Sarcopenia is a term utilized to define the loss of muscle mass and strength that occurs with aging. Sarcopenia is believed to play a major role in the pathogenesis of frailty and functional impairment that occurs with old age. Progressive muscle wasting occurs with aging. The prevalence of clinically significant sarcopenia is estimated to range from 8.8% in young old women to 17.5% in old old men. Persons who are obese and sarcopenic (the “fat frail”) have worse outcomes than those who are sarcopenic and non-obese. There is a disproportionate atrophy of type IIa muscle fibers with aging. There is also evidence of an age-related decrease in the synthesis rate of myosin heavy chain proteins, the major anabolic protein. Motor units innervating muscle decline with aging, and there is increased irregularity of muscle unit firing. There are indications that cytokines—especially interleukin-1β, tumor necrosis factor-α, and interleukin-6—play a role in the pathogenesis of sarcopenia. Similarly, the decline in anabolic hormones—namely, testosterone, dehydroepiandrosterone growth hormone, and insulin-like growth factor-I—is also implicated in the sarcopenic process. The role of the physiologic anorexia of aging remains to be determined. Decreased physical activity with aging appears to be the key factor involved in producing sarcopenia. An increased research emphasis on the factors involved in the pathogenesis of sarcopenia is needed. (J Lab Clin Med 2001;137:231-43)

Abbreviations: CRP = C-reactive protein; DXA = dual energy x-ray absorptiometry; IGF-1 = insulin-like growth factor-1; IL-1 = interleukin-1; IL-1Rα = IL-1 receptor antagonist; MHC = myosin heavy chain; PBMC = peripheral blood mononuclear cell; RSMI = relative skeletal muscle mass; TNF-α = tumor necrosis factor-α
Disability is a major cause of nursing home institutionalization and hospitalization of elderly adults, with projected costs approaching $50 billion by the year 2000. Physical impairment leading to disability has been shown to be associated with old age, female sex, non-white ethnicity, low socioeconomic status, chronic morbidity, falls, smoking and alcohol use, obesity, and physical inactivity. Recent reports suggest that sarcopenia (sarc = muscle, penia = lack of), or the loss of muscle mass and strength with age, may be an important correlate of impairment and disability. Other factors such as decrease in endurance capacity and increased muscle fatiguability also contribute to the age-related disabilities. These factors together contribute to increased fatness, because the decrease in lean mass decreases energy expenditure. Whereas there are currently a variety of studies of underlying mechanisms and treatments for age-related muscle loss, there are very few epidemiologic studies of the prevalence, incidence, pathogenesis, and consequences of sarcopenia in elderly populations.

Harris postulated in a recent review that the loss of muscle mass and strength with age has a multifactorial basis in female gender, hormones, sedentary lifestyle, smoking, disuse atrophy, poor health, genetics, body size, and body composition. There are few studies to date, however, for multivariate associations of morbidity, gender, and ethnicity and hormonal, nutritional, behavioral, genetic, and health factors with muscle mass and strength in samples of community-dwelling elderly people. There are very few data comparing elderly men and women for differences in rates of muscle loss, underlying pathogenesis, or consequences of sarcopenia. There has been little investigation of the roles of various health behaviors such as smoking and drinking, although many studies have reported that smoking is associated with a low body mass index, suggesting an association with sarcopenia. Surprisingly, the association of malnutrition with sarcopenia is not well established except in sick, hospitalized elderly people. Although low energy and low protein and vitamin intakes may be associated with muscle wasting and dysfunction, the strength of the association with sarcopenia in the community-dwelling elderly is unknown. It is not well established whether increased body fatness, or obesity, protects against muscle loss or exacerbates disability associated with sarcopenia. Some epidemiologic studies indicate that risk of disability is increased in those with high, rather than low, body mass indexes. The impact of morbidity on age-related muscle loss has been assumed, but there are few data from population studies. Although muscle mass, fiber-type composition, and strength exhibit genetic variation, genetic factors that influence age-related variation in muscle mass and strength have not been identified.

There are presently no studies showing direct relationships between sarcopenia and consequences such as physical and cognitive impairment, disability, and injurious falls in the elderly. Most studies have analyzed associations with indirect measures of muscle function such as grip strength, balance, gait speed, or timed chair stands. There are no studies that we are aware of for associations of sarcopenia with cognitive impairment.

A major gap in knowledge is the lack of data for minority ethnic groups. Ethnic differences in the prevalence or incidence of sarcopenia, its pathogenesis, and its consequences are largely unknown. Most epidemiologic studies of impairment, disability, falls, and other risk factors for sarcopenia have been of white, middle-class, elderly cohorts, and few studies have included ethnic minorities. Only a handful of studies are presently looking at the epidemiology of sarcopenia, impairment, and disability in Hispanic elders, who are the fastest growing minority group in the United States.

In summary, the magnitude of the public health problem posed by sarcopenia is not well established. A recognized impediment to epidemiologic studies of sarcopenia is the lack of suitable approaches for estimating its prevalence and incidence in elderly populations. To establish the public health importance of sarcopenia we need the following: (1) improved methods for measuring and predicting muscle mass; (2) better criteria for defining at what level muscle mass and strength become “deficient”; (3) a focus on epidemiologic measures of association to identify risk factors and consequences.

**EPIDEMIOLOGIC STUDIES**

The New Mexico group has developed methods for estimating the prevalence of sarcopenia and associations with risk factors and consequences in two studies of community-dwelling elderly populations in New Mexico. The first study is the New Mexico Aging Process Study, which consists of a cohort of approximately 400 elderly men and women who are being followed over time for the onset of sarcopenia, falls, morbidity, impairment, and disability. The second study is the New Mexico Elder Health Survey, which is a population-based cross-sectional survey of about 883 Hispanic and non-Hispanic white elderly men and women. In both studies, DXA was used for estimating skeletal muscle mass. Only 199 of the 883 subjects in the New Mexico Elder Health Survey had direct estimates of muscle mass by DXA; muscle mass was predicted by using an anthropometric equation for the remaining 684 subjects. It is recognized that DXA...
may underestimate the prevalence of sarcopenia. The present report is based on data for direct DXA estimates in the 199 subjects only.

Because skeletal muscle mass is highly correlated with skeletal size, an index of RSMI that adjusts for variation in skeletal size as muscle mass (kg) divided by stature (m) squared (kg/m²) was derived. This index is conceptually similar to the body mass index that is widely used to grade variation in body fatness and to classify individuals as overweight and obese. Using data for a reference population of younger adults (mean age = 29 years), sarcopenia was defined as values less than −2 SD below the sex-specific mean for RSMI, or less than 7.26 kg/m² in men and less than 5.45 kg/m² in women. Sarcopenic individuals were further characterized as sarcopenic-lean and sarcopenic-obese based on their percent body fat. Sarcopenic-obese individuals were those with an RSMI less than −2 SD below the young adult reference mean and percent body fat greater than sex-specific cutoff values that correspond approximately to a body mass index of 27 kg/m² (ie, >27% body fat in men and 38% body fat in women). These methods are described in detail in previous publications.

Figs 1 and 2 show increases with age in the prevalences of sarcopenia in each sex when using combined data from the two studies for direct estimates of muscle mass by DXA in 630 subjects. In the men, the percent classified as sarcopenic-lean increased with age from about 13.5% in those less than 70 years of age to about 29% in those older than 80 years. The prevalence of sarcopenic-obesity increased from about 13.5% in those less than 70 years of age to about 17.5% in those over 80 years. In the women, the percent who were sarcopenic-lean increased with age from about 8.8% in those less than 70 years of age to about 16% in those older than 80 years. The prevalence of sarcopenic-obesity increased from about 5.3% in those less than 70 years of age to about 8.4% in those over 80 years.

Hispanic women were not significantly more likely than non-Hispanic white women to be either sarcopenic-lean or sarcopenic-obese. Hispanic men, however, were significantly more likely to be sarcopenic-obese than were non-Hispanic white men (age-adjusted odds ratio = 3.0, 95% confidence interval = 1.3 to 6.9). The prevalence of sarcopenia (both lean and obese subgroups) was increased in those with low incomes (<$15,000 per annum). There were no statistically significant differences between the sarcopenic groups and those with normal body composition for reported energy or protein intakes. The prevalences of type 2 diabetes and gall bladder disease were increased in the sarcopenic-obese group and were similar to those in the obese group without sarcopenia. The prevalence of chronic obstructive pulmonary disease was increased in both sarcopenic groups. There was no association with cancer, stroke, coronary heart disease, or osteoarthritis.
Serum total testosterone and IGF-1 were significantly lower in men with sarcopenic-obesity than in the other groups. In the women, there were no significant differences between groups for serum estrone or IGF-1. Serum leptin, additionally adjusted for body fat mass, was significantly elevated in both the men and the women with sarcopenic-obesity. Fasting insulin was significantly increased in the obese groups, regardless of muscle mass. There were no differences among groups for serum albumin or total cholesterol.

Both obesity and sarcopenia were associated with functional impairment, disabilities, and falls independent of age, ethnicity, smoking, and co-morbidity. The strongest associations within each sex, however, were with sarcopenic-obesity. In the New Mexico Elder Health Survey, the odds ratio for 3 or more physical disabilities in the men was 8.72 (95% confidence interval 2.52 to 32.8) in sarcopenic-obese men compared with 3.8 (1.36 to 11.7) in the sarcopenic-lean group, and it was 1.34 (0.4 to 4.2) in the obese subjects. In the women, the odds ratio for 3 or more physical disabilities was 11.98 (3.07 to 61.6) in the sarcopenic-obese group, as compared with 2.96 (1.4 to 6.6) in the sarcopenic-lean and 2.2 (1.1 to 4.3) in the obese groups.

FUTURE DIRECTIONS

These data suggest that many of the deleterious health and functional sequelae of old age are concentrated in a small group of people with sarcopenic-obesity. Because sarcopenic-obese, elderly individuals have increased body fat that masks their sarcopenia, they may not be recognized as “frail” unless muscle mass and strength are additionally measured.

Sarcopenia, obesity, and sarcopenic-obesity may be considered “syndromes of disordered body composition” that have different associations with age, health, and functional status. It is not yet clear exactly how these syndromes evolve, especially sarcopenic-obesity. Future research with the longitudinal New Mexico Aging Process Study may help to elucidate this question. Such studies will be important to determine optimal methods for preventing both sarcopenia and obesity in old age. It is also useful to question whether these syndromes might require different tailored approaches to treatment that combine either aerobic or resistive exercise, dietary supplements, hormone replacement, or possibly appetite-stimulating drugs. Improved methods of identifying different patterns of disordered body composition in elderly people are needed so that such optimal treatments can be prescribed and improvement measured.

AGE-RELATED CHANGES IN MUSCLE

Muscle accounts for approximately 40% of the total body mass and 75% of the body’s cell mass. A quarter of all protein synthesis in the body occurs in mus-
ple. There is a decrease in muscle mass and muscle strength with aging.\(^1\)\(^9\) In addition, there is a decline in age-related muscle efficiency (ie, muscle strength per unit of muscle mass).\(^1\)\(^9\)\(^2\)\(^0\) This appears to be related to a decrease in total muscle fitness with aging with a disproportionate atrophy of the type IIA (fast-twitch) muscle fibers.\(^2\)\(^1\) The decrease in muscle efficiency is responsible for the decline in muscle power that occurs with aging.\(^1\)\(^9\) Power is defined as the product of force generation and speed of muscle contraction. Foldvari et al.\(^2\)\(^2\) have demonstrated that leg power accounts for 40% of the decline in functional status with aging. Men who maintain physical activity into their 80s show compensatory hypertrophy of muscle fibers to compensate for a decrease in fiber number.\(^2\)\(^3\)\(^2\)\(^4\)

With aging there is a decrease in muscle protein synthesis.\(^2\)\(^5\) This is particularly prominent in the mitochondria, perhaps because of the mutations and deletions that occur in mitochondrial DNA with aging.\(^1\)\(^8\)\(^2\)\(^6\) Mitochondrial oxidative enzymes show a decline parallel to the decrease in mitochondrial protein synthesis and VO\(_2\) max that occurs with aging.\(^2\)\(^7\)

The two major structural proteins of striated muscle are actin and myosin. The levels of muscle protein are determined by the balance between muscle protein synthesis and breakdown. The continuous process of breakdown and synthesis occurs as part of the process of remodeling of muscle tissue. The ability to synthesize the MHC is strongly correlated with muscle strength.\(^2\)\(^8\) MHC synthesis declines with aging.\(^2\)\(^8\) A similar decline in synthesis rate of actin also has been reported.\(^2\)\(^6\) In addition, with aging there is a relative increase in muscle fibers coexpressing two MHC isoforms.\(^2\)\(^9\) This suggests that with aging there may be a less clear separation into slow and fast fibers. The decline in MHC fractional synthesis rate is correlated with free testosterone and to a lesser extent with IGF–1.\(^2\)\(^8\)

Two studies have demonstrated that testosterone replacement in young hypogonadal men increased muscle protein synthesis.\(^3\)\(^0\)\(^3\)\(^1\) MHC synthesis was also increased,\(^3\)\(^0\) as was local expression of IGF-1 mRNA.\(^3\)\(^1\) Short-term resistance training increased the synthesis rate of mixed muscle proteins\(^3\)\(^2\); however, this could not be demonstrated to be sustained over a longer period of time.\(^3\)\(^3\)

In addition to the changes in muscle there are also changes in the motor unit innervating muscle that occur with aging. In old rats there is a reduction in the number of muscle fibers innervated per motor axon.\(^3\)\(^4\) In old human beings there is a decrease in functional motor units.\(^3\)\(^5\) This is associated with enlargement of the cross-sectional area of the remaining units. This decrease in motor unit populations is more prominent in distal than in proximal muscle innervation.\(^3\)\(^6\) Endplates have a reduction in subsynaptic fold number associated with thickening of the remaining ones.\(^3\)\(^7\) This motor unit remodeling seems to be caused by selective denervation of muscle fibers with re-innervation by axonal sprouting from juxtaopposed innervated units.\(^3\)\(^8\) There is evidence of increased irregularity of muscle unit firing.\(^3\)\(^9\)

To summarize, the decrease in muscle mass, strength, and power with aging is caused by atrophy in muscle fibers, particularly the type IIA. This is associated with a decline in protein synthesis, particularly that involved in the synthesis of MHC. Changes in the motor units innervating muscle with aging lead to a decline in coordinated muscle action.

**THE ROLE OF CYTOKINES IN THE DEVELOPMENT OF SARCOPENIA**

Loss of muscle with age may be caused by loss of anabolic factors such as neural growth factors, growth hormone, androgens and estrogens, and physical activity; by an increase in catabolic factors such as inflammatory cytokines; or by a combination of the two. The last is the most likely, but relatively little is currently known about the contribution of cytokines to the development of sarcopenia. It is clear that several of the cytokines are capable of causing muscle amino acid export in vivo in rodents and to some extent in human beings.\(^4\)\(^0\)–\(^4\)\(^4\) The cytokines for which the most data are available are IL-1\(\beta\), TNF-\(\alpha\), and IL-6.

Much is known about the role of these cytokines in acute illness. In a typical acute immune response, antigen-presenting cells encountering a foreign peptide secrete IL-1 and TNF, which assist in the recruitment of T cells and the development of a specific immune response to the antigen.\(^4\)\(^4\) IL-1 and TNF up-regulate the production of each other and also stimulate endothelial, hepatic, and immune cells to secrete IL-6. IL-1 and TNF are both endogenous pyrogens and have massive effects on metabolism in acute illness, including increased or decreased secretion of insulin and counter-insulin hormones (glucagon, epinephrine, cortisol), increased gluconeogenesis, increased protein breakdown, and increased hepatic glucose production. These cytokines and IL-6 also engender the acute phase response, with up-regulation of CRP and other positive acute phase reactants and down-regulation of albumin gene transcription.\(^4\)\(^5\) Although these changes are largest in acute illness such as sepsis, trauma, or post-operative states, in chronic inflammatory diseases such as rheumatoid arthritis, these changes persist for months to years and are associated with loss of muscle, elevated metabolic rates, and accelerated muscle protein breakdown.\(^4\)\(^6\)
Although these effects underscore the capability of the inflammatory cytokines to induce a catabolic state that leads to muscle loss, it does not necessarily follow that they play a role in the sarcopenia of aging. Indeed, the changes mentioned above are much more typical of more aggressive conditions such as wasting (unintentional weight loss) and cachexia (hypermetabolism and hypercatabolism with variable changes in weight but large changes in muscle mass). What is needed is evidence that the much slower, less aggressive muscle loss seen in normal aging (sarcopenia) may also be affected by excessive inflammatory cytokine production. To examine this question, Roubenoff et al measured PBMC production of IL-1, TNF, and IL-6 in a group of nearly 800 participants in the Framingham Heart Study of ages 72 to 92 years. The cytokine production from PBMCs from the elderly subjects were compared with those in young, healthy control subjects from the same study. The elderly subjects were further divided into four groups based on indication of active inflammation as measured by serum CRP. The groups were those with undetectable CRP, low CRP (<1 µg/dL), intermediate levels of CRP (1 to 2 µg/dL), and high levels of CRP (>2 µg/dL).

There were no differences between young and old subjects in PBMC production of either TNF or IL-1, either in unstimulated cells or after ex vivo stimulation with 1 or 100 ng/mL lipopolysaccharide. In contrast, IL-6 production in elderly patients was significantly higher than that in the young control subjects, beginning in persons with no detectable CRP and rising exponentially with higher CRP levels (Fig 3). In addition, PBMC production of IL-1Rα was also elevated in the elderly, but this time with no relationship to CRP level, suggesting that increased IL-1Rα production is a feature of aging and not of inflammation (Fig 4).

How do we reconcile the apparent increase in a pro-inflammatory, moderately catabolic cytokine like IL-6 and the increase in an anti-inflammatory, protective cytokine like IL-1Rα with the absence of a rise in the putatively upstream cytokines IL-1 and TNF? One possible explanation is predicated on the observation that IL-6 is in fact both an anti-inflammatory and a pro-inflammatory cytokine. True, increased IL-6 production causes wasting in rats, but on the other hand, the IL-6 knockout mouse has increased levels of TNF, suggesting that IL-6 may serve as a negative feedback signal to suppress TNF production. IL-6 also induces soluble TNF receptor and IL-1Rα production. This may also explain the observations of Roubenoff et al that there is a plateau in the amount of IL-1Rα produced in response to IL-6, so that above a certain level, additional IL-6 does not induce additional IL-1Rα. In addition, many of the acute phase responses that IL-
6 mediates serve to wall off inflammation and control it rather than to directly accelerate it.\textsuperscript{50} Thus it is possible that IL-6 and IL-1R\textsubscript{α} up-regulation represents a combined approach on the part of the older individual to suppress inflammation rather than promote it. However, given the catabolic effect of IL-6 on muscle protein, we hypothesize that although IL-6 has a possible beneficial effect in terms of reducing inflammation, the cost is paid by the muscle, because the low-grade catabolic effect of IL-6 promotes a negative muscle protein balance over time that helps foster sarcopenia.

But in the absence of a demonstrable increase in IL-1 and TNF secretion from elderly persons' PBMCs, where is the inflammatory signal coming from that the IL-1R\textsubscript{α} and IL-6 could be responding to? This is unclear. IL-1R\textsubscript{α} is generally thought to be secreted in response to IL-1, while IL-6 production is stimulated by both IL-1 and TNF. However, it should first be pointed out that although there was no increase in IL-1 or TNF secretion by elderly PBMCs in the study of Roubenoff et al,\textsuperscript{48} there was no reduction, either. This is in marked contrast to the reduction in T cell function and IL-2 secretion that happens with age, and it may in fact be a relative increase in IL-1 and TNF as compared with the rest of the cytokine milieu. In any case, the lack of increased TNF and IL-1 production by PBMCs does not eliminate the possibility of increased production by other tissues such as adipocytes and endothelial cells, which in turn triggers the increased IL-1R\textsubscript{α} and IL-6 observed in the circulating white cells. For example, serum TNF increases with age and obesity and is thought to represent adipocyte TNF production. Yet the correlation between PBMC TNF and serum TNF is weak—on the order of $r = 0.2$ (Roubenoff R, unpublished observation). Thus the issue of the compartmentalization of cytokines and the idea that cytokine production is differentially regulated in different tissues—and the possible breakdown of that compartmentalization with age—have yet to be adequately addressed.

Despite the gaps in our present knowledge, the currently available data suggest that an alteration in the cytokine milieu does occur with age and is even more pronounced in older persons with evidence of chronic inflammation. Because sarcopenia develops over many decades, only a small change in the balance of muscle protein catabolism and anabolism is needed to effect a large change in body composition over such a long time span. The combination of the withdrawal of anabolic stimuli (growth hormone, estrogens, androgens, central nervous system innervation) and the possible increase in catabolic stimuli (IL-6, tissue IL-1) may thus weave a complex web of signals whose ultimate result is a decline in muscle mass and strength that we now recognize as sarcopenia.

**ANOREXIA OF AGING AND SARCOPENIA**

It is now well established that food intake declines with aging both in the general population and in highly healthy persons.\textsuperscript{51} The decline in food intake is greater in males than in females. The reasons for this physiologic decline in food intake are multiple and are reviewed briefly below. The role of this physiologic anorexia of aging in the pathogenesis of sarcopenia is uncertain.

The regulation of food intake is complex and involves both peripheral and central mechanisms.\textsuperscript{52} The major reason for the early satiation seen with aging appears to be an inability of the fundus to respond by adaptive relaxation to the same extent in older as in younger persons.\textsuperscript{53} This appears to be due to a decrease in the ability of the fundus to produce nitric oxide with aging.\textsuperscript{54} This results in earlier and more rapid antral stretch leading to early satiation.\textsuperscript{55} In addition, older persons have an increase in the release of cholecystokinin in response to a fat load as compared with the release in young persons,\textsuperscript{56} and cholecystokinin has a greater satiating effect with advancing age (reference 57, and unpublished observations). When glucose is infused directly into the duodenum, older persons tend to become less satiated than younger persons, supporting the concept that the stomach is the major organ involved in producing early satiation in older persons.\textsuperscript{58}

Leptin is a hormone produced by adipose cells that may play a role in decreasing food intake.\textsuperscript{59} In postmenopausal women, elevated leptin levels are associated with a decrease in food intake.\textsuperscript{60} With aging, leptin levels increase at middle age but decline in old age in men,\textsuperscript{61} but the relative ability to increase leptin with an increase in fat mass seems to decrease with age. This increase in leptin in older males is related to the fall in testosterone that occurs with aging, and testosterone treatment decreases leptin levels.\textsuperscript{62} Thus the anorexia of aging may, in part, be related to the increase in leptin levels related to fatness that occurs with the middle aged. The greater degree of anorexia that occurs in males with aging may be due to the continued increase in leptin throughout the lifespan.

There are numerous neurotransmitters involved in the regulation of food intake. There is little knowledge concerning the effects of aging on the central regulation of food intake. Animal studies have implicated a role for opioids\textsuperscript{64} and neuropeptide Y\textsuperscript{65} in the physiologic anorexia of aging. Whether this physiologic anorexia plays a role in the pathogenesis of sarcopenia by reducing protein intake below the levels necessary to main-
tient muscle mass or by decreasing the intake of essential dietary nutrients for muscle such as creatine will be determined by future studies. However, the anorexia of aging does place older individuals at marked risk of developing protein energy malnutrition with the onset of disease that can lead to severe cachexia.

Cytokines appear to be an important mediator of increasing anorexia and muscle mass loss as well as declining albumin levels when disease develops in older persons. Ciliary neurotrophic factor appears to be a particularly potent anorectic cytokine in both animals and human beings. Increased obesity in middle age is associated with an increase in circulating TNFα levels. This in turn would decrease food intake and result in loss of lean mass. The role of cytokines in sarcopenia has been discussed in detail in the previous section.

Severe anorexia leading to cachexia is not uncommon in older persons when they develop disease processes. Cancer appears to account for less than 20% of the anorexia leading to severe weight loss in older persons. A number of studies have suggested that depression is the most common cause of protein energy malnutrition. Older persons are more likely to develop weight loss than younger persons when they are depressed. Iatrogenic causes, both drugs and therapeutic diets, are commonly implicated in weight loss in older persons. Table I provides a simple mnemonic to help remember the majority of the reversible causes of weight loss in older persons.

The reversal of anorexia and associated protein energy malnutrition is often extremely difficult. Treatment of depression or other reversible causes is the cornerstone of treatment. Mirtazapine is an antidepressant that is also a potent appetite enhancer and may be the drug of choice for the management of cachectic older persons with depression. Oral liquid caloric and protein supplements have been demonstrated to improve outcomes in patients with hip fractures and in some other situations. The utility of both enteral and parenteral nutrition remains controversial in older persons. In most situations enteral nutrition is preferred over parenteral nutrition because of its positive effects on gut flora.

Another controversial area is the use of orexigenic drugs. Anabolic steroids, such as nandrolone and oxandrolone, have been demonstrated to reverse weight loss in patients with kidney failure and AIDS. No adequate studies have been published in older persons. Megestrol acetate enhances appetite and produces weight gain in cancer and AIDS patients. One controlled study has suggested that it may have positive effects in older persons, but the weight gain was not seen until after the drug was discontinued. It has been suggested that megestrol acetate produces its effect by inhibiting cytokine release. Growth hormone was suggested to be a useful agent for the management of catabolic states; however, a recent study of severely ill malnourished patients suggested that growth hormone produced an excess of deaths.

When older persons lose weight they lose both fat and muscle mass. To restore muscle mass after weight loss requires exercise in addition to calories. Thus it would appear reasonable to consider that both physiologic and pathologic anorexia in older persons may play a role in the development of sarcopenia or cachexia. Anorexia may be particularly important in the development of the fat/fit or sarcopenia-obesity.

### OTHER NUTRITIONAL FACTORS AND SARCOPENIA

There is now excellent evidence that homocysteine levels increase with aging and that elevated homocysteine levels are correlated with atherosclerosis. Peripheral vascular disease is associated with decreased lower limb function. Atherosclerosis is associated with accelerated blood flow to muscles and metabolic efficiency of muscles. Although deficiencies of both vitamin B₁₂ and folate are associated with elevated homocysteine level, it appears that they do not account for the majority of the elevated homocysteine levels seen in older persons. Kidney failure, hypothyroidism, and estrogen deficiency are other causes of hyperhomocystinemia. Whether high-dose folate will sufficiently lower homocysteine levels to slow the progression of atherosclerosis and decrease the loss of muscle mass in some individuals remains to be determined.

There is evidence of variable quality in young athletes that creatine supplementation together with exercise

### Table I. Simple “MEALS ON WHEELS” mnemonic for the reversible causes of weight loss in older people

<table>
<thead>
<tr>
<th>Medications (eg, digoxin, theophylline)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emotional (eg, depression)</td>
</tr>
<tr>
<td>Alcoholism, obesity, anorexia tardive</td>
</tr>
<tr>
<td>Late-life paranoia</td>
</tr>
<tr>
<td>Swallowing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nosocomial infections (eg, tuberculosis, clostridium difficile, Helicobacter pylori)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wandering and other dementia-related behaviors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism, hypoadrenalinism, hypercalcemia</td>
</tr>
<tr>
<td>Entepe problems (eg, gluten enteropathy)</td>
</tr>
<tr>
<td>Eating problems</td>
</tr>
<tr>
<td>Low-salt, low-cholesterol diet</td>
</tr>
<tr>
<td>Stones (cholecystitis)</td>
</tr>
</tbody>
</table>
enhances muscle strength.97 One study in older persons has suggested that muscle strength may also be improved with a combination of creatine and exercise.98 Further studies are necessary to explore this observation.

**HORMONES AND SARCOPENIA**

Both testosterone99,100 and the adrenal androgens101 decline with age. There is epidemiologic evidence supporting the relationship of the fall in testosterone with the decline in muscle mass,17 muscle strength,17,102 and functional status102 with aging. Interventional studies with testosterone have demonstrated an increase in muscle mass103 and an increase in upper arm strength.58,104 One study suggested an increase in lower limb strength, but the study was not placebo controlled.105 Another failed to show an increase in lower limb strength.103

Dehydroepiandrosterone at doses of 100 mg daily has been shown to increase muscle mass and strength in males but not in females.106 Numerous studies have shown that growth hormone in pharmacologic doses increased muscle mass but not muscle strength.107 The administration of growth hormone at these doses is associated with multiple side effects.108 Whether growth hormone secretagogues that produce more physiologic levels of growth hormone will reverse sarcopenia without producing side effects remains to be determined.109

At present the available data suggest that strengthening exercises are more efficacious at reversing sarcopenia than are hormones.

**EXERCISE AND SARCOPENIA**

It is now well established that exercise, particularly that which increases mechanical force by strength training (resistance exercise), can increase muscle mass and strength even in very elderly persons.110 In elite Olympic oarsmen there was a decline in VO2 and in peak power. This decline was attenuated to some extent in those who continued to do regular aerobic training.111 Nelson et al112 demonstrated that high-intensity strength training exercises are an effective and feasible means to improve muscle mass, strength, and balance in postmenopausal women. Fiatarone et al113 reported similar findings in an extremely old cohort living in a nursing home. McCartney et al114 reported continued improvement in dynamic strength and endurance in 142 elderly persons 60 to 80 years of age who did weight training for 42 weeks a year for each of 2 years. Ivey et al115 demonstrated an improvement in muscle quality in older persons in response to strength training, and this improvement could still be demonstrated after 31 weeks of detraining. Resistance training also increased power in older persons, with men showing greater gains than women.116 Muscle power has been shown to be closely associated with functional status in community-dwelling older women.22 The decline in muscle power with aging appears to be best correlated with muscle volume and...
muscle fiber type changes rather than with the contractile properties of the muscle.\textsuperscript{117}

Hagerman et al\textsuperscript{118} showed that the response of skeletal muscle to high-intensity resistance training was accompanied by major increases in muscle fiber size and capillary density in the vastus lateralis muscle. There was an increase in the number of type IIa fibers and a decrease in type IIb fibers. There was a tendency for the number of myonuclei per fiber and myonuclei per unit length of muscle fiber to increase.\textsuperscript{119} The increase in use of type IIa fibers (together with type I fibers) and a decrease in type IIb fibers was also found in another study.\textsuperscript{120}

Yarasheski et al\textsuperscript{121} reported that in a group of men and women of 76 to 92 years of age, resistance training over a 3-month period resulted in an increase in mixed muscle protein synthesis. Hasten et al,\textsuperscript{122} utilizing a 2-week period of resistance training in a group of 74- to 84-year-olds, found an increase in both MHC and mixed protein synthesis of over 100% as compared with baseline.

Overall, it is clear that resistance training appears to be the best approach to reversing sarcopenia. Rooks et al\textsuperscript{123} have demonstrated that a self-paced, minimally expensive exercise protocol in subjects of 65 to 95 years of age was effective at improving neuromotor and functional capacity in community elders. An even simpler exercise program reversed frailty in very elderly people in the nursing home.\textsuperscript{124}

**CONCLUSION**

The loss of muscle mass with aging represents a major cause of functional decline and disability. There is a paucity of data examining the pathogenesis of sarcopenia in older persons. The available data suggest that the pathogenesis of sarcopenia is multifactorial (Fig 5). Intrinsic aging changes in the muscle and nerve represent one set of causes, but poor nutritional status, a decline in anabolic hormones and cytokines, and atherosclerosis all appear to accelerate the process. At present, only exercise has been proved to reverse sarcopenia. Future studies should focus on the interaction of anabolic hormones and exercise.

**REFERENCES**


242 Morley et al

90. Evans WJ. Exercise strategies should be designed to increase muscle power. J Gerontol 2000;55A:309-10.
gressive decreases in bioavailable testosterone, dehy-
droepiandrosterone sulfate, and the ratio of insulin-like
growth factor 1 to growth hormone. Proc Natl Acad Sci
USA 1997;94:7537-42.

102. Perry HM III, Miller DK, Patrick P, Morley JE. Testosterone
and leptin in older African-American men: relationship to
age, strength, function, and season. Metabolism 2000;49:
1085-91.

103. Snyder PJ, Peachery H, Hannoush P, Berlin JA, Loh L,
Lenrow DA, et al. Effect of testosterone treatment on body
composition and muscle strength in men over 65 years of

104. Morley JE, Perry HM III, Kaiser FE, Kraenzle D, Jensen J,
Houston K, et al. Effects of testosterone replacement ther-
apy in old hypogonadal males: a preliminary study. J Am

105. Urban RJ. Effects of testosterone and growth hormone on

The effect of six months treatment with a 100 mg daily dose
of dehydroepiandrosterone (DHEA) on circulating sex
steroids, body composition and muscle strength in age-
advanced men and women. Clin Endocrinol 1998;49:421-
32.

107. Lieberman SA, Hoffman AR. The somatopause: should
growth hormone deficiency in older people be treated


RL, Alberti KG, et al. Effect of aging on the sensitivity of
growth hormone secretion to insulin-like growth factor-I
negative feedback. J Clin Endocrinol Metab 1997;82:2996-
3004.

110. Evans WJ. Exercise strategies should be designed to
55A: M309-10.

111. Hagerman FC, Fielding RA, Fiatarone MA, Gault JA, Kirk-
endall DT, Ragg KE, et al. A 20-year longitudinal study of

112. Nelson ME, Fiatarone MA, Morganti CM, Trice I,
Greenberg RA, Evans WJ. Effects of high-intensity
strength training on multiple risk factors for osteoporotic
fractures: a randomized controlled trial. JAMA 1994;272:
1909-14.

113. Comright KC, Evans JP, Nassralla SM, Tran MV, Silver AJ,
Morley JE. A walking program improves gait and balance

114. McCartney N, Hicks AL, Martin J, Webber CE. A longitudi-
nal trial of weight training in the elderly: continued
51A: B425-33.

115. Ivey FM, Tracy BL, Lemmer JT, Ness AIVER, Metter EJ,
Fozard JL, et al. Effects of strength training and detraining
on muscle quality: age and gender comparisons. J Gerontol

116. Jozsi AC, Campbell WW, Joseph L, Davey SL, Evans WJ.
Changes in power with resistance training in older and
1999;54A:M591-6.

117. Martin JC, Farrar RP, Wagner BM, Spiriduso WW. Maximal
power across the lifespan. J Gerontol A Biol Sci Med

118. Hagerman FC, Walsh SJ, Staron RS, Hikida RS, Gilders
RM, Murray TF, et al. Effects of high-intensity resistance
training on untrained older men. I. Strength, cardiovascu-
lar, and metabolic responses [review]. J Geront A Biol Sci

119. Hikida RS, Staron RS, Hagerman FC, Walsh S, Kaiser E,
Shell S, et al. Effects of high-intensity resistance training
on untrained older men. II. Muscle fiber characteristics and
nucleo-cytoplasmic relationships. J Gerontol A Biol Sci

120. Hakkinen K, Newton RU, Gordon SE, McCormick M,
Volek JS, Nindl BC, et al. Changes in muscle morphology,
electromyographic activity, and force production character-
istics during progressive strength training in young and
B415-23.

121. Yarasheski KE, Pak-Loduca J, Hasten DL, Obert KA,
Brown MB, Sinacore DR. Resistance exercise training
increases mixed muscle protein synthesis rate in frail
women and men ≥76 yr old. Am J Physiol 1999;40:E118-
25.

122. Hasten DL, Pak-Loduca J, Obert KA, Yarasheski KE. Resis-
tance exercise acutely increases MHC and mixed muscle
protein synthesis rates in 78-84 and 23-32 yr olds. Am J

123. Roos DS, Kiel DP, Parsons C, Hayes WC. Self-paced
resistance training and walking exercise in community-
dwelling older adults: effects on neuromotor performance.

124. Fiatarone MA, O’Neill EF, Ryan ND, Clements KM,
Solares GR, Nelson ME, et al. Exercise training and nutri-
tional supplementation for physical frailty in very elderly