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Timothy J. Doherty

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*Exp Physiol*, June 13, 2014; .

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## Physiology of Aging

### Invited Review: Aging and sarcopenia

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**Doherty, Timothy J.** Invited Review: Aging and sarcopenia. *J Appl Physiol* 95: 1717–1727, 2003;10.1152/jappphysiol.00347.2003.—Aging is associated with progressive loss of neuromuscular function that often leads to progressive disability and loss of independence. The term sarcopenia is now commonly used to describe the loss of skeletal muscle mass and strength that occurs in concert with biological aging. By the seventh and eighth decade of life, maximal voluntary contractile strength is decreased, on average, by 20–40% for both men and women in proximal and distal muscles. Although age-associated decreases in strength per unit muscle mass, or muscle quality, may play a role, the majority of strength loss can be accounted for by decreased muscle mass. Multiple factors lead to the development of sarcopenia and the associated impact on function. Loss of skeletal muscle fibers secondary to decreased numbers of motoneurons appears to be a major contributing influence, but other factors, including decreased physical activity, altered hormonal status, decreased total caloric and protein intake, inflammatory mediators, and factors leading to altered protein synthesis, must also be considered. The prevalence of sarcopenia, which may be as high as 30% for those  $\geq 60$  yr, will increase as the percentage of the very old continues to grow in our populations. The link between sarcopenia and disability among elderly men and women highlights the need for continued research into the development of the most effective interventions to prevent or at least partially reverse sarcopenia, including the role of resistance exercise and other novel pharmacological and nutritional interventions.

skeletal muscle; muscular strength; muscle quality; motoneuron; countermeasures; muscle protein

IT IS WELL ESTABLISHED THAT the human aging process, from maturity to senescence, is associated with a significant decline in neuromuscular function and performance (34, 51, 109, 128). Characteristic of this decline is the inevitable reduction in skeletal muscle mass and associated loss of strength that occurs even in the healthy elderly. Rosenberg (110) first coined the term *Sarcopenia*, from the Greek, which literally means poverty of flesh, to describe age-associated loss of skeletal muscle mass. Sarcopenia is now generally used to describe age-related changes that occur within skeletal muscle and thus encompasses the effects of altered central and peripheral nervous system innervation, altered hormonal status, inflammatory effects, and altered caloric and protein intake. These multiple factors all contribute to sarcopenia and to the characteristic skeletal muscle atrophy and weakness, both of which

are considered major contributing factors to the loss of functional mobility, independence, and frailty present in many older adults (111, 113). As our population ages, it is clear that we require greater understanding of the underlying mechanisms leading to sarcopenia. Only then can we begin to develop effective targeted interventions to prevent disability and optimize independence in older men and women. This review will examine sarcopenia from the context of age-related losses of muscle mass and strength, potential etiological factors, and its epidemiology. In particular, the role of motoneuron loss and its impact on muscle fiber numbers and muscle mass will be examined. Interventions to reverse or counter sarcopenia, including resistance training, are briefly examined.

#### AGE-RELATED LOSS OF STRENGTH

Loss of skeletal muscle strength is a commonly recognized consequence of aging. Age-related decline in strength has been well established with multiple cross-sectional studies of limb muscles tested under isometric and dynamic conditions, most often comparing

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groups of healthy young, middle-aged, and older men and women (34, 103, 128). The knee extensors, because of their functional importance, ease of testing, and presence of comparative histological data, have been the most frequently examined.

As outlined in Table 1, multiple studies have compared knee extensor strength in groups of young and healthy older subjects in their seventh and eighth decades. The average reported age-related decreases in strength are on the order of 20–40% (71, 93, 94, 140, 141). Even greater losses (50% or more) have been reported for those in their ninth decade and beyond (93, 94). 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 (6, 25, 26, 35, 43, 62, 84, 131). Relative losses appear similar for men and women; however, because 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 (18, 26, 32, 35, 69, 95, 129), some reports have shown more significant losses of strength with isokinetic testing at higher angular velocities (25, 71, 97). One important exception to these observations is the consistent finding of relative preservation of strength under eccentric testing conditions (104, 130). It has been postulated that this may be related to slower contractile properties and increased or altered connective tissue content and muscle stiffness in older adults.

Although it has been well established that resistance training interventions can partially reverse losses of strength in even the very old (42, 46, 103, 128), the extent to which lifelong activity patterns and training can prevent age-related declines in strength has not

been prospectively examined. However, Klitgaard and coworkers (70), in a cross-sectional study, compared elderly men (mean age 69 yr) who had either trained with running, swimming, or strength training regularly for between 12 and 17 yr with young and elderly sedentary controls. Compared with the young controls, they reported that strength declines in the sedentary elderly group for maximal isometric torque for the knee extensors (44%) and elbow flexors (32%). However, although the older swimmers and runners exhibited similar declines in strength as the sedentary elderly, the strength-trained elderly men had maximal isometric strength and muscle cross-sectional areas (CSAs) similar to the young controls. These results are clearly limited by the cross-sectional study design but do provide evidence that, at least in a selected population, strength losses with aging may be attenuated by resistance exercise.

The rate of strength decline with aging remains largely unknown. Vandervoort and McComas (131) used a cross-sectional design whereby they examined young, middle-aged, and elderly men and women. Maximal voluntary and electrically evoked maximal twitch forces were determined for the ankle plantar flexor and dorsiflexor muscles. Men were stronger than women at all ages, and aging was associated with substantial declines in force for both muscle groups. Strength losses were relatively similar for men and women, and these declines were similar for both evoked and voluntary contractions. In an attempt to determine the extent to which reduced central drive may contribute to decreased volitional strength, the twitch interpolation technique was used (9). An important finding of this study, in keeping with the observations for other muscle groups (35, 101), was that most older men and

Table 1. Age-related changes in knee extensor strength

Study	Gender	Age, decade	Testing Condition	% of Young Adult Strength
Larsson et al. (71)	M	7th	Isometric	75
Murray et al. (94)	M	8–9th	Isometric	55
Murray et al. (93)	F	8–9th	Isometric	63
Young et al. (140)	F	8th	Isometric	65
Young et al. (141)	M	7th	Isometric	61
Overend et al. (97)	M	7–8th	Isometric	76
Ivey et al. (59)	M	7–8th	Isometric	76
Poulin et al. (104)	F	7–8th	Isometric	75
	M	7–8th	Isokinetic (90°/s)	
			Concentric	68
			Eccentric	81
			Isokinetic (180°/s)	
Vandervoort et al. (130)	F	7–8th	Concentric	69
			Eccentric	98
			Isokinetic (90°/s)	
Lynch et al. (77)	M	8th	Concentric	50
			Eccentric	64
			Isokinetic (30°/s)	
	F		Concentric	65
			Eccentric	67
			Concentric	69
			Eccentric	73

Percentage of young adult strength refers to the percentage of strength remaining in the older group compared with the younger group. M, male; F, female.

women were able to maximally activate the lower motoneuron pool for maximal force production. Thus the reduced volitional strength with aging was predominantly attributed to decreased muscle mass as opposed to the inability to adequately recruit the available contractile tissue. From these data, it was established that ankle strength did not begin to decline until the sixth decade of life and then proceeded at a rate of  $\sim 1.3\%$  per year thereafter.

Longitudinal studies have provided important insights into the rate of strength decline with aging. For example, Bassey and Harries (6) reported a 3% loss of grip strength per year for men and 5% for women over 4 yr. These losses were greater than those reflected in their initial cross-sectional analysis. Alternatively, Kallman et al. (62), from cross-sectional analysis of 847 subjects from 20 to 100 yr, reported that grip strength peaked in the fourth decade and then declined in a curvilinear fashion thereafter, such that by the ninth decade strength had declined by 37%. Their longitudinal analysis, however, showed that 15% of the subjects aged 60 yr and over exhibited no strength decline during an average 9-yr follow-up, suggesting significant interindividual variability. Similarly, Rantanen et al. (106) reported declines in grip strength of  $\sim 1\%/yr$  in a large cohort (3,680) of Japanese-American men with a 27-yr average follow-up. A more significant rate of decline was present in those older at baseline or with chronic diseases such as diabetes and arthritis.

A number of studies have longitudinally examined age-related strength decline in the knee extensors. Aniansson et al. (2) reported a decline of  $3.2\%/yr$  in a 7-yr follow-up of 23 men aged 73–86 yr, whereas Greig et al. (49) found that strength was essentially unchanged over 8 yr in a group of men and women aged 79–89 yr. Frontera et al. (44) reexamined the strength of 9 of 12 men who had taken part in a training study 12 yr earlier. Isokinetic strength losses for the knee and elbow flexors and extensors ranged from 9% for elbow extension at  $180^\circ/s$  to 30% for knee extension at  $240^\circ/s$ . These changes were accompanied by significant reductions in muscle CSA as shown by computerized tomography scanning. Winegard et al. (136) longitudinally examined 22 men and women from the 69 initially studied by Vandervoort and McComas (131). Over the 12-yr follow-up period, significant decreases of 30% for men and 25% for women were noted for ankle plantar flexors, whereas less dramatic losses of 9.5 and 3.3% were reported for dorsiflexors. Hughes and coworkers (56) longitudinally studied a large cohort of men and women initially examined cross-sectionally  $\sim 10$  yr earlier. They obtained a 64% response rate and reexamined the knee flexors and extensors and elbow dorsiflexors and plantar flexors in 68 women and 52 men. Rates of decline were similar for men and women for knee flexors and extensors (11.8–17.6% per decade). Women, however, demonstrated substantially lower rates of decline for elbow flexors and extensors (2% per decade) than men (12% per decade). Although knee extensor strength was related to total muscle mass (estimated from 24 urine creatinine collections),

this accounted for only 5% of the observed variance in strength. This observation is limited by the comparison of strength in a specific muscle group with an estimate of total body muscle mass; however, it does point out the importance of other factors, including neural, metabolic, and cellular changes, that may have an impact on strength decline with aging. In particular, this study also highlights that there may be differential effects in men and women with regard to age-related changes in upper and lower body strength.

Thus it appears that healthy men and women in their seventh and eighth decades exhibit, on average, 20–40% less strength compared with 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) compared with 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 CSA decreases by  $\sim 40\%$  between the ages of 20 and 60 yr (34, 103, 128). CSAs have been determined for various limb muscle groups with ultrasound, computed tomographic scanning, magnetic resonance imaging (MRI), and direct measurement of whole muscle cross sections from cadaveric specimens. For example, Young et al. (140, 141), using ultrasonographic imaging, reported 25–35% reductions in the CSAs of the quadriceps muscles in older men and women compared with young controls. Computed tomographic scanning has shown similar results for the quadriceps muscle (70, 98), the biceps brachii (70, 108), and triceps brachii (108) in men. Additionally, highlighting the inaccuracy of simple anthropometric measures of limb circumference, Rice et al. (108) 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. (98) reported increases in nonmuscle tissue of 59% for the quadriceps and 127% for the hamstrings. CSA measurements taken directly from whole muscle obtained postmortem showed similar average reductions of 40% for subjects between 20 and 80 yr old (76). The average reduction was 10% at 50 yr and accelerated thereafter.

The above studies used small sample sizes, measured the CSA of only one to three muscles, and comprised only male subjects. Two recent studies, however, have overcome many of these limitations. Gallagher et al. (48) measured arm skeletal muscle mass, leg skeletal muscle mass, and total appendicular skeletal mus-



cle mass (TASM) using dual-energy X-ray absorptiometry (DEXA) in a sample of 148 women and 136 men between 20 and 90 yr of age. After adjustments for height, body weight, and age were made, men were shown to have larger TASM than women. Moreover, men exhibited larger age-related decreases in TASM compared with women (14.8 vs. 10.8%). Similarly, Janssen et al. (61) used whole body magnetic resonance imaging to determine skeletal muscle mass in a sample of 268 men and 200 women between 18 and 88 yr of age. Again, men had significantly greater skeletal muscle mass than women with greater losses of skeletal muscle mass with aging. The mechanisms leading to greater losses of muscle mass with aging in men compared with women are unknown but have been postulated to relate to hormonal factors, including growth hormone, insulin-like growth factor, and testosterone (61). Although greater losses of muscle mass occur with aging in men, it has been suggested that sarcopenia may be a greater public health concern for women since they live longer and generally exhibit higher rates of disability (113).

#### AGE-RELATED CHANGES IN MUSCLE QUALITY

The term muscle quality (MQ) refers to strength per unit CSA or strength per unit muscle mass and is considered a more meaningful indicator of muscle function than strength alone (113).

There are significant challenges in setting out to determine MQ *in vivo* in humans. There is the obvious assumption that both the measurements of force and muscle mass or CSA are valid and accurate. Measurements of maximal voluntary strength, especially of large proximal or intermediate muscles (e.g., knee flexors and extensors, biceps and triceps, and ankle dorsi- and plantar flexors) are dependent on multiple factors, including the need for full central activation, difficulties in ensuring that only the muscles of interest participated in force or torque production, and the effects of pain and other neural inhibitory factors limiting or modifying central drive. Additionally, there are potential limitations and errors related to the method used for determination of muscle mass or CSA. Given these potential limitations, early studies provided variable results. For example, Young et al. (140) found no difference in force/CSA in the knee extensors of older women in the eighth decade vs. young controls. Alternatively, losses in MQ were reported for older men by a number of investigators (45, 62, 97, 107, 141). The differing methods for determining muscle mass or CSA and force measurement may be largely responsible for the variability in these earlier studies. More recently, Kent-Braun and Ng (67) reported no age-related impairment in force/CSA for the ankle dorsiflexors. They had carefully controlled for central activation and used MRI scanning to accurately quantify the CSA for the anterior compartment of the leg. Alternatively, Klein et al. (69) reported that, although the physiological CSA of the elbow flexors and extensors significantly declined with age in older men, the force/CSA was

decreased for the flexors, but not extensors. Proposed mechanisms for this finding included changes in the architecture of the triceps brachii, increased coactivation of the biceps, and reduced muscle fiber-specific tension. The observations of Macaluso et al. (78) have further supported potential reductions in force/CSA in older women. They reported decreased force/CSA in both the knee flexors and extensors of elderly women in their seventh decade. The decreased force/CSA in the knee extensors was accompanied by increased coactivation of the antagonist knee flexors, again suggesting a potential neural mechanism for the decreased force/CSA.

Some potential sex differences in MQ with aging have been demonstrated. For example, in a recent comprehensive study, Lynch et al. (77) set out to determine differences in MQ between arm and leg muscles across the life span. Reliable measures were used for both concentric and eccentric strength, and muscle mass was determined from whole body DEXA scanning with estimation of arm and leg muscle mass. They reported that the age-associated losses in arm MQ were greater for men than for women, whereas leg MQ declined similarly. Second, arm MQ was higher than leg MQ across all age groups for men and women; however, although arm MQ declined at the same rate as leg MQ for men, the decline in leg MQ was greater than arm MQ for women. These age-related losses in MQ are potentially related, among other factors, to changes in neural drive, altered muscle pennation, and increases in connective tissue. With regard to this latter point, Kent-Braun et al. (68) recently reported a two- to threefold increase in intramuscular noncontractile tissue in the anterolateral compartment muscles. Although similar increases were noted for men and women, an inverse relationship was found between physical activity and the extent of noncontractile tissue in women.

Finally, gender differences in MQ with aging may be related to altered contractile properties of the muscle fibers themselves. Frontera et al. (47) examined whole muscle strength and whole muscle cross-sectional area (WMCSA) as well as the contractile properties of chemically skinned segments from single fibers of the vastus lateralis in young men and older men and women. Strength and WMCSA of the knee extensors were significantly higher in younger men compared with older subjects and in older men compared with older women. The age-related but not the gender-related differences were eliminated after controlling for WMCSA. Moreover, muscle fibers expressing the same myosin heavy chain isoform from young men were stronger than fibers from older men, and type I and IIA fibers from older men were stronger than similar fibers from older women, even after adjustments for size. These important findings provide direct evidence for differences in MQ in older men and women. The mechanisms underlying such gender-related differences with aging remain in question. However, hormonal factors may play a role, as it has been demonstrated that specific force is similar in men and premenopausal

women, whereas there was a dramatic decline in specific force around the time of menopause; the latter, however, was diminished in women who used hormone replacement therapy (HRT) (102).

**THE EPIDEMIOLOGY OF SARCOPENIA**

Age-associated loss of muscle mass appears inevitable and is likely the most significant contributing factor to the decline in muscle strength (109, 111, 113, 128). Although all men and women experience some degree of sarcopenia, this is variable and on a continuum. However, in a similar fashion to bone mineral density scores for osteoporosis, it is possible to dichotomize this continuous process by establishing a lower limit of normal such as 2 SD below the mean appendicular muscle mass for healthy young adults. For example, Baumgartner et al. (7), 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 losses greater than 2 SD below the mean for young healthy controls. The prevalence of sarcopenia ranged from 13 to 24% in persons aged 65 to 70 yr and was over 50% for those older than 80 yr. In this study, the prevalence was higher for men over age 75 yr (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 yr and 40 and 18%, respectively, for men and women over 80 yr (85). Because 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. (58) used DEXA to quantify appendicular skeletal muscle mass in 195 women aged 64–93 yr and 142 men aged 64–92 yr. They defined sarcopenia as 2 SD below the muscle mass/height (m)<sup>2</sup> 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 yr. Similarly, Janssen et al. (61) used whole body MRI to examine skeletal muscle mass and distribution in a large cohort of 468 men and women from 18 to 88 yr of age. They observed a decline in body skeletal muscle mass beginning in the third decade; however, this did not become substantial until the end of the fifth 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.

Although sarcopenia most specifically refers to loss of skeletal muscle mass, clearly, functional ability is of the utmost importance to elderly men and women. 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 study in which sarcopenic women had 3.6 times higher rates of disability and men had 4.1-fold higher

rates compared with those with greater muscle mass (7). The use of assistive walking aids and the number of falls were also higher in these subjects. More recently, Janssen et al. (60) reported a higher prevalence of more severe sarcopenia in women compared with men over 60 yr. These researchers found that functional impairment and disability were two times greater in older men and three times greater in older women.

**MECHANISMS UNDERLYING SARCOPENIA**

Multiple, interrelated factors contribute to the development and progression of sarcopenia (Fig. 1). These factors, no doubt, contribute in varying degrees to the age-related losses of muscle mass, strength, MQ, 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 comorbid states.

Regardless of any potential age-related impairment in MQ, loss of muscle mass is the largest contributing factor to strength decline and associated disability in older men and women. Histological data, predominately from needle biopsy sampling, has provided some insight into the cause of the age-related atrophy. The majority of these studies have been undertaken on the vastus lateralis muscle, and the overall findings are reasonably consistent. That is, the average type II fiber size is diminished with age, whereas the size of type I fibers is much less affected (34, 51, 72–74, 76, 109, 128). Although 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.

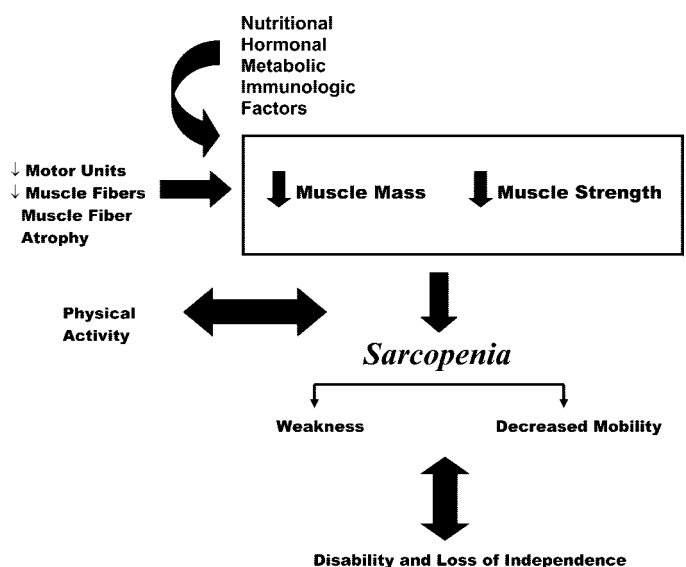


Fig. 1. Factors contributing to sarcopenia. This figure summarizes the influence of multiple factors that lead to age-associated declines in muscle mass and strength and the subsequent impact on disability and loss of independence.

The above reductions in fiber size, however, are moderate compared with the reductions in muscle mass; therefore, reductions in muscle fiber number have been proposed. Lexell et al. (76), using whole muscle cross-sections from the vastus lateralis muscle obtained postmortem, reported that, by the ninth decade, ~50% fewer type I and type II fibers were present compared with muscles from those 20 yr old. The fact that similar losses of muscle fibers were present for type I and II fibers stood in contrast to earlier work from samples obtained with muscle biopsy (71, 72). Further analysis determined that the CSA of the vastus lateralis, at least, is mainly determined by the total number of fibers and, to a lesser extent, by the size or number of type II fibers (73, 74, 76).

Further to this, in concert with type II atrophy, there is histochemical evidence of fiber type grouping, fiber atrophy, and increased coexpression of myosin heavy chain isoforms in the same fiber, thought consistent with a progressive denervation and reinnervation process secondary to a chronic neuropathic process (1, 36, 96). Given these findings and the previously noted losses of muscle fibers, it has been suggested that  $\alpha$ -motoneuron loss may be largely responsible for age-related loss of muscle mass (15, 31–33, 36, 109).

Is there any support for such a hypothesis? Electrophysiological studies that used either macro electromyographic techniques (118) or motor unit number estimation techniques (30, 33) have demonstrated substantive losses of whole functioning motor units in proximal and distal muscles in the upper and lower extremities (28, 33, 119). These reported losses are on the order of 50% for the thenar, hypothenar, and biceps/brachialis muscle groups (15, 16, 31, 35, 115) and are consistent with anatomic data that has demonstrated losses of anterior horn cells and ventral root fibers with aging (31, 35, 64, 65, 86, 125). These findings, taken together with muscle morphological changes consistent with a chronic neuropathic process, point toward age-associated losses of motoneurons as an important contributing factor to reduced muscle fiber number and muscle mass (3, 17, 34, 35). No longitudinal studies have examined this process, but cross-sectional studies would suggest that motoneuron or motor unit numbers are well maintained until the seventh decade and then begin to decline precipitously thereafter (18, 81, 82). Whether the progressive loss of motor units continues to occur to the same extent into the eighth and ninth decade has not yet been examined, especially for larger proximal muscles. If so, as occurs in the postpolio syndrome, this may be an important factor leading to progressive atrophy in the very old as losses of muscle mass become exponential as progressively larger motor units drop out (33, 83). It is unknown whether physical activity or hormonal or genetic factors potentially influence the extent or rate of motor unit loss.

Loss of muscle mass secondary to muscle fiber loss and secondarily fiber atrophy appear largely responsible for sarcopenia. However, other hormonal, metabolic, nutritional, immunologic, and molecular factors

also contribute to sarcopenia. (see Refs. 113 and 132 for recent reviews). In general, it has been postulated that with aging there is a withdrawal of, or resistance to, anabolic factors and potential development of catabolic influences on skeletal muscle.

The relationship between hormonal mediators and sarcopenia has been the topic of a number of recent reviews (11, 63, 88, 91, 114). Serum levels of both testosterone and the adrenal androgens decline with age (120–122), and there are epidemiological data supporting the relationship between the fall in testosterone and the decline in muscle mass (8), strength (8, 100), and functional status (100). The decline in estrogen in women associated with menopause is well recognized; estrogen may also have anabolic effects on muscle, possibly as a result of its conversion to testosterone (113). Estrogen and testosterone may also inhibit the production of IL-1 and IL-6, suggesting that decreased levels of these hormones may have an indirect catabolic effect on muscle (113).

Testosterone replacement has resulted in increased muscle mass (92) and strength in hypogonadal populations (10) and elderly men (116, 127) and increased strength in elderly women (27). A recent randomized, placebo-controlled trial reported increased total and leg lean body mass and leg and arm strength resulting from 6 mo of testosterone treatment designed to maintain serum testosterone within the physiological range for younger men (40). These changes were accompanied by increased expression of insulin-like growth factor I (IGF-I), which may point toward it as an important mechanism for muscle anabolism in older men. Although these data are promising, further work is required to determine the ideal dosing regimen, potential risks with long-term use, and perhaps, most importantly, the impact on functional outcomes.

Menopause is associated with decreased levels of circulating  $17\beta$ -estradiol concentrations in middle-aged and older women (29). Impaired muscle performance has been observed during perimenopause in concert with rapid and dramatic decreases in ovarian hormone production (117). This observation suggests that female sex steroids may play an important role in regulating muscle performance in middle-aged and older women. It has been demonstrated that HRT attenuates the loss of muscle mass that occurs in the perimenopausal period (29, 102), whereas a recent study reported that the rate of sarcopenia was as common in nonobese long-term HRT users as those not using HRT (66). HRT did not augment the increases in fat-free mass or leg strength in postmenopausal women aged 60–72 yr after 11 mo of high-impact weight-bearing exercise (14), whereas another recent study reported improvements in lower extremity power and muscle CSA in response to resistance training and HRT in a group of younger postmenopausal women (117). These limited data suggest that HRT, possibly in concert with resistance exercise, may be most beneficial in the early postmenopausal period; however, more studies are required to further elucidate the role of



HRT in relation to improving or maintaining muscle mass, strength, and function.

Levels of both growth hormone and IGF-I decline with age, and, based on their known anabolic effects, there has been interest in their potential therapeutic benefit to counter sarcopenia (87) (91). In general, however, studies have shown that growth hormone administration in pharmacological doses increases muscle mass but not strength (142). For example, 1 mg of growth hormone or IGF-I in older women increased nitrogen balance, protein turnover, and muscle protein synthesis; however, in response to a 16-wk resistance training program, growth hormone conferred no greater gains in strength or protein synthesis (139). It is believed, given the side effects, cost, and equivocal results in the literature, that growth hormone cannot be recommended now as an efficacious intervention for sarcopenia (139, 142).

It is well recognized that aging is associated with a decline in food intake; this so-called anorexia of aging is considered an important factor in the development and progression of sarcopenia (89–91). Anorexia increases the risk of developing severe muscle wasting, such as occurs during illness or other potential catabolic states such as after hip fracture. This wasting, if severe, can lead to cachexia and progressive functional decline (89, 90).

The multiple complex mechanisms and interactions leading to decreased food intake with aging have recently been reviewed (91). They include early satiety secondary to decreased relaxation of the fundus, increased release of cholecystokinin in response to fat intake, increased leptin levels, which may in part be due to increase in fat mass with aging, and the effects of neurotransmitters such as opioids and neuropeptides (91). It remains unclear whether this physiological anorexia contributes to sarcopenia because the intake of protein is below the levels necessary to maintain muscle mass or because the intake of essential dietary nutrients, including creatine (91), is decreased.

Reversal or treatment of age-related anorexia and associated protein malnutrition is challenging and often focused on the treatment of coexisting disorders such as depression, the effects of polypharmacy, and other potentially reversible causes (91). Oral liquid caloric and protein supplements have been demonstrated to be effective in randomized trials in patients with hip fracture (5, 91). The roles of enteral feeding and pharmacological agents to reverse anorexia, including anabolic steroids, megestrol acetate, growth hormone, and cannabis derivatives, remain in question (5, 91).

Eating one-half the recommended dietary allowance (RDA) of protein of  $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  has been shown to lead to significant declines in strength, body cell mass, and IGF-I in postmenopausal women (23). The extent to which less substantial reductions in dietary protein intake contributes to sarcopenia is unknown. This is an important consideration, however, as it has been shown that 15% of those over 60 yr eat less than 75% of the RDA (113). Furthermore, the extent to

which the RDA for protein is adequate for elderly men and women remains in question. Several studies have suggested that the dietary protein requirements for older adults are greater than the currently recommended  $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  (19–22). For example, reduced thigh muscle CSA was associated with a diet containing  $0.8 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$  in men and women aged 55–77 yr (22), and gains in fat-free mass with resistance training were greater in men aged 51–69 yr who consumed a meat-containing diet compared with an isonitrogenous lacto-ovo vegetarian diet (19). These differences were unlikely because of increased myofibrillar protein synthetic rate, as this was unchanged in response to progressively higher protein intakes in older men and women (135).

In addition to declines in anabolic stimuli with advanced age, there is evidence for an increase in catabolic stimuli. For example, Roubenoff et al. (112) have reported increased production of IL-6 and IL-1 receptor antagonist (IL-1ra) by peripheral blood mononuclear cells in elderly subjects. IL-6 is mildly catabolic, whereas IL-1ra is a pure cytokine antagonist without direct catabolic effects (123). In this same study, however, there was no increase in production of the more catabolic cytokines TNF- $\alpha$  or IL-1 $\beta$  (112). It has not been established whether aging is associated with directly increased cytokine production within muscle; thus their direct role in sarcopenia remains in question (113). Again, this may be an important consideration in the setting of illness or injury superimposed on aging.

The role of altered protein turnover and protein metabolism in the development of sarcopenia has been the topic of a number of excellent reviews (99, 105, 124). In general, regardless of the mechanisms, muscle atrophy occurs when protein breakdown exceeds synthesis. To this end, there is evidence that aging is associated with a lower fractional synthetic rate of mixed muscle protein (54, 138), myofibrillar protein

Table 2. *Strength gains of the knee extensors after resistance training interventions in older adults*

Study	Gender	Age, yr	Duration, wk	Strength Gain, %
Frontera et al. (46)	M	60–72	12	1 RM: 107 MVC: 7
Charette et al. (24)	F	64–86	12	1 RM: 28
Grimby et al. (50)	M	74–84	8	Con: 10 Ecc: 19
Fiatarone et al. (42)	M + F	72–98	10	1 RM: 113
Lexell et al. (75)	M + F	70–77	11	1 RM: 152
McCartney et al. (79)	M + F	60–80	84	1 RM: 32
Hakkinen et al. (53)	M + F	X = 70	26	1 RM: 26
Hunter et al. (57)	M + F	64–79	12	1 RM: 39
Tracy et al. (126)	M + F	65–75	9	1 RM: 28
Yarasheski et al. (137)	M + F	76–92	12	1 RM: 41
Hagerman et al. (52)	M	X = 64	16	1 RM: 50
Hortobagyi et al. (55)	M + F	66–83	10	1 RM: 35
Brose et al. (12)	M + F	X = 68	14	1 RM: 49
Ferrir et al. (41)	M	65–81	16	1 RM: 30

1 RM, maximum weight that could be lifted once; MVC, maximal voluntary contraction; con, concentric contraction; ecc, eccentric contraction, X, mean.



(actin/myosin) (4, 134, 138), and mitochondrial proteins. The reduced basal muscle synthetic rate is associated with a reduction in mRNA responsible for myofibrillar protein gene expression (133).

Given these findings and the relationship between muscle mass and function, there has been obvious interest in examining the capacity for increased anabolic activity in older adults in association with resistance exercise. For example, Yaresheski et al. (139) reported increased mixed muscle protein synthesis (~50%) accompanied by strength gains after 16 wk of progressive resistance training in older men (65–75 yr). Additionally, a subsequent study reported that 3 mo of resistance training increased the mixed protein synthetic rate in the vastus lateralis muscles of men and women between 72 and 92 yr (137). Thus, in concert with other studies (see below) that have reported increased strength and muscle mass with resistance training, even the very old retain the ability to upregulate protein synthesis in response to progressive overload.

Finally, physical inactivity is a significant contributing factor to age-related sarcopenia. It is well established that older men and women who are less physically active have less skeletal muscle mass and increased prevalence of disability (37–39, 103, 113, 128). Clearly, it is difficult from cross-sectional studies to draw inferences regarding causation. However, the results of numerous studies that have documented that resistance exercise can reverse sarcopenia provide sound evidence for the relationship between activity and skeletal muscle mass and strength (38, 103, 128). As summarized in Table 2, short-term training studies, typically of 10- to 12-wk duration, with training two or three times per week have consistently resulted in significant strength gains in elderly men and women (13, 24, 42, 46, 79, 80, 103, 128). Increased strength and muscle mass with resistance exercise has been achieved even for the frail elderly  $\geq 90$  yr old (42). Strength gains were variable across studies, which reflects multiple factors, including the study population, intensity, and duration of the training and the outcome measured. Typically, increases in muscle CSA were on the order of 5–10%, suggesting a significant neural adaptation associated with the reported strength gains. Nevertheless, increases in muscle fiber CSA ranging from 5% to over 40% have also been reported, confirming that strength gains likely result from a combination of both central (neural) and peripheral (muscle mass) factors. Further in depth discussion of resistance training for sarcopenia is beyond the scope of this review; however, it should be noted that, so far, no other intervention has proven to be as efficacious as resistance exercise in reversing sarcopenia. The optimal exercise modality, duration, and intensity for healthy older men and women to maintain muscle mass remain in question; moreover, the benefits of resistance or other forms of exercise for specific targeted populations of at-risk elderly patients have not been adequately addressed.

The extent to which countermeasures, including exercise and nutritional and pharmacological interventions, are able to not only reverse or partially reverse sarcopenia but improve function and decrease disability in the elderly remains to be established. To this point, although numerous resistance training studies, for example, have successfully shown gains in muscle mass and strength, these studies have typically either not included or were underpowered from the standpoint of establishing the relationship between such gains and functional outcomes. Well-designed intervention trials, including meaningful functional outcome measures, directed toward well-defined populations, are required to begin to answer these important questions.

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