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Review Article

Sarcopenia: Effects on Body Composition and Function

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Sarcopenia is the loss of muscle mass that happens to everyone with age. However, the rate of sarcopenia and the severity of its sequelae vary greatly according to health status, physical activity, and possibly diet. In this review, I discuss the potential mechanisms of sarcopenia and some ideas about prevention and treatment.

TO give a little perspective on body composition changes with aging and illness, first of all, let me remind you that the world can be divided into ''lumpers'' and ''splitters.'' On the issue of losing lean body mass (LBM), I am in the splitting camp. We have proposed (1) that loss of LBM has slow, medium, and fast lanes, kind of like freeways, with *wasting*, *cachexia*, and *sarcopenia* as terms that can be used to indicate the fast, medium, and slow loss of muscle (Table 1). *Wasting* has been co-opted by the HIV field to indicate the unintentional loss of weight, meaning both lean and fat, and both our data and that of others suggest that the real issue here is negative protein and energy balance. Muscle is simply lost along the way. Wasting is rapidly fatal, if untreated, the ultimate example being starvation. Mortality is uniform by approximately 40 days if one is adequately hydrated, but may not occur for up to 60 days. *Cachexia* is a slower process where there is loss of cell mass but weight remains stable or can even be increasing. This is because mass of another compartment, typically extracellular fluid (ECF) or fat, is increasing; depending on the situation. Examples are the organ failure syndromes (e.g., renal, liver, heart), where ECF is going up, or rheumatoid arthritis, where body fat may go up. The prewasting phase of HIV infection may also be cachectic. In these situations, our data indicate that dietary intake is usually good, often better than in healthy controls. The reason for that is presumably because there is not an anorexigen present as there is in medically driven wasting. What is altered is metabolism, and this alteration, our data suggest, is primarily related to excess production of inflammatory cytokines.

Finally, *sarcopenia* is the age-associated loss of muscle mass, which clearly is related to a decrease in anabolic stimuli with aging. Our interest has been whether there are also additional catabolic stimuli with normal aging and to what extent these might play a role in sarcopenia. We care about this because people die when they lose about 40% of their normal LBM. The question ''What is normal?'' can take hours to discuss, but if you take the rather arbitrary definition of the LBM at age 25 years as normal for each individual, which has a long historical precedent, the fact is that you do not find people alive once they fall below about 60% of what normal 20-to-30-year-olds have. However, because the main subcompartments of LBM—muscle, viscera, and immune system—decline with all of the 3 processes mentioned above, there are functional sequelae to this loss, and morbidity is demonstrable with even a 5% loss (2). Muscle, of course, is the source of strength and therefore of independence. Muscle plus viscera together are the main determinants of resting energy expenditure, and therefore caloric requirements and immune function declines with advancing malnutrition. The nice thing, of course, is that all these things are reversible. The extreme example of wasting and immune dysfunction is that the original descriptions of *Pneumocystis carinii* pneumonia, which is the hallmark of AIDS, of course, were in starving children in India in the 1960s, long before there was an HIV epidemic. So the degree of immune suppression, you can see, is quite severe, but fortunately is reversible.

To use a metaphor from the beef industry, we transition from free range to USDA (U.S. Department of Agriculture) prime as we age (Figure 1). Which change is more important in terms of health sequelae, the loss of the lean or the gain of the fat, is one that bears some discussion. Cross-sectional studies suggest that this is primarily a type II fiber loss (3). There are few longitudinal data. Now if this loss is an age-related phenomenon, it ought to be universal because we are all aging. But if you are going to create case definitions for clinical trials, you have to dichotomize what is essentially a continuous process. Baumgartner did that, and so did the group at the Mayo Clinic (4,5). Baumgartner used two standard deviations below the mean for normal, healthy young men and women under age 30 in the Rosetta Study (New York), to define sarcopenia in old people. He then looked at the prevalence of sarcopenia by whole-body dual X-ray absorptiometry (DEXA) scan in white and Hispanic men and women in New Mexico and found that, whereas below age 70, only about 10%–20% of people can be defined as sarcopenic, by the time they are in their 80s, a majority of healthy, successfully aging people have

Table 1. Lean Loss Syndromes

Syndrome
Wasting
Loss of all compartments
Negative energy and protein balance
Cachexia
Loss of cell mass ≫ weight or fat
Intake near adequate or better
Altered metabolism and cytokines
Sarcopenia
Age-associated loss of muscle
Generalized withdrawal of anabolic stimuli?

sarcopenia (Figure 2). Extrapolated to a population basis, these data indicate that approximately 8.9 million persons in the United States have sarcopenia. At least cross-sectionally, there was a relatively strong relationship between the sarcopenia and disability, with odds ratios between 2.5 and 4 for various measures of disability (Table 2). Difficulties in carrying out instrumental activities of daily living (IADLs), along with poor balance, need to use a cane or walker, or falls during the preceding year, are all associated with sarcopenia in men, whereas in women, the main association was with IADL (4).

Functional Implications of Sarcopenia

Sarcopenia is associated with increased mortality, even after adjusting for major clinical variables (6,7). Moreover, sarcopenia goes hand in hand with functional decline: There are data from Guralnick and colleagues (8) suggesting that a very simple measure of physical performance, scored on a 12-point scale, is a good predictor of future requirement for nursing home institutionalization or mortality (Figure 3). The data show that requirement for help with activities of daily living increases rapidly after scores drop below approximately 8. It is known that the relationship between muscle mass and muscle strength is quite linear. However, the relationship between muscle strength and physical function things is not. Thus, one of the complicating factors in understanding the importance of sarcopenia is the problem of identifying parameters other than loss of muscle mass that contribute to decline in physical function. Nevertheless, strength itself is a good predictor of mortality. Data from Rantanen and colleagues (9) on measurement of hand-grip strength between ages 40 and 50 with follow-up 30 years later show that, regardless of whether participants were thin, of medium weight, or heavy, people in the lowest strength category had the highest mortality 30 years later. Thus, sarcopenia and osteopenia may be analogous in that both peak mass and rate of decline of bone mineral are important determinants of fracture risk. It may well be that both peak muscle mass and rate of loss of muscle mass are interacting to determine the outcome.

It is also important to point out, as have others, that, although everybody declines with age, training has a huge effect on function. For example, longitudinal VO_{2max} data from people who maintain their level of physical activity stay on the athlete curve (10), whereas those who stop their physical activity drop down rapidly to the untrained curve. So in addition to a genetic component and a component of chronologic age, there is also a very large component that is under direct behavioral control. Knowing this may or may not be helpful in terms of devising strategies to prevent sarcopenia, since compliance is a major issue.

Factors Associated With Sarcopenia

Next, let us examine some of the changes we have seen in a longitudinal study. In a group of 130 healthy men and women aged approximately 60 years, at first visit, with normal body mass indexes (BMIs), seen twice at 10-year intervals from the late 1980s to the late 1990s, we observed decreases in isokinetic strength of the knee extensors and flexors and elbow extensors and flexors in both women and men (11). In the lower extremity, men and women are similar, losing a little more than 1% per year in knee extensor and flexor strength. There is a disparity between men and women in upper extremity strength, where the women maintained their strength quite well while the men did not. There may be complex hormonal, cytokine, and other differences between men and women that explain this phenomenon, but we favor the explanation that, in this generation, during the time period of follow-up, the men retired and stopped working, whereas the women were still doing housework. In any case, these data indicate that it may not be appropriate to combine genders or even upper and lower extremity measurements without due care. We consider lower extremity strength important because that is what keeps people out of nursing homes, but older people may care more about being able to use their arms. Significant predictors of strength loss included age, at least for the knee, and loss of weight. Change in muscle mass was significant at the knee, although measurement of muscle mass at the elbow is imprecise. Health did not appear to be an issue in this study, as our study participants remained remarkably healthy. Using computed tomography, cross-sectional area of muscle showed changes consistent with the observed changes in strength, approximately a 1% per year decline in thigh muscle area in both extensors and flexors (12). Thus, change in anatomy and change in function were similar.

What are determinants of sarcopenia that might relate to these observations? One is weight change. In a review of studies of 3 to 404 participants measuring body composition longitudinally (13), there were some gains of lean body mass in young people starting in their 20s, but past age 30 nearly all studies show loss of lean and gain of fat. In our longitudinal 10-year series, there were a few people who gained or did not lose muscle mass, but nearly everybody who lost muscle lost strength (11). People who maintained their muscle mass tended to be clustered around zero in terms of change in strength, and there were very few people who actually gained strength and muscle. So, there is heterogeneity, at least between ages 60 and 70, in healthy aging. The next question is what happens between 70 and 75? Is there a natural break point? Does exercise prevent or merely delay the natural decline?

However, most people do not exercise. Data from the Centers for Disease Control show that two thirds of people

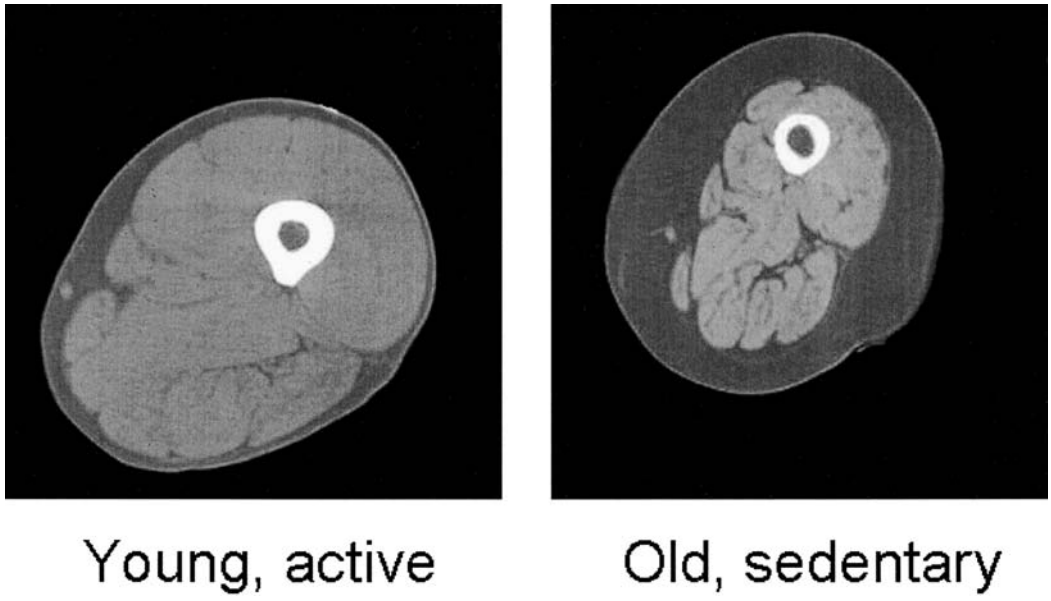

Figure 1. Sarcopenia. Magnetic resonance images through the midthigh of a 25-year-old healthy adult (**left**) and a 75-year-old healthy adult (**right**) demonstrating sarcopenia. Note the smaller muscle mass (light gray), larger subcutaneous fat (dark gray), and increased intramuscular fat (dark gray lines) in the older participant's leg.

over 75 do absolutely nothing in terms of leisure time/physical activity, half of people aged 65–74 do nothing, and roughly 42% of people between 45 and 64 do nothing (14). This is, I think, part of the impetus to the loss of muscle mass that we see, and if you chronicle vigorous physical activity, the rate drops even more dramatically. In the best group, ages 18–24, only one third of persons engage in vigorous physical activity on a regular basis, and that drops to below 10% by the time people are in their 70s.

Qualitative Changes in Muscle with Age

Another important issue is the question of muscle quantity versus quality. Is the loss of strength simply due to decreased mass, perhaps caused by fiber dropout due to apoptosis, or is there also a qualitative decline in the strength of the muscle over time? There are different ways of defining quality of muscle. The simplest way is to obtain some measure of strength and divide by a measure of cell lean mass. One can also quantify the amount of tension produced by the muscle per unit of area in different locations. From a simplistic whole-body point of view, body cell mass, measured as total body potassium, divided by fat-free mass by DEXA gives us an estimate of the cellular versus extracellular contents of LBM. After midlife, there is a linear decline in this value in men, and, probably, a decline in women as well (15). Thus, there seems to be a faster loss of the cellular components of lean mass with age than there is of the structural extracellular proteins, collagen, and so on, which have slower turnover.

However, even if one examines muscle quality at the cellular level in vastus lateralis biopsy specimen, by measuring contractility of the actin myosin complex in skinned fibers in vitro, one sees that there is a difference between young and old cells. The force produced by single muscle cells from young men versus old men, by type I or IIa fibers, plotted against the size of those fibers, show that type II fibers are stronger than type I fibers, as expected, and also that young fibers are stronger than old fibers (12). We do not know if there is less myosin in aged muscle fibers, but these data suggest that the muscle deficit goes beyond cellular dropout with a diminished number of cells and that there is a decline in force production with age at the cellular level. Differences between men and women present a more complicated story. When force production is plotted against fiber size, one sees an interaction with sex, such that large fibers in men's cells are stronger than women's, whereas smaller fibers show no difference between men and women. Also, there is no difference between type I and II fibers from women (12).

If one tries to extrapolate from the single cell to the whole muscle level, one finds yet another level of complexity, in that there is nonlinearity. Plotting single-fiber specific-force production against the whole-muscle specific-force production from isokinetic measurements shows that, at the low end of force production, the relationship is linear, and at the high end, it is *again* linear, but in between, there is really no relationship at all. This probably indicates the role of the central nervous system in integrating single-cell contractility into muscle function. We hypothesize that when weak cells are called upon to do minimal work, muscle weakness is apparent, but with higher levels of demand, the brain coordinates weak cells together, compensating for the deficit so that no effect of individual cell weakness is apparent, then, as work demand increases further, one again sees that weak cells lead to weak muscle because neural compensation is no longer effective. If one asks whether quality or quantity is more important, using a multivariate model, one finds that 92% of variability is explained by strength at

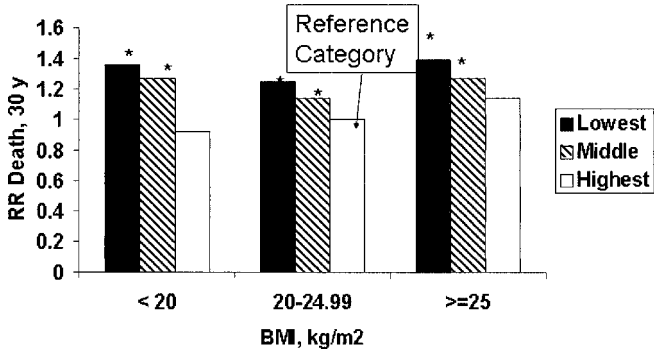

Figure 2. Grip strength predicts mortality after 30 years, independently of body mass index (BMI). Prevalence of sarcopenia in ambulatory men and women in New Mexico (from Ref. 32). *$p < .05$.

baseline and the change in muscle cross-sectional area (i.e., quantity), and only 8% is related to quality. However, multivariate modeling is very sensitive to the precision of the measurement of the variables, and we are much more precise at measuring the quantitative aspect than the qualitative aspect, so we are probably overestimating the effect of the quantity with this approach. Nonetheless, this analysis does suggest that measurements of body composition and muscle size are good surrogates for muscle function.

The Multivariate Etiology of Sarcopenia

With regard to the etiology of sarcopenia, when Nathan Shock first started the Baltimore Longitudinal Study on Aging, an elderly patient complaining, "I'm old and I feel weak," would be asked, "What do you expect at your age?," because that was all we knew. Twenty years ago, we recognized the decline in growth hormone secretion, which starts in the late 30s, and found even earlier that estrogen and androgen decrease with aging. While the hormonal role in altering muscle mass and strength in older persons is not fully understood, both growth hormone (16) and testosterone (17–19) decline with aging, and have been suggested to play a role in the pathogenesis of sarcopenia. This is discussed in more detail in this series of review articles by Marcell (20) and Bhasin (21). There is also a decline in physical activity and an increase in fat mass, but none of this provides a mechanistic understanding. More recently (Figure 4), it has become clear that there is a decline in central motor system alpha motor neurons. Studies in which motor units were counted show that healthy people in their 60s have lost up to half their motor units compared with people in their 20s (22). This very large change may well be the most important single factor driving loss of muscle. It could also be that it is the result, rather than the cause, of the muscle loss because there can be retrograde atrophy of those neurons. Moreover, increase in fat mass, which plays a role in insulin resistance, may also be important for sarcopenia. It is now clear that adipocytes are not just inert fat depots. Not only do they make leptin and a variety of other hormones, they also make tumor necrosis factor (TNF) and other cytokines. Interleukin (IL)-6 increases with age, and TNF increases with adiposity (23). TNF is catabolic and IL-6 has both proinflammatory and anti-inflammatory activities and may be both protective and catabolic.

Table 2. Correlates of Sarcopenia with Disability

	Men		Women	
Disability	%	OR	%	OR
≥3 IADL	16	3.7 (1.4–10)	33	4.1 (1.5–11)
Balance poor	28	3.2 (1.1–9.7)		
Cane/walker	14	2.3 (1.1–4.9)		
Fell during year	22	2.6 (1.4–4.7)		

Notes: From Reference (4).
IADL = Instrumental Activities of Daily Living; OR = odds ratio.

USDA surveys of household food intake have shown reproducibly that approximately 25% of women over age 65 do not meet the recommended daily allowance (RDA) for protein, which is only 0.8 grams/kilo, and 6% of women take-in less than two thirds of the RDA of protein (see http://www.barc.usda.gov/bhnrc/foodsurvey/home.htm). Therefore protein malnutrition may also play an important role in sarcopenia, driven largely by inadequate overall dietary intake and suboptimal variety of foods eaten. Data from Castaneda and colleagues (24) show that feeding healthy elderly women 0.4 grams/kilo of protein (half the RDA), compared to 0.8 grams/kilo, for 9 weeks produces a marked reduction in cell mass, muscle mass, and nitrogen balance, as well as weakness by electrical stimulation testing. Thus, in a few months nutrition can make a dramatic difference in muscle function and mass.

Our group has been interested in whether cytokines provide a catabolic signal to muscle with age that is not just disease related. Muscle is highly sensitive to catabolic cytokines such as IL-1, TNF, IL-6, and myostatin. There are also some anabolic cytokines, such as IL-15, insulin-like growth factor-I and its muscle congener, muscle growth factor, and perhaps transforming growth factor beta. Muscle itself makes significant quantities of cytokines, including all of the above. Under certain circumstances, muscle can also behave like antigen-presenting cells, and can be a pretty good immune cell, presenting human leukocyte antigen class I and II antibodies and complement factors, and so forth. So, muscle is probably not just an inert target here, no more than is fat, but appears to be an active participant in signaling.

We showed several years ago in the Framingham Heart Study (23) that white blood cells from old people make more cytokines in vitro than white cells from young people. In a group from Cycle 22 of Framingham, average age about 84 years, subdivided by blood level of C-reactive protein as undetectable, low, medium, and high, in vitro IL-6 production by white cells from those with undetectable C-reactive protein is about twice that of young people. With increasing C-reactive protein, as evidence of systemic inflammation, one sees even more IL-6 produced. We also measured IL-1 receptor antagonist (RA), a normal product of white cells that serves primarily to prevent catastrophic reactions to IL-1, which is a catabolic cytokine and a major pyrogen. IL-1 RA is a competitive inhibitor that binds to the IL-1 receptor but does not activate it because it does induce signal transduction. Healthy young persons have levels of

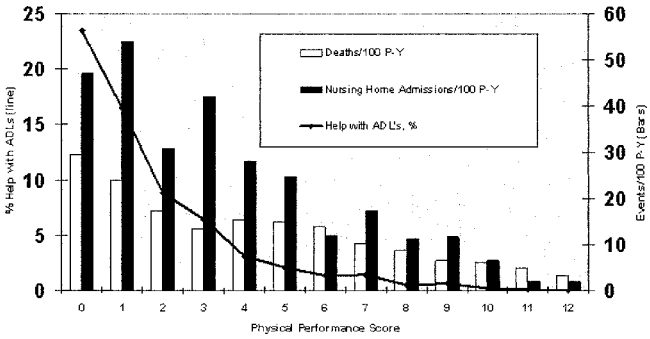

Figure 3. Physical performance and outcomes in elderly people. Risk of death (white bars), nursing home admission (black bars), and disability (needing help with activities of daily living [ADLs]) in elderly adults based on their score on the Short Physical Performance Battery (from Ref. 8).

IL-1 RA about 100-fold higher that those of IL-1. We found that white cells from old people make about 5 times as much IL-1 RA as those of young people, whereas their IL-1 production was exactly the same. It would be interesting to know where the signal is coming from to make IL-1 inhibitor in the absence of an increase in IL-1. One possibility is that IL-1 RA is simply an acute-phase reactant. This raises the issue whether, with aging, there are subclinical inflammatory processes going on that do not directly relate to diagnosable disease, but are part of a generalized catabolic milieu.

There is also a question of whether there is a decline in muscle protein synthesis with age. Data from Yarasheski and colleagues (25) show that exercise can increase muscle protein synthesis approach, whereas there is not as large an effect in studies by Welle (26). However, data from Volpi showed no difference in synthesis of muscle protein with age during the fasting state, suggesting that any age-related defect in protein handling relates to the efficiency with which postprandial protein is incorporated into muscle tissue (27). The jury is still out on this issue.

What about exercise? We have also found in human studies that exercise can partly reverse the age-related decline in muscle strength and muscle mass. In our study, approximately 40% of the 10-year strength loss and 75% of the mass loss is restored by 12 weeks of exercise training. People who exercise are also less depressed and they sleep better, so there are a lot of benefits to exercise. Exercise is a multifunctional intervention that is a good way to address a multifunctional problem. If we are trying to reduce sarcopenia down to a single molecule, we are going to have more difficulty. What about falls? Data show that people who exercise fall less (28). They also seem to be more functional (29). It is even possible that the more frail you are, the better you respond to exercise (30). Inactivity kills people (6,31).

If we are going to convince the medical world and—more importantly, the insurance world—that interventions for sarcopenia are worth paying for, we will need much larger scale intervention trials to examine clinical outcomes. We, and others, have done a variety of multicenter grassroots community-based programs that have involved thousands of participants. If we truly want to improve sarcopenia as a national health problem, what we must do is to make this kind of program widely available to reach people at the local level.

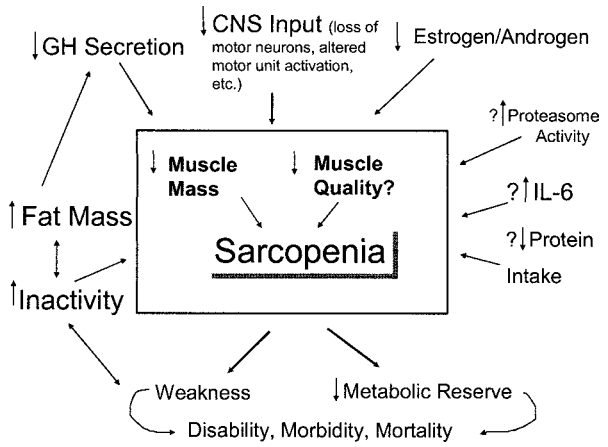

Figure 4. Potential mechanisms leading to sarcopenia, and its sequelae. CNS = central nervous system; GH = growth hormone; IL = interleukin.

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