

# Muscle weakness in the elderly: role of sarcopenia, dynapenia, and possibilities for rehabilitation

Teet Seene · Priit Kaasik

Received: 22 November 2011 / Accepted: 18 April 2012 / Published online: 4 May 2012  
© European Group for Research into Elderly and Physical Activity (EGREPA) 2012

**Abstract** Aging is a multifactorial process leading to changes in skeletal muscle quantity and quality, which cause muscle weakness and disability in the aging population. This paper discusses the reasons for muscle weakness—and its biological and physiological mechanisms—in the elderly and describes the role of sarcopenia and dynapenia, and the possibilities to modify the age-associated decline in muscle function and decelerate the development of muscle weakness and disability. Resistance and endurance training are effective measures of exercise therapy in the elderly, which improve muscle metabolism and thereby muscle function and life quality.

**Keywords** Aging · Sarcopenia · Dynapenia · Muscle weakness · Exercise therapy

## Introduction

Sarcopenia has been considered to be a minor modifiable risk factor for health outcomes, and it plays a significant role in the etiology of disability [14, 45]. Sarcopenia is understood as an age-related loss of muscle mass, muscle strength, and physical function [23]. The term sarcopenia has been defined as the age-related loss of muscle mass and dynapenia as the age-related loss of muscle strength [13].

The rate of muscle loss has been established to range from 1 to 2 % per year past the age of 50 years, as a result of which 25 % of people under the age of 70 years and 40 % of

those over the age of 80 years are sarcopenic [34, 52]. If the loss of muscle mass is more than 5 % in 6–12 months, the term myopenia has been suggested for use [25]. Aging and inactivity or disuse is associated with a decline in muscle mass, structure, and strength [23, 77]. A sedentary lifestyle, bed rest, spaceflight, and hindlimb suspension lead the skeletal muscle to microcirculatory disturbances, atrophy, protein loss, changes in contractile properties, and fiber-type switching [23, 33, 63, 95]. In both young and aged skeletal muscle, oxidative stress increases in response to unloading [84] and may have an important role in mediating muscle atrophy. Unloading results in a decrease in the number of myonuclei and an increase in the number of apoptotic myonuclei in skeletal muscle [46].

Heat-shock protein 70 inhibits caspase-dependent and caspase-independent apoptotic pathways and may function in the regulation of muscle size via the inhibition of necrotic muscle fiber distribution and apoptosis in aged muscle [59]. The decline in muscle mass primarily results from type II fiber atrophy and loss in the number of muscle fibers. Increased variability in fiber size; accumulation of non-grouping, scattered, and angulated fibers; and the expansion of extracellular space are characteristic of muscle atrophy [8]. Beyond the loss of muscle size due to reduced fiber number and myofibrillar proteins that underlie muscle weakness in the elderly [13, 23], impairments in neural activation have been found, as well as potential alterations in other muscular properties that may reduce contractile quality defined as a reduction in involuntary force production per unit muscle size [31, 86, 100]. The functional and structural decline of the neuromuscular system is a recognized cause of decreased strength, impaired performance of daily activities, and loss of independence in the elderly [51]. Loss of muscle strength in older adults is weakly associated with the loss of lean body mass [29]. It means that muscle

T. Seene (✉) · P. Kaasik  
Institute of Exercise Biology and Physiotherapy,  
University of Tartu,  
Ülikooli Str 18,  
Tartu 50090, Estonia  
e-mail: teet.seene@ut.ee

weakness in older adults is more related to impairments in neural activation and/or reductions in the intrinsic force-generating capacity of skeletal muscle [51].

Research data suggest that the number and magnitude of associations for low physical performance or disability are greater for low muscle strength than low muscle mass [29]. At the same time, it has been shown that higher aerobic capacity is related to an increase in the abilities of cardiovascular factors in the elderly [73]. But it is still unclear whether aerobic exercise training is superior to resistance training or other exercise models in altering effect on the elderly [58]. However, it is clear that purposeful life-long physical activity (exercise therapy) has been proven to have a positive effect on health via many disease-specific mechanisms and seems to provide the highest health benefits [44].

The purpose of the present review was to analyze the reasons for aging skeletal muscle weakness and the role of sarcopenia and dynapenia in this process and to evaluate possibilities for decelerating the development of muscle weakness and disability in the aging population. We also intend to examine the decelerative effect of exercise therapy on the structure and function of aging skeletal muscle.

## Etiology of muscle weakness and disability in the elderly

### Sarcopenia

Aging leads to changes in skeletal muscle quantity and quality, and these changes are a major cause of the increased prevalence of disability in the aging population [23, 24, 71, 77]. In addition to sarcopenia, osteopenia and organopenia are characteristic of increasing age [50] and may contribute to the development of disability.

About two decades ago, sarcopenia was already defined as the age-related loss of muscle mass [37]. Nowadays, we know that muscle mass and strength are causally linked and that changes in mass are responsible for changes in strength [29]. About three decades ago, it was shown that muscle strength does not solely depend on muscle mass [56]. In elderly people, the decline in muscle strength is more rapid than the concomitant loss of muscle mass [11, 19, 28, 31], and loss of muscle mass during disuse is associated with loss of strength only in the range of 10 % [12, 15]. This standpoint is also supported by the experiments where muscle mass is gained but the age-related decline in muscle strength is not prevented [19].

Thus, the aforementioned standpoint that the loss of muscle strength in elderly people is weakly associated with the loss of lean body mass demonstrates that the loss of strength is more related to impairments in the neural activation of muscle [29].

### Regeneration capacity of sarcopenic muscle

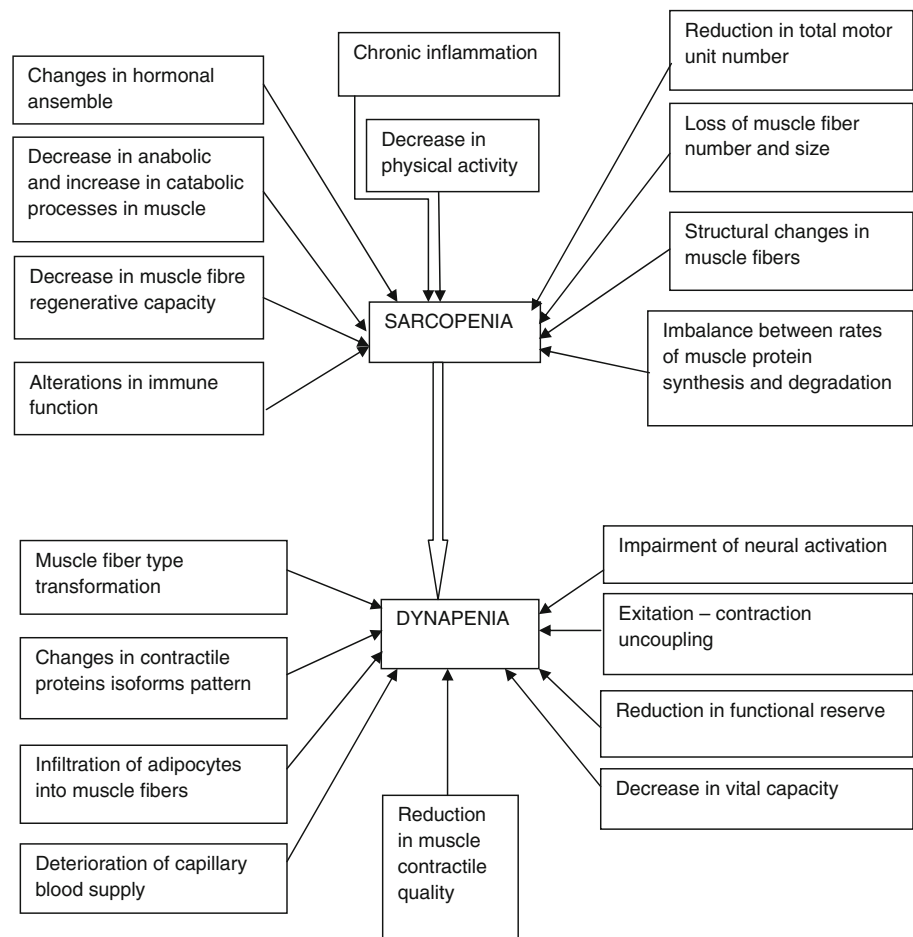
Aging is a physiological process that includes a gradual decrease in skeletal muscle mass, strength, and endurance coupled with an ineffective response to tissue damage [18]. Aging and a reduced physical level are mainly responsible for the progressive decline in several physiological capacities in the elderly [39]. Decrease in the protein synthesis rate is affected by the translational process occurring in older human skeletal muscle, whereas the transcriptional process appears to be unaltered when compared with those in younger men [69]. Skeletal muscle fibers have a remarkable capacity to regenerate [5, 69], and this depends on the number of satellite cells under the basal lamina of fibers and their oxidative capacity [83]. Autografting of gastrocnemius muscle in old rats shows that regeneration proceeds at a significantly slower rate in comparison with young animals [38]. A decrease in the number of satellite cells has been shown in fast-twitch muscle fibers of elderly subjects [98]. In sarcopenic muscle, the decrease in the satellite cell pool and the length of telomeres might explain the higher prevalence of muscle injuries and delayed muscle regeneration [39]. Functionally heterogeneous satellite cells with different properties may be recruited for different tasks, for example, muscle regeneration [49, 61, 92].

After severe damage, muscles in old rodents did not regenerate as well as muscles in adults [10, 17]. The decreased regeneration capacity of muscles is likely due to extrinsic causes rather than an intrinsic limitation of muscles [10, 17]. A contraction-induced muscle injury to weight-bearing muscles in old rodents causes deficits in muscle mass and force [67]. It has been shown that the degradation rate of contractile proteins in rat skeletal muscle during aging increased about two times, and muscle strength and motor activity decreased at the same time [38]. Aging-induced sarcopenia is a result of decreased synthesis and increased degradation of myofibrillar proteins, which leads to the slower turnover rate of muscle proteins, particularly contractile proteins, and this, in turn, leads to the decrease in muscle strength [23, 24, 38]. It has been shown that increasing dietary protein intake in combination with the use of anabolic agents attenuates muscle loss [23]. In essence, sarcopenia is an imbalance between protein synthesis and degradation rate (Fig. 1).

### Dynapenia

As muscle size is not the sole contributor to loss in physical activity in the elderly, it is important to evaluate all aspects in the etiology of disability. In the literature, there are many descriptions for the identification of risk factors for loss in physical activity among the elderly [6, 14]. The decline in muscle strength is a result of a combination of neurologic

**Fig. 1** Factors supporting the development of loss of muscle mass and strength in the elderly



and muscular factors, such as the impairment of neural activation due to a reduction in descending excitatory drive from supraspinal centers, suboptimal motor unit recruitment, and neuromuscular transmission failure [14, 31, 86, 100]. Muscle atrophy, reduced contractile quality due to changes in the myofibrillar machinery, and infiltration of adipocytes into muscle fibers are also reasons for the decrease of muscle strength and physical activity [14, 19, 72, 77]. Taking all these into account, Clark and Manini [13, 14] described the age-related loss of muscle strength using the term dynapenia.

A decrease in skeletal muscle strength contractile protein synthesis rate and an increase in muscle protein degradation rate demonstrate that the contractile machinery in the elderly is structurally and functionally damaged (Fig. 1). Such an integral indicator of contractile protein metabolism as their turnover rate shows that in senescent rats, myosin heavy chain (MyHC) turned over about 35 % and actin about 10 % more slowly than in young elderly [38, 76]. Functional rearrangements in the contractile apparatus of senescent rats also show a decrease in MyHC fastest isoform relative content in skeletal muscle [64]. Changes in MyHC isoform's composition in skeletal muscle may be related to slower ATP splitting in the elderly because of a decrease in muscle

mitochondrial ATP production [1]. It has been demonstrated that in both humans and rodents, skeletal muscle mitochondrial dysfunction occurs with age [4, 70]. The reason is a decrease in mitochondrial DNA copy numbers, decreased mRNA in genes encoding muscle mitochondrial proteins [4], reduced oxidative enzyme activity, and a decreased mitochondrial protein synthesis rate [82]. Neuronal or chemical mediators may also play a role in signaling hypothalamus from the periphery to stimulate the center of sympathetic nerves signaling the paraventricular nucleus of the hypothalamic center [57]. It is generally known that skeletal muscle protein synthesis in humans decreases with age [3, 70, 81, 102]. Studies have shown that the synthesis rate of MyHC and mitochondrial proteins decreases, but others like sarcoplasmic proteins have a relatively high synthesis rate in the elderly [57]. It has been shown that the age-related decrease in muscle protein is not a global effect on all proteins, but is selective for certain proteins [57]. Proteins that have a faster turnover rate contribute more to the skeletal muscle synthesis rate despite their small amount. Proteins which constitute a major part of muscle proteins but have a slow turnover rate play a smaller role in the synthesis rate of skeletal muscle proteins [57].

## Effect of unloading and reloading on muscle quantity and quality in the elderly

### Unloading

The gradual development of functional limitations over an extended period of time is affected by a natural age-related decline in physical and biological properties, which already starts in midlife and increases the risk for a decline in physical functioning in later life [99].

During aging, the physical system suffers to a different extent and rate in diverse parts of the body. This results in reduced functional reserve, a decrease in vital capacity, deterioration of the capillary blood supply, and a decrease in muscle mass [53].

Due to living a sedentary life in older age, inactivity can lead to a loss of functional health due to deficits in strength, endurance, and flexibility [53]. “Use it or lose it” has been shown to be a key rule for maintaining physical independence in the elderly [68]. One of the reasons for the development of muscle weakness in the elderly is decreased physical activity [66]. Inactivity and aging cause a marked relative increase in the endo- and perimysial connective tissue, which results in changes in the mechanical properties of the skeletal muscle [22]. Myofibrillar basal lamina becomes thicker and more rigid with age, and increased cross-linking of collagen molecules makes fibrils more resistant to degradation by collagenase [30]. The muscle tissue response to unloading seems to be more expressed than the connective tissue response [41, 48]. The connective structures are protected from rapid changes in tissue mass, while the muscle, which is known to act as a protein store of the organism, is subject to substantial and fast changes in tissue mass. Despite the small changes in connective tissue mass, important changes occur in the tissue structures during unloading and aging [77].

Unloading has been shown to decrease the protein synthesis rate in skeletal muscle by 46 % [27]. Decreased muscle mass, reduction in strength, and aerobic capacity are the typical changes in the elderly during bed rest [23]. An increase of dietary protein intake attenuates protein degradation rate during bed rest [87] and, in combination with anabolic agents, prevents muscle loss [23, 40, 91].

### Reloading

Due to the differences in the plasticity of young and old skeletal muscle, young muscle mass increases faster than old after reloading [88], but the recovery of muscle strength, both in young and old, takes more time than gain of muscle mass [65]. Regaining muscle strength after unloading takes longer in old than in the young [88]. The recovery of locomotory activity after hindlimb suspension is as fast as

the recovery of muscle strength and is related to the regeneration of muscle structures from disuse atrophy [36]. Muscle metabolism can be restored faster than the full recovery of muscle function as the cross-sectional area and myonuclear domain size require more time for restoration of neural and mechanical properties of muscle [20, 60].

It has also been proposed that aging militates against the loss of collagen stability due to mechanical overextension [101], but the growth hormone is more important in strengthening the matrix tissue than forming muscle fiber hypertrophy in aged musculotendinous tissue [21]. After severe damage, muscle in old rodents does not regenerate as well as muscle in adults [17]. A contraction-induced muscle injury to weight-bearing muscles in old age causes deficits in muscle mass and force [67]. The fact that an increase in muscular strength lags behind that in muscular mass shows that an increase in muscular mass contains functionally immature muscle fibers during the recovery process following disuse atrophy [77].

## Effect of exercise therapy on muscle weakness in the elderly

### Resistance exercise training

Muscle weakness is the main factor in the dysfunction of locomotory activity and balance not only in the elderly but also during the first months of a newborn’s life activity. It has been shown that an increase in muscle strength is in good agreement with the development of the baby’s controlled movements during the first 5 months of life [79]. This fact in turn shows the importance of muscle strength in human everyday activity. It has been demonstrated that exercise programs incorporating balance training are effective in reducing falls in older people [90].

Elderly people were 59 % weaker than young, but a 6-month resistance training improved muscle strength in the old group and was only 38 % lower than in the young group [54]. During aging, muscle power declines more rapidly than strength [55]. Resistance training improves the power-producing capacity of skeletal muscle fibers in the elderly due to the increase of contractile velocity [96].

Resistance training is a strong stimulus for skeletal muscle metabolism in the elderly, particularly for the contractile apparatus as the fractional synthesis rate of myofibrillar proteins in the skeletal muscle increases [64]. Compensatory hypertrophy of *plantaris* muscle by tenotomy of the *gastrocnemius* muscle decreased the relative content of MyHC IIb and IIa isoforms in old rats. Simultaneous compensatory hypertrophy and heavy resistance training increased the proportion of MyHC IIb and decreased the relative content of MyHC IIc isoform in old animals’ muscles [64]. If the

intensity and volume ratio is properly regulated in heavy resistance training, it may prevent the age-related decrease in the relative content of MyHC IIB isoform in skeletal muscle.

In the elderly, skeletal muscle atrophy and mitochondrial dysfunction coexist and maybe causally related [7]. There is convincing evidence of the existing link between muscle mitochondrial dysfunction and insulin resistance in the elderly [2]. It has been shown that resistance training in older adults can increase mitochondrial capacity in skeletal muscle [62]. Muscle contraction induce(s) the mobilization of local lipid reserves in obese skeletal muscle and promotes beta-oxidation while discouraging glucose utilization [93]. Resistance training helps elderly skeletal muscle preserve fat-free mass during body mass loss [9].

Rapid recovery from resistance exercise in young age supports the increase in muscle strength [77], but recovery from more damaging resistance exercise is slower as a result of age, whereas there are no age-related differences in recovery from less damaging metabolic fatigue [26]. Recent evidence suggests that the difference in the regenerative capacity of skeletal muscle between young and very old rats is only about 10 %, but regeneration of the myofibrillar apparatus is much slower in the elderly [38].

This is obviously related to the greater amount of resistance exercise-induced damage in skeletal muscle as there is relatively slow repair of muscle tissue after exercise in the elderly [26]. Finding possibilities to rehabilitate the loss of physical function by exercise therapy in the elderly is one of today's burning issues due to an increase in elderly people in the society.

#### *Changes in the turnover rate of muscle proteins during resistance exercise training*

Resistance exercise may modify muscle fiber structure and metabolism and promote the release of growth factors and other signaling molecules, such as nitric oxide, which activates the satellite cells through the paracrine system [94]. Myosatellites, which develop further into myoblasts, contain lots of ribosomes, branching granular sarcoplasmic reticulum with widened canals, and a Golgi apparatus. Myosatellitocytes may also contain centrioles, and this confirms that these cells are divided by mitosis [78]. Myosatellitocytes sarcoplasm close to the nucleus contains bundles of filaments, which may turn out to be myofilaments [97]. In adults and aged persons, resistance training causes muscle hypertrophy in two ways: firstly, damaged fibers regenerate as a result of the fusion with the satellite cells; secondly, satellite cells divide and, later, myosimplasts fuse with each other and form myotubes [78]. It has been shown that contractile proteins turned over faster in type I and IIA muscle fibers than in IIB fibers, and the turnover rate of

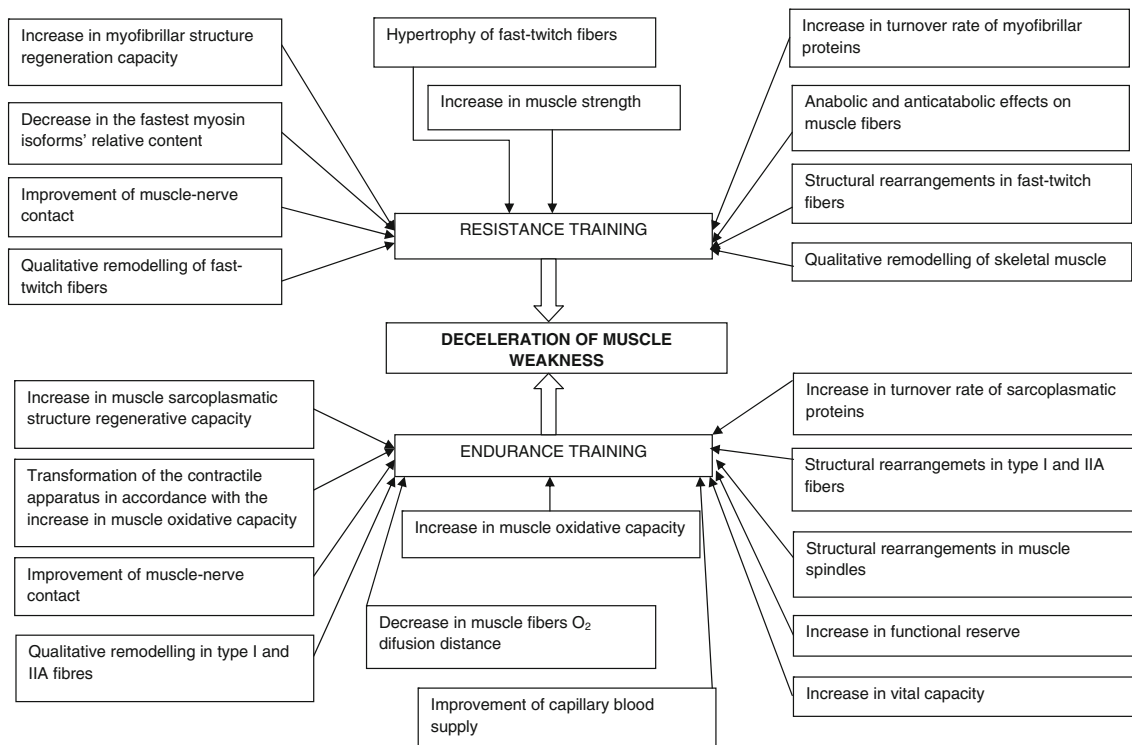
skeletal muscle proteins depends on the functional activity of the muscle [78]. The turnover rate of contractile proteins in skeletal muscle seems to be related to age-related changes in the composition of the MyHC isoform [77]. Resistance training increases the turnover rate of contractile proteins, but the changes in old age are relatively slower than in young age [77, 78].

Even if it does not cause hypertrophy of muscle fibers, resistance exercise in the aging population avoids muscle atrophy as the myonuclear number increases slightly as a result of the fusion of satellite cells with damaged fibers. Via this or as a result of myoblasts' fusion forming myotubes, which develop into new muscle fibers, muscle functional capacity increases. Exercise causes adaptational changes in the contractile apparatus, primarily in newly formed fibers via the remodeling of myosin isoforms. A faster turnover rate of contractile proteins in resistance-trained muscles supports the strength generation capacity of muscle fibers in elderly skeletal muscle (Fig. 2). Naturally, this process is more effective in muscle fibers with higher oxidative capacity than in muscle fibers with low oxidative capacity.

#### Endurance exercise training

Structural and functional rearrangements in skeletal muscle depend on the oxidative capacity of the fibers [78]. The integral indicator of muscle protein metabolism, muscle protein turnover, fiber recovery from exercise-induced injury, and regeneration capacity is faster in fibers with higher oxidative capacity [74, 75, 80]. As a physiological process, aging also includes a gradual decrease in skeletal muscle endurance [18, 77], and this is related to the reduction in fitness. A decrease in physical fitness gives theoretical background to use both endurance and resistance exercise for health outcomes in the elderly. The turnover of muscle protein provides a mechanism by which resistance training can change the contractile protein renewal in accordance with the needs of the contractile machinery of skeletal muscle [75]. As the oxidative capacity of skeletal muscle decreases in the elderly, endurance training seems to be effective in its restoration as it stimulates mitochondrial biogenesis and improves their functional parameters [35, 47]. A combination of endurance and resistance exercise in the elderly for the purpose of increasing muscle oxidative capacity and the contractile protein turnover rate is an effective measure for enhancing quality of life in the elderly by improving skeletal muscle functional capacity and plasticity (Fig. 2). It has recently been shown that the individual development of muscle plasticity in the elderly makes it possible to modify the age-associated decline even in maximal physical performance at least for some time [89]. The higher aerobic capacity in trained elderly people is related to an increase in the abilities of the cardiovascular system and, to a lesser extent, to an increase in muscle mitochondrial concentration and capacity [73]. Here, the lesser





**Fig. 2** Effect of exercise therapy on the deceleration of muscle weakness and, via this, improvement of quality of life in the elderly

extent means that regular aerobic activity provides a foundation for an increase of muscle oxidative capacity in the elderly. At this point, it is useful to repeat the viewpoint of Suominen [89] that adequate physical performance is an essential element of a healthy and productive life among the elderly. Although factors such as health, physical function, and independence constitute components of the quality of life in the elderly, physiological functioning is significant in determining the ability to maintain independence and an active interaction with the environment [85]. The mode of exercise plays a significant role in elderly training. It has shown that high-intensity aerobic exercise training efficiently reduced visceral fat in elderly and overweight adults [16]. However, with older age, managing everyday activities becomes less self-evident, although there are gender differences in physical functioning [43]. Functional limitation in old age is an objective measure of the consequences of disease and impairment [32]. There is increasing need in the society to encourage elderly people to follow the motto of Kramer and Erickson [42] for successful aging to use widespread participation in low-cost and low-tech exercise to further improve their fitness and reduce the risk of disability.

### Summary and conclusions

Both sarcopenia and dynapenia are risk factors for health outcomes and play a significant role in the etiology of disability in the elderly. As a complex of factors contributes

to the development of muscle wasting and weakness in the elderly, it is complicated to find one certain measure for rehabilitation. As lack of strength is one of the main reasons for muscle weakness, it seems to be most realistic to use resistance training for this purpose in the elderly. Resistance training is a strong stimulus for muscle metabolism in the elderly, particularly for the contractile machinery of muscle. The contractile protein turnover rate provides a mechanism by which the effect of exercise-caused changes can be assessed in accordance with the needs of the contractile apparatus. As the contractile protein turnover rate depends on the oxidative capacity of muscle and muscle oxidative capacity decreases in the elderly, it is obvious that endurance exercise stimulates an increase in the oxidative capacity of skeletal muscle by an increase in mitochondrial biogenesis and supports faster protein turnover during resistance training, as a result of which muscle function, and thereby quality of life, in the elderly improves. The regeneration of skeletal muscle from the damage caused by exercise is faster in muscles with higher oxidative capacity. Using both resistance and endurance exercise in the elderly makes it possible to modify the age-associated decline in muscle function and decelerate the development of muscle weakness.

**Acknowledgments** This study was supported by the funds of the Ministry of Education and Research of Estonia, research project no. TKKSB1787.

## References

- Abate N, Chandalia M (2003) The impact of ethnicity on type 2 diabetes. *J Diabet Complicat* 17:39–58
- Abbatecola AM, Paolisso G, Fattoretti P, Evans WJ, Fiore V, Dicioccio L, Lattanzio F (2011) Discovering pathways of sarcopenia in older adults: a role for insulin resistance on mitochondria dysfunction. *J Nutr Health Aging* 15:890–895
- Balagopal P, Schimke JC, Ades P, Adey D, Nair KS (2001) Age effect on transcript levels and synthesis rate of muscle MHC and response to resistance exercise. *Am J Physiol Endocrinol Metab* 280:E203–E208
- Barazzoni R, Short KR, Nair KS (2000) Effects of aging on mitochondrial DNA copy number and cytochrome c oxidase gene expression in rat skeletal muscle, liver, and heart. *J Biol Chem* 275:3343–3347
- Bassaglia Y, Gautron J (1995) Fast and slow rat muscles degenerate and regenerate differently after crush injury. *J Muscle Res Cell Motil* 16:420–429
- Brown M (2009) Too many weak days—diagnosis: physical frailty. *Mo Med* 106:121–125
- Bua E, Johnson J, Herbst A, DeLong B, McKenzie D, Salamat S, Aiken JM (2006) Mitochondrial DNA-deletion mutations accumulate intracellularly to detrimental levels in aged human skeletal muscle fibers. *Am J Hum Genet* 79:469–480
- Buford TW, Anton SD, Judge AR, Marzetti E, Wohlgemuth SE, Carter CS, Christiaan Leeuwenburgh C, Pahor M, Manini TM (2010) Models of accelerated sarcopenia: critical pieces for solving the puzzle of age-related muscle atrophy. *Ageing Res Rev* 9:369–383
- Campbell WW, Haub MD, Wolfe RR, Ferrando AA, Sullivan DH, Apolzan JW, Iqbal HB (2009) Resistance training preserves fat-free mass without impacting changes in protein metabolism after weight loss in older women. *Obesity (Silver Spring)* 17:1332–1339
- Carlson BM, Dedkov EI, Borisov AB, Faulkner JA (2001) Skeletal muscle regeneration in very old rats. *J Gerontol A Biol Sci Med Sci* 56:B224–B233
- Chabi B, Ljubicic V, Menzies KJ, Huang JH, Saleem A, Hood DA (2008) Mitochondrial function and apoptotic susceptibility in aging skeletal muscle. *Ageing Cell* 7:2–12
- Clark BC, Fernhall B, Ploutz-Snyder LL (2006) Adaptations in human neuromuscular function following prolonged unweighting: I. Skeletal muscle contractile properties and applied ischemia efficacy. *J Appl Physiol* 101:256–263
- Clark BC, Manini TM (2008) Sarcopenia ≠ dynapenia. *J Gerontol A Biol Sci Med Sci* 63:829–834
- Clark BC, Manini TM (2010) Functional consequences of sarcopenia and dynapenia in the elderly. *Curr Opin Clin Nutr Metab Care* 13:271–276
- Clark BC, Manini TM, Bolanowski SJ, Ploutz-Snyder LL (2006) Adaptations in human neuromuscular function following prolonged unweighting: II. Neurological properties and motor imagery efficacy. *J Appl Physiol* 101:264–272
- Coker RH, Williams RH, Kortebein PM, Sullivan DH, Evans WJ (2009) Influence of exercise intensity on abdominal fat and adiponectin in elderly adults. *Metabolic Syndr Relat Disord* 7:363–368
- Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, Rando TA (2005) Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 433:760–764
- Degens H, Alway SE (2006) Control of muscle size during disuse, disease, and aging. *Int J Sports Med* 27:94–99
- Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Valasquez-Mieryer P, Boudreau R, Manini TM, Nevitt M, Newman AB, Goodpaster BH (2009) Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *Am J Clin Nutr* 90:1579–1585
- Desaphy JF, Pierno S, Liantonio A, De Luca A, Didonna MP, Frigeri A, Nicchia GP, Svelto M, Camerino C, Zallone A, Camerino DC (2005) Recovery of the soleus muscle after short- and long-term disuse induced by hindlimb unloading: effects on the electrical properties and myosin heavy chain profile. *Neurobiol Dis* 18:356–365
- Doessing S, Heinemeier KM, Holm L, Mackey AL, Schjerling P, Rennie M, Smith K, Reitelseder S, Kappelgaard AM, Rasmussen MH, Flyvbjerg A, Kjaer M (2010) Growth hormone stimulates the collagen synthesis in human tendon and skeletal muscle without affecting myofibrillar protein synthesis. *J Physiol* 588:341–351
- Ducomps C, Mauriege P, Darche B, Combes S, Lebas F, Doutreloux JP (2003) Effects of jump training on passive mechanical stress and stiffness in rabbit skeletal muscle: role of collagen. *Acta Physiol Scand* 178:215–224
- Evans WE (2010) Skeletal muscle loss: cachexia, sarcopenia, and inactivity. *Am J Clin Nutr* 91(Suppl):1123S–1127S
- Evans WJ, Paolisso G, Abbatecola AM, Corsonello A, Bustacchini S, Strollo F, Lattanzio F (2010) Frailty and muscle metabolism dysregulation in the elderly. *Biogerontology* 11:527–536
- Fearon K, Evans WJ, Anker SD (2011) Myopenia—a new universal term for muscle wasting. *J Cachexia Sarcopenia Muscle* 2:1–3
- Fell JW, Williams AD (2008) The effect of aging on skeletal muscle recovery from exercise: possible implications for aging athlete. *J Aging Phys Act* 16:97–115
- Ferrando AA, Lane HW, Stuart CA, Davis-Street J, Wolfe RR (1996) Prolonged bed rest decreases skeletal muscle and whole body protein synthesis. *Am J Physiol* 270:E627–E633
- Frontera WR, Suh D, Krivickas LS, Huges VA, Goldstein R, Rubenoff R (2000) Skeletal muscle fiber quality in older men and women. *Am J Physiol Cell Physiol* 279:C611–C618
- Gandevia SC (2001) Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 81:1725–1789
- Goldspink G, Fernandes K, Williams PE, Wells DJ (1994) Age-related changes in collagen gene expression in the muscles of mdx dystrophic and normal mice. *Neuromuscul Disord* 4:183–191
- Gonzales E, Messi ML, Delbono O (2000) The specific force of single intact extensor digitorum longus and soleus mouse muscle fibers declines with aging. *J Membr Biol* 178:175–183
- Guralnik JM, Ferrucci L (2003) Assessing the building blocks of function: utilizing measures of functional limitation. *Am J Prev Med* 25:112–121
- Haus JM, Carrithers JA, Trappe SW, Trappe TA (2007) Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. *J Appl Physiol* 103:2068–2076
- Hiona A, Leeuwenburgh C (2008) The role of mitochondrial DNA mutations in aging and sarcopenia: implications for the mitochondrial vicious cycle theory of aging. *Exp Gerontol* 43:24–33
- Hood DA (2009) Mechanisms of exercise-induced mitochondrial biogenesis in skeletal muscle. *Appl Physiol Nutr Metab* 34:465–472
- Itai Y, Kariya Y, Hoshino Y (2004) Morphological changes in rat hindlimb muscle fibres during recovery from disuse atrophy. *Acta Physiol Scand* 181:217–224
- Janssen I (2010) Evolution of sarcopenia research. *Appl Physiol Nutr Metab* 35:707–712
- Kaasik P, Umnova M, Pehme A, Alev K, Aru M, Selart A, Seene T (2007) Ageing and dexamethasone associated sarcopenia: peculiarities of regeneration. *J Steroid Biochem Mol Biol* 105:85–90
- Kadi F, Ponsot E (2010) The biology of satellite cells and telomeres in human skeletal muscle: effects of aging and physical activity. *Scand J Med Sci Sports* 20:39–48

40. Katsanos CS, Chinkes DL, Paddon-Jones D, Zhang X, Aarsland A, Wolfe RR (2008) Whey protein ingestion in elderly results in greater muscle protein accretal than ingestion of its constituent essential amino acid content. *Nutr Res* 28:651–658
41. Kjaer M, Magnusson P, Krogsgaard M, Moller JB, Olesen J, Heinemeier K, Hansen M, Haraldsson B, Koskinen S, Esmarck B, Langberg H (2006) Extracellular matrix adaptation of tendon and skeletal muscle to exercise. *J Anat* 208:445–450
42. Kramer AF, Erickson KI (2007) Capitalizing on cortical plasticity: influence of physical activity on cognition and brain function. *Trends Cogn Sci* 11:342–348
43. Kuh D, Bassey EJ, Butterworth S, Hardy R, Wadsworth MEJ (2005) Grip strength, postural control, and functional leg power in a representative cohort of British men and women: associations with physical activity, health status, and socioeconomic conditions. *J Gerontol A Biol Sci Med Sci* 60:224–231
44. Kujala UM (2011) Physical activity, genes, and lifetime predisposition to chronic disease. *Eur Rev Aging Phys Act* 8:31–36
45. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM, Ferrucci L (2003) Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *J Appl Physiol* 95:1851–1860
46. Leeuwenburgh C, Gurley CM, Strotman BA, Dupont-Versteegden EE (2005) Age-related differences in apoptosis with disuse atrophy in soleus muscle. *Am J Physiol Regul Integr Comp Physiol* 288:R1288–R1296
47. Ljubicic V, Joseph AM, Saleem A, Ugucioni G, Collu-Marchese M, Lai RY, Nguyen LM, Hood DA (2010) Transcriptional and post-transcriptional regulation of mitochondrial biogenesis in skeletal muscle: effects of exercise and aging. *Biochim Biophys Acta* 1800:223–234
48. Mackey AL, Heinemeier KM, Koskinen SOA, Kjaer M (2008) Dynamic adaptation of tendon and muscle connective tissue to mechanical loading. *Connect Tissue Res* 49:165–168
49. Malatesta M, Perdoni F, Muller S, Pellicciari C, Zancanaro C (2010) Pre-mRNA processing is partially impaired in satellite cell nuclei from aged muscles. *J Biomed Biotechnol* 2010:410405. doi:10.1155/2010/410405
50. Manini TM (2009) Organ-o-penia. *J Appl Physiol* 106:1759–1760
51. Manini TM, Clark BC (2012) Dynapenia and aging: an update. *J Gerontol A Biol Sci Med Sci* 67:28–40. doi:10.1093/gerona/67.10.28
52. Marzetti E, Leeuwenburgh C (2006) Skeletal muscle apoptosis, sarcopenia and frailty at old age. *Exp Gerontol* 41:1234–1238
53. Mechling H, Netz Y (2009) Aging and inactivity—capitalizing on the protective effect of planned physical activity in old age. *Eur Rev Aging Phys Act* 6:89–97
54. Melov S, Tarnopolsky MA, Beckman K, Felkey K, Hubbard A (2007) Resistance exercise reverses aging in human skeletal muscle. *PLoS One* 2:e465
55. Metter EJ, Conwit R, Tobin J, Fozard JL (1997) Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci* 52:B267–B276
56. Moritani T, deVries HA (1979) Neural factors versus hypertrophy in the time course of muscle strength gain. *Am J Phys Med* 58:115–130
57. Nair KS (2005) Aging muscle. *Am J Clin Nutr* 81:953–963
58. Netz Y (2009) Type of activity and fitness benefits as moderators of the effect of physical activity on affect in advanced age: a review. *Eur Rev Aging Phys Act* 6:19–27
59. Ogata T, Machida S, Oishi Y, Higuchi M, Muraoka I (2009) Differential cell death regulation between adult-unloaded and aged rat soleus muscle. *Mech Ageing Dev* 130:328–336
60. Ohira Y, Yoshinaga T, Ohara M, Kawano F, Wang XD, Higo Y, Terada M, Matsuko Y, Roy RR, Edgerton VR (2006) The role of neural and mechanical influences in maintaining normal fast and slow muscle properties. *Cells Tissues Organs* 182:129–142
61. Ono Y, Boldrin L, Knopp P, Morgan JE, Zammit PS (2010) Muscle satellite cells are a functionally heterogeneous population in both somite-derived and branchiomeric muscles. *Dev Biol* 337:29–41
62. Parise G, Brose AN, Tarnopolsky MA (2005) Resistance exercise training decreases oxidative damage to DNA and increases cytochrome oxidase activity in older adults. *Exp Gerontol* 40:173–180
63. Pasiakos SM, Vislocky LM, Carbone JW, Altieri N, Konopelski K, Freaque HC, Anderson JM, Ferrando AA, Wolfe RR, Rodriguez NR (2010) Acute energy deprivation affects skeletal muscle protein synthesis associated intracellular signaling proteins in physically active adults. *J Nutr* 140:745–751
64. Pehme A, Alev K, Kaasik P, Seene T (2004) Age related changes in skeletal muscle myosin heavy-chain composition: effect of mechanical loading. *J Aging Phys Act* 12:29–44
65. Pottle D, Gosselin LE (2000) Impact of mechanical load on functional recovery after muscle reloading. *Med Sci Sports Exerc* 32:2012–2017
66. Powers SK, Kavazis AN, McClung JM (2007) Oxidative stress and disuse muscle atrophy. *J Appl Physiol* 102:2389–2397
67. Rader EP, Faulkner JA (2006) Recovery from contraction-induced injury is impaired in weight-bearing muscles of old male mice. *J Appl Physiol* 100:656–661
68. Rejeski WJ, Brawley LR (2006) Functional health: innovations in research on physical activity with older adults. *Med Sci Sports Exerc* 38:93–99
69. Roberts MD, Kerksick CM, Dalbo VJ, Hassell SE, Tucker PS, Brown R (2010) Molecular attributes of human skeletal muscle at rest and after unaccustomed exercise: an age comparison. *J Strength Cond Res* 24:1161–1168
70. Rooyackers OE, Adey DB, Ades PA, Nair KS (1996) Effect of age in vivo rates of mitochondrial protein synthesis in human skeletal muscle. *Proc Natl Acad Sci USA* 93:15364–15369
71. Russ DW, Grandy JS, Toma K, Ward CW (2011) Ageing, but not yet senescent, rats exhibit reduced muscle quality and sarcoplasmic reticulum function. *Acta Physiol* 201:391–403
72. Russ DW, Grandy JS, Toma K, Ward CW (2011) Ageing, but not yet senescent, rats exhibit reduced muscle quality and sarcoplasmic reticulum function. *Acta Physiol (Oxf)* 201:391–403
73. Sagiv M, Goldhammer E, Ben-Sira D, Amir R (2010) Factors defining oxygen uptake at peak exercise in aged people. *Eur Rev Aging Phys Act* 7:1–2
74. Seene T, Alev K, Kaasik P, Pehme A (2007) Changes in fast-twitch muscle oxidative capacity and myosin isoforms modulation during endurance training. *J Sports Med Phys Fitness* 47:124–132
75. Seene T, Kaasik P, Alev K (2011) Muscle protein turnover in endurance training: a review. *Int J Sports Med* 32:905–911. doi:10.1055/s-0031-1284339
76. Seene T, Kaasik P, Pehme A, Alev K, Riso EM (2003) The effect of glucocorticoids on the myosin heavy chain isoforms' turnover in skeletal muscle. *J Steroid Biochem Mol Biol* 86:201–206
77. Seene T, Kaasik P, Riso EM (2012) Review on aging, unloading and reloading: changes in skeletal muscle quantity and quality. *Arch Gerontol Geriatr* 54:374–380. doi:10.1016/j.archger.2011.05.002
78. Seene T, Kaasik P, Umnova M (2009) Structural rearrangements in contractile apparatus and resulting skeletal muscle remodeling: effect of exercise training. *J Sports Med Phys Fitness* 49:410–423
79. Seene T, Lellep J, Tungal E, Kaasik P, Seene M (2011) Modelling of newborns' strength development. In: Puman E, Lellep J (eds) International Conference on Optimization and Analysis of Structures, Tartu, 42 pp



80. Seene T, Umnova M, Kaasik P, Alev K, Pehme A (2008) Overtraining injuries in athletic population. In: Tiidus PM (ed) Skeletal muscle damage and repair, Human Kinetics, IL, pp 173–184 and 305–307
81. Short KR, Vittone JL, Bigelow ML, Proctor DN, Nair KS (2004) Age and aerobic exercise training effects on whole body and muscle protein metabolism. *Am J Physiol Endocrinol Metab* 286:E92–E101
82. Short KR, Vittone JL, Bigelow ML, Proctor DN, Rizza RA, Coenen-Schimke JM, Nair KS (2003) Impact of aerobic exercise training on age-related changes in insulin sensitivity and muscle oxidative capacity. *Diabetes* 52:1888–1896
83. Shultz E, Darr K (1990) The role of satellite cells in adaptive or induced fiber transformations. In: Pette D (ed) The dynamic state of muscle fibers. W.de Gruyter, Berlin, pp 667–681
84. Siu PM, Pistilli EE, Alway SE (2008) Age-dependent increase in oxidative stress in gastrocnemius muscle with unloading. *J Appl Physiol* 105:1695–1705
85. Spirduso WW, Gronin DL (2001) Exercise dose–response effects on quality of life and independent living in older adults. *Med Sci Sports Exerc* 33:S598–S610
86. Stackhouse SK, Stevens JE, Lee SC, Pearce KM, Snyder-Mackler L, Binder-Macleod SA (2001) Maximum voluntary activation in nonfatigued and fatigued muscle of young and elderly individuals. *Phys Ther* 81:1102–1109
87. Stuart CA, Shangraw RE, Peters EJ, Wolfe RR (1990) Effect of dietary protein on bed-rest-related changes in whole-body-protein synthesis. *Am J Clin Nutr* 52:509–514
88. Suetta C, Hvid LG, Justesen L, Christensen U, Neergaard K, Simonsen L, Ortenblad N, Magnusson SP, Kjaer M, Aagaard P (2009) Effects of aging on human skeletal muscle after immobilization and retraining. *J Appl Physiol* 107:1172–1180
89. Suominen H (2011) Ageing and maximal physical performance. *Eur Rev Aging Phys Act* 8:37–42
90. Suttanon P, Hill K, Said C, Dodd K (2010) Can balance exercise programmes improve balance and related physical performance measures in people with dementia? A systematic review. *Eur Rev Aging Phys Act* 7:13–25
91. Symons TB, Sheffield-Moore M, Chinkes DL, Ferrando AA, Paddon-Jones D (2009) Artificial gravity maintains skeletal muscle protein synthesis during 21 days simulated microgravity. *J Appl Physiol* 107:34–38
92. Tatsumi R (2010) Mechano-biology of skeletal muscle hypertrophy and regeneration: possible mechanism of stretch-induced activation of resident myogenic stem cells. *Anim Sci J* 81:11–20
93. Thyfault JP, Gree MG, Tapscott EB, Bell JA, Koves TR, Ilkayeva O, Wolfe RR, Dohm GL, Muoio DM (2010) Metabolic profiling of muscle contraction in lean compared with obese rodents. *Am J Physiol* 299:R926–R934
94. Toigo M, Boutellier U (2006) New fundamental resistance exercise determinants of molecular and cellular muscle adaptations. *Eur J Appl Physiol* 97:643–663
95. Trappe T (2009) Influence of aging and long-term unloading on the structure and function of human skeletal muscle. *Appl Physiol Nutr Metab* 34:459–464
96. Trappe S, Williamson D, Godard M, Porter D, Rowden G, Costill D (2000) Effect of resistance training on single muscle fiber contractile function in older men. *J Appl Physiol* 89:143–152
97. Umnova M, Seene T (1991) The effect of increased functional load on the activation of satellite cells in the skeletal muscle of adult rats. *Int J Sports Med* 12:501–504
98. Verney J, Kadi F, Charifi N, Feasson L, Saafi MA, Castells J, Piehl-Aulin K, Denis C (2008) Effects of combined lower body endurance and upper body resistance training on the satellite cell pool in elderly subjects. *Muscle Nerve* 38:1147–1154
99. von Bonsdorff MB, Rantanen T (2011) Progression of functional limitations in relation to physical activity: a life course approach. *Eur Rev Aging Phys Act* 8:23–30
100. Weisleder N, Brotto M, Komazaki S, Pan Z, Zhao X, Nosek T, Parness J, Takeshima H, Ma J (2006) Muscle aging is associated with compromised  $Ca^{2+}$  spark signaling and segregated intracellular  $Ca^{2+}$  release. *J Cell Biol* 174:639–645
101. Willett TL, Labow RS, Aldous IG, Avery NC, Lee JM (2010) Changes in collagen with aging maintain molecular stability after overload: evidence from an in vitro tendon model. *J Biomech Eng* 132:031002. doi:10.1115/1.4000933
102. Yarasheski KE, Welle SL, Nair KS (2002) Muscle protein synthesis in younger and older men. *JAMA* 287:317–318