muscle factors, and that biologic properties of both of these systems are altered with aging. Accordingly, numerous scientists and clinicians have used the term “muscle quality” to describe the relationship between voluntary muscle strength and muscle size. In this review article, we discuss the age-associated changes

in the neuromuscular system—starting at the level of the brain and proceeding down to the subcellular level of individual muscle fibers—that are potentially influential in the etiology of dynapenia (age-related loss of muscle strength and power).

Keywords Sarcopenia · Dynapenia · Muscle · Strength · Weakness · Aging

1 Introduction

In 2006, there were 37.3 million adults over the age of 65 years living in the USA [1], and it is expected that this number will double by the year 2050. Among these individuals, it is estimated that 42% have limitations in performing one or more daily tasks (e.g., walking two to three blocks, transferring from sitting to standing) that are essential for maintaining physical independence [1]. While the causes of physical disability are multifactorial, it is well established that contributing factors associated with age-related physical disability are low levels of voluntary muscle strength and power [2–7]. Indeed, over the past several decades, the scientific and medical communities have recognized that both skeletal muscle wasting and weakness are a debilitating—and even life-threatening—condition in older persons [8].

It was originally thought that the loss of skeletal muscle mass largely explained the muscle weakness observed in older adults [9]; however, recent longitudinal data suggest that other physiologic factors—independent of tissue size—play an important role in muscle weakness. Specifically, data from the Health ABC study indicate that the decline in muscle strength is much more rapid than the concomitant loss of muscle mass and that the change in quadriceps muscle area only explains ~6–8% of the between-subject

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variability in the change in knee extensor muscle strength [10]. Moreover, maintaining or gaining muscle mass does not prevent aging-related declines in muscle strength [10]. Accordingly, these findings indicate that the loss of muscle strength in older adults is weakly associated with the loss of lean body mass. Our findings using animal models of aging and experimental disuse models of muscle weakness (e.g., cast immobilization and unilateral lower limb suspension) also suggest that the relative contribution of muscle atrophy to the disuse-induced muscle weakness is only modest [11–13]. In recent years, we have attempted to highlight the paucity of knowledge and our lack of understanding of the mechanisms of weakness in the elderly, and in 2008, a new term to more accurately define the loss of muscle strength with age was coined: *dynapenia* [14].

Numerous scientists and clinicians have used the term “muscle quality”—and other related terms such as specific force—to describe the relationship between voluntary muscle strength and muscle size (i.e., decreased muscle quality is indicative of lower muscle strength relative to muscle size) [2, 10, 15–24]. Recent longitudinal data from the Health ABC study of more than 1,600 older adults indicate that knee extensor muscle quality—as defined above—decreases at a staggering rate of ~2.5%/year (in contrast to muscle cross-sectional area decreasing at a rate of ~1%/year) [10]. Similar findings have also been observed in cross-sectional studies [2]. These findings further indicate that changes in neurological function and/or the intrinsic force-generating properties of skeletal muscle contribute to dynapenia in older adults. These potential contributors to reduced muscle quality are numerous and likely even vary within the context of specific tasks. In general though, the mechanisms determining muscle quality largely arise from two factors: (1) neurological and (2) skeletal muscle properties, as it is well known that the output from these sources controls muscle force production. Specifically, within the neuromuscular system, there are several potential sites affecting muscle quality, such as excitatory drive to the lower motor neurons, α -motor neuron excitability, neuromuscular transmission, and excitation–contraction (E–C) coupling [25]. In this review article, starting at the level of the brain and proceeding down to the muscle fiber level, we will discuss and describe the potential physiological factors leading to reductions in muscle quality in older adults.

2 Effects of aging on the mechanisms determining optimal force output

2.1 Neural contributors to force generation

In this section, we will discuss age-related changes in central (voluntary) activation, followed by discussing the effects of aging on supraspinal and spinal form and function.

2.1.1 Age-related changes in central (voluntary) activation

As stated earlier, aging is commonly associated with muscle weakness. This loss of muscle strength is likely due to a wide variety of physiologic reasons, including reductions in muscle mass and changes in the excitation–contraction coupling process. However, it is also probable that a portion of the strength loss is attributable to the nervous systems ability—or lack thereof—to fully activate skeletal muscle. Thus, it is imperative that scientists and clinicians understand the role of the central nervous system in mediating the muscle weakness observed with advancing age.

There is evidence to suggest that aging results in impaired agonist activation and/or increased antagonistic coactivation [26]; however, age-related differences in voluntary activation appear to vary between muscle groups. Prior to more fully discussing the effects of aging on voluntary activation, we will first provide a brief overview of the assessment of voluntary activation. A voluntary effort, or a voluntary contraction of a muscle, comprises the recruitment of motor neurons, and hence muscle fibers, by increased descending drive. Hence, with an increased force of contraction, there is increased activation of neurons in the primary motor cortex with increased firing of corticospinal neurons [27]. Increased descending drive recruits greater numbers of motor neurons in the spinal cord. While there are many influences on motor neurons during voluntary contractions, such as excitatory and inhibitory sensory feedback, and alterations in motor neuron properties that may make them more or less responsive to synaptic input [28], descending drive from the motor cortex is the major determinant of the timing and strength of voluntary contractions. Voluntary activation is commonly assessed using the interpolated twitch method, or a derivative thereof (e.g., central activation ratio) [29–32]. Here, the motor nerve to the muscle is electrically stimulated during a voluntary effort. During maximal voluntary efforts, any increment in force evoked by a stimulus indicates that voluntary activation is less than 100%. That is, some motor units are not recruited or are not firing fast enough to produce fused contractions [33]. The extra force evoked by stimulation during contraction can be quantified by comparison to the force produced by the whole muscle. Thus, voluntary activation represents the proportion of maximal possible muscle force that is produced during a voluntary contraction. Measurement of voluntary activation does not quantify the descending drive reaching the motor neurons, nor whether motor neuron firing rates are maximal, nor does it take into account the source of drive to the motor neurons [30].

There are equivocal reports in the literature on whether or not advancing age reduces voluntary activation capacity [34–53] (for review, see [2]). A synthesis of the literature provides some insight into potential explanations of these

equivocal reports. Specifically, several studies examining the effect of age on voluntary isometric activation of the knee extensors (Fig. 1a) and the elbow flexors (Fig. 1b) suggest that older adults, particularly those greater than 70–75 years of age, exhibit a decrease in voluntary activation,

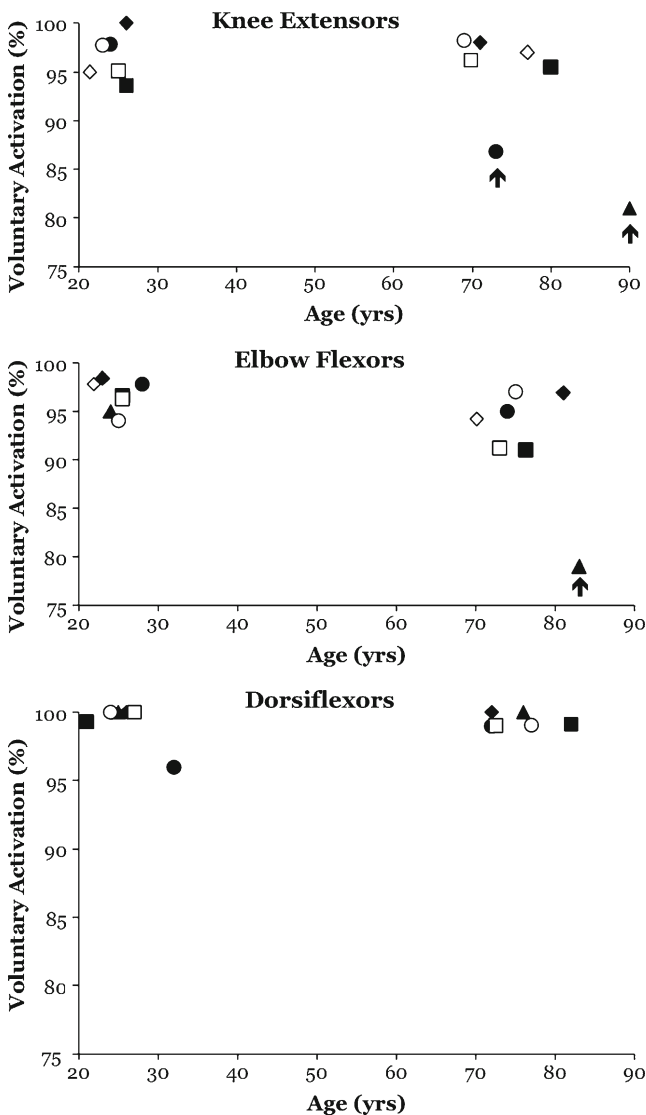


Fig. 1 Age-related changes in voluntary activation (a measure of how much of a muscle’s possible force is produced by a voluntary contraction) is muscle group specific. Studies quantifying age-related differences in voluntary activation of the knee extensors (a), elbow flexors (b), and ankle dorsiflexors (c) during isometric contractions. Selected studies have been highlighted with an arrow pointing to them (see main text for further discussion on these specific papers). Data points in a correspond to the following articles: filled circles: [50], filled squares: [48], filled diamonds: [35], filled triangle: [40], open circles: [51], open squares: [36], open diamonds: [46]. Data points in b correspond to the following articles: filled circles: [38], filled squares: [34], filled diamonds: [45], filled triangle: [42], open circles: [52], open squares: [41], open diamonds: [53]. Data points in c correspond to the following articles: filled circles: [43], filled squares: [38], filled diamonds: [47], filled triangle: [44], open circles: [49], open squares: [37]. Reprinted with permission from [233]

whereas investigations on the age-related changes in voluntary activation of the dorsiflexors yield null findings (Fig. 1c). Due to the functional differences between these muscles, as well as differences in their physiologic profiles (e.g., motor unit innervations and fiber-type characteristics), these muscle group-specific effects are not overly surprising. We should note that three studies indicating a dramatic impairment in voluntary activation are highlighted with an arrow in Fig. 1. Two of these (Fig. 1a) relate to the knee extensor muscles and one relates to the elbow flexors (Fig. 1b). With regards to the knee extensors, a number of reports show no differences between old and young adults, but two reports stand out as showing a deficit in voluntary activation with aging (Fig. 1a, vertical arrows) [40, 42, 50]. One of these represents data from the oldest known cohort of individuals that has been examined to date ($n=11$, age range 85–97 years) [40], and this observation suggests that deficits in the neural drive can contribute to much of the muscle weakness observed in the very elderly—at least in the knee extensor muscles. The second of the highlighted studies deserves particular attention because it is the largest to date (young adults: $n=46$, 18–32 years; older adults: $n=46$, 64–84 years) [50]. Here, the voluntary activation of older adults was calculated to produce 87% of maximal muscle force in comparison to 98% maximal force produced by younger subjects. With regards to the elbow flexors, one study is highlighted as this study averaged voluntary activation across numerous trials (as opposed to a single best trial or two) and thus provides some evidence that voluntary activation is less consistent across trials in older men compared to younger men [42]. Together, these studies provide proof of principle that older adults likely exhibit impairments in voluntary activation and that this likely varies with the specifics of a given task and the muscle group being examined.

2.1.2 Age-related changes in supraspinal properties

The neurons in the premotor and primary motor cortex form a complex network of glutamatergic interneurons, afferent projections, and pyramidal neurons that project to the striatum and spinal cord, among other areas of the central nervous system. Although it is often widely assumed that there is a progressive decay in the number of primary motor cortex (M1) neurons in normal aging, it does not appear that an actual decrease in cortical neurons occurs [54, 55]. However, there are substantial morphometric changes in the motor cortex that do occur with normal aging. For example, cadaveric dissections from humans who died without neurological signs suggest that individuals over 65 years of age exhibit a 43% volumetric reduction in the premotor cortex neuron cell body size in comparison to adults younger than 45 years [54], which have more recently been corroborated in living humans using high-resolution magnetic resonance imaging [56]. Furthermore, there is also evidence to suggest

that age-related differences exist in mass of white matter and of myelinated nerve fiber length with individuals losing ~45% of the total length of the myelinated fibers, mostly in the smallest white matter nerve fibers [57]. Also, cross-sectional studies further suggest that aging disrupts the integrity of white matter [58]. Functionally, it appears that these changes due to aging would affect the connectivity of the cortex with itself as well as the rest of the central nervous system.

In addition to morphometric changes, there has long been interest regarding the neurochemical changes within the basal ganglia that can be attributed to aging. This interest was largely driven by the hypothesis that changes in neurotransmitters and their receptors may be attributed to decreases in cognitive as well as motor functions. Certainly, it has been shown that impaired neurotransmission is responsible for at least some age-related behavioral abnormalities [59], including the serotonergic [60, 61], cholinergic [62], adrenergic [61], dopaminergic [63–66], GABAergic [63, 65], and glutamatergic systems [63, 65]. Reductions in neurotrophic factors have been shown within the motor cortex as well [67]. Age-related changes in the dopaminergic system are perhaps the best understood from work on different neurological conditions such as Parkinson's disease. Older adults have been reported to exhibit reduced dopamine transporter availability [68], and animal findings show that older rodents have decreased dopamine (D_2) receptors [69].

Aging also affects motor cortical properties at the systems level. Specifically, aging has been shown to result in decreased cortical excitability [70–73], increased activation in areas of sensorimotor processing and integration [74–76], and reduced cortical plasticity [77, 78]. In the following exposition, we will briefly summarize some of the evidence indicating these pertinent changes.

The effect of aging on cortical excitability is most commonly examined using paired-pulse transcranial magnetic stimulation (TMS), which also allows for the assessment of intracortical excitability [79, 80]. More specifically, paired-pulse TMS permits the assessment of short- and long-interval intracortical inhibition, which is generally thought to be mediated by gamma-aminobutyric acid (GABA) type A [81, 82] and B [81, 83] receptors, respectively ($GABA_A$, $GABA_B$). Additionally, intracortical facilitation—a measure that is mediated by excitatory glutamatergic interneurons and *N*-methyl-D-aspartate (NMDA) receptors [82, 84, 85]—can also be quantified. A recent investigation on age-related changes in intracortical facilitatory and inhibitory properties using paired-pulse TMS suggests that middle-aged adults exhibit reduced cortical excitability in comparison to younger adults, as it has been observed that individuals in their late 50s and early 60s exhibit more intracortical inhibition and less intracortical facilitation than adults in their 20s [70]. Our

recent findings in the elderly (mean age of 71 years) support these previous data, as we have observed that older adults exhibit substantially more intracortical inhibition and less intracortical facilitation in comparison to young adults under resting conditions, but that when these data were elicited during a submaximal contraction these differences disappeared [73]. Collectively, these findings suggest that aging results in cortical atrophy, altered neurochemistry, and reduced motor cortical excitability, all of which could be mechanistically link to impairments in voluntary activation capacity and contribute to age-related reductions in motor performance.

2.1.3 Age-related changes in spinal properties and the neuromuscular junction

The neuromuscular system is comprised of individual motor units, with the neuromuscular junction serving as the communication bridge between the nerve terminal and the muscle fibers they innervate. While the motor neuron and its behavior are the “final common pathway” for all motor commands, each motor neuron typically has 50,000 synapses to convey these commands [86] and can thus be influenced by numerous factors. It is well known that motor unit recruitment is primarily regulated on a biophysical basis with low-threshold motoneurons being recruited first [87]. However, in addition to the size principle of recruitment, discharge patterns of motor neurons are influenced by both the characteristics of their presynaptic input and their intrinsic properties. For instance, the discharge properties of motor neurons can be influenced by their prominent post-spike after hyperpolarization [88], their “bistable” behavior [89], as well as persistent inward currents. This phenomenon is thought to be explained from dendrite properties known as the persistent inward currents that act to amplify synaptic input [89, 90]. Motor units demonstrate numerous age-related adaptations, including changes in morphology, behavior, and electrophysiology. With regards to changes in morphology, advancing age is thought to result in a reduced motor unit number as well as an increased number of fibers per motor unit (increased innervation ratio) due to the compensatory collateral sprouting by surviving neurons [91–94]. Aging also elicits remodeling of the neuromuscular junctions endplate. Specifically, aged neuromuscular junctions exhibit elevations in presynaptic nerve terminal branching, and in the post-synaptic distribution of receptor sites for neurotransmitter [95–100]. Interestingly, recent evidence indicates that disuse further compounds these age-associated changes as muscle unloading was observed to result in significant remodeling of aged rats neuromuscular junction, but not in those of young, healthy rats [99]. Accordingly, these findings may indicate that the combination of aging and disuse, at least among aged rats, results in partial denervation leading

to morphological remodeling of the neuromuscular junction [101].

Aging has also been shown to result in changes in spinal excitability. For example, Kido and colleagues reported that both the maximum soleus H-reflex (H_{\max} , a measure of global spinal excitability) and the maximum soleus M-wave (M_{\max} , also known as the compound muscle action potential or CMAP) decrease gradually with age, with the decrease in the H_{\max} being more pronounced (reduced H_{\max} to M_{\max} ratio; Fig. 2). The H-reflex only provides a global measure of spinal excitability, as it can be modulated by a number of potential factors (e.g., presynaptic inhibition, variation in the amount of neurotransmitter released by the Ia terminal, fluctuations in the membrane potential arising, alterations in the intrinsic properties in the motoneurons, etc.). As such, the aforementioned findings suggest that overall spinal excitability is depressed in older adults. However, others have observed that heteronymous facilitation [102] and oligosynaptic reflexes [2] also decrease with age, which provides collective evidence that there is a general decrease in the excitability of spinal reflexes with age.

The end result of the morphological and physiological adaptations in motor units with aging is alterations in the behavioral discharge properties of motor units. For instance, older adults have been reported to exhibit mean motor unit firing rates of the tibialis anterior across a variety of contraction intensities that are ~30–35% lower than young adults [103], and the maximum motor unit firing rate of an intrinsic hand muscle is also comparably reduced [103]. These lower firing rates appear to be largely inter-related to the longer twitch contraction durations in older muscle,

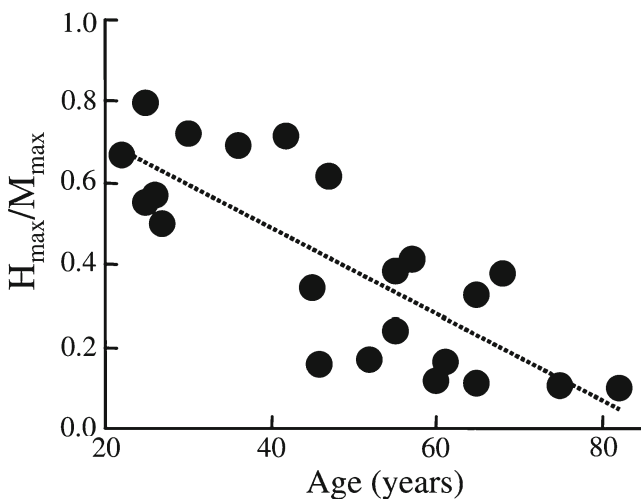


Fig. 2 Age-related decline in the human soleus muscles H_{\max} to M_{\max} ratio suggesting that advancing age results in a decrease in global spinal excitability. Data were obtained during standing while the muscle was activated at an intensity equal to 15% of its maximum voluntary contraction. Reprinted with permission from [234]

which further illustrates the critical integrative control processes involved between the nervous and muscular systems as it relates to overall neuromuscular function. More recent evidence suggests that more subtle age-related differences exist in motor unit behavior. Specifically, older adults have been reported to exhibit a greater variability in motor unit discharge rates that appears to largely influence their ability to maintain steady forces [104], and the occurrence of motor unit doublet discharges is lower in older adults (Fig. 3) [105].

Collectively, these findings suggest that aging results in morphological changes in motor units, including an actual reduction in functional motor units. A change of this nature (i.e., loss of motor units resulting in some muscle fibers not undergoing re-innervation) would theoretically result in a reduction in muscle quality. Additionally, age-related changes in spinal properties and the neuromuscular junction, such as decreased spinal excitability and a reduction in maximal motor unit discharge rates, may contribute to impairments in voluntary activation capacity (and thus reduced muscle quality).

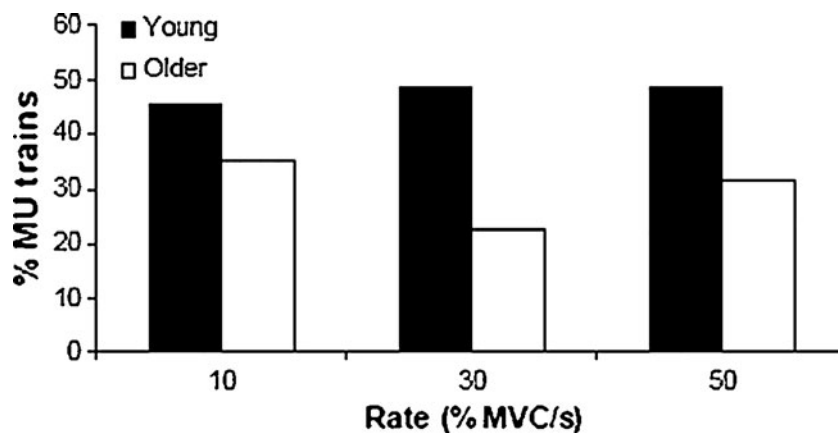
2.2 Muscular contributors to force generation

In this section, we will discuss age-related changes in muscular properties as it relates to muscle size and composition, excitation–contraction coupling, and crossbridge function and energetics.

2.2.1 Age-related changes in muscle size and composition

Much atrophy undoubtedly occurs with advancing age. In fact, data from the Health, Aging, and Body Composition (Health ABC) Study—which followed 1,678 older adults between 70 and 79 years of age longitudinally over a 5-year period—indicate that, on average, older men lose approximately 1% of their thigh muscle area per year and older women lose approximately 0.65% of their thigh muscle area per year [10]. With this stated, it should be noted that there is a large between-subject variability in the degree of atrophy observed with aging, and some older adults appear to exhibit no or nominal losses in muscle mass [10]. To study the effects of increasing age on human skeletal muscle size and composition, Lexell et al. examined 15- μm cross sections of autopsied whole vastus lateralis muscle from 43 previously physically healthy men between 15 and 83 years of age [106]. They reported that age-related muscle atrophy begins during the third decade of life and accelerates thereafter. The observed atrophy appeared to be primarily caused by a loss of fibers, with no predominant effect on any fiber type, and to a lesser extent by a reduction in fiber size—predominantly type II fibers. This finding was later corroborated by Lee and colleagues who reported that aging

Fig. 3 Percentage of motor unit trains in which doublets were observed in young (*black*) and older (*white*) individuals at three rates of force production. There were no significant differences among rates of force production, but significant differences between groups were found, indicating that the young subjects tended to display more doublet discharges. Reprinted with permission from [105]



resulted in a decreased fiber area percentage, fiber number percentage, and mean fiber area of type IIA and IIB muscle fibers, but that type I fibers increased in area and number but not in size [107]. Moreover, the type II fibers appeared morphologically smaller and flatter, which is consistent with other reports suggesting pathological abnormalities in aged human muscle fibers such as central nuclei, ring fibers, fiber splitting, scattered highly atrophic fibers, moth-eaten fibers, and even vacuoles [108]. Hence, as both the size and structure of a muscle deteriorate, the force-generating capacity is influenced.

There are many interacting factors leading to muscle wasting in older adults, and they often present themselves concurrently (for review, see [109]). Changes in muscle protein metabolism have been proposed as an explanatory factor in muscle wasting in older adults, as the balance between protein synthesis and degradation is largely responsible for the maintenance of lean mass [110]. However, recent findings suggest that basal muscle protein synthesis rates do not differ between young and old adults [111–116], and today, it is generally accepted that the difference in fasted rates of muscle protein synthesis or breakdown are not altered in healthy older adults [110]. Current hypotheses related to causative factors affecting muscle protein turnover surround the concept of older adults being resistant to anabolic stimuli, such as that associated with feeding, insulin, or physical activity. For example, while the ingestion or infusion of large quantities of amino acids/protein (~30–40 g) yields similar increases in muscle protein synthesis in both young and older individuals [114, 117–122], recent studies indicate that older adults exhibit a diminished accretion of muscle proteins after the ingestion of smaller amounts of essential amino acids (6–15 g) [112, 113]. Similarly, several recent studies have reported a blunted muscle protein synthesis response following an acute bout of resistance exercise in older subjects [123–125]. These effects are likely due to deficits in the mammalian target of rapamycin signaling pathway [111, 126], extracellular-related kinase 1/2 signaling pathway [127], and/or upregulation of the ubiquitin proteasome pathway in the elderly [128].

In addition, an increasing number of investigations report an age-related decline in autophagy (for recent reviews, c.f. [129, 130]). Sometimes referred to as “cell death type II,” autophagy is a process of cell and organelle degradation similar to, but distinct from, apoptosis [131, 132]. Although it can contribute to cell death in a number of situations (e.g., starvation, growth factor deprivation), autophagy also serves valuable housekeeping functions in normal, healthy cells by removing damaged or dysfunctional organelles [132]. This latter function is often referred to as macroautophagy, and recent evidence suggests that this process is lost or impaired in aging muscles. It is hypothesized that impaired autophagy leads to the accumulation of dysfunctional, damaged proteins, lipids, and nucleic acids that function at a suboptimal level. Dysfunctional contractile proteins, for example, might produce less force than normal ones and, thus, could contribute to impaired muscle quality. Moreover, the accumulation of these damaged cellular components may initiate cellular apoptosis, leading to a loss of muscle mass, thus contributing to sarcopenia. In support of this hypothesis, caloric restriction has been shown to restore markers of autophagy in skeletal muscle [132] and preserve muscle size and function [133, 134].

In addition to muscle size and anatomical structure, aged muscle also appears to differ in other compositional manners. For instance, over the past decade, numerous studies have reported that aging increases the adipocyte content between muscle groups (intermuscular adipose tissue) and between muscle fascicles (intramuscular adipose tissue) [10, 92, 93, 135, 136]. The earliest of these studies suggested that greater muscle fat content was associated with reduced muscle strength [135], suggesting a potential mechanistic link between increases in fat infiltration in muscle and muscle weakness. Indeed, cytokine production from adipose tissue has been linked to depressed muscle force production [94, 137], thus providing a theoretical basis to this assertion. However, more recent longitudinal data have failed to observe a direct relationship between increased levels of intermuscular adipose tissue and strength loss with age [10].

2.2.2 Age-related changes in contractile filaments

As noted, age-related declines in muscular force production were considered to be solely a function of reduced muscle mass for some time. It is no surprise then, that substantial attention has been devoted to age-related changes in the contractile proteins actin and myosin, which make up the majority of the volume of a skeletal muscle cell. Although sarcomeric actin seems to be quite uniform across muscle cells, myosin, in particular the myosin heavy chain (MHC), is not. In fact, muscle cells (fibers) are frequently differentiated by which isoform(s) of myosin they express. These different myosin isoforms are associated with different levels of ATP consumption—type I (i.e., slow) consume less ATP than type II (i.e., fast) isoforms at maximum levels of contractile activation [138–142]. Studies suggest that metabolic cost of type I < type IIa < type IIx < type IIb fibers. While humans do not express type IIb myosin, this pattern appears to hold for the three principal isoforms expressed in human muscle. Aging is associated with a loss of skeletal muscle mass (sarcopenia), and since actin and myosin are the predominant proteins in skeletal muscle, an overall loss in these proteins is observed with aging [143–146].

Some investigators have reported an age-related decline in the myosin/actin ratio in rat muscles [146], which might be expected to alter force production, as has been suggested in studies of disuse and microgravity [147, 148]. Of note, this change occurred in the semimembranosus, but not the soleus muscle, and was observed only in very old, but not old animals [146]. Our own data from aging, but not very old, rats indicate no significant changes in this ratio in any of the principal plantar flexor muscles (Fig. 4), further suggesting that this change may be muscle specific.

In addition to loss of muscle mass, aging is also generally associated with a shift in fiber type. Although not universal, most studies of aging muscle reflect a shift in overall muscle phenotype from faster to slower MHC, such that a larger proportion of the remaining contractile mass is composed of slower MHC isoforms [149, 150]. Consistent with a slower overall muscle phenotype are observations of reduced potentiation in aged skeletal muscle [151–153]. This shift is believed to be the result of both greater atrophy of type II fibers as well as a relatively small loss of fast, type II fibers [106, 154, 155]. Such a shift may inherently alter muscle quality, as the specific tension of type II fibers is greater than that of type I fibers [156, 157]. Although the underlying mechanisms are not entirely clear, apoptotic loss of the α -motor neurons has been implicated [91, 158, 159]. A decline in overall habitual physical activity has been shown to occur with increasing age, but MHC changes due to disuse and detraining are typically observed to be the opposite of those seen with aging (i.e., from slower to faster isoforms).

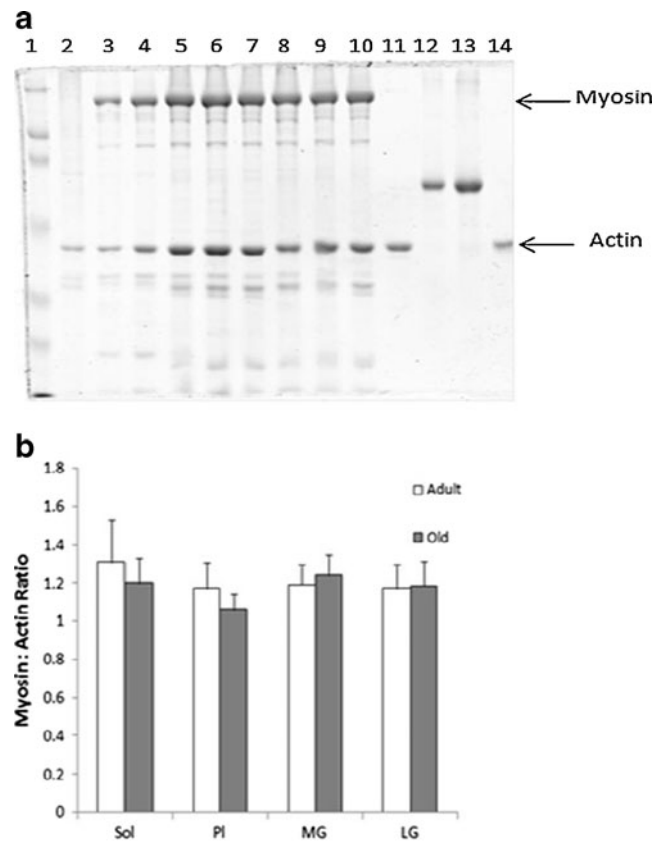


Fig. 4 Lack of difference in myosin/actin ratio between adult (6–8 months) and old (24 months) muscles. **a** Representative Coomassie-stained gel. Lane 1, molecular weight markers; lane 2, myofibrillar fraction from a previous experiment for positive control; lanes 11 and 14, actin standards of 2.0 and 1.0 µg, respectively; lanes 12 and 13, BSA standards of 2.5 and 5 µg, respectively; lanes 3 and 4, adult and old soleus; lanes 5 and 6, adult and old plantaris; lanes 7 and 8, adult and old medial gastrocnemius; lanes 9 and 10, adult and old lateral gastrocnemius. **b** Mean (\pm SE) myosin/actin ratio for adult and old muscles ($n=8$ /group). Unpublished data from Russ Laboratory

In addition to the absolute amount of contractile protein, some investigators have reported age-related functional impairments of these proteins within single fibers [160] and even at the level of isolated myosin molecules [161, 162]. Lowe and colleagues demonstrated a reduction in the number of strongly bound crossbridges in maximally activated fibers of aged vs. young rats using electron paramagnetic resonance [97, 163, 164]. These functional deficits may be the result of a reduced mixed muscle protein and MHC turnover [165–168], which could in turn contribute to the accumulation of post-translational modifications that impair crossbridge function. These findings are also consistent with the role of age-related impairments of autophagy described earlier in this paper.

Finally, the thin filaments also contain tropomyosin and the troponin isoforms. Although these regulatory proteins are not part of the actin–myosin crossbridge, they are critical in opening up the myosin binding site on actin, which makes

crossbridge formation possible. If either tropomyosin or troponin are not functioning properly, it is possible that fewer crossbridges will form (in effect reducing the calcium sensitivity of the muscle), generating less force which would result in reduced muscle quality [169]. Recent proteomics studies have suggested that increased age is associated with reduced expression of these proteins and increased post-translational modifications (e.g., nitration) [170–172], either of which could impair protein function. These proteins have received much less attention in the aging literature than the contractile proteins, and this area clearly needs more study in the future.

2.2.3 Age-related changes in muscular force transmission

Although actin and myosin are proteins responsible for the generation of muscular force (via the crossbridge cycle), functional force needs to be effectively transmitted to produce optimal function. Much force transmission in skeletal muscle takes place through a complex array of cytoskeletal proteins, and it is possible that deficiencies in these cytoskeletal proteins could reduce muscle quality by impairing force transmission. This topic has been largely unexplored, despite evidence from knockout animals that loss of at least one cytoskeletal protein, desmin, is associated with reduced muscle quality [173–176]. However, the few existing studies indicate that, if anything, desmin is increased with aging [145, 177, 178]. Interestingly, one group [179] has reported increased specific force in muscles from desmin knockout mice, speculating that desmin acts a “viscous element that dissipates mechanical energy.” If this is the case, then an age-associated increase in desmin could indeed contribute to impaired muscle quality with aging. Clearly, much further work needs to be done to explore the potential role of cytoskeletal changes in aging muscle function.

2.2.4 Age-related changes in excitation–contraction coupling

Excitation–contraction coupling (E–CC) converts the neural signal for muscle activation (muscle action potential) into muscle contraction and force development through a series of biophysical steps (Fig. 5). Briefly, the action potential spreads throughout the muscle via the t-tubular system, activating the voltage-sensitive dihydropyridine receptors (DHPRs), which subsequently open the ryanodine receptors (RYRs; Ca^{2+} release channels). This releases Ca^{2+} from its membranous storage area known (the sarcoplasmic reticulum (SR)). The newly released Ca^{2+} binds to troponin C which promotes crossbridge formation and force production. The Ca^{2+} is then returned to the SR by the sarcoplasmic reticulum Ca^{2+} pump (SR-ATPase) [180].

Reuptake of Ca^{2+} , in and of itself, contributes more to force relaxation than force generation. Thus, age-associated

impairments of reuptake, if present, are more likely to play a significant role in phenomena such as task performance (i.e., motor coordination) and muscle fatigue than in weakness. However, impaired Ca^{2+} reuptake could lead to unwanted elevations of intramyocellular Ca^{2+} that could activate specific proteases (e.g., calpains). Although the main myofibrillar proteins actin and myosin are not believed to be substrates for calpains, many of the cytoskeletal elements that anchor the myofibrillar proteins are. Thus, increased calpain activity could disrupt myofibrillar integrity of the myofibrils, making them susceptible to degradation by the ubiquitin–proteasome system (for recent reviews, c.f. [181, 182]). In addition, elevated Ca^{2+} could activate several cell signaling pathways that could contribute to weakness by inducing muscle cell apoptosis [181]. Several investigators have reported reduced SR Ca^{2+} reuptake with aging [13, 183, 184], although if SR Ca^{2+} release declines with age as well (see below), this may not be a major issue, as there may be no net increase in calcium. The rest of this section will focus on SR Ca^{2+} release, as this is the aspect of E–CC most directly related to force production, and thus weakness.

The description of E–CC above outlines the predominant mechanism of Ca^{2+} release in skeletal muscle, also referred to as voltage-induced calcium release (VICR) and does not require transmembrane movement of extracellular calcium [185]. However, Ca^{2+} -induced calcium release (CICR), which predominates in cardiac muscle, has also been shown to occur in skeletal muscle [186–188]. In this process, direct entry of extracellular Ca^{2+} into the myoplasm via activation of DHPRs that are not associated with RyRs occurs and triggers further mobilization of intracellular Ca^{2+} stores by activating RyRs. It has been suggested that this CICR may amplify the effects of VICR [189]. Finally, store-operated calcium entry (SOCE) is thought to serve to renew depleted Ca^{2+} in the SR via the opening of plasma membrane-located store-operated Ca^{2+} channels [190]. This allows extracellular Ca^{2+} to accumulate in the cytoplasm in order replenish SR Ca^{2+} [191]. Theoretically, disruption at any point in the E–CC process can prevent optimal activation of muscle mass and thus reduce muscle quality.

Impairments in SR Ca^{2+} release have been suggested to explain deficits of muscle quality in aged muscle [192–195], and in this regard, the role of Osvaldo Delbono must be acknowledged. Arguably, the idea that changes in E–CC were contributing to age-related weakness began with his reports of “excitation–calcium release uncoupling” in single fibers from aged human muscles [196]. Perhaps the most obvious mechanism for “uncoupling” of E–CC to account for loss of force production would be a reduction in the expression of the principal proteins in VICR. Although some early work indicated that RYR expression might be reduced with age, at least in fast muscles [194], a number of studies have not supported this hypothesis [184, 197–199].

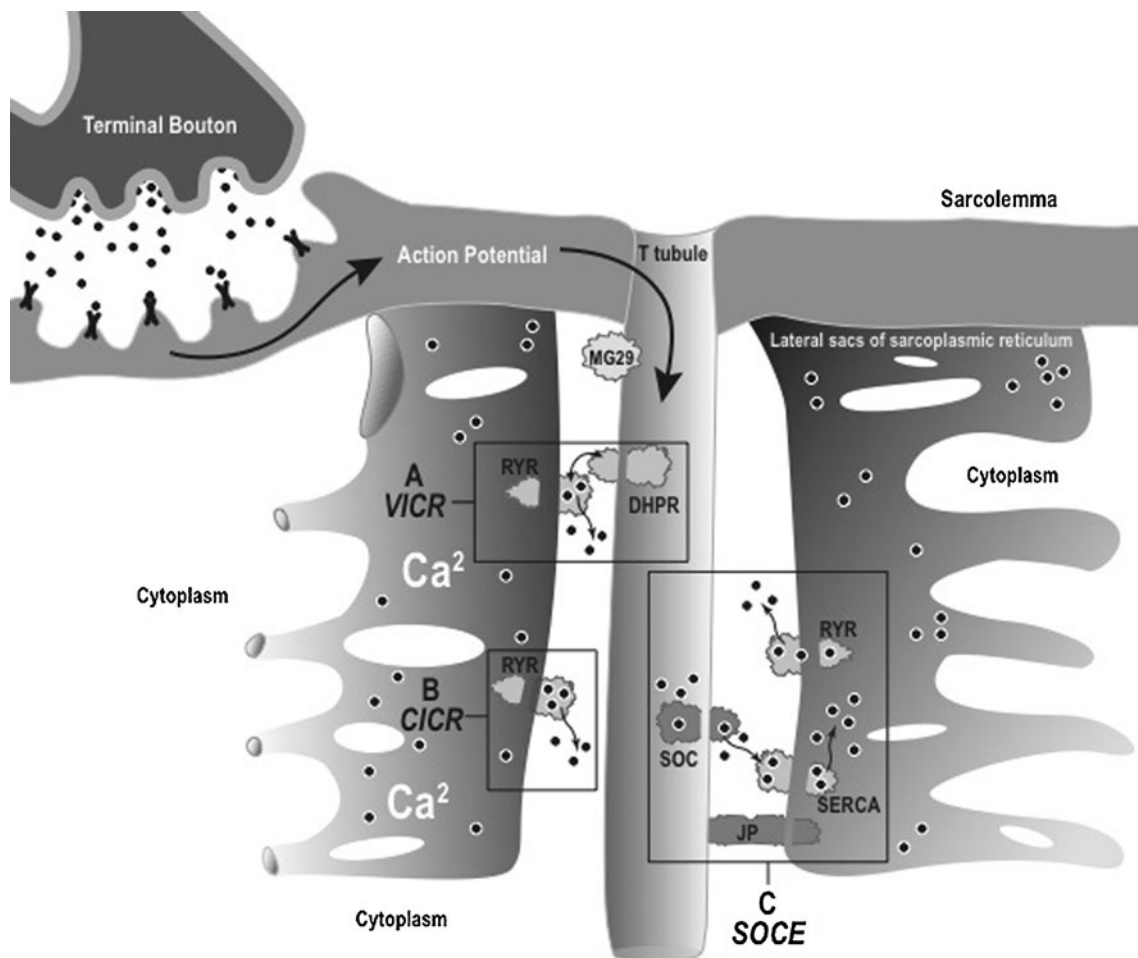


Fig. 5 Graphical illustration of the excitation–contraction coupling process. *VICR* voltage-induced calcium release, *CICR* calcium-induced calcium release, *SOCE* store-operated calcium entry, *RYR*

ryanodine receptor, *DHPR* dihydropyridine receptor, *SERCA* sarcolemmal/endoplasmic reticulum calcium ATPase, *JP* junctophilin

There is more support for the age-related loss of DHPR (particularly the α -1s subunit), such that a greater number of RYRs are not associated with DHPR, causing the uncoupling and disrupting the VICR process [199–201]. More recently, attention has been focused on the β -1a subunit of the DHPR. This subunit has roles in chaperoning the α -1s subunit to the t-tubule membrane and regulating Ca^{2+} current [202–204]. It also interacts directly with RyR [205] and may impair E–CC by binding to charged residues on RyR [206]. Taylor et al. determined that DHPR- β 1a increases significantly with age in fast, slow, and mixed murine muscle fibers and that overexpression of the subunit results in a decrease in α -1s subunits and a decline in specific force [207]. Finally, Payne et al. found that RNA inhibition of DHPR- β 1a expression in FDB muscles of young and old mice caused a significant reduction of charge movement in young mice, but restored charge movement to young control levels in old mice [208].

Although the case for alterations of DHPR contributing to the age-related decline in muscle quality is compelling, other processes may be impaired as well. Data from our

laboratory [13] and others [184] suggest that aging may impair SR calcium release, independent of DHPR function. In these experiments, the RYR was stimulated directly through pharmacological means in an SR vesicle preparation. Thus, SR function was compromised. Interestingly, we found that the older muscles also exhibited a reduced RYR–FKBP binding [13]. FKBP is a small immunophilin known to associate with the RYR, and reduced RYR–FKBP interaction has been linked to reduced muscle quality and impaired calcium release in models of aging, heart failure, and exhaustion [209–211]. While the cause of the reduced protein–protein interaction has not been definitively identified, data suggest that an age-related increase in RYR oxidation may be at work [209, 210]. Such a modification may be the result of reduced protein turnover with increasing age, allowing for greater accumulation of post-translational modifications such as oxidation [212]. Again, impaired autophagy may contribute to the problem, as oxidized RYR may not be removed and thus dysfunctional RYR will accumulate. Given that normal turnover of RYR is more

rapid than that of myosin [212, 213], it could be that impaired autophagy may affect RYR earlier in the aging process than it does myosin.

Investigators have also begun examining a potential role for SR-related proteins that are not directly involved in SR Ca^{2+} release, with much attention given to junctophilin and mitsugumin 29 (MG29). These proteins are both associated with the triadic junctions between the t-tubules and terminal cisternae, and both appear necessary for normal triad organization and optimal E–CC [214–218]. Interestingly, MG29 has been linked to SOCE and has been shown to decline with aging [191, 195], and may contribute to the fragmentation of the SR, resulting in fragments of Ca^{2+} -containing SR disconnected from the t-tubule membranes [219]. It has been hypothesized that this fragmentation occurs in a sub-population of fibers that became at least partially dependent on extracellular Ca^{2+} for SR Ca^{2+} . This phenomenon essentially shifts the E–CC mechanism from VICR to CICR [220]. Muscles containing higher percentages of such fibers dependent on SOCE would be at a force-generating disadvantage compared to normal skeletal muscle fibers that are not dependent upon the influx of Ca^{2+} from the t-tubule, particularly if the SR were depleted of Ca^{2+} . The role for an age-associated decline in SOCE in impaired muscle quality remains unclear, however, as others have not found that age adversely affects either SOCE or calcium stores [208], and the conditions under which impairments in SOCE may affect force (i.e., prolonged, high-rate stimulation with long-duration pulses) may not occur during normal muscle function [221].

Because of the role of E–CC in linking neural signals to muscular responses, it is not surprising that a direct biochemical interaction between muscle and nerve may influence E–CC. There is evidence to suggest that muscle-specific IGF-1 may act in a paracrine, retrograde manner to preserve motor neuron function [222, 223]. This in turn is thought to lead to the preservation of E–CC and muscle quality [223, 224], possibly through the regulation of DHPN expression [225]. However, questions regarding the exact mechanisms and outcomes of IGF-1 overexpression remain [201].

Finally, it is worth noting that age-related changes in membrane composition of the SR itself may occur. While much attention has been focused on the age-related alterations of the proteins associated with the SR, it is well known that the function of integral membrane proteins is affected by the composition of the membranes in which they are situated [226–229]. Investigation along these lines has been quite limited. However, age-related changes in the SR phospholipid and fatty acid composition have been demonstrated [230, 231]. The contribution of such alterations in membrane composition on age-related changes in muscle function has not been characterized, but at least one group has observed an increased susceptibility to heat inactivation of SERCA function in the SR of aging rats [230].

2.3 Future directions

Muscle weakness is undoubtedly a debilitating and life-threatening condition in the elderly as it is highly associated with both mortality and physical disability. As argued in this article, voluntary muscle force production is not solely dependent upon muscle size, but rather results from a combination of neurologic and skeletal muscle factors, and that biologic properties of both of these systems are altered with aging. The scientific and medical communities have made substantial progress in recent years on developing a better understanding of the clinical significance of muscle weakness in older adults and the physiological mechanisms involved in muscle weakness; however, there is still substantial progress that needs to be made. For example, virtually all studies conducted to date examining age-related mechanisms of muscle weakness have used cross-sectional study designs. Unfortunately, delineating the true cause and effect relationships with designs of this nature—and thus determining the mechanistic underpinnings of muscle weakness in older adults—is difficult. Accordingly, longitudinal studies are needed, or at a minimum, case–control studies whereby healthy older adults are compared to older adults with low levels of muscle strength are needed. Experiments of this nature would help determine the relative contribution of the various segmental components of the neuromuscular system associated with muscle weakness and thereby identify potential therapeutic targets.

Acknowledgments This work was supported in part by Award Number R15HD065552 from the Eunice Kennedy Shriver National Institute of Child Health & Human Development to BC Clark. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Eunice Kennedy Shriver National Institute of Child Health & Human Development or the National Institutes of Health. The authors would like to thank Danette Pratt, a Biomedical Illustrator in the Office of Communication at the Ohio University Heritage College of Osteopathic Medicine, for developing Fig. 5 depicting the excitation–contraction coupling process. The authors declare that they have no conflict of interest. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the *Journal of Cachexia, Sarcopenia and Muscle* [232].

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