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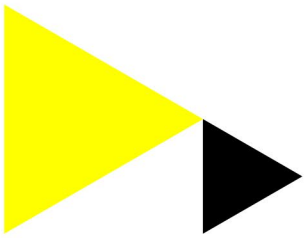

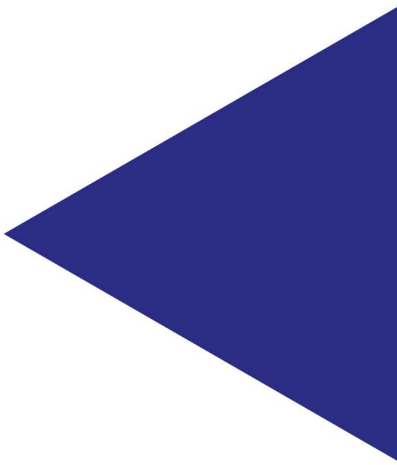

REVIEW

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Skeletal muscle performance and ageing

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Abstract

The world population is ageing rapidly. As society ages, the incidence of physical limitations is dramatically increasing, which reduces the quality of life and increases healthcare expenditures. In western society, ~30% of the population over 55 years is confronted with moderate or severe physical limitations. These physical limitations increase the risk of falls, institutionalization, co-morbidity, and premature death. An important cause of physical limitations is the age-related loss of skeletal muscle mass, also referred to as sarcopenia. Emerging evidence, however, clearly shows that the decline in skeletal muscle mass is not the sole contributor to the decline in physical performance. For instance, the loss of muscle strength is also a strong contributor to reduced physical performance in the elderly. In addition, there is ample data to suggest that motor coordination, excitation–contraction coupling, skeletal integrity, and other factors related to the nervous, muscular, and skeletal systems are critically important for physical performance in the elderly. To better understand the loss of skeletal muscle performance with ageing, we aim to provide a broad overview on the underlying mechanisms associated with elderly skeletal muscle performance. We start with a system level discussion and continue with a discussion on the influence of lifestyle, biological, and psychosocial factors on elderly skeletal muscle performance. Developing a broad understanding of the many factors affecting elderly skeletal muscle performance has major implications for scientists, clinicians, and health professionals who are developing therapeutic interventions aiming to enhance muscle function and/or prevent mobility and physical limitations and, as such, support healthy ageing.

Keywords Sarcopenia; Physical performance; Mobility; Dynapenia; Muscle quality

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Introduction

The world population is ageing rapidly. Since 1980, the number of people aged 60 years and over has doubled to approximately 810 million.[1] The elderly population will continue to grow to approximately 2 billion in 2050.[1] It has been predicted that 22% of the total population will be older than 60 years and around 5% will be older than 80 years in 2050.[1] As society ages, the incidence of physical performance limitation will increase as well. In western society, as much as 42% of those over 60 years of age have difficulties in performing activities of daily living (e.g. walking speed or standing up from a chair), 15–30% report being unable to lift or carry 10 pounds (4.5 kg), and >30% are confronted with physical disabilities.[2] These physical limitations increase the risk of falls, institutionalization, co-morbidity, and premature death. In addition, the higher age-related prevalence of physical disability (i.e. impairment in body function or structure, activity limitations, and participations restrictions[3]) will increase the demand on our healthcare system. Prevention and treatment of physical disability are, therefore, relevant for public health and healthy ageing. While there are a number of contributors to physical limitations with advancing age, one of the more prominent contributors is undoubtedly a reduction in skeletal muscle performance. One of the hallmark changes of ageing that is linked to reductions in muscle performance is the loss of skeletal muscle mass, which is commonly referred to as sarcopenia.[4,5]

However, it should be noted that skeletal muscle loss is not always related to sarcopenia but may also occur in the context of chronic systemic diseases such as heart failure, COPD, cancer, and others as a sign of cachexia (i.e. excessive weight loss in the setting of ongoing disease, usually with disproportionate muscle wasting).[6] Beyond muscle wasting, however, a plethora of other factors, however, contribute to reductions in skeletal muscle performance with advancing age. As illustrated in Figure 1, elderly skeletal muscle performance is regulated by factors associated with the nervous, muscular, and skeletal systems. The relative contribution of each of these factors on determining 'muscle performance' depends on the type of performance task being considered. Broadly speaking, degeneration of the anatomical and/or physiological processes governing these systems will result in impairments in muscle performance. These systems are all influenced by lifestyle, biological, and psychosocial factors. For example, the levels of physical activity and nutritional intake are important lifestyle factors[7,8] and genetics, hormones, and low-grade inflammation are examples of biological factors.[9–12] Psychosocial factors, such as fear of falling,[13] psychological resiliency,[14] self-efficacy,[15] and loneliness,[16] are also direct and indirect determinants of elderly skeletal muscle performance.

In the present review, we aim to provide a broad overview on the underlying mechanisms associated with elderly skeletal muscle performance, with a primary focus on age-related changes in muscle function, structure, and metabolism. We start with a system level discussion and progress to a discussion on the influence of lifestyle, biological, and psychosocial factors. The goal of this review is to not extensively cover the literature *per se* within each of the systems or factors, as there are many excellent reviews that have delved deeply into these specifics. Rather, we aim to provide a broad overview illustrating the integrative nature of these systems and factors and how they interact together in a multifactorial manner to ultimately regulate elderly skeletal muscle performance. We encourage the reader to also refer to the many review articles referenced herein for more specific reviews for in-depth information. Additionally, it should be noted that this article primarily concentrates on the role of skeletal muscle in movement and does not address another major function of skeletal muscle: joint and skeletal stability.

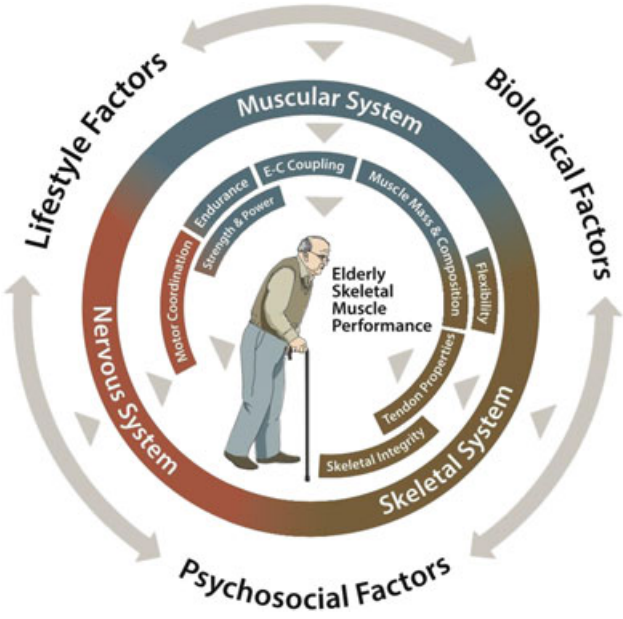
Physiological systems that contribute to the decline in elderly skeletal muscle performance

Role of the muscular system

Overview of skeletal muscle form and function

The body consists of more than 500 skeletal muscles[17] which are controlled by the nervous system and which connects and supports the skeletal system. Skeletal muscles consist of muscle fibres, each containing sarcomeres, which are the smallest repeating functional units in the muscle. Via a series of complex events, sarcomeres are responsible for muscle contraction and relaxation. This allows the body to perform

Figure 1 The multifactorial determinants of elderly skeletal muscle performance. *Diagram by Tim Goheen, Associate Professor, Ohio University School of Visual Communication*.



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a wide variety of different movements, ranging from fast and powerful movements to small and fine motions. Since skeletal muscles are responsible for all the voluntary movements, logically, skeletal muscles are essential for optimal physical performance. Physiological changes, such as a loss of motor units, changes in fibre type, muscle fibre atrophy, and reduced neuromuscular activation, could affect the velocity, force, and strength of movements, leading to reduced physical performance, potentially leading to functional disability and institutionalization.[18]

Not only are skeletal muscles important for physical performance, they are also an important contributing factor in maintaining optimal health throughout life. As such, skeletal muscles are involved in different metabolic pathways. Since muscles are the primary site for the insulin-stimulated glucose uptake from the blood, the muscles are crucial in maintaining glucose homeostasis.[19] Muscles are also involved in other metabolic functions providing a site for fatty acid metabolism and glycogen synthesis. Metabolic disturbances in muscle could, therefore, lead to insulin resistance, the metabolic syndrome, and obesity.[20] Furthermore, muscles interact with other organs via the excretion of myokines, which can exert autocrine, paracrine, or endocrine effects. Myokines support the metabolic function of different tissues, such as the bones, pancreas, liver, and adipose tissue.[21] The metabolic function of skeletal muscle and the role of myokines both illustrate the importance of the muscles in maintaining optimal health throughout life.

Age-related changes in muscle size and fibre types

Skeletal muscle atrophy undoubtedly occurs with advancing age. A recent quantitative review showed that the median decline in muscle mass throughout the lifespan is 0.37% per year in women and 0.47% per year in men.[22] According to longitudinal studies in people aged 75 years or over,[22] muscle mass is lost at a rate of 0.64–0.70% per year in women and 0.80–0.98% per year in men. However, during periods of physical inactivity, skeletal muscle atrophy is substantially accelerated. For instance, data from immobilization and bed rest studies show a substantial 1 kg loss of muscle mass in 10 days.[23–31] This substantial loss of skeletal muscle mass is accompanied by a major decline in strength that ranges between 0.3% and 4.2% per day.[29,31] As a consequence, multiple episodes of prolonged muscle disuse atrophy accelerate the degradation of muscle performance and physical performance and, as such, increases the risk for physical disability at later life.[32–36]

At the myocellular level, many studies have reported a substantial decrease in muscle fibre size in the elderly.[37–39] This reduction in muscle fibre size has been shown to be fibre type specific, with 10–40% smaller type II fibres observed in the elderly as compared with young adults. In contrast, type I muscle fibre size seems to be largely sustained with ageing.[38–41] The type I, or slow twitch fibres, are recruited first and, as such, are mainly responsible for endurance-type activities. The type II, or fast twitch fibres, are recruited later and predominantly responsible for higher intensity or highly fatiguing activities. The reduction in type II fibres may therefore result in a decline in muscle strength in the elderly and may decrease the ability to rise from a chair or to lift a heavy load. Next to muscle fibre size decrease with age, several studies reported a decrease in total number of muscle fibres with age.[42–44] Lexell *et al*.[44] reported an 18% smaller vastus lateralis muscle size in the elderly, with a 25% lower total number of muscle fibres, suggesting that muscle atrophy with ageing could be largely contributed to the loss of muscle fibres.[42–44] Nilwik *et al*. [45], however, clearly showed that the number of muscle fibres in the vastus lateralis muscle did not differ between young and old subjects but that predominantly type II muscle fibre size is declined with ageing.[45] These studies illustrate that full consensus on this topic is lacking.

The decline in type II muscle fibre size is reported in some studies to be accompanied by an age-related reduction in type II muscle fibre satellite cell content and function.[30] These satellite cells are the stem cell of human muscular tissue and essential for skeletal muscle fibre growth, repair, and regeneration throughout human life. The specific reduction in type II muscle fibre satellite cell content and function could therefore possibly represent a key factor responsible for specific type II muscle fibre atrophy with ageing. However, although some studies support this finding by reporting an association between muscle fibre satellite cell content of the tibilais anterior, masseter, and biceps brachii and increasing age,[46,47] others did not in the vastus lateralis.[48,49]

The primary cause of skeletal muscle loss is the disruption in the regulation of skeletal muscle protein turnover, leading to a negative balance between muscle protein synthesis and muscle protein breakdown.[50,51] Literature suggests an important role of a blunted protein synthetic response to anabolic stimuli in elderly, the so called anabolic resistance.[51] This is supported by a study of Cuthbertson *et al*. [52] who compared the myofibrillar and sarcoplasmic protein synthesis rates in the vastus lateralis muscles of young and older men, in response to a bolus of amino acids, and reported about 1.5-fold higher synthesis rates in the young.[52] In a more recent study, Wall *et al*. [53] showed a 16% lower skeletal muscle protein response to dietary protein intake in the vastus lateralis of older adults as compared with younger counterparts.[53] In addition, the protein synthetic signalling proteins p70 ribosomal S6 kinase and eukaryotic initiation factor 4E binding protein 1 were 30–40% lower phosphorylated in older adults vastus lateralis muscle.[54] In addition to the lower postprandial skeletal muscle response to anabolic stimuli, some studies suggest an increase in protein breakdown with age. In a study where vastus lateralis muscle biopsies were obtained from old and young women, messenger mRNA expression of atrogin-1, a ubiquitin proteasome-related gene,

was up-regulated (2.5-fold) in older women after resistance exercise.[55] The ubiquitin-proteasome pathway is responsible for the breakdown of muscle protein synthesis[56] and could possibly contribute to muscle protein breakdown with ageing.[57] However, full consensus is lacking as some studies reported inconsistencies regarding the relationship between the ubiquitin proteasome pathway, muscle protein breakdown, and ageing.[58]

Age-related changes in skeletal muscle contractile function and exctiation–contraction coupling

In addition to the pronounced muscle atrophy, a reduction in the force per unit area of skeletal muscle is also observed at the single fibre and whole muscle level in the elderly.[59,60] For instance, when the rat plantarflexor muscle group is electrically stimulated (eliminating the potential neural impairments in force production) and force is expressed relative to muscle mass (controlling for size), aged rats (24 months) exhibit a 34% reduction in 'muscle quality' (force/unit area or mass) in comparison to young rats (6–8 months).[61] One of the causes of this intrinsic reduction in the force-generating capacity of elderly muscle is changes in the excitation–contraction coupling (E-CC) processes.

Excitation–contraction coupling involves the physiological processes that convert the neural signal for muscle activation (i.e. the muscle fibre action potential) into muscle contraction and subsequently into force development. Briefly, the action potential spreads throughout the muscle via the t-tubular system, activating the voltage-sensitive dihydropyridine receptors, which subsequently open the ryanodine receptors. This releases Ca^{2+} from the sarcoplasmic reticulum (SR) that binds to troponin C creating cross bridge formation, leading to muscle contraction and consequently to force production. After the contraction phase, Ca^{2+} is returned to the SR by the SR Ca^{2+} pump, allowing the muscle to relax.[60] Theoretically, disruption at any point in the E-CC process results in reduced muscle performance. Impairments in SR Ca^{2+} release have been suggested to explain deficits in physical performance in aged muscle.[62] Indeed, data from Russ *et al*. [63] showed a 17% decline in SR Ca^{2+} release in older rats' gastrocnemius muscle compared with younger rats.[63] This decline in SR Ca^{2+} release might be attributed to a disruption of ryanodine receptor expression[64]; however, it is suggested that predominantly, the loss of dihydropyridine receptor (particularly the α-1 s subunit) might cause disruption of SR Ca^{2+} release.[65–67] In addition, Hunter *et al*. [68] showed a reduction of about 33% SR Ca^{2+} reuptake with ageing in the vastus lateralis.[61,68] The reuptake of Ca^{2+} to the SR by the SR Ca^{2+} pump is an energy-dependent process and contributes to muscle relaxation. As such, age-associated impairments of Ca^{2+} reuptake are more likely to play a role in motor coordination and muscle fatigue than in force production. The impaired Ca^{2+} reuptake could lead to unwanted elevations of intramyocellular Ca^{2+}, which is associated with various negative outcomes including calpain activation and muscle cell apoptosis, leading to muscle weakness and fatigue.[69,70] However, this may not be a major issue if SR Ca^{2+} release declines as well with age, resulting in absence of unwanted elevations of intramyocellular Ca^{2+}. Elegant work from Delbonno and colleagues has demonstrated reduced expression of the voltage sensor calcium channel α1 subunit (Cav1.1) with ageing in three different groups of muscles (soleus, extensor digitorum longus, and in a pool of several skeletal muscles consisting of a mixture of fast-twitch and slow-twitch muscle fibres), which has been shown to lead to excitation–contraction uncoupling.[71] This group recently reported that fast skeletal muscle troponin T3 (TnT3) is fragmented in ageing mice[72,73] and that the full-length TnT3 and its carboxyl-terminal fragment shuttle to the nucleus and regulate the gene encoding Cav1.1.[74] Further, systemic administration of a calpain inhibitor (BDA-410) prevented TnT3 fragmentation and Cav1.1 down-regulation and improved soleus muscle quality by ~20–30 + % depending on the stimulation frequency ration in sedentary old mice (23–25 month old C57BL/6 female mice).[74] These findings suggest that excitation–contraction uncoupling contributes significantly to the reduction in muscle quality observed with advancing age and highlights the processes in the E-CC pathway as a potential therapeutic target.

Age-related changes in skeletal muscle structure and composition

In addition to changes in the E-CC processes, there are several other physiological contributors to reduced muscle quality with one being age-related changes in the muscle architectural structure.[59] Skeletal muscle displays a strong structure–function relationship by which several architectural characteristics factor into its functional capacity. Architectural changes with ageing include, among others, a change in the elastic fibre system and an increase in fat infiltration of skeletal muscle.[75] A number of studies have indicated that elderly muscle exhibits higher levels of intermuscular adipose tissue.[76–78] In a five-year longitudinal study of older adults between 70 and 79 years of age at study entry, intermuscular adipose tissue was observed to increase ~30% in the mid-thigh for women and nearly 50% for men, although it should be noted that large standard deviations for percent change over time were noted.[78] Intermuscular adipose tissue has been shown to be associated with the loss of physical performance and limited mobility in older adults.[79,80] Little is known regarding the mechanisms that underlie the relation between fat accumulation and physical performance; however, some suggest that the endocrine metabolism may explain the relation. Ectopic fat can induce a pro-inflammatory state with the secretion of several cytokines. Elevated cytokines may lower skeletal muscle mass and physical performance in older adults as they interact with hormones such as insulin, testosterone, and growth hormone[81,82] and may

cause resistance to anabolic stimuli such as physical activity and dietary protein.[83]

Architectural changes also likely include an increased level of muscle fibrosis. Muscular fibrosis is the excessive formation of fibrous bands of scar tissue in between muscle fibres. The development of pathological fibrosis in tissue is the end result of a series of events including injury, infiltration of inflammatory cells, tissue degeneration, and proliferation of fibroblasts that result in remodelling of tissue architecture.[84] There is no direct evidence of muscle fibrosis with age in humans due to the difficulty in assessing fibrosis in population studies, but animal work indicated >17% increase in fibrotic tissue in older rats as compared with younger rats.[85] Clearly, more data are warranted in humans and older adults to assess the impact of muscle fibrosis on muscle performance.

Age-related changes in muscle endurance capacity

With regard to muscle energetics, the vast majority of studies have focused on the effects of ageing on aerobic metabolism (i.e. mitochondrial function or oxidative phosphorylation). There is evidence that aerobic capacity, measured by the peak treadmill oxygen consumption (peak VO_2), which is the maximal ability to use oxygen to meet the energy demands of physical activity, may decline at an accelerated rate already after the age of 20, with a rate up to >20% per decade in community-dwelling men and women over 70.[86] Aerobic capacity reflects not only cardiovascular adaptation to transport oxygen but also adaptations within the muscle to use oxygen to meet the energy demands of physical activity. When the age-related decline in maximal oxygen consumption is adjusted for forced expiratory volume in 1 s and maximal exercise heart rate, the decline is closer to 10%/decade,[87] which likely more accurately reflects the contribution of the age-related changes in the skeletal muscle.

Mitochondria are important cellular organelles that are responsible for the production of energy by both aerobic and anaerobic respiration and oxidative phosphorylation. Cross-sectional evidence from 74 healthy men and women aged 18–90 years indicates that age is inversely related with vastus lateralis mitochondrial DNA (-0.62, $P < 0.001$) and with mRNA transcription ($r = -0.48/-0.54$, $P < 0.001$).[88] This decline may result in lower mitochondrial muscle protein synthesis rates in older adults.[89] Not only the mitochondrial content is important for elderly skeletal muscle performance, the mitochondrial function (i.e. the ability to produce ATP) is important as well. High-energy phosphates (i.e. ATP and creatine phosphate) provide the chemical energy necessary to satisfy the energy cost of cross-bridge cycling and ion pump activity during muscle contraction and are therefore important for performance. It has been suggested that several pathways of ATP synthesis may be impaired in ageing skeletal muscle, including anaerobic glycolysis and oxidative phosphorylation.[90] Some studies suggested a decline in anaerobic capacity with ageing, probably due to reduced enzyme activity of lactate dehydrogenase and hexokinase[38,91–93]; others, however, could not confirm the declined anaerobic capacity and found similar enzyme activity between young and older individuals.[94] This discrepancy might be attributed to the limited studies available and the differences in methodology. Furthermore, these studies were performed in healthy elderly subjects, whereas no data are available on weaker or frail elderly. More research is warranted to elucidate the impact of ageing on the anaerobic capacity in the elderly and their impact on muscle performance.

Role of the nervous system

Overview of the neural control of muscles and movement

The vast range of motions and forces that humans can achieve arises from the activity of more than 600 skeletal muscles, which are under the control of the nervous system. After processing sensory information about the body and its surroundings, the motor centres of the brain and spinal cord generate neural commands that effect coordinated, purposeful movements. The process is complex, as the nervous system is a cellular network of up to 10 billion neurons and 60 trillion synapses communicating together.[95] Each neuron is a component in the system of distinct circuits whose computational processing precision ultimately determines every aspect of behaviour. The discharge behaviour of these neurons, including the motor neuron, represents a complex interplay between the excitatory and inhibitory synaptic inputs they receive and the cells' intrinsic electrical properties. The patterns of interneuronal connections and communication, as well as the discharge behaviours, are not permanently fixed; they show variability and can be reorganized.

Motor systems are organized hierarchically, with each level concerned with a different decision. The highest and most abstract level, likely requiring the prefrontal cortex, deals with the purpose of a movement. The next level, which is concerned with the formation of a motor plan, involves interactions between the posterior parietal and premotor areas of the cerebral cortex. The premotor cortex conveys the spatial characteristics of a movement based on sensory information arising from the posterior parietal cortex about the situation (i.e. the environment) and about where the body is in space. The lowest level coordinates the space and time details of the muscle contractions needed to execute the planned movement. These supportive motor regions include the contralateral sensorimotor cortex, supplementary motor area, and the cingulate cortex. Control circuits located in the cerebellum and basal ganglia are then initiated to trigger activity in descending motor tracts, which signals the spinal interneurons and lower motor neurons to contract skeletal muscle fibres to produce movement. While this hierarchical view is useful in understanding the system, many of these processes can

occur simultaneously. This brief overview of the neural control of movement and muscle force generation illustrates the complexities of this system and highlights how a problem in a variety of different 'neural factors' associated with advancing age could lead to impairments in skeletal muscle performance.

Age-related changes in supraspinal properties

There is clear evidence that alterations in nervous system form and function contribute to declines in skeletal muscle impairment with age, namely diminished motor coordination, muscle strength, and power. Conceptually, a breakdown in a large number of neural processes can lead to functional impairments in skeletal muscle control and/or force generation. There are an overwhelming number of morphometric changes in the motor cortex that occur with ageing. For example, cadaveric studies suggest that individuals over 65 years of age exhibit a >40% volumetric reduction in the premotor cortex neuronal cell body size in comparison to adults younger than 45 years.[96] *In vivo*, imaging-based studies have corroborated these findings, suggesting that cortical thinning occurs by middle age and that areas near the primary motor cortex demonstrate prominent atrophy.[97] Reduced cerebellar grey matter has been linked to weakness, low activity, and slowness.[89] Additionally, age-related differences also exist in white matter mass and length of myelinated nerve fibres.[98] Recently, Rosano and colleagues[99] reported that smaller volume of the prefrontal area was associated with a slower gait speed in the elderly and that this may be due to slower information processing,[99] suggesting a need to better understand the causal relationship between focal brain atrophy with slowing in information processing and gait.

In addition to morphometric changes, neurochemical changes within the basal ganglia are observed with ageing. It has been shown that impaired neurotransmission is responsible for at least some age-related behavioural abnormalities, including the serotonergic, cholinergic, adrenergic, dopaminergic, GABAergic, and glutamatergic systems.[100–106] Reductions in neurotrophic factors have been shown within the motor cortex as well.[107] 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,[108] and animal findings show that older rodents have decreased dopamine (D2) receptors.[109] These changes can lead to delayed and uncoordinated motor functions.

Ageing also affects motor cortical properties at the electrophysiological systems level. Using magnetic brain stimulation techniques, ageing has been shown to be associated with decreased motor cortical excitability of the wrist flexor muscles,[110] and weaker seniors, in particular, have been reported to exhibit more cortical hypoexcitability than their stronger counterparts.[111] Moreover, ageing has been shown to require significantly higher activation of several motor areas of the brain to perform the same motor grip task as younger adults,[112] as well as reduced deactivation of the ipsilateral primary motor cortex (i.e. the side of the brain not directly responsible for performing a given motor task). This suggests a reduced ability to modulate activity in appropriate motor networks when required.[113] Collectively, these findings suggest that ageing results in cortical atrophy, altered neurochemistry, and alterations in motor cortical excitability and plasticity, all of which could be mechanistically link to impairments in the nervous systems ability to optimally activate the musculature and ultimately reduce muscle performance.

Age-related changes in spinal properties

Motor units demonstrate numerous age-related adaptations, including changes in morphology, behaviour, and electrophysiology. Conceptually, these adaptations result in reductions in muscle performance. Advancing age is thought to result in a reduced motor unit number as well as an increased number of muscle fibres per motor unit (increased innervation number) due to the compensatory collateral sprouting by surviving neurons.[114,115] More specifically, age-related remodelling of motor units may involve denervation of fast muscle fibres with re-innervation by axonal sprouting from slow motor neurons.[116] Therefore, motor unit remodelling leads to changes in fibre-type distribution towards a predominantly slow muscle fibre phenotype.[116] Re-innervation of muscle fibres tends to compensate for denervation; however, a net loss of fibres across age has been detected.[116] Whether long-life physical activity can minimize the loss of motor units is questionable. Whereas some studies suggest that lifelong high-intensity physical activity, such as running, may minimize the loss of motor units associated with ageing in the biceps brachii and tibialis anterior,[117,118] others showed that tibialis anterior motor units were not spared in older adults athletes.[119] Moreover, it is unclear whether sarcopenia is associated with reductions in motor unit number.[120,121]

There is also evidence that the behavioural discharge properties of motor units are altered with age. For instance, older adults exhibit reduced motor unit firing rates in a variety of muscle groups, with the intrinsic hand muscles and leg extensor muscles demonstrating a 30–40% lower motor unit firing rate during maximal isometric contractions in the elderly.[122,123] Similarly, age-related declines in the rate of voluntary torque development during a rapid (ballistic) dorsiflexion contraction are accompanied by a lower maximal motor discharge frequency as well as incidence of doublet discharges in the tibialis anterior.[124] These lower firing rates appear to be largely inter-related to the longer twitch contraction durations in older muscle, which further illustrates the critical integrative control processes involved between the nervous and muscular systems as it relates to overall neuromuscular function. Older adults have also been

reported to exhibit a greater variability in motor unit discharge rates that appears to largely influence their ability to maintain steady forces.[125] Recent technological advances now permit the decomposition of single motor unit action potentials using non-invasive, surface electromyographic techniques.[126–128] Thus, it is likely that the understanding of age-related changes in motor unit behavioural discharge properties will dramatically increase in the near future.

Ageing also elicits remodelling of the neuromuscular junction endplate. Specifically, rodent studies indicate that in the lightly recruited plantaris muscle, significant signs of denervation were noted in aged rats, while the same muscles displayed no change in myofiber profile.[129] In the heavily recruited soleus, however, there was little evidence of denervation, and again no alterations in myofiber profile.[129] These results suggest that age-related denervation occurs before myofiber atrophy and that high amounts of neuromuscular activity may delay the onset of age-related denervation and sarcopenia. However, whether changes in the neuromuscular junction precede or follow the decline of muscle mass and strength is still debated.[130] Recent animal data do suggest that exercise training may improve neuromuscular junction morphology and function in young and older rats.[131] Collectively, these findings clearly indicate that there are a plethora of changes in motor unit and neuromuscular junction form and function, with these changes all likely culminating in impaired muscle performance.

Are 'neural factors' related to muscle weakness in the elderly?

A voluntary effort, or a voluntary contraction of a muscle, comprises the recruitment of motor neurons, and hence muscle fibres, 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.[132] 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,[133] descending drive from the motor cortex is the major determinant of the timing and strength of voluntary contractions.

'Voluntary activation' (also referred to as 'central activation') is the term commonly used to describe the nervous system's overall ability to fully activate skeletal muscle (i.e. the ability to optimally recruit and discharge motor units). There are a number of methodological approaches to quantify voluntary activation, such as amplitude measures of the voluntary electromyogram signal (although caution should be taken with this approach[134,135]) as well as by comparing voluntary and electrically stimulated muscle forces. While these approaches do not give insight about where in the nervous system impairment may occur, they do provide insight into whether the nervous system may have a global involvement in weakness. Voluntary activation is assessed by supramaximally electrically stimulating the motor nerve to the muscle, or the muscle itself, during a maximal voluntary effort.[136–138] Any increment in force evoked by a stimulus indicates that voluntary activation is less than 100%, which indicates that some motor units are not recruited or are not firing fast enough to produce fused contractions.[139] Thus, voluntary activation represents the proportion of maximal possible muscle force that is produced during a voluntary contraction.

Over the past several decades, numerous studies have investigated the question of 'does voluntary activation become impaired with advancing age?'.[111,140–163] These studies largely report discrepant findings, but a critical examination indicates several notable observations. First, many older people, particularly those who are healthy and physically active, do not exhibit impairments in voluntary activation.[154,160,163,164] Second, weaker older people, as well as the oldest old, do exhibit impairments in voluntary activation.[111,146,159] Thus, it appears that many older people are indeed able to preserve their nervous systems ability to optimally activate their motor units and musculature while many, particularly the older old, the weakest, and/or those with poor physical function exhibit impairments in voluntary activation.

Role of the skeletal system and tendons

The adult human skeletal system consists of 206 bones, as well as a network of tendons, ligaments, and cartilage that connects them. The skeletal system provides form, support, and stability to the body, and when coupled with the muscular system, it permits movement. The basic fundamentals of form-function relationships suggest that any fundamental change in form (e.g. skeletal alignment) will affect elderly skeletal muscle performance. While few studies have examined the effect of age-related changes in skeletal structural integrity on muscle mass and performance, the evidence to date indicates that it is a contributing factor. For instance, data from The Study of Osteoporotic Fractures reported that women who experienced accelerated bone mineral density loss were more likely to develop disability and older women who maintained their bone mineral density over a 15 year period were less likely to develop disability.[165] Further, hyperkyphosis has been shown to increase the risk of an injurious fall in elderly people,[166] and individuals who have experienced a vertebral fracture have lower levels of physical function and muscle strength.[167]

In addition to skeletal aspects, connective tissue changes are also occurring with advancing age. For instance, a series of experiments by Narici and colleagues[168,169] using ultrasonography to study tendon mechanical properties *in vivo* suggest tendon deterioration with old age.[168,169] These age-

related changes include a reduction in tendon stiffness and in Young's modulus (the ratio of stress, or force per unit area, and strain, which is the ratio of deformation over initial length), suggesting that a deterioration in tendon material properties accounts for most of the decline in stiffness.[168,169] A decline in stiffness seems counterintuitive as data indicate that the collagen in the tendon becomes stiffer with ageing because there is an increase in the intermolecular cross-linking through the accumulation of advanced glycation end products.[170] Thus, there appears to be a mechanism that prevails over the stiffening effect of increased collagen cross-linking. Potential mechanisms include a reduction in ground substances, a reduction in the number of longitudinally aligned collagen fibres, a reduction in fibril diameter, and inflammatory cytokines increasing the activity of matrix metalloproteinases and resulting in collagen degradation.[170] The alterations in tendon properties with ageing are believed to directly impact the mechanical behaviour of muscle-tendon systems function. During locomotion, the muscle-tendon system functions as a spring when the muscle lengthens while activated, before subsequently shortening.[171] Thus, this unit effectively act as a shock absorber (i.e. they cyclically absorb and recover elastic recoil energy).[171] Accordingly, changes in tendon properties likely alter the muscle spring properties and affect the degree of shortening of muscle fibres and the rate of force development upon contraction[168,169] and, as such, physical performance in older adults.

While rarely discussed, collective degenerative changes in both the muscular and skeletal systems result in reductions in flexibility (e.g. decreased range of motion). Evidence suggests that upper body flexibility is negatively associated with physical function in nonagenarians.[172] Unfortunately, the impact of age-related changes in flexibility has on physical performance characteristics is not clear as this has received very little scientific attention.

Biological factors that contribute to the decline in elderly skeletal muscle performance

Hormones

Ageing results in a significant decline in different anabolic hormones.[173] As such, a longitudinal observational study in 221 community-dwelling men that found that plasma testosterone declined 7% in 4 years,[174] and daily plasma production of growth hormone (GH), decreased about 14% per decade of age.[175] In addition, oestrogen and other female hormones decline after entering the menopause.[176] Furthermore, plasma insulin-like growth factor-1 (IGF-1) concentrations were significantly associated with age in both men and women.[177] Circulating IGF-1 plays an active role in processes of protein synthesis via activation of the protein synthesis regulating Akt-mTOR pathway,[178,179] and in regulating GH secretion through a negative feedback mechanism. Both testosterone and GH are powerful anabolic agents that promote muscle protein synthesis and subsequent muscle mass accretion.[180–182] Also, oestrogen may play a significant role in stimulating muscle repair and regenerative processes, including the activation and proliferation of satellite cells.[176] The pathways by which hormones regulate muscle protein metabolism are complex and multifactorial[173] and go beyond the scope of this review.

Inflammation

Epidemiological data of 1411 subjects aged between 25 and 91 showed that the inflammatory cytokine interleukin-6 levels increased up to a 2.4-fold in the elderly compared with the young and tumour necrosis factor-α (TNF-α) is doubled in elderly people.[183] Elevated levels of interleukin-6 were reported to be associated with a two-fold to three-fold risk in losing more than 40% of the muscle strength, after 3 years of follow up,[82] with similar results found for TNF-α.[82,184] Animal studies have demonstrated that TNF-α induced skeletal muscle protein breakdown in rats which lead to significant loss of muscle mass,[10,185,186] which is likely to occur via the activation of the ubiquitin–proteasome pathway and apoptosis, and perhaps via reduced basal muscle protein synthesis rates.[187] In addition, TNF-α potentially negatively affects the muscle regenerating capacity by destabilizing MyoD and myogenin.[188,189] These muscle-specific transcription factors are involved in the transition from proliferation to differentiation of satellite cells.[188] Thus, in elderly people, the relatively high levels of inflammatory cytokines over many years may inhibit differentiation of satellite cells, and hence maintenance of the muscle, resulting in a slow but progressive loss of muscle mass and quality and subsequent sarcopenia.

Insulin resistance

Observational cross-sectional studies reported that advanced age is related to decreased ability to maintain similar glucose levels during the euglycemic–hyperinsulinemic clamp ($P < 0.01$), indicating a decreased sensitivity to insulin, mediated by increased fat mass, with age.[190,191] Longitudinal observational studies have shown that insulin-resistant individuals show an accelerated loss of muscle mass over time, compared with non-insulin-resistant subjects,[192,193] increasing their risk for the development of sarcopenia. To illustrate, non-diabetic elderly lost on average 193 ± 22 g of muscle mass per year compared with 293 ± 72 g per year in elderly with diagnosed diabetes.[192] The loss of muscle

mass could possibly be explained by the similar structure of insulin to IGF-1, and likewise, they are very similar in function,[194] and therefore potentially involved in the activation of the anabolic mTOR pathway.[195] Similarly, insulin potentially inhibits the catabolic ubiquitin-proteasome pathway, both contributing to maintenance of a positive muscle protein balance.[196] The resistance to insulin potentially contributes to suppression of these pathways, resulting in a lower net protein balance.

Other biological factors

Next to the role of hormones, inflammation, and insulin resistance, other biological factors may also be involved in elderly skeletal muscle performance. Several studies emphasize the important role of genetics on physical performance later in life.[197–200] For instance, a twin study on the role of genes in physical performance in elderly (>75 years) found that about 33–50% of the variation in physical performance in elderly women could be attributed to age-related genetic factors.[197] An example of age-related gene modulations is the reduced expression of vitamin D,[201] as a low vitamin D level is associated with lower muscle mass and impaired physical performance.[202–204] Another example is the two-fold higher level of myostatin protein and myostatin mRNA in elderly, compared with younger controls, which was associated with lower fat-free mass.[205,206] Myostatin is a protein that acts as a negative regulator of muscle growth and has been linked to the development of sarcopenia.[207,208] Inhibition of myostatin has been suggested as a promising therapeutic therapy for sarcopenia, which could affect skeletal muscle performance.[208]

In addition to genetics, other biological factors such as gender and physical resilience (i.e. the ability to withstand infection or other stressors) may affect muscle mass loss in elderly leading to an increased risk for a decline in elderly skeletal muscle performance.[209]

Lifestyle factors that contribute to the decline in elderly skeletal muscle performance

Nutritional status

The ageing process is associated with a decline in appetite and food intake known as anorexia of ageing.[210] Approximately, 21% of the older adults present with anorexia of ageing, and it is even more prevalent in frail and institutionalized elderly people.[211] Anorexia and subsequent weight loss have been associated with adverse health outcomes, such as falls, immobility, and sarcopenia. In fact, recent epidemiological data from the ilSIRENTE study showed an 88% higher risk of sarcopenia in elderly suffering from anorexia compared with non-anorexic elderly people.[212] Anorexia is closely related to malnutrition, which is highly prevalent among hospitalized elderly patients. In geriatric wards, prevalence rates of 35% have been recorded.[213] Malnutrition is strongly related to a decline of dietary protein intake and micronutrient intake. Adequate dietary protein intake is a key factor for maintaining skeletal muscle mass in the elderly. The amount of protein intake, the distribution, and the source of protein intake are all important to maximally stimulate postprandial muscle protein synthetic response and muscle mass accretion in the elderly. Tieland[214] observed that habitual dietary protein intake is between 0.8 and 1.1 g/kg/bw/day in elderly, showing the lowest intakes in institutionalized and hospitalized elderly people.[214,215] Although the average protein intake of 0.8 g/kg-bw/day reaches the recommended daily allowance, 35% of institutionalized and hospitalized elderly people reported an insufficient protein intake below the estimated average protein requirement of 0.7 g/kg-bw/day.[214] Recent consensus statements have argued that protein intakes between 1.2 and 1.5 g/kg-bw/day may be necessary to slow down or counteract sarcopenia in the elderly.[216,217] Indeed, data from the Health ABC study showed that elderly consuming a daily protein intake of 0.8 g/kg-bw lost a dramatic 40% more muscle mass compared with elderly who consumed 1.2 g/kg-bw/day of protein.[218] This suggests that not only institutionalized/hospitalized elderly but also community-dwelling and frail elderly people may need to increase their dietary protein intake in order to prevent the loss of muscle mass loss and, as such, skeletal muscle performance. In addition, several studies suggest that omega 3-fatty acid supplementation may enhance muscle protein synthesis and promote muscle mass gain in older adults.[219–221] Although omega 3-fatty acid supplementation is found to promote muscle protein synthesis, no strong evidence is present in the literature showing that insufficient omega 3-fatty acid intake is linked to lower muscle mass or decreased skeletal muscle performance.[222,223]

Some minerals have been identified to play a role in maintaining optimal muscle function and metabolism. Recent cross-sectional studies in community-dwelling elderly showed that elderly with the lowest tertiles of calcium intake had a three-fold to four-fold higher risk of being sarcopenic compared with the elderly with the highest tertile of calcium intake[224] and had a significant lower gait speed.[225] Also, a case–control study reported 6% lower intakes of magnesium in sarcopenic adults compared with non-sarcopenic adults,[226] and supplementation of magnesium even showed a significant improvement in the chair stand, short physical performance battery, and 4 m walking speed in a 12 week randomized controlled trial.[227] A cross-sectional study with 315 community-dwelling elderly found that men with a low walking gait had a significant lower intake of iron

(−2.5 mg/day) compared with faster walking men.[225] Moreover, some vitamins have been linked to elderly skeletal muscle performance, such as vitamin D deficiency, which has been associated with poor muscle mass and impaired physical performance in elderly people.[202–204,228–230] Mechanistically, it is suggested that the activation of the vitamin D receptor in skeletal muscle tissue plays an important role in muscle protein turnover[231] and it has been suggested that 1,25-dihydroxyvitamin D, the active form of 25-hydroxyvitamin D, regulates muscle calcium concentrations by modulating the activity of calcium pumps in SR and sarcolemma,[202] which may impact force production. Collectively, both macronutrients and micronutrients play an important role in impaired skeletal muscle performance in elderly.

Exercise

Resistance-type exercise training is currently the most effective intervention to initiate muscle hypertrophy and to elicit improvements in muscle strength and physical performance.[8,232–236] A meta-analysis of 49 randomized intervention studies showed that after an average of 20.5 weeks of resistance-type exercise training, elderly people gained 1.1 kg (CI: 0.9–1.2) of lean body mass.[237] Furthermore, an additional meta-analysis showed that elderly people improved 1-RM leg press strength by 29 ± 2% and 1-RM leg extension strength by 33 ± 2% after an average of 18 weeks of resistance-type exercise training.[237] In addition, it has been suggested that exercised muscles become more sensitive to nutrients, allowing more of the available amino acids to be synthesized into muscle protein. In sedentary elderly subjects, however, the sensitivity of skeletal muscle tissue to anabolic stimuli such as physical activity or protein intake might be reduced.[238–240] To illustrate, postprandial rates of muscle protein synthesis were significantly reduced by 26% after a 14 day reduction in physical activity (on average a 76% decrease in daily step count) in 10 healthy elderly.[238] As such, it could be speculated that a more sedentary lifestyle is responsible for the anabolic resistance to physical activity and protein intake in frail elderly people.[239]

Although resistance exercise is effective in maintaining, and in many cases improving, muscle mass and strength, aerobic exercise is also important in maintaining optimal skeletal muscle performance.[241] Aerobic capacity gradually declines with age, resulting in the decrease ability to perform physical activities such as walking or cycling. As such, a longitudinal observational study reported a significantly decrease in 6 min walking distance (−11%) in healthy elderly after 3 years of follow up, indicating a decrease in aerobic capacity.[242] Furthermore, aerobic exercise results in mitochondrial adaptation,[243] enhances cardiovascular function (e.g. increased stroke volume capacity),[244] and thus improves aerobic capacity and optimizing elderly skeletal muscle performance.[245,246]

Psychosocial factors that contribute to the decline in elderly skeletal muscle performance

There are a number of psychosocial factors that directly and indirectly influence physical performance in elderly people. Self-efficacy is one classic example. Self-efficacy refers to an individual's belief in their capacity to execute behaviours necessary to produce specific performance attainments. It reflects confidence in the ability to exert control over one's own motivation, behaviour, and social environment. Self-efficacy has been associated with gait speed[247] and self-reported limitations in physical function.[248] Perhaps more importantly, self-efficacy is also a determinant of exercise participation[249–251] and has been reported to mediate the relationship between physical activity and functional limitations in elderly people.[250,252,253] Thus, there is strong evidence that self-efficacy is a salient determinant of physical function and should be targeted in interventions designed to improve physical function in elderly people. Fear of falling is another classic example.[254,255] Fear of falling is independently associated with increased sedentary behaviour time[256] and decreased physical activity,[257] which negatively affects physical function in elderly people.[258] Similarly, higher levels of social isolation are associated with lower levels of physical activity.[259]

Psychological resiliency—the ability to overcome or bounce back from adversity—is a well-known construct that has historically focused on children and adolescents who encounter numerous trials and tribulations. Recently, this has gained attention within the context of ageing, particularly as it relates to the very old.[260–262] Hayman, Kerse and Consedine[262] recently contended that because late life is characterized by a unique balance between losses, associated with vulnerability and resource restrictions, and potential gains based upon wisdom, experience, autonomy, and accumulated systems of support, that it (late life) provides a specific context for the expression of resilience.[262] They suggested that post-adversity growth is possible, but maintenance of everyday abilities may be more relevant to resilience in advanced age.[262] While there is still little known about how the construct of psychological resilience influences physical function in the elderly, it is an area of study that deserves additional focus. Other psychosocial factors, such as depression and idiopathic tiredness or exhaustion, are linked to reduced physical performance in elderly people. For instance, depressive symptoms have been shown to predict declines in all domains of physical

function.[263] Exhaustion is a common complaint that is also associated with decreased physical function performance in elderly people.[264]

Final remarks and conclusions

The loss of exercise capacity with ageing is the net result of lack of regular physical exercise (i.e. inactivity), age-related functional, metabolic, and structural changes in the skeletal muscle and the neuromotor control, and disease-related functional impairment resulting from catabolic effects of chronic systemic illness (e.g. heart failure, COPD, and cancer). Developing a clear understanding of the many factors affecting elderly skeletal muscle performance and physical function has major implications for scientists, clinicians, and health professionals who are developing therapeutic interventions aiming to enhance muscle function and/or prevent mobility and physical limitations and, as such, support healthy ageing. There are still many unanswered questions related to both the physiological causes and mechanisms of reduced muscle and physical function with advancing age as well as interventional strategies to promote muscle and physical function in the elderly. For instance, key questions that remain include the following:

- determining the relative contribution of various neurophysiologic, psychosocial, muscular, tendonous, and skeletal factors on the age-related changes in physical function;
- optimizing exercise (e.g. mode, frequency, and intensity) and nutritional interventions for enhancing physical function in the elderly; and
- determining the impact of illness and hospitalization on rapid decrements in physical function in the elderly and identifying approaches to mitigate the impact of these acute events.

Note that the authors certify that they comply with the ethical guidelines for publishing in the Journal of Cachexia, Sarcopenia and Muscle: update 2015.[265]

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