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MUSCLE WEAKNESS IN THE ELDERLY: MECHANISM AND BENEFITS OF EXERCISE*

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ABSTRACT

The 20th century was characterized by a dramatic increase in the number and percentage of people joining the group of men and women older than 60 years. Life expectancy has increased around the world. Aging, as a biological process, impacts all physiological systems in the human body. One of the most typical findings in the elderly is the loss of functional capacity including significant losses in muscle mass, strength, and power. As a result, simple daily tasks, such as rising from a chair and climbing stairs, require a larger percentage of the voluntary strength and lead to early fatigue. Longitudinal studies show that muscle strength is lost at a rate of approximately 1% per year but women appear to maintain the strength of the muscles of the upper limbs. Muscle power is lost at a faster rate. Muscle atrophy contributes to these losses but there is scientific evidence suggesting that muscle quality (strength adjusted for size) is also affected. The molecular mechanism underlying these losses is unknown but it could include changes in the biochemistry and function of the motor protein myosin. Exercise has been shown to significantly enhance muscle strength and mass in the elderly. Typical exercise programs require progressive resistance, 3-4 sets for various muscle groups, 8-10 repetitions per set, and a training intensity of 60-80% of the maximal capacity. Free weights as well as special weight training devices can be used. Strength training increases muscle strength, cross-sectional area, and muscle fiber specific force. Muscle protein synthesis is activated. Strength training also enhances cardiovascular function and joint flexibility and restores functional capacity in frail elderly.

Key words: sarcopenia, aging, muscle strenght, exercise training

Why is aging important?

The population growth and the aging of the population are two of the most important challenges facing scientists, clinicians, governments, and modern societies. The population of the Earth grew about 10 fold from 600 million in the year 1700 to approximately 6.3 billion in 2003 (1). This accelerated growth was most noticeable in the 20th century. For example, it took from the beginning of time until about 1927 to put the first 2 billion people on the planet, less than 50 years to add the next 2 billion (1974), and just 25 years to add the next 2 billion (1999).

A closely associated phenomenon is the aging of the population. Life expectancy increased dramatically in the 20th century (WHO report; Fig. 1) and it is more than 70 years in many countries around the world.

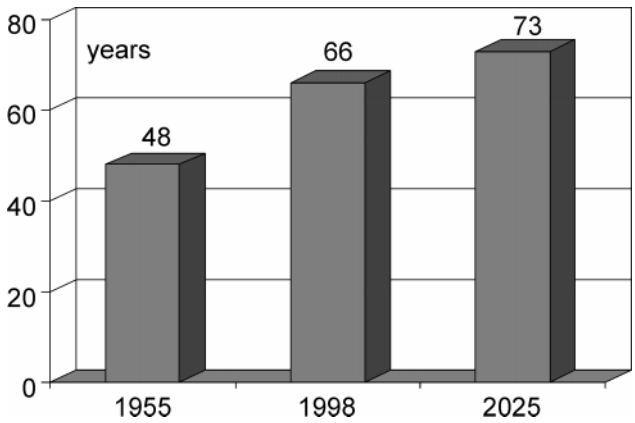

Fig. 1. *Global average life expectancy at birth (modified from: WHO Report, 1998)*

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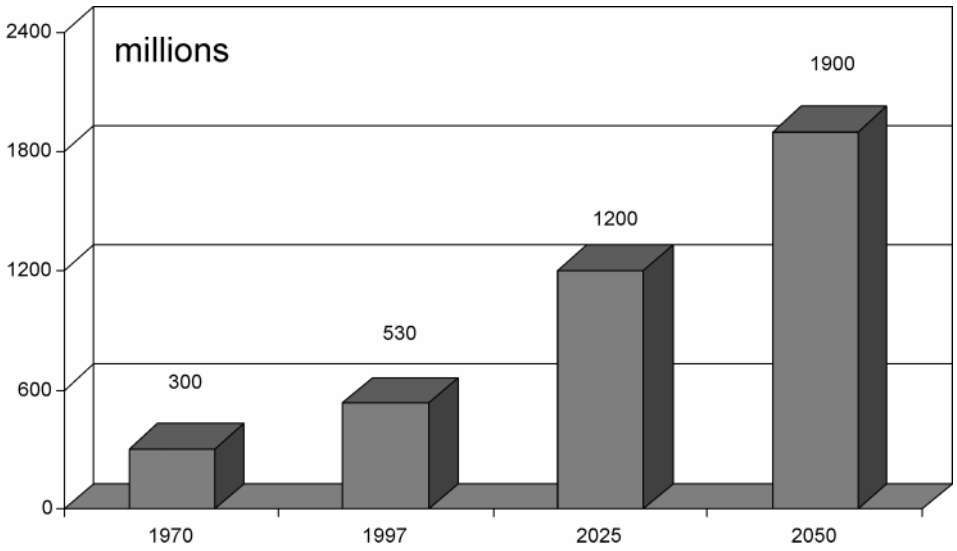

Fig. 2. *Population above age 60 for the world in 1970, 1997, and projected for 2025 and 2050 (modified from Vaupel (2) and Cohen (1))*

In some countries like Japan, average life expectancy has exceeded 80 years. Further, the number of people above age 60 is increasing in all continents of the world and will be reaching 1.2 billion (Fig. 2) by the year 2025 (1,2). Of special interest, the increase in the number of individuals in a particular age group is occurring at a faster rate in the old-old group (>85 years) and the number of centenarians is increasing almost exponentially in some parts of the world.

Defining aging

The process that we all recognize as ***"aging"*** is not easy to define. Many epidemiological, physiological, and clinical studies frequently use chronological age to define population groups but there is no precise way to define true physiological age. Thus, Banks and Fossel (3) have argued, and with good reasons, that age per se does not determine aging. Recent advances in genetics and animal cloning support this idea. For example, Dolly, the cloned sheep, forced a reexamination of what it means to grow old (4). Her DNA taken from the donor cell of the adult animal was approximately 6 1/2 years old at the time of her birth (Dolly's chronological age).

From a physiological point of view, aging can be defined as the sum of all changes that occur in a living organism with the passage of time (5). But these changes may affect different cell types, tissues, organs, and individuals at different rates (6). Thus, to talk about a homogeneous process of aging that affects the human body may be misleading. The incidence and prevalence of many degenerative and chronic illnesses such as osteoarthritis and coronary heart disease increases with advanced adult age. But aging must be understood independently from associated illnesses. Hayflick (6) argues that "one general distinction is that physiological losses characteristic of aging eventually occur in the cells, tissues and organs of ***all*** older members of a species, while changes due to disease occur only in ***some*** members." In a clinical research setting this distinction is difficult because some pathophysiological changes may not be detectable with methods and techniques used for subject selection in aging studies. Finally, it is of interest to define the onset of the aging process. When does aging start? Not an easy question because it is many times answered using an arbitrary chronological age that has occupational (for example retirement age) or social relevance and implications but it is not based on biological changes. Aging is associated with an increase in mortality, so, as stated by Austad (7), "it makes sense to say that aging begins at the point at which the probability of death is at the minimum -or, in other words, from the point at which the probability of dying forever after increase".

In this article we will take a functional approach to the aging question. It is the objective of this discussion to examine one of the changes that impacts functional capacity in the elderly, the decline in skeletal muscle performance, and the potential role of exercise training in slowing down or reversing these alterations. It is not the intent of the authors to provide the reader with an extensive review of the literature but to highlight some scientific observations that can help us understand the problem and suggest a solution.

Aging as a functional challenge

All human beings would welcome a longer life expectancy if we could maintain an acceptable functional capacity and quality of life as we grow older. In other words, living longer is not a problem but adding years to our lives is not acceptable to many if the end result is losing our functional independence. In the words of H. Nakajima, former Director General of the World Health Organization (1998), "Increased longevity without quality of life is an empty prize …... that health expectancy is more important than life expectancy".

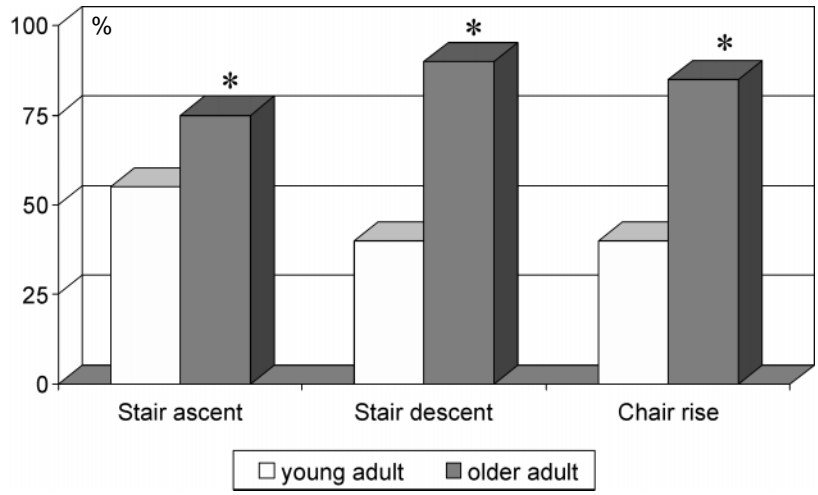

Fig. 3. *A comparison of relative effort at the knee joint in young and old healthy volunteers. Effort is expressed as %left knee extensor moment during an activity of daily living in relation to the maximal knee extensor. Moment during supine leg press *=significantly higher (modified from Hortobagyi (58)).*

It is well known that the incidence of functional limitations increases with age (8). Although this can be explained, at least partially, by an increase in the incidence of chronic conditions (9), age-related declines in physiological capacities are significant contributors to this deleterious situation. In other words, while the physiological demands of a particular task remain constant as we grow older, the maximal capacity of physiological systems to support the performance of the task declines with aging.

One way of understanding this problem is illustrated in figure 3. For an older person, the muscle force necessary to perform simple activities of daily living (ADL's) such as ascending and descending stairs and rising from a chair represents, in relative terms, a higher percentage of the muscle strength (maximal force-generating capacity) of the individual. Younger persons, on the other hand, easily perform the same tasks because muscle strength is generally preserved in this age group and the force needed for the same task represents a lower percentage of their strength. Thus, it should not be a surprise that older persons limit, voluntarily or involuntarily, their level of physical activity and participation in daily activities to avoid fatigue or failure.

The health implications of these functional changes can be best appreciated if we examine statistics related to the utilization of health services. In the United States it has been reported that older people account for 36% of hospital stays, 49% of all days of hospital care, 50% of all physician hours, and approximately 50% of all health care expenditures (in the foreseeable future). An elegant example of the relationship between an impairment resulting in functional loss, such as the decline in muscle strength, and health outcomes has been published by Rantanen and collaborators (10). They studied mortality after a bone fracture in older people with different levels of muscle strength at baseline. The results of the study showed that the number of deaths per 1000 person months was 8.9 times higher in the group with the lowest initial muscle strength (15.2) compared to those in the group with the highest strength (1.7). Clearly, physiological and functional capacities and health are intimately related.

Skeletal muscle as a source of the problem

Galileo once said "there is perhaps nothing in nature older than motion". The ability to move defines our functional capacity and quality of life in many respects and the primary organ responsible for motion is skeletal muscle. Aging has a noticeable impact on skeletal muscle function and structure and late in life a substantial portion of the population reaches low levels of muscle mass (sarcopenia) that are associated with increased disability (11,12). Sarcopenia is associated with a number of functional limitations including deficits in gait, mobility, activities of daily living, and risk for osteoporotic fractures.

A review of performance records in weightlifting sports events shows a decline in all categories with advancing age (13). To examine this trend in the general population we conducted a cross-sectional study several years ago and demonstrated that isokinetic strength of the knee and elbow extensors and flexors was 15.5-26.7% lower in 65-to78-yr-old men and women compared to their younger counterparts (14). In a 10 yr. longitudinal follow-up study we retested 64% of the initial sample and demonstrated a 60% faster decline compared to the cross-sectional data (15,16). However, this decline is by no means homogeneous. Muscles of the lower limbs lose strength at a faster rate than muscles of the upper limbs. Also, men lose strength in the upper limbs while women tend to maintain it. More striking is the observation that a large percentage of subjects actually showed an increase in muscle strength over the ten-year period (7 to 13% in the lower limbs and 8 to 32% in the upper limbs). It must be noted that

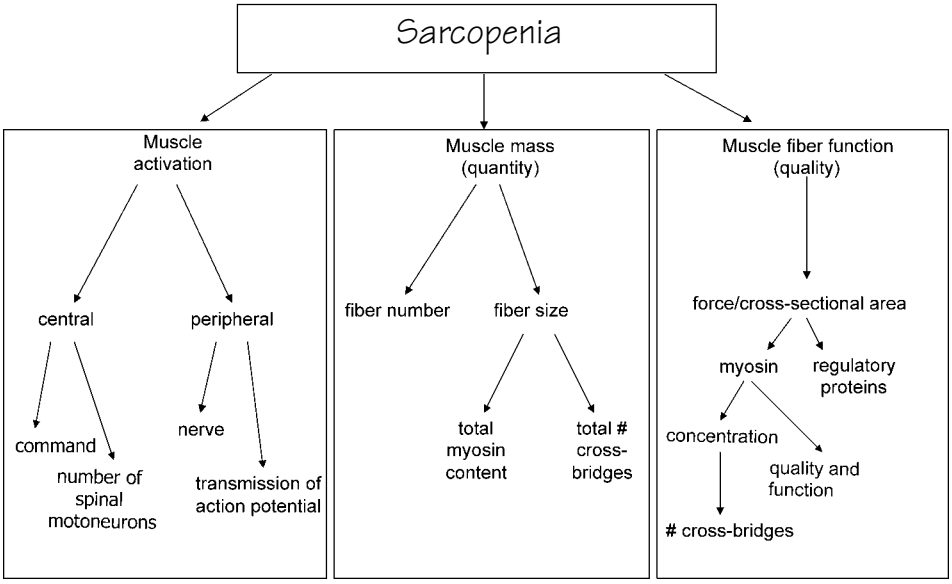

Fig. 4. *A schematic representation of some of the determinants of muscle strength that could be altered by aging and explain muscle dysfunction in older men and women*

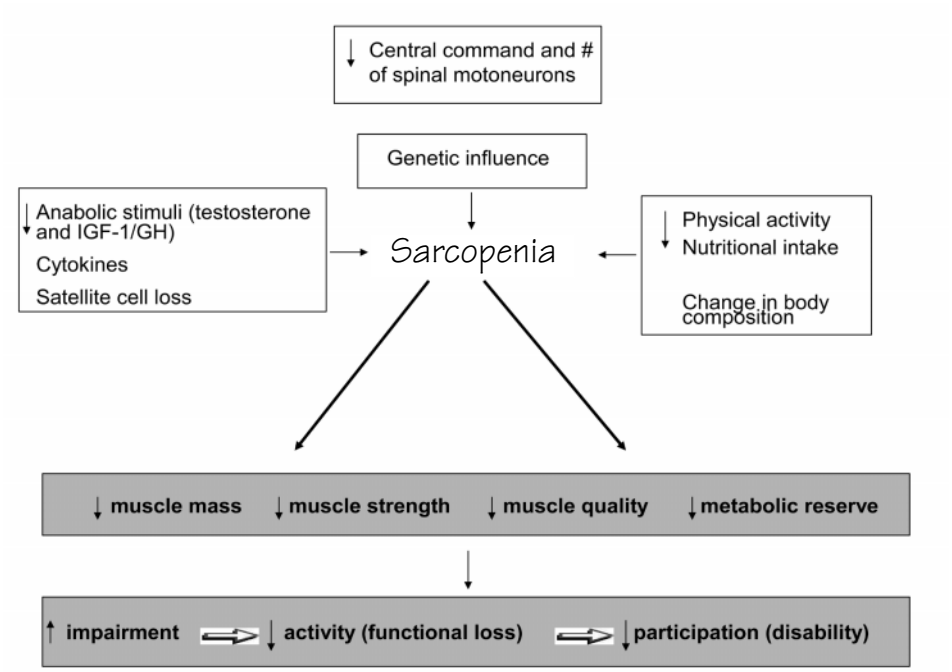

Fig. 5. *Diagram of some of the determinants of sarcopenia leading to disability*

the study group was considered to be a fairly active group. Our findings are not unique and similar reductions in muscle strength have been reported by other investigators using larger populations (12). Further, aging has a negative impact not only on muscle strength but also on muscle power; the product of force and velocity and a predictor of functional performance (17).

Physiological mechanism underlying muscle dysfunction

What is the mechanism underlying the reduction in muscle force production? Several possibilities exist (Fig. 4) including changes in the central and peripheral nervous systems (18). For the purpose of this discussion, we will concentrate on those determinants of muscle performance that are directly related to skeletal muscle size and cellular function.

A significant contributor to muscle weakness in the elderly is the loss of muscle mass (12,19,20,21) resulting mainly from a reduction in muscle fiber number (22) and a smaller contribution from muscle fiber atrophy. The fact that lean soft tissue is lost faster in the lower limbs compared to the upper limbs and that women preserve lean tissue better than men may explain the relative preservation of strength of the upper limbs in women mentioned above (19).

Another important contributor is the change in the composition of the muscular compartments. For exam-

ple, in the case of the leg anterior compartment, Kent-Braun and collaborators (20) showed that older men and women have a smaller cross-sectional area than younger subjects and that non-contractile tissue represents a larger percentage of the total area. For example fat and connective tissue represents 6% of the total area in younger men and women but 14 and 16% of the total area in older women and men, respectively; more than a two-fold increase. In other words, muscle tissue is replaced to some degree by tissue that does not contribute to force generation and the production of movement.

Based on the above observations it is generally accepted that muscle atrophy is part of the problem. However, other lines of investigation have suggested that there may be important additional contributing factors to the muscle weakness frequently seen in the elderly. Investigations using skinned single muscle fibers obtained with the percutaneous biopsy technique allow the study of the contractile properties of human muscle fiber segments under controlled conditions and in the absence of the influence of the nervous system. Because fibers are activated using maximal calcium concentrations, the degree of activation is not a limiting factor in the experiments. These studies have demonstrated a reduction in the force generating capacity of single fibers expressing type I or type IIA myosin heavy chain even after adjusting for differences in muscle fiber size (15). This parameter (force adjusted for muscle size) is known as specific force and is used as an indicator of muscle quality. Again, these observations are statistically significant only in men but not in women emphasizing the sex-dependent nature of the changes. Thus it has been suggested that, not only muscle mass (the quantitative point of view) but also the quality of the remaining muscle cells is compromised in older skeletal muscles; at least in men.

Molecular mechanism changes in muscle fiber quality

If the quality of muscle fibers is compromised with aging, what could be the underlying cellular/molecular mechanisms that explain this important change? A detailed discussion of the molecular biology and genetics of aging is beyond the scope of this article but a few observations are warranted.

Some investigators have reported important alterations in the excitation-contraction coupling of skeletal muscle with age (23). Uncoupling of the excitation of the transverse tubules and the release of calcium from the sarcoplasmic reticulum, events that are nicely coordinated in normal muscle, results in a reduction of calcium release and supply for force generation. Our experiments on muscle fiber quality referenced above were conducted in the absence of nervous influence (isolated single fibers with no innervation). In addition, the skinning process used to prepare the muscle fibers for the experiments removes the sarcolemma and the sarcoplasmic reticulum. Therefore, muscle fiber dysfunction under these conditions can only be explained by alterations in events happening beyond the excitation-contraction coupling steps and in the contractile or regulatory protein cellular infrastructure. Of these proteins, myosin has received a lot of attention in recent years and it is believed to play a significant role in sarcopenia of the aged.

When considering underlying mechanisms, at least three possibilities exist: 1) a reduction in gene transcription and protein synthesis resulting in a lower concentration of myosin in muscle fibers; 2) a genetic abnormality resulting in abnormal protein synthesis or regulation; 3) post-translational modifications of normal proteins.

It is generally believed that older muscles have impaired protein synthesis and that the balance between muscle protein synthesis and degradation favors the progressive loss of muscle protein content (24). Given our interest in myosin, it is significant that the *in vivo* synthesis of **myosin heavy chain** is impaired in older humans (25). However, a decline in protein synthesis with age is not a universal finding and in carefully controlled experiments, Volpi and coworkers (26) have reported recently no difference in **mixed muscle protein** fractional synthesis rate between young and old. This question needs further investigation. It is possible that the variability seen among studies is due to methodological differences and limitations. In spite of this disagreement, D'Antona and co-workers (27) have reported lower myosin concentrations in single human muscle fibers from older subjects expressing type I or IIA myosin heavy chain isoforms. Because, myosin concentration correlates directly with force, these data suggest that a lower myosin concentration in individual fibers leads to a reduction in the number of cross-bridges producing force and contributes to muscle weakness in the elderly.

Genetic mechanisms have also been explored in the search for the mechanism of sarcopenia. Examples of genetic abnormalities leading to muscle atrophy or hypertrophy have been reported in the literature in mice (28), cattle (29), and recently in humans (30).

It is possible that genes involved in the regulation of muscle size are affected by the aging process. Up- or down regulation of these genes could result in the absence of substances that promote muscle growth or the synthesis of a product that inhibits muscle protein accretion; the end result of either is sarcopenia. One example of the latter situation is the growth and diffe-

rentiation factor known as myostatin. Myostatin is a negative regulator of skeletal muscle mass. An increase in the levels of myostain may result in muscle protein wasting. Increased levels of myostatin have been reported in older men and women (31) suggesting that this could be one of the mechanisms leading to muscle atrophy in this age group (32).

The final possibility is that the myosin molecule suffers post-translational modifications with advanced adult age in men and women. Some investigators have shown this to be the case using the in vitro motility assay to measure the speed of the actin filament sliding on single myosin molecules (33,34,35). These modifications may result from biochemical processes such as glycation and oxidation that alter the molecular structure and leads to functional failure. It must be noted that these experiments measure filament-sliding speed and not force generation. Others, using paramagnetic resonance, have observed a reduction in the number of myosin heads in the strong-binding structural state in aged rat muscle during maximal isometric actions (36,37). The 30% age-related reduction in myosin heads in the force-producing state reported by Lowe and coworkers coincided very nicely with a 27% reduction in specific force seen in older animals in the same studies.

Other mediators and determinants of sarcopenia

A number of additional age-related alterations may be important mediators or determinants of muscle weakness and wasting in the elderly. Hormonal deficiencies such as a reduction in testosterone levels have been reported (38,39) and the incidence of hypogonadism, as reflected by low testosterone levels or reduced free testosterone index is higher in older age groups (40). Parallel changes have been observed in the insulin growth factor 1/growth hormone axis (38,39). These data suggest that sarcopenia is associated with an anabolic-deficient state that becomes progressively worse with age.

Another line of investigation proposes a role for the immunological system and suggests that inflammation can explain some of the alterations in skeletal muscle. The production of interleukin-6 (IL-6) by polymorphonuclear cells has been shown to be higher in elderly subjects (41). Further, physically active men have lower levels of IL-6 than less active men, emphasizing the potential preventive role of regular exercise (41). Finally, higher levels of the tumor necrosis factor α have been reported both, at the mRNA and protein content levels (42). Together, these observations support a role for inflammation and cytokines in the development of sarcopenia.

The loss of muscle cells would not represent a significant problem if skeletal muscle retained the capacity for regeneration and growth in old age. Recent evidence, however, shows a reduction in satellite cell population with increasing age in healthy men and women (43). Further, human satellite cells from older subjects studied in culture have a lower replicative potential (44). Because satellite cells are myogenic precursor cells that play an important role in cell repair and that can generate new muscle cells, this reduction may limit the ability of older muscles to repair itself and to regenerate in response to the age-related fiber loss.

The role of exercise

The development of disability in older people is a dynamic process and newly disabled people can recover functional independence (45). One of the most effective interventions shown to alter the process leading to disability is exercise training. In fact, exercise is the only intervention that has been shown to have significant anabolic effects, long-term functional benefits, and a very low risk profile. For the purpose of this article we will concentrate on exercise programs design to increase muscle strength otherwise known as resistance training, progressive resistance training, heavy resistance training, strength conditioning or simply strength training.

Some of the basic assumptions and principles of strength training in the elderly are: 1) muscle overload increases strength and results in muscle hypertrophy; 2) skeletal muscle of older men and women retain the capacity to respond to the training stimulus; 3) initial training load should be small to avoid injuries and to enhance compliance; 4) training loads must be progressively increased to maintain the training stimulus relatively constant; 5) activities of daily living using body weight as resistance (stair climbing, chair rises, and others) may be used to provide an activity-specific training stimulus; and 6) strengthening exercises must be done as part of a comprehensive training program including flexibility exercises and endurance type activities.

Many studies have been conducted during the last 15 years in different countries clearly demonstrating the physiological, health-related, and functional benefits of strength training in the elderly. The duration of these studies have ranged from 8 weeks to 2 years and although the exercise prescription has varied significantly among studies, almost all contain variations of the basic elements presented in Table 1. In the elderly population strength training can be conducted using the weight of a body segment as resistance or devices such as elastic tubing, free weights, pulley systems or more sophisticated equipment such as isokinetic machines. There is no scientific evidence to show that one type of equipment is more effective than the others. In practice, the selection depends more on factors such as access and availability of the equipment, comfort, cost, mobility level (can the individual travel to a gym?), and related considerations.

Table 1. *Strength training in older men and women: basic exercise prescription*

Device	Activities of daily living; Elastic or surgical tubing; Free weights; Special equipment (hydraulic, accomodating resistance, isokinetic)
Type	Progressive resistance including concentric and eccentric muscle actions
Frequency	2-3 days / week (on alternate days)
Duration	3-5 sets of 8-10 repetitions each; 1-3 minutes of rest between sets
Intensity	60-80% of the one repetition maximum

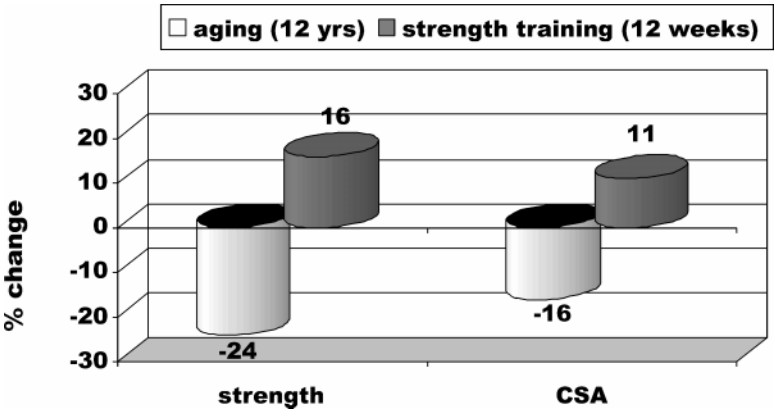

Fig. 6. *Isokinetic muscle strength (measured at 60 deg/s) and cross-sectional area (CSA, determined using computerized tomography) of the extensors of the knee: effects of 12 years of aging and 12 weeks of strength training (adapted from Frontera (48) and Frontera (59))*

Another important matter is the type of muscle action to be used for training. Many programs include a combination of concentric and eccentric actions. The latter has been shown to be quite effective and safe in this population (46). More recently, power training programs (as opposed to strength training) in which the speed of the movement plays an important role have become popular and shown to be effective and useful in community settings outside the laboratory or fitness centers (46,47).

Taken together, strength-training studies in older human have reported significant gains in several physiological parameters of muscle function including strength (higher relative gains when the testing and training modalities are similar), endurance, power, and force-velocity and power-velocity relationships. These changes have been accompanied by increases in whole muscle size and hypertrophy of both type I and II fiber types (48). It could be argued that the gains with strength training over 12 weeks are significant enough to partially offset losses in muscle strength and mass that have accumulated over 12 years of aging (Fig. 6).

The gains in strength are, in relative terms, much larger than the increases in muscle size. This observation combined with the fact that strength increases early in the absence of hypertrophy supports the notion that early strengthening is due to adaptations in the nervous system (for example a learning effect) and that hypertrophy is an important contributor only later (after 8-12 weeks) in the training process. More recently, improvements have also been reported at the single fiber level in diameter, maximal force production, and specific force (50,51). It is particularly impressive that even octogenarians and nonagenarians can experience positive adaptations to this type of exercise training and that study participants show continued gains even after many months of training.

An essential adaptation to strength training in both, men and women, is an increase in mixed muscle protein synthesis that is similar in nature to that reported in younger individuals (52,53). This includes proteins responsible for calcium handling during muscle contraction. Another important effect of strength training is an increase in the satellite cell proportion (number of cells relative to total myonuclei) reported by Roth and collaborators (54). Given the relevance of the satellite cells in muscle repair and regeneration, the functional implications of this finding deserve further study. Finally, given the potential role of cytokines in the development of sarcopenia it is encouraging that resistance training in frail elderly has been shown to reduce the levels of tumor necrosis factor α in skeletal muscle (42) thus reducing a catabolic stimulus.

One interesting question regarding the benefits of exercise training relates to the use of nutritional sup-

plementation. Nutritional intake is many times suboptimal in elderly persons and physical activity results in a higher protein intake than the typical recommendation for sedentary individuals. Some studies have suggested that the ingestion of amino acids alone or in combination with glucose after exercise enhances protein synthesis in young volunteers (55). At least one study suggests that protein intake, immediately after the exercise session, can enhance the benefits of strength training in the elderly (56). More research is needed to test this idea and to define the optimal combinations of exercise and nutrients and timing of ingestion for older men and women during training.

In addition to the physiological benefits mentioned above, strength training has been shown to have positive functional consequences. Although not all studies report improvements in functional performance, some have demonstrated increases in gait speed and ability to climb stairs for example. The nature of the functional tests may require larger sample sizes to detect significant differences. The health-related benefits of strength training in healthy individuals of all ages and patients with particular pathologies have been reviewed in a book edited by Graves and Franklin (57). In the elderly, health-related benefits of strength training include an increase in bone mineral density, a decrease in fall risk, a reduction in adipose tissue (improving body composition), enhanced cardiovascular performance in patients with coronary heart disease, improved function after stroke, reduced high blood pressure, improvements in insulin sensitivity, among others. It is clear that strength training should be considered not only as an effective way of enhancing muscle performance but also as a means to improve health and function in the elderly.

Concluding remarks

In conclusion, muscle impairment and dysfunction in the elderly is an important problem that must be understood and treated accordingly. Sports medicine professionals should get involved in the design of exercise training programs for older individuals. Strength training has many physiological and health-related benefits and could enhance quality of life in old age.

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