Sarcopenia: Prevalence, Mechanisms, and Functional Consequences

Michael J. Bergera • Timothy J. Dohertya,b

aSchool of Kinesiology, and Departments of Clinical Neurological Sciences and Physical Medicine and Rehabilitation, Schulich School of Medicine, University of Western Ontario, London, Ont., Canada

Abstract

Aging is associated with significant decline in neuromuscular function and performance. Sarcopenia, often defined as age-related loss of muscle mass, strength, and functional decline, is the most characteristic feature of age-related changes in the neuromuscular system. Strength decline in upper and lower limb muscles is typically 20–40% by the 7th decade and greater in older adults. This is accompanied by similar losses of limb muscle cross-sectional area. Whole body or appendicular muscle mass determination has become the method of choice for defining sarcopenia. Large population studies have reported that sarcopenia affects over 20% of 60- to 70-year-olds, and approaches 50% in those over 75 years. While loss of muscle mass explains a significant component of weakness, other factors are emerging as important contributors. In particular changes at the level of the motor neuron and motor unit are discussed. Muscle power has emerged as an important indicator of function in older adults, and we discuss knee osteoarthritis as a model of accelerated limb sarcopenia.

It is well established that the human aging process is associated with a significant decline in neuromuscular function and performance [1–3]. Characteristic of this decline is the inevitable reduction in skeletal muscle mass and associated loss of strength, so-called Sarcopenia, that occurs even in the absence of disease specifically affecting the neuromuscular system. Rosenberg [4] first coined the term sarcopenia in 1989, literally meaning poverty of flesh, to describe age-associated loss of skeletal muscle mass. Subsequently, the definition has been broadened to imply loss of muscle mass, strength, muscle contractile quality and functional decline. To date, there is no universally accepted definition of sarcopenia, which, in part, is related to the absence of well-accepted standardized methodology or criteria to establish its presence in a given population. Nevertheless, recent expert opinion [5] has suggested that the definition of sarcopenia encompass age-related alteration in muscle mass, strength, and function and this broader definition will be adopted in this chapter.
This review will examine sarcopenia in the context of age-related losses of muscle mass and strength, its epidemiology, and potential etiologic factors. In particular, the role of motor neuron loss and its impact on muscle fiber numbers and muscle mass will be examined. Age-related reduction in muscle power has recently emerged as a stronger influence on function than strength, and this will be reviewed in greater detail. Finally, knee osteoarthritis as a potential model of ‘accelerated sarcopenia’ in the lower limb is discussed.

Age-Related Decline in Strength

Loss of skeletal muscle strength is a commonly recognized consequence of aging. Age-related decline in strength has been demonstrated in multiple cross-sectional studies of limb muscles tested under isometric and dynamic (usually isokinetic) conditions, most often comparing groups of healthy young subjects with, middle-aged, and older men and women [1, 6, 7]. The knee extensors, because of their functional importance, ease of testing, and presence of comparative biopsy data, have been most frequently examined.

Multiple studies have compared knee extensor strength in groups of young with healthy older subjects in their seventh and eighth decades. The average reported age-related decreases in strength are on the order of 20–40% [8–12]. Even greater losses (50% or more) have been reported for those in their 9th decade and beyond [11–13]. In general, similar declines in strength have been reported for proximal and distal limb muscles including the ankle plantar and dorsiflexors, elbow flexors and extensors, and hand grip [14–20]. Relative losses appear similar for men and women; however, since men typically start from higher baseline values, their absolute losses of strength are greater. In concert with age-related slowing of electrically evoked muscle contractile properties [16, 21–26], some reports have shown more significant losses of strength with isokinetic testing at higher angular velocities [8, 15, 27]. One important exception to these observations is the consistent finding of relative preservation of strength under eccentric testing conditions [28, 29]. It has been postulated that this preservation of high velocity strength may be related to slower contractile properties, slower cross-bridge cycling, and increased or altered connective tissue content and muscle stiffness in older adults.

While it has been well established that short duration resistance training interventions can partially reverse losses of strength in even the very old [6, 7, 30, 31], the extent to which life-long activity patterns and training can prevent age-related declines in strength has not been prospectively examined. However, Klitgaard et al. [32], in a cross-sectional study, compared elderly men (mean age 69 years) who had either trained with running, swimming or strength training regularly for between 12 and 17 years with young and elderly sedentary controls. In comparison to the young controls, they reported strength declines in the sedentary elderly group for maximal
isometric torque for the knee extensors (44%) and elbow flexors (32%). However, while the older swimmers and runners exhibited similar declines in strength to the sedentary elderly, the strength-trained elderly men had similar maximal isometric strength and muscle cross-sectional areas as the young controls. These results are clearly limited by the cross-sectional study design and potential selection bias, but do provide evidence that, at least in a selected population, strength losses with aging may be attenuated by long durations of resistance exercise.

Thus, it appears that healthy men and women in their seventh and eighth decades exhibit, on average, 20–40% less strength in comparison to their younger counterparts. These losses are even greater (50% or more) for the very old. In general, similar losses are present for proximal and distal muscles in the upper and lower extremities and men and women experience similar losses on a relative basis. Longitudinal studies, with some exceptions, have reported somewhat greater losses of strength over time (1–3%/year) in comparison to cross-sectional studies. The majority of these studies, however, have examined older populations over a limited duration of follow-up, and thus may not predict the rate of decline in young or middle-aged populations.

Age-Related Loss of Skeletal Muscle Mass

Age-related declines in strength are directly impacted by, and correlated with, losses of skeletal muscle mass. It has been demonstrated that total muscle cross-sectional area decreases by about 40% between the ages of 20 and 80 [3, 6, 7]. Cross-sectional areas have been determined for various limb muscle groups using ultrasound, computed tomographic scanning, magnetic resonance imaging, and direct measurement of whole muscle cross sections from cadaveric specimens. For example, Young et al. [11, 12] using ultrasonographic imaging, reported 25–35% reductions in the cross-sectional areas of the quadriceps muscles in older men and women as compared to young controls. Computed tomographic scanning has shown similar results for the quadriceps muscle [33], the biceps brachii [34] and triceps brachii [34] in men. Additionally, highlighting the inaccuracy of simple anthropometric measures of limb circumference, Rice et al. [34] found 27, 45, and 81% more nonmuscle tissue (fat and connective tissue) for the arm flexors, arm extensors and plantar flexors, respectively. Similarly, Overend et al. [33] reported increases in nonmuscle tissue of 59% for the quadriceps and 127% for the hamstrings. Cross-sectional area measures taken directly from whole muscle obtained postmortem showed similar average reductions of 40% between 20 and 80 years of age [35]. The average reduction was 10% at 50 years and accelerated thereafter.

More recent studies have attempted to define sarcopenia through quantifying whole body muscle mass or appendicular skeletal muscle mass (ASM) by a variety of methods, with magnetic resonance imaging (MRI) and dual energy X-ray absorptiometry (DEXA) emerging as the two most well accepted methods. Indeed, current
expert opinion suggests that determination of whole body, or appendicular muscle mass comprises an important aspect of defining sarcopenia [5]. Baumgartner et al. [36], in the New Mexico Elder Survey, measured appendicular muscle mass by DEXA in 883 randomly selected elderly Hispanic and white men and women. Sarcopenia was defined as loss of muscle mass greater than 2 SD below the mean for young healthy controls. The prevalence of sarcopenia ranged from 13 to 24% in persons aged 65–70 years and was over 50% for those older than 80 years. In this study, the prevalence was higher for men over age 75 (58%) than for women (45%). In a similar study, the prevalence based on total skeletal mass determined by DEXA was 10% for men and 8% for women between 60 and 69 years, and 40% and 18%, respectively, for men and women over 80 years [37]. As these prevalence rates are relative to gender-specific younger control populations they suggest greater declines in muscle mass for men than women. Iannuzzi-Sucich et al. [38] used DEXA to quantify appendicular skeletal muscle mass in 195 women aged 64–93 years and 142 men aged 64–92 years. They defined sarcopenia as 2 SDs below the muscle mass/height (m)2 for young controls. The overall prevalence of sarcopenia so defined was 22.6% in women and 26.8% in men. These values climbed to 31 and 45%, respectively, for women and men over 80. Similarly, Janssen et al. [39] used whole body MRI to examine skeletal muscle mass and distribution in a large cohort of 468 men and women from 18 to 88 years of age. They observed a decline in whole body muscle mass beginning in the third decade; however, this did not become substantial until the end of the 5th decade. An important finding of this study was that the loss of muscle mass with aging was greater in the lower body in men and women. This finding may reflect decreased activity or altered patterns of activity of the lower extremity muscles with aging and has important implications for functional mobility and disability. In summary, the prevalence of sarcopenia is partially dependent on the population studied, the measurement technique employed and the operational definition used. However, in general, sarcopenia affects at least 20% of men and women in their 7th decade and often approaches 50% or greater for those over 75 years.

While sarcopenia most literally refers to loss of skeletal muscle mass and has been extended to imply loss of strength, clearly functional ability is of the utmost importance to elderly men and women in terms of independence and quality of life. It would seem intuitive that a relationship should exist between muscle mass, strength and the ability to carry out functional tasks. This was evident in the New Mexico Elder study where sarcopenic women had 3.6-fold higher rates of disability and men had 4.1-fold higher rates in comparison to those with greater muscle mass [36]. The use of assistive walking aids and falls were also higher in these subjects. More recently, Janssen et al. [40] reported a higher prevalence of more severe sarcopenia in women as compared to men over 60 years. Functional impairment and disability were two times greater in older men and three times greater in older women.

Alternatively, Visser and colleagues [41] examined 3,075 adults over 70 years and reported that whole body and lower limb strength, as opposed to leg muscle mass
(based on DEXA), were independent predictors of lower extremity performance. Similar results were reported by their group from a cross-sectional analysis of 449 men and women 65 years of age and older whereby low strength (grip strength), but not low muscle mass (from DEXA), were associated with poor lower extremity performance as measured by gait speed and chair rise. The results of a 5-year longitudinal study of thigh muscle mass, intramuscular fat infiltration and strength in men and women over 70 years of age reported 2- to 5-fold greater losses of muscle strength (isokinetic torque) than muscle mass. This was accompanied by significant increases in intramuscular fat, which was thought to contribute to decreased muscle contractile quality. Others have reported similar greater losses of strength over time, with one longitudinal study reporting that the decline in strength over time was 60% greater than predicted from cross-sectional analysis and that age-related loss of muscle mass accounted for only 5% of the variance in the loss of strength [42]. As a result of these and other observations, it has become clear that loss of muscle mass is only partially responsible for age-related loss of strength and functional mobility and other factors including central drive, muscle contractile quality, and altered excitation-contraction coupling to name a few are implicated [43].

**Mechanisms Underlying Sarcopenia**

Multiple, inter-related factors contribute to the development and progression of sarcopenia [44]. These factors, no doubt, contribute in varying degrees to the age-related losses of muscle mass, strength, muscle quality and the degree of functional impairment and reserve present in older men and women. It is also probable that certain underlying mechanisms are of greater influence than others when considering any specific age group, gender or association with co-morbid states. Among others, altered endocrine function (growth hormone, insulin, estrogen, testosterone), increased levels of proinflammatory cytokines (e.g. IL-6, TNF), mitochondrial dysfunction, cellular apoptosis, and inadequate nutrition (particularly dietary protein) have all been implicated as potential contributing factors to loss of muscle mass, strength and contractile quality. These potential etiologic factors have recently been reviewed in detail [44]. In addition to these factors, we and others have shown in multiple studies that there is a strong neurogenic component underlying age-related loss of muscle mass and strength. This has been established primarily through the use of electrophysiological techniques and specifically ‘motor unit number estimation’ or MUNE [45, 46]. MUNE techniques estimate the numbers of functioning MUs in a muscle group by dividing a size parameter of the electrically evoked compound muscle action potential (the muscle’s maximal output) by the mean size of its constituent motor unit potentials. These observations related to aging and sarcopenia are summarized below.

Regardless of any potential age-related impairment in contractile quality, loss of muscle mass remains as a significant contributing factor to strength decline and
associated disability in older men and women. Histologic data, predominately from needle biopsy sampling, has provided some insight into the cause of the age related atrophy. The majority of these data are from the vastus lateralis muscle and the overall findings are reasonably consistent. That is, the average type II fiber size is diminished with age while the size of type I fibers is much less affected [3, 7, 8, 35, 47–50]. While reductions in type II area range from 20 to 50%, type I fiber area losses range from 1 to 25%. The variability noted in these studies relates to sampling variability, potential sampling bias with muscle biopsy, and the undoubted inherent variability in both the older and younger control populations.

The above reductions in fiber size, however, are typically moderate in comparison with the reductions in muscle mass, and therefore reductions in muscle fiber number have been proposed. In a landmark study, Lexell's group [35, 48] using whole muscle cross-sections from the vastus lateralis muscle obtained postmortem, reported that by the ninth decade approximately 50% fewer type I and type II fibers were present in comparison to muscles from 20-year-olds. The observation that similar losses of muscle fibers occurred for both type I and II fibers stood in contrast to earlier work from samples obtained with muscle biopsy [8, 51]. Further analysis determined that the cross-sectional area of the vastus lateralis was mainly determined by the total number of fibers and, to a lesser extent, by the size or number of type II fibers [35, 48, 49]. There was no way, however, based upon these analyses to determine the etiology of the fiber loss.

Further to this, in concert with type II atrophy, there is histochemical evidence of fiber type grouping, fiber atrophy, and increased co-expression of myosin heavy chain isoforms in the same fiber, thought consistent with a progressive denervation and reinnervation process secondary to a chronic neuropathic process [52–54]. Given these findings and the previously noted losses of muscle fibers, it has been suggested that alpha motor neuron loss may be largely responsible for age-related loss of muscle mass [23, 46, 50, 55, 56].

Is there any support for such a hypothesis? Electrophysiological studies using either macro electromyographic techniques [57] or motor unit number estimation techniques [45, 46] have demonstrated substantive losses of whole functioning motor units in proximal and distal muscles in the upper and lower extremities [46, 58, 59]. These reported losses are on the order of 50% for the thenar, hypothenar, and biceps/brachialis muscle groups [23, 55, 56, 60, 61] and are consistent with anatomic data that have demonstrated losses of anterior horn cells and ventral root fibers with aging [62–65]. These findings, taken together with muscle morphologic changes consistent with a chronic neuropathic process point toward age-associated losses of motor neurons/motor nerves as an important contributing factor to reduced muscle fiber number and muscle mass [3, 66, 67]. No longitudinal studies have examined this process, but cross-sectional studies would suggest that motor neurons or motor unit numbers are well maintained until the seventh decade and then begin to decline precipitously thereafter [21, 68, 69].
Our group recently examined the impact of MU loss as a potential contributing factor to progressive or accelerated strength loss in the ankle dorsiflexors of very old men [70]. Voluntary strength, evoked twitch strength, maximum compound muscle action potential (CMAP) size, and MUNE (the number of functioning motor units) were determined in a cross-sectional study from a group of young (mean age 27 years), old (66 years) and very old (82 years) men. The number of MUs in the tibialis anterior muscle was reduced in the older men (91 MUs) in comparison to the young (150 MUs); further reductions still were observed in the very old (59 MUs). Despite significant MU losses, twitch strength, CMAP size and MVC were maintained in the old group – likely as a result of effective collateral reinnervation of denervated muscle fibers [3]. However, in the very old, collateral reinnervation was unable to maintain pace with the extent of motor unit loss resulting in substantive loss of both voluntary and evoked strength. This raises the concept that the neuromuscular system may be able adapt to loss of motor units until a threshold is reached, after which progressive losses of muscle mass and strength occur – this, in part, may explain the rapid decline in strength that occurs in the very old leading to mobility disability and subsequent frailty. Interestingly, there appears to be variability in these findings in different muscle groups, as in a second series of experiments, we did not observe the same extent of age-related losses of motor units in the soleus [71]. Perhaps this relates to differences in the underlying fiber type/MU type (soleus is predominantly composed of type 1 muscle fibers), altered patterns of use or function of a given muscle group.

The extent to which chronic physical activity might affect motor neuron function is intriguing. To that end, we recently examined the numbers of motor units in a group of masters distance runners (mean age 65 years). While their MVC strength was lower than young controls and sedentary older adults (a common observation for endurance athletes likely related to low body mass), the estimated number of motor units in the tibialis anterior muscle of the masters runners was similar (140 MUs) to young control data [72]. These preliminary results require further substantiation, but provide support for physical activity as a potential protective factor in maintaining the health and function of the motor neuron, possibly as a result of reduced oxidative stress.

**Age-Related Changes in Power**

Age-related reduction in muscle power has received far less attention than strength. Muscle power is the product of force and velocity of movement and may be measured during dynamic and isokinetic (constant velocity) contractions. There is evidence to suggest that power declines earlier in the lifespan and more precipitously than force [73, 74]. Additionally, power may be a more robust predictor of functional ability in the elderly [75]. Our discussion of muscle power will consider: (1) reports of age-related power deficits and altered force-velocity relationships in the elderly with