Origins and Clinical Relevance of Sarcopenia

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Abstract/Résumé

Sarcopenia is the loss of muscle mass and strength that occurs with normal aging. Because sarcopenia is not the result of a disease, it is seen in all aged adults. Sarcopenia markedly increases the risk of disability and loss of functional capacity in the elderly. The mechanisms underlying sarcopenia are complex and are reviewed here. It is not clear at this time which factors are most important in determining the severity or rate of development of sarcopenia. While progressive resistance training clearly can reverse and prevent sarcopenia, little is known about the mechanisms by which aged muscle adapts to training, or whether these adaptations reflect reversal of direct pathophysiological processes or compensation by activation of separate pathways from those leading to the deterioration in the first place. As populations in developed countries continue to age, diagnosing, treating, and preventing sarcopenia will be progressively more important to the health and well-being of modern societies.

La sarcopénie est définie comme une diminution normale de masse et de force musculaires au cours du vieillissement. Comme la sarcopénie n’est pas une maladie, on l’observe chez toutes les personnes âgées. La sarcopénie accroît notablement le risque d’incapacité et la perte de capacité fonctionnelle chez la personne âgée. Les mécanismes à la base de ce processus sont complexes et sont analysés ci-après. Les facteurs les plus importants impliqués

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dans le développement de la sarcopenie ne sont pas encore connus. Bien que l’entraînement à la force puisse renverser le processus et prévenir la sarcopenie, on ne connaît pas très bien les mécanismes d’adaptation du muscle âgé avec l’entraînement et on ne sait pas si les adaptations correspondent à une inversion directe du processus pathophysiologique ou si ces adaptations se manifestent par l’activation de mécanismes qui diffèrent de ceux des processus de détérioration habituelle. Au fur et à mesure que les populations des pays développés vieillissent, le diagnostic, le traitement et la prévention de la sarcopenie seront des actions de plus en plus importantes pour la santé et le bien-être des sociétés modernes.

Sarcopenia, from the Greek meaning poverty of flesh, was a term proposed by Irwin Rosenberg to indicate the loss of muscle mass and strength caused by normal aging (Rosenberg, 1989). It is distinct from muscle loss (cachexia) caused by inflammatory disease or from the weight loss and attendant muscle wasting caused by starvation or advanced disease (Roubenoff et al., 1997a). A truly age-driven phenomenon should be universal with advanced age. Indeed, reduced muscle mass and strength are evident in all elderly persons compared to young, healthy, physically active young adults. If the sarcopenia progresses beyond a threshold of functional requirements, it leads to disability and frailty, and this can occur independently of any disease-induced frailty. Of course, superimposed illness will accelerate the loss of muscle mass and thus increase the risk of disability, frailty, and death.

There is no absolute level of lean mass, body cell mass, or muscle mass at which one can definitely say that sarcopenia is present. However, it is important to consider two important and generally agreed-upon concepts in relation to lean body mass. First, there is a direct structure-function link between muscle mass and strength, in that more muscle generally equals greater strength and vice versa. However, the function defining the relationship between muscle loss and strength loss is not the same as that applying to muscle and strength gain. Pharmacologic interventions such as growth hormone or testosterone, which increase lean mass (and evidently muscle mass as well) do not alter strength much, while progressive resistance training, which causes large increases in strength, can do so with little evident muscle hypertrophy, at least in the first few months of training. Thus, defining sarcopenia solely on compositional terms may be useful and attractive for research purposes, but it may be simplistic in explaining functional changes caused by treatment of sarcopenia.

Second, there is reasonable evidence that there is a limit on how much lean body mass can be lost before death supervenes. The available data, based on starvation (Winick, 1979), AIDS patients (Kotler et al., 1989), and critical illness (Tellado et al., 1989), suggest that loss of more than about 40% of baseline lean mass is fatal. Baseline is a slippery concept here, because again absolute mass is not explanatory—basketball players do not necessarily outlive jockeys—but rather the amount of loss as a function of the baseline mass that the individual started with. Reference Man and Woman are one benchmark, based on a few cadaver studies in generally healthy persons (Ellis, 1990). Kehayas and colleagues (1997) defined baseline as the mean for adults aged 20–30 years; no healthy subjects were found below approximately 70% of that standard, and there was a steady decline in body cell mass for both men and women across age groups between 30 and 100 years.
The latter point also raises the issue of the importance of sarcopenia as an indicator of reduced protein stores for times of stress. It is well accepted that during illness, gluconeogenesis increases in importance, while ketogenesis is relatively suppressed, so that protein is burned for energy in excess of the levels seen in starvation adaptation. Given the anorexia caused by acute illness, and by the iatrogenic limitation on dietary intake that often obtains in hospitals, endogenous protein stores are crucial in determining the availability of metabolic substrate to cope with the illness and thus the ability to survive it. Therefore, it is no wonder that elderly, sarcopenic patients fare worse than young, healthy adults for almost all diseases. Tellado and colleagues (1989) have shown that measurement of body cell mass was the only independent determinant of survival in intensive care unit patients in multivariate analysis, removing the significance of univariate predictors such as albumin, age, and even diagnosis. Thus, the metabolic significance of sarcopenia in illness should be considered independently of its functional impact during times of better health, as both are important to the survival and well being of elderly persons.

**Prevalence of Sarcopenia**

There is one population-based study of the prevalence of sarcopenia with advancing age. Data are available from the New Mexico Elder Health Survey by Baumgartner and colleagues (1998), who measured appendicular muscle mass by dual-energy x-ray absorptiometry (DXA) in 883 elderly Hispanic and non-Hispanic white men and women. The subjects were selected randomly from the Health Care Financing Administration (HCFA) Medicare listing for Bernalillo County, New Mexico. A total of 2,200 subjects were sampled; 534 had died, moved, could not be contacted, or were ineligible. Of the 1666 eligible subjects contacted, 1,130 (67.8%) completed the home interview and 883 (53%) underwent DXA. Sarcopenia was defined as a muscle mass 2 or more standard deviations below the mean for young healthy participants in the Rosetta Study, a large cross-sectional study of body composition in New York. The prevalence of sarcopenia by this definition increased from 13–24% of persons under age 70 to over 50% of those over age 80 years.

Kehayias and colleagues (1997) found that the quality of the lean body mass, defined as the ratio of cell mass (measured by whole body potassium counting) to lean mass (measured by hydrodensitometry or neutron activation), declined with age in a cross sectional analysis. These data suggest that sarcopenia is universal, and indeed this would be consistent with an age-related phenomenon and complement the data of Baumgartner and colleagues (1998) where a cutoff was used to define sarcopenia. Gallagher and colleagues (1997) have shown that the cross-sectional change in appendicular muscle mass measured by DXA parallels the decline in total body cell mass measured by total body potassium (TBK), the reference method for this compartment. Cross-sectional studies of muscle fiber distribution have suggested that the loss of muscle is largely confined to type II fibers, the fast twitch cells that are most responsible for strength and anaerobic, short-term movements (Lexell, 1995).
However, one cannot easily come to conclusions about the phenomenology of sarcopenia based on cross-sectional data. Longitudinal data are harder to come by, but a few studies do exist. Forbes and Reina (1970) reported longitudinal change in total body potassium in 18 men and 2 women aged 22–53 (mean 33 yr), followed for a mean of 7.8 years. There was a decline in lean mass of 0.25 kg/yr over this time span. Flynn and colleagues (1989) measured body cell mass by TBK at two-year intervals over 18 years in a group of 564 male and 61 female faculty and employees of the University of Missouri. Lean mass (calculated from TBK) declined in the men who were first measured after age 40, with a median loss of 0.3 kg/yr. No significant change was seen in women, although this is likely to be due to their smaller sample size, as the point estimates for change were negative in this group after age 50. These observations raise the question of whether menopause accelerates sarcopenia as it does osteopenia. A small study by Poehlman and colleagues (1995) suggests that this is indeed the case, as women who experienced menopause had a much greater decline in lean body mass, gain in fat mass, and drop in metabolic rate than did women of similar ages who continued to have menses.

A recent study by Forbes (1999) highlights the importance of weight change in determining change in muscle mass with age. Using longitudinal data from various sources, Forbes found that subjects who lost weight lost more lean mass than those whose weight was stable or rising. We have seen similar results in a 10-year follow-up study (Hughes et al., unpublished).

As noted earlier, these data all define sarcopenia in terms of its compositional rather than functional (strength) aspect. However, there are data suggesting that the decline in strength with age exceeds the decline in lean mass. Kallman and colleagues (1990), using the Baltimore Longitudinal Study on Aging data, showed that older men have a weaker grip strength, and young men have a stronger grip, than would be predicted by arm muscle mass alone. This finding may be partly limited by reliance on anthropometric measures of muscle mass, which are relatively imprecise; data using CT scans are discussed below. Nevertheless, 71% of men aged 40–59 and 85% of men over age 60 had a decline in strength over a 9-year follow-up, again suggesting the universal nature of sarcopenia at the functional as well as structural level.

Other studies of change in muscle strength over time have shown declines (Bassey and Harries, 1993; Rantanen et al., 1997), no change (Greig et al., 1993), or even gains (Bassey and Harries, 1993; Rantanen et al., 1997) in strength over 4–25 years. A reduction in type II muscle fibers has been shown in some studies, but no change was found in others (Klitgaard, Bergman, et al., 1990; Klitgaard, Zhou, and Richter, 1990; Klitgaard, Zhou, Schiaffino, et al., 1990). Recently Frontera, Hughes, and colleagues (2000) examined changes in thigh skeletal muscle mass by CT scanning and strength by isokinetic dynamometry in 9 healthy men studied on two occasions 12 years apart. Thigh extensor and flexor cross-sectional area declined by 16.1% and 14.9%, respectively, while strength fell by 20–30%. However, specific force (strength/cross sectional area) did not change, and loss of muscle explained 50% of the variance in strength loss in the knee extensors. There was also a decline in the percentage of type I fibers on histologic examination of biopsies.
of the vastus lateralis muscle (from 60% to 42%) but no change in the mean area of either type I or type II fibers. The capillary/fiber ratio was also significantly reduced (1.39 vs. 1.08, p < .05). These data indicate that longitudinal change in the amount of muscle is strongly linked to change in strength in healthy elderly men.

Relevance of Sarcopenia

There is a strong direct relationship between muscle mass and strength. Thus, sarcopenic persons are weaker than persons with normal muscle mass. In reality, there may be a feedback loop between muscle mass and function that can be driven in either a positive (healthy) or a negative (disabling) direction. In the positive direction, people who are fit tend to be physically active, and people with chronic diseases who enter an exercise program demonstrate an increase in their physical activity outside of the training program. Studies from our laboratory have previously shown this for adults with rheumatoid arthritis (Rall et al., 1996a, 1996b), HIV infection (Roubenoff et al., 1997b), as well as for frail elderly nursing home residents (Fiatarone et al., 1994). In the negative direction, as people become weaker, either because of disease or because of age-related sarcopenia, the proportion of maximal effort required to perform daily tasks increases, so that it becomes progressively uncomfortable to perform these tasks, and they are abandoned. While both cardiopulmonary fitness and muscle strength are important determinants of functional capacity in frail, elderly persons with advanced sarcopenia but without heart failure or emphysema, muscle weakness may be more limiting than aerobic fitness (Shephard, 1987). Weakness in turn leads to further disuse, as people avoid activities that are uncomfortable. Thus, reduced physical activity follows loss of muscle mass, and then accelerates it by removing the trophic stimulus of the activity. The improved survival and reduced disability of elderly athletes who remain physically active suggest that such a vicious cycle is avoidable under some circumstances (Paffenbarger et al., 1986, 1993). More importantly, perhaps, the ability to reverse these changes with PRT suggests that they are modifiable effects of aging.

The New Mexico study (Baumgartner et al., 1998) gives an idea of the relationship between sarcopenia and functional status. Sarcopenic women had 3.6 times higher rates of disability, and men 4.1 times higher rates, compared to study participants with normal muscle mass. There were significantly greater risks of use of cane or walker, and a history of falling, in the sarcopenic subjects as well. These odds ratios were significant after adjustment for age, race, obesity, income, alcohol intake, physical activity, current smoking, and comorbidity. Thus, sarcopenia is independently associated with important health outcomes and disabilities in this relatively healthy, ambulatory population.

Mechanisms Underlying Sarcopenia

It is unlikely that sarcopenia has only a single cause. We have approached the problem as a multifactorial one with a range of possible explanations, in the expectation that several, if not many, factors will turn out to be important when
sarcopenia is better understood. Figure 1 shows our current understanding of important etiologic factors. Several have been addressed over the past few years by studies and have thus risen or fallen in terms of their relative importance.

CEN tRAL NERVOUS SYSTEM

Our current concept is that loss of alpha motor units from the spinal cord is a critical feature of sarcopenia that differentiates it from cachexia or wasting. Loss of neurons is a continuous process throughout life and is currently considered irreversible. Older adults have larger motor units than young adults, as the dropout of neurons and muscle cells is partially compensated for by the “adoption” of muscle fibers by surviving neurons. These motor units are less efficient as a result and in the extreme case can cause tremor as well as weakness (Enoka, 1997). Clearly neuronal death can and does lead to muscle atrophy, as noted in strokes and peripheral neuropathic conditions. It is highly likely that this change also occurs in sarcopenia, although it is possible that the primary event is loss of muscle fibers, with subsequent “dying back” of the neuron.

The change in strength in response to exercise that occurs in the first few weeks after beginning a training program is thought to occur via changes in CNS output to the motor units, as there is no change in muscle mass during this time (Akima et al., 1999). The CNS may respond to training by increasing neuronal firing rates, improving the recruitment of motor units in response to the signal to contract a muscle, and by increasing the innervation of muscle over time. Additional evidence for the importance of the CNS in determining strength (if not muscle
mass) comes from the cross-education effect seen in contralateral muscles when only one leg or arm is trained. The increase in strength on the untrained side is often as much as half of that seen on the exercised side (Sale, 1988). Even imagining exercise can significantly increase strength (Herbert et al., 1998). Finally, the specificity of training is such that the greatest strength gains occur at or near the angular velocity and joint angle at which training is done: strength gains fall off markedly above and below this target (Fleck and Kraemer, 1997).

Intrinsic Changes in Muscle Contractility and Muscle Cell Biology

There is a decline in the specific force produced by single muscle cells from elderly adults (muscle quality), in addition to the decline in number of muscle cells with age (muscle mass; Frontera, Suh, et al., 2000). A handful of studies of the contractile properties and biochemical composition of human single muscle fiber have been published (Fitts et al., 1989; Galler et al., 1997; Harridge et al., 1995; Klitgaard, Bergman, et al., 1990; Klitgaard, Zhou, and Richter, 1990; Klitgaard, Zhou, Schiaffino, et al., 2000; Lankford et al., 1995; Larsson et al., 1995, 1996, 1997; Larsson and Moss, 1993; Widrick et al., 1996, 1997). Only two studies (Larsson et al., 1995; Larsson and Moss, 1993) have included women (one in one study and three in another) and, to our knowledge, only one group of researchers included any elderly subjects, a total of only four men (Larsson et al., 1997). Three studies have examined the effects of physical activity levels or exercise training on force production, maximal shortening velocity, and the expression of myosin heavy and light chains in single muscle fibers, but again only one (Larsson et al., 1997) included elderly subjects. In that study, however, the sample size (two physically active and two sedentary men) was small and the results must be interpreted with caution. The type of exercise in two of the three studies (Fitts et al., 1989; Widrick et al., 1996) was aerobic (swimming or running), and of the two active subjects in the third study (Larsson et al., 1997), only one was involved in regular strength training sessions. These studies demonstrate the response of muscle fibers to various types of aerobic exercise training by the adaptability of shortening velocity (Fitts et al., 1989; Widrick et al., 1996) and maximal force (Widrick et al., 1996). Further studies are needed to define the extent to which single muscle fibers adapt to strength training, and whether this adaptation is modified by age. Finally, the relationship between these adaptations and changes in whole muscles and functional tasks important for independent living must be evaluated.

HUMORAL FACTORS

Many hormones and cytokines have metabolic effects that can alter muscle mass and function. Anabolic hormones such as growth hormone (GH), testosterone, and estrogen are reduced with age, and the withdrawal of their trophic effects may lead to muscle atrophy and sarcopenia. As mentioned earlier, there is evidence of accelerated loss of lean mass (and gain in fat) around menopause, suggesting that estrogen could have a role in supporting muscle mass (Poehlman et al., 1995). In addition,
estrogen and testosterone have been shown to suppress catabolic cytokine expression in animal models and may have an indirect role in modulating subclinical inflammation in aging.

Because the decline in GH begins in the fourth decade of life and parallels the decline in lean mass, it is intuitively appealing that loss of GH could act as a central coordinating mechanism driving the loss of muscle in aging (Rudman et al., 1990). If this is so, it follows that people with lower GH secretion should have lower lean body mass, and that this relationship should extend into middle and old age. However, we have recently shown that this is not the case: postmenopausal women with the lowest 24-hour GH levels had the highest body cell mass, not the lowest (Roubenoff et al., 1998b). In fact, the relationship between GH and lean mass is highly confounded by fat mass, and there is some evidence that leptin suppresses GH production. In addition, we have now shown that patients with rheumatoid arthritis, a model for inflammatory cachexia and muscle loss, do not have lower GH levels than age- and BMI-matched healthy controls (Rall and Roubenoff, unpublished observations). As a result, it appears that GH is not central to the development of sarcopenia.

Activation of the immune system leads to production of inflammatory cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), and interleukin-6 (IL-6), which can cause amino acid export from muscle (Baracos et al., 1983; Clowes et al., 1983; Tsujinaka et al., 1996). Such a situation has been clearly demonstrated for acute illness and for chronic inflammatory conditions such as rheumatoid arthritis and HIV infection (Roubenoff et al., 1994). There is evidence that aging is associated with immune senescence that includes loosening of the tolerance, which allows a healthy immune system to correctly identify “self” from “non-self” antigens and avoid targeting self antigens. For example, autoimmune phenomena such as production of rheumatoid factors (antibodies against other antibodies) and anti-nuclear antibodies increase with age, as does the prevalence of most autoimmune disease (Vaughan, 1980).

These changes suggest, but do not prove, the theory that aging is associated with a subclinical inflammatory state, which leads to increased production of catabolic cytokines and with it an increased rate of muscle catabolism and thus sarcopenia. We have shown that, consistent with this idea, there is an increase in IL-6 and indirect evidence of increased IL-1 (measured as increased production of the natural neutralizer of IL-1, IL-1 receptor antagonist) produced by peripheral blood mononuclear cells from elderly participants in the Framingham Heart Study compared to young controls (Roubenoff et al., 1998a).

LIFESTYLE FACTORS

Finally, there is clear evidence that sarcopenia is worsened with disuse, and that physical inactivity leads to faster and greater muscle loss than seen in physically active elders. However, even master athletes develop sarcopenia, so it is not completely prevented by exercise, and remains a result of aging and not purely of disuse. Nevertheless, the overwhelming trend in industrial and post-industrial societies is toward a decline in physical activity with advancing age, and there is no
doubt that this sedentary lifestyle promotes loss of muscle and gain in fat, with their attendant morbidity and mortality.

References


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