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REVIEW ARTICLE

Sarcopenia: Current Concepts

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Sarcopenia, the loss of muscle mass and strength with age, is becoming recognized as a major cause of disability and morbidity in the elderly population. Sarcopenia is part of normal aging and does not require a disease to occur, although muscle wasting is accelerated by chronic diseases. Sarcopenia is thought to have multiple causes, although the relative importance of each is not clear. Neurological, metabolic, hormonal, nutritional, and physical-activity–related changes with age are likely to contribute to the loss of muscle mass. In this review, we discuss current concepts of the pathogenesis, treatment, and prevention of sarcopenia.

SARCOPENIA, from the Greek for "poverty of flesh," is a term coined by Rosenberg (1) in 1989 to denote the decline in muscle mass and strength that occurs with healthy aging. Sarcopenia can be thought of as both a process and an outcome. As befits an age-related trait, the process of sarcopenia is universal with age. Whether the outcome of sarcopenia becomes a clinically evident problem depends on many factors, including the starting level of muscle mass and the rate of its decline, both of which are dependent on many factors, including the individual's habitual level of physical activity. Like osteopenia, the determinants of sarcopenia are likely to be a combination of genetic and environmental factors, with a complex series of interactions between them. Unlike bone mass loss at menopause, however, which is primarily determined by estrogen status, muscle homeostasis is dependent on many anabolic and catabolic signals. Thus, it follows that the etiology of sarcopenia will turn out to be multifactorial and resist scientific reductionism in the classic sense. In this review, we will describe current understanding of the prevalence of sarcopenia, its pathogenesis, etiology, and treatment.

The Nature of Sarcopenia

As noted previously, all humans lose muscle mass and function as they age. This is true even of master athletes who, although they continue to be physically active and perform at levels well above those of sedentary adults, demonstrate a decline in lean tissue with age (2,3). Similarly, aerobic capacity declines with age, even in active runners and swimmers (2), reflecting both a decline in muscle and in cardiopulmonary reserves (4). Cross-sectional data also show that body cell mass is systematically lower in older adults than in middle-aged or young adults (5–7) and so is strength (8,9). The decline in cell mass with age is largely due to loss of muscle mass (10).

In addition, there is a decline in the "quality" of lean body mass, as cell mass declines faster than intercellular connective tissue and water (11). That is, a pound of lean tissue from an elderly person is systematically different than a pound of lean tissue from a young person, in that it has relatively less intracellular tissue and relatively more extracellular tissue (11). In men aged 20 to 29 years, cell mass represents 59% of lean body mass; in contrast, in men aged 80 to 89 years, cell mass is only 46% of lean mass (12) and lean mass itself has also fallen significantly. Thus, there is both a quantitative and a qualitative change in lean body mass with age. However, the change in cell mass to lean mass ratio cannot be detected by density-based methods, such as underwater weighing, because the density of lean tissue remains stable with age (13). However, sarcopenia is really a disorder of muscle cells, which drive the decline in body cell mass. At the muscle level, as at the total body level, there is both quantitative and qualitative decline. The quantitative loss occurs both by loss of myocyte numbers and by reduction in the protein content of the remaining muscle cells. As muscle quantity falls, it is matched by a decline in "muscle quality," defined functionally in terms of the strength of muscle (14,15). This occurs both on a macroscopic level (i.e., the force produced by a muscle per unit area, measured using computed tomography or magnetic resonance imaging) and on a cellular level (the force produced by single muscle fibers adjusted for fiber size) (14,16,17).

Longitudinal studies are fewer than cross-sectional ones and, by and large, only report on white men, but those that exist also show that over a period of 5 to 18 years, total body potassium, the reference measure of body cell mass that is largely driven by muscle mass, declines in a linear fashion (3,18). An open question at this time is whether menopause accelerates muscle loss in women the same way that it does bone loss. Acceleration of lean tissue loss is seen during the menopausal years in women (19,20). Poehlman and colleagues (20) demonstrated a decline in resting metabolic rate, physical activity, and lean mass, and an increase in fat mass, waist-to-hip ratio, and fasting insulin levels during 6 years of follow-up in 18 women who were premenopausal at baseline but experienced menopause during follow-up. No such changes occurred in 17 other women of comparable age who remained premenopausal. Although these results have not been replicated in larger samples, they do suggest that the acute changes in estrogen availability and effectiveness may have a profound role in the accelera-

tion of sarcopenia during the menopausal years. This suggests that this is the crucial time to concentrate on interventions that will attenuate muscle loss in women.

In Figures 1 and 2, we have summarized the findings of several studies evaluating the longitudinal changes in body composition that occur at various ages in men and women. The pattern in men shows a tendency to gain fat and lean mass through their 40s, followed by a trend toward weight loss, resulting in the loss of both compartments after age 60 years (Figure 1) (21–28,111). Studies in women show consistent gains in fat across the age spectrum (Figure 2), but there are few data describing the body composition changes in women older than 60 years of age (20,21,23,27,29–31,111). Note that nearly all these data were obtained in Caucasian adults, and little is know about racial and ethnic differences in sarcopenia.

At the tissue level, aging is associated with a decline in the synthesis of muscle protein and, in some studies, in whole-body protein turnover, after adjustment for lean body mass (32). The decline in protein synthesis is not uniform for all proteins, however. There is a greater decline in mitochondrial protein synthesis and myosin heavy-chain synthesis than in sarcoplasmic protein synthesis, which actually increases with age (33,34). In contrast to the increased protein turnover seen with inflammatory conditions, aging per se is probably more of a problem of synthetic failure than of excess catabolism (35).

Prevalence of Sarcopenia

If sarcopenia is indeed a ubiquitous process, then its prevalence should be 100%. However, if one dichotomizes the otherwise continuous process of muscle loss according to a boundary condition, such as 2 *SD* below the mean appendicular muscle mass for young healthy adults, one can determine the prevalence of sarcopenia at this level of severity. Data are available from the New Mexico Elder Health Survey by Baumgartner and colleagues (36), who measured appendicular muscle mass by dual-energy x-ray absorptiometry in 883 randomly selected elderly Hispanic and white men and women. Sarcopenia was defined as a muscle mass $\geq$2 *SD* below the mean for young healthy participants in the Rosetta Study (37), a large cross-sectional study of body composition in New York. The prevalence of sarcopenia by this definition increased from 13% to 24% of persons aged 65 to 70 years to over 50% of those older than 80 years of age. The prevalence increases in both men and women, but is actually higher in men older than 75 years of age (58%) than in women (45%). The higher prevalence of sarcopenia in men in this study is consistent with the greater change in the quality of lean mass that occurs in men, as discussed earlier (12). Nevertheless, conventional wisdom has it that sarcopenia is a greater public health problem in women, because women live longer and have higher total rates of disability (38). However, the results of Baumgartner and colleagues (36) and of Ellis (12) suggest that the biological process of sarcopenia occurs in both sexes, perhaps to a greater extent in men.

Sarcopenia and Physical Function

Although we have focused largely on the decline in muscle mass with age, what matters most to elderly persons is their ability to function. The New Mexico study (36) lends insight into the relationship between sarcopenia and functional status. Sarcopenic women had 3.6 times higher rates of disability, and men had 4.1 times higher rates, compared with 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.

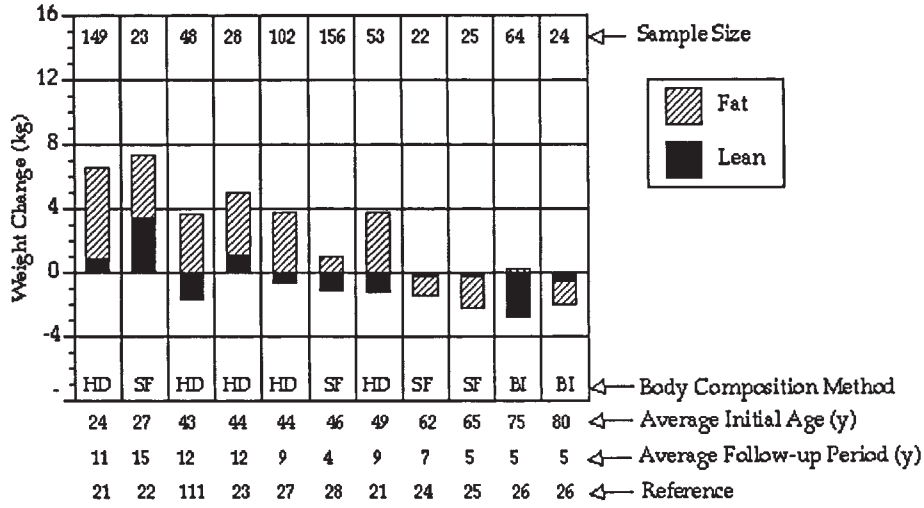

Figure 1. Absolute fat and lean changes per decade as a function of age in men. Studies are ordered by age at baseline. All changes are standardized to 10-year follow-up. HD = hydrodensiometry; SF = skinfold; BI = bioimpedance.

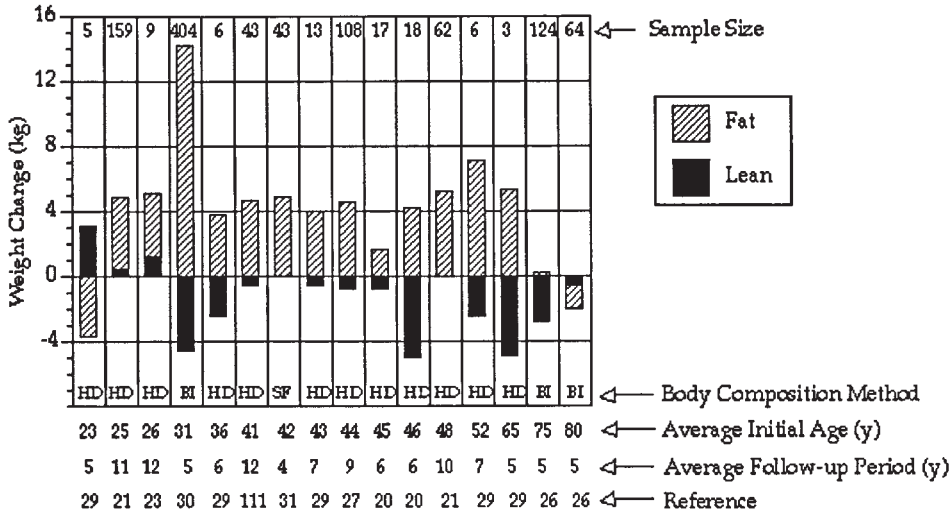

Figure 2. Absolute fat and lean changes per decade as a function of age in women. Studies are ordered by age at baseline. All changes are standardized to 10-year follow-up. HD = hydrodensiometry; SF = skinfold; BI = bioimpedance.

Although the simplest conceptual framework is that muscle loss causes weakness, which in turn causes loss of physical functioning, this may be an oversimplification. Clearly, in advanced sarcopenia, muscle weakness is the limiting factor that determines functional capacity and performance. This is commonly the case in nursing homes (39,40). However, in milder sarcopenia, such as is seen in ambulatory persons, the relationship between structure and function may be more complex. For example, in young adults, the changes in muscle strength and size seen in response to resistance training or inactivity are not always related to each other (41,42). Furthermore, resistance exercise can lead to large improvements in function with little or no change in muscle mass, or even in strength (43). Recent studies also suggest that an important effect of sarcopenia is the loss of power (work performed per unit of time) as well as strength (44,45).

Mechanisms of Sarcopenia

Although the causes of sarcopenia are not yet clearly understood, there are many potential mechanisms that have been investigated to greater or lesser extent (Figure 3). Overall, aging can be thought of as the withdrawal of, or resistance to, several anabolic stimuli to muscle (central nervous system [CNS] input, growth hormone, estrogen, testosterone, dietary protein, physical activity, insulin action) and possibly the development of several catabolic ones (subclinical inflammation, production of catabolic cytokines, such as tumor necrosis factor-α [TNF-α], interleukin-6 [IL-6], and possibly interleukin-1β [IL-1β; identified directly or indirectly via increase in its antagonist protein, IL-1 receptor antagonist, IL-1Ra]). Whether any one of these is more important than the others, or even paramount, remains to be seen.

If there is a single most important cause of sarcopenia, it is probably the loss of α-motor neuron input to muscle that occurs with age (46). Since innervation is crucial to the maintenance of muscle mass as well as strength, it is likely that this decline is at the heart of sarcopenia. Neuron loss with age occurs in many places in the CNS, including the primary motor cortex, subcortical nuclei, cerebellum, and hippocampus. However, the recent data suggest that the degree of neuronal loss in aging is more restricted, and older neurons may retain more plasticity, than previously thought (47,48). It is also not known what role physical activity, hormone levels, or genetic factors have in preserving motor unit numbers in elderly persons.

Of the hormonal anabolic inputs that decline with age, the sex steroids are probably the most important. Both estrogen and testosterone have important anabolic effects on muscle, although the effect of estrogen may also be mediated through its conversion to testosterone (49). In women, the decline in estrogen is well defined during menopause, although in men, decline in testosterone is more variable in its speed and trajectory (50). Between the ages of 25 and 75 years, mean serum testosterone levels decline by about 30% and free testosterone levels decline by up to 50%; the declines continue as age becomes more advanced (50,51). Furthermore, both estrogen and testosterone can inhibit production of catabolic cytokines, such as IL-1 and IL-6 (52–54), suggesting that loss of these hormones with age could have both direct and indirect catabolic effects on muscle.

Growth hormone (GH) begins to decline in the fourth decade and declines progressively over the ensuing years. It is not clear that GH deficiency is an important cause of sarcopenia, however. Roubenoff and colleagues (55) found that among postmenopausal women, 24-hour GH secretion was highest in those with the lowest body cell mass, which is the opposite of what is predicted by a straightforward GH-deficiency hypothesis. GH production is known to be lower in obese persons, and it is likely that fat mass is a major confounder of the relationship between GH and sarcopenia. Thus, Roubenoff and colleagues found a strong inverse relationship ($r = -.67$, $p < .006$) between serum leptin level, an index of body fat, and GH production. Similar suppression of GH production has been noted in obese children, in whom higher leptin was associated with lower GH re-

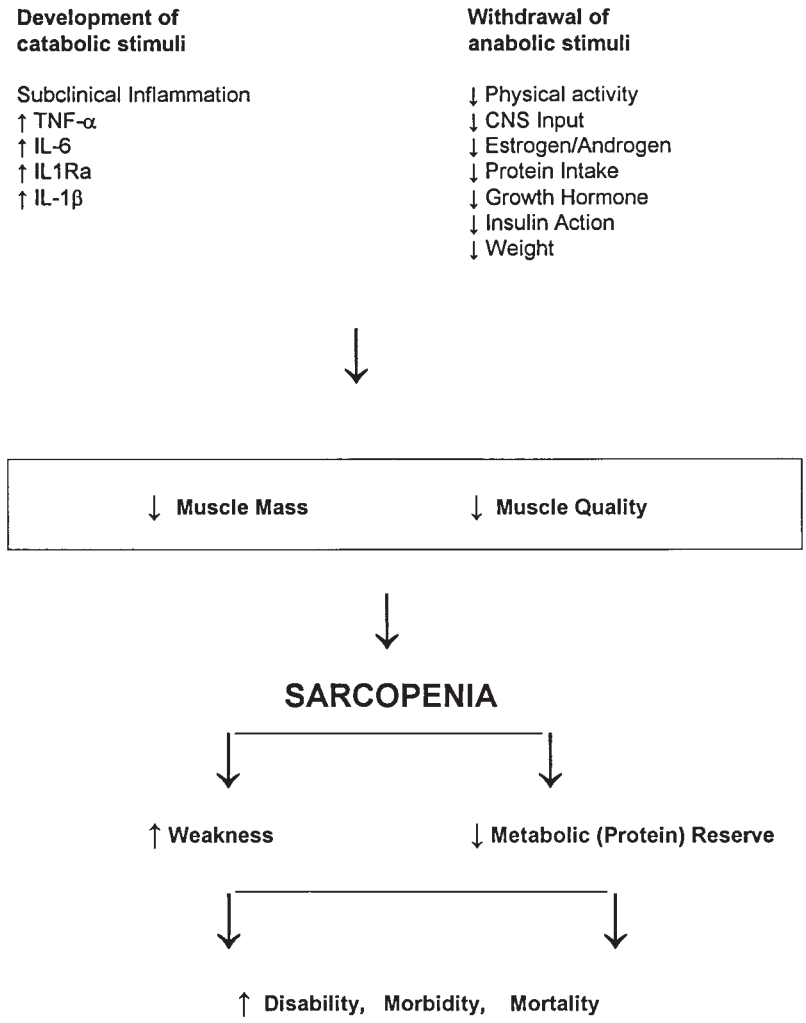

Figure 3. Potential etiologic factors in the development of sarcopenia.

sponse to stimulation with GH-releasing hormone (GHRH) (56), although higher leptin was found in children with GH deficiency due to a defect in the GHRH receptor (57). In contrast, animal data suggest that leptin stimulates GH secretion in rats (58). In vitro data show that short-term (30-minutes) incubation of pituitary cells with leptin increases GHRH-stimulated GH secretion, although longer (24-hour) incubation suppresses it (59). Thus, the role of leptin in modulating the decline in GH seen with aging remains unclear.

Insulin, one of the major anabolic hormones with respect to muscle, also appears to decline in its action as people age. In the pre-insulin era, diabetes mellitus was associated with severe muscle wasting, and insulin increases body cell mass and body nitrogen in diabetics (60,61). Insulin's action on muscle appears to be primarily one of inhibiting protein breakdown, although it has been difficult to demonstrate a sustained effect of insulin in increasing muscle protein synthesis (62,63). It is not clear to what extent loss of the anticatabolic effect of insulin occurs in nondiabetics as they age, but insulin resistance could certainly play a part in the development of sarcopenia. Insulin resistance increases with age, fat mass (especially visceral fat mass), and physical inactivity (64–68). In addition, TNF-α has been shown to increase insulin resistance by dissociating the heterodimers of the insulin receptor, and serum TNF increases with obesity, if not directly with age (69,70). The reduction in insulin action that occurs in many elderly people because of these multiple etiologies may well have a procatabolic effect on muscle.

Concurrent with the withdrawal of endocrine anabolic stimuli in elderly persons is a loss in body weight. General patterns of weight gain are observed in men and women up to approximately age 60, after which time a greater percentage of individuals lose weight (71–74). Loss of body weight in older adults may be caused by many factors, some of which may be part of biological aging, but others are surely related to disease. Weight loss may reflect changes in appetite, dentition, taste, depression, comorbidity, poverty, isolation, constipation, and other factors. Regardless of cause, however, loss of lean mass is a necessary result of this age-related weight loss.

Physical activity declines with age, especially in developed societies, depriving muscle of what is probably its most important environmental stimulus to maintaining its mass and function. Elderly persons who are less physically

active have less strength and lean mass than do active elderly individuals and live less long (2,75–78), but is this cause or effect? It may be that the persons who are the least physically active are genetically deprived of adequate muscle mass, and the relationship between physical activity and body composition is not a causal one. Perhaps the most convincing evidence of the importance of physical activity comes from the demonstrated capacity of exercise to reverse sarcopenia (as discussed later). However, there is also clear evidence from studies of bed rest and microgravity that muscle disuse causes a large decline in muscle size and strength, even with adequate protein and energy intake (79–81).

The role of protein deficiency in the development of sarcopenia is more problematic. Castaneda and colleagues (82) have shown that eating half the recommended dietary allowance (RDA) of protein of 0.8 g/kg/d led to significant declines in strength, body cell mass, and insulin-like growth factor-1 (IGF-1) levels in postmenopausal women. However, it is not known if modest reductions in dietary protein intake also contribute to sarcopenia. However, such reductions are common. The USDA Survey of Food and Nutrient Intakes by Individuals (www.barc.usda.gov/bhnrc/foodsurvey/home.htm) shows that approximately one third of men and women older than 60 years of age eat less than 0.8 g/kg of protein per day, and approximately 15% eat less than 75% of the RDA. Among Hispanics, the fastest-growing minority group in the United States, approximately 30% of adults older than 20 years of age do not meet the RDA for protein, and 13% consume less than 75% of the RDA (www.barc.usda.gov/bhnrc/foodsurvey/home.htm). These data are surprising, given that the average intake of protein in the United States is nearly 1.2 g/kg/d, or 50% above the RDA level (83). In addition, it is not clear whether the RDA for protein is adequate for elderly persons. Studies are divided on this issue, and more research is needed before this question can be settled (84–89).

In addition to the decline in anabolic stimuli that occurs with age, there is some evidence of an increase in catabolic stimuli as well. For example, Roubenoff and colleagues (90) found that production of IL-6 and IL-1Ra by peripheral blood mononuclear cells (PBMC) from ambulatory elderly participants (72–92 years old) in the Framingham Heart Study was significantly higher than from younger controls (<40 years old) (90). IL-6 is a mildly catabolic cytokine that also has anti-inflammatory properties (91), while IL-1Ra is a pure cytokine antagonist without catabolic effects. There was no difference in the production of the more catabolic cytokines, TNF-α or IL-1β. However, plasma TNF has been shown to be increased and may reflect production of the cytokine by adipocytes (92). As noted previously, TNF is especially important because it has been implicated as a cause of insulin resistance (69,70). These data suggest several points: (i) unlike the situation in cachexia caused by inflammatory or infectious disease, aging is not associated with excess PBMC production of IL-1 or TNF; thus, if there is a role for catabolic cytokines in the development of sarcopenia, it is likely to be a more gradual and mild problem than in acute illness; (ii) the increase in IL-6 and IL-1Ra may be an attempt to downregulate an upstream inflammatory stimulus that is catabolic to muscle and not a direct cause of sarcopenia; and (iii) the cytokine response seen may differ by compartment, with different regulatory and functional roles for cellular and circulating cytokines.

How can we rank the importance of these possible contributors to sarcopenia? To date, no single study has attempted to develop an integrated model with adequate data on all the variables listed previously. However, Baumgartner and colleagues (93), using the New Mexico data, recently performed a cross-sectional analysis evaluating the relative contributions of physical activity, dietary energy and protein, health status, serum testosterone, estrone, sex hormone-binding globulin, IGF-1 in 121 men and 180 women aged 65 to 97 years. The authors found that muscle mass in men was significantly associated with free testosterone (partial $R^2 = .11$, $p < .004$), physical activity ($R^2 = .05$, $p < .002$), heart disease ($R^2 = .03$, $p < .01$), and IGF-1 ($R^2 = .02$, $p < .04$). In women, however, muscle mass was only associated with total fat mass ($R^2 = .10$, $p < .0001$) and physical activity ($R^2 = .04$, $p < .001$). Grip strength was also measured and was associated with muscle mass in both sexes and weakly with IGF-1 in women ($R^2 = .02$, $p < .02$). These data are limited by the cross-sectional nature of the analysis, the absence of data on cytokines, and by a relatively small sample size for this type of statistical analysis. However, these results suggest that (i) determinants of sarcopenia may differ between men and women; (ii) androgen status is important in men but not women; (iii) fat may play an important and generally unrecognized role, especially in women; and (iv) physical activity is important in both sexes.

Countermeasures Against Sarcopenia

Countermeasures should be aimed at the list of etiologic factors reviewed previously. However, given the imperfect state of knowledge about the relative importance of the various identified risk factors and the amount of variability left unexplained and requiring identification of additional risk factors, a comprehensive approach to prevention and treatment of sarcopenia remains out of our reach. We have suggested that senescent changes in the CNS, in terms of motor unit numbers and function, may be the main arbiters of sarcopenia. Unfortunately, for the foreseeable future, there is no treatment that can reverse this decline. However, much of the weakness of sarcopenia can be reversed with strength training, even though the number of nerve cells is probably not altered by this intervention (as discussed later). It is not known whether genetic or environmental factors are the key determinants of the loss of motor units with age.

In terms of anabolic hormonal interventions, both estrogen and testosterone can be replaced, making them inviting targets for therapeutic trials. Pharmacological doses of testosterone certainly increase muscle mass and strength in both young and elderly men (94–97). Furthermore, hypogonadism should be treated in elderly men when it is found, and physicians should consider this diagnosis in elderly men, even if they do not spontaneously complain of erectile dysfunction. However, there is at present no evidence that testosterone replacement impacts the course of sarcopenia in elderly men with normal testosterone levels or that estrogen replacement affects muscle loss in women at and after

menopause. Treatment with GH is less appealing, because of the higher costs and side effects of GH treatment, which may improve aerobic capacity, increase lean mass, and reduce fat mass, but has little effect on strength (98,99).

Many studies have now documented that exercise training can reverse sarcopenia, and that people who retain a high level of physical activity throughout their lives maintain a higher level of physical functioning and live longer (39,40,100). In addition, physical activity is one of the few factors that are within the control of nearly everyone, and it does not require pharmacological treatment. Moreover, Fiatarone and colleagues (39) showed that it is never too late to begin strength training and that even frail elderly nursing home patients in their 90s retain the plasticity of muscle in response to training. The effectiveness of strength training is clear, and the effect can be obtained in as little as 8 weeks with training 2 to 3 times per week. Strength training can be done with low-tech, relatively low-cost equipment in the home or in congregate settings, such as gyms or senior centers. In addition, strength training can be used safely in people with arthritis, coronary artery disease, heart failure, and renal failure (101,102). In obese persons, adding a program of resistance exercise training during caloric restriction has been effective in attenuating or preserving lean tissue loss in younger subjects (103,104). Whether this can be an effective means to prevent muscle loss in older obese individuals who try to lose weight remains to be seen. The difficulty with strength training is translating it into an effective public health intervention on a large scale. This requires training an adequate number of exercise leaders who can, in turn, train others. Unlike physical therapy, which is covered by insurance, exercise training has not been "medicalized" and is not reimbursed. This is a serious impediment to application of this therapy.

Another important countermeasure is to ensure adequate intake of energy and protein. Although this sounds simple, in practice, it may be quite difficult to ascertain whether an elderly person is eating enough. However, consultation with a registered dietitian to obtain a diet history and prescription is an important part of the evaluation, prevention, and treatment of sarcopenia. The optimal level of protein intake for elderly persons is a surprisingly controversial issue, and studies have shown that the RDA for protein, 0.8 g/kg/d, is (85,86,88,105) or is not (84,87,106) adequate. Further study of this question is clearly needed.

Finally, what about weight gain, which is almost universal during middle age in developed societies? Much public policy is appropriately aimed at preventing weight gain and the attendant complications of obesity. Positive energy balance leading to weight gain in midlife may be another anabolic stimulus that facilitates the gain in lean tissue (107,108). The timing of peak muscle mass in the fourth decade of life may result from a more favorable endocrine milieu in the younger subjects in combination with higher activity profiles and possibly better nutrition. Thus, maximizing lean tissue by promoting muscle-building activities in the younger years may be one mechanism for delaying sarcopenia in later life. In longitudinal studies of men, without specific interventions, lean mass accretion is only seen when weight gain is greater than 5 kg and in individuals less than 44 years of age (Figure 1) (21–23). Whether these factors are independent or synergistic remains to be determined.

Is weight gain all bad? Is there a role for modest (e.g., 3–5 kg) weight gain to prevent sarcopenia in people with a starting body mass index (BMI) below 25 kg/m^2? Such a question may be heretical, but there are no data to either refute or support the benefit of such a strategy. Excessive weight gain can clearly cause more disability, and the combination of low muscle mass and high fat mass (sarcopenic obesity) is the worst of both worlds (38). However, it is noteworthy that ambulatory, free-living, successfully aging persons in the Framingham Heart Study had a mean BMI of 28 kg/m^2, while their institutionalized counterparts in nearby nursing homes had a mean BMI of about 23 kg/m^2 (109). Moreover, at any level of body fat and age, more fit men had lower all-cause and cardiovascular mortality than men with lower cardiorespiratory fitness (110), suggesting that physical activity can affect survival, independent of body weight or composition. If weight gain optimized with an appropriate exercise program can add lean mass without increasing cardiovascular risk factors substantially, it may be of benefit to a segment of the population at high risk for sarcopenia. We are not advocating sedentary retirement with laissez-faire weight gain. However, legitimate concern about obesity can lead to the stigmatizing of lean gain, even when it is desirable. It is much more appropriate, we believe, to focus attention and resources on developing population-wide programs of strength training for adults older than 60 years of age. Clearly, such a program is a public health and communication challenge of the first order.

Summary

Sarcopenia is a normal part of aging, but if unchecked it can lead to weakness, disability, falls, and loss of independence. Sarcopenia has many causative factors, including sedentary lifestyle and neurological, hormonal, nutritional, and immunological determinants. The treatment of sarcopenia with resistance training is effective but difficult to implement. Interventions to prevent sarcopenia may need to begin at a much younger age than is currently common: life-long improvements in physical activity and diet are probably the most effective public health interventions for this condition. Further research is needed to identify treatments based on an understanding of the pathophysiology of sarcopenia and to better implement treatments that are already available.

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