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Sarcopenia and Aging

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Sarcopenia refers to the gradual decline in muscle mass and quality noted with advancing age. There is growing evidence linking sarcopenia to functional disability, falls, decreased bone density, glucose intolerance, and decreased heat and cold tolerance in older adults. Factors implicated in the etiology of sarcopenia include decreased physical activity, malnutrition, increased cytokine activity, oxidative stress, and abnormalities in growth hormone and sex steroid axes. At present, progressive resistance training is the best intervention shown to slow down or reverse this condition. Preliminary studies show that the utilization of several trophic factors, notably testosterone and DHEA, may have a salutary effect on muscle mass and/or strength in older adults. More research is needed, however, before drawing definite conclusion as to the clinical utility of these substances in the management of sarcopenia.

Key Words: sarcopenia, frailty, muscle, aging

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Introduction

Sarcopenia refers to the loss of muscle mass and decline in muscle quality observed with increasing age.[1] Sarcopenia has been linked to multiple morbid outcomes in older adults such as falls, functional decline, osteoporosis, impaired thermoregulation, and glucose intolerance.[2–5] The development of these morbid outcomes during life depends on the starting level of muscle mass and the rate of its decline.[6] Unlike age-related decline in bone density, however, a quantitative relationship between pathology and morbidity is largely undetermined. If unchecked, sarcopenia may transform from an age-related physiologic change to a pathologic condition with a negative impact on the function and quality of life of affected individuals. Currently available data are insufficient to form a consensus on when such a transition may occur. Baumgartner et al.[7] arbitrarily defined clinically significant sarcopenia (pathologic sarcopenia) as an appendicular skeletal mass more than two standard deviations (<–2 SD) below the mean of a young reference group; they reported a prevalence of more than 50% in persons over 80 years of age. The presence of this degree of muscle loss was associated with a three- to fourfold increase in the likelihood of disability in older individuals independent of age, sex, obesity, ethnicity, socioeconomic status, chronic morbidity, and health behaviors. Melton and collegues[8] used dual-energy X-ray absorptiometry (DEXA) to estimate the muscle mass of 669 community-dwelling individuals, and reported a prevalence of sarcopenia ranging from 6 to 15% in older subjects based on the normal values used to define cut-off levels. In this study, subjects with sarcopenia had more physical and functional limitations compared with those who did not. Although the validity of this approach to define pathologic sarcopenia remains to be determined, the evidence cited by both studies raises concerns that sarcopenia constitutes a threat to the functional independence and quality of life of older adults. This paper reviews current knowledge on the pathophysiology of sarcopenia. The functional and metabolic consequences of sarcopenia will be discussed, and the therapeutic interventions that may help prevent or reverse this condition will be explored.

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Anatomic Changes in the Aging Muscle

There are several anatomic changes that have been reported in the aging muscle (Table 1). One of the most noticeable effects of increasing age is the reduction in muscle mass. In 1960, Allen et al. published one of the first reports demonstrating a loss of muscle mass with increasing age using total body potassium in relation to age.[9] Later, excretion of creatinine was used to measure muscle mass in 959 healthy individuals between the ages of 20 and 97 years, and a reduction of approximately one-third in muscle mass with age was found.[10] With the introduction of modern radiologic imaging techniques, muscle mass and muscle cross-sectional area could be estimated more directly. Young et al. used ultrasonogra-

Table 1. Anatomic Changes in the Aging Muscle

1. Decreased muscle mass and cross-sectional area
2. Infiltration of fat and connective tissue
3. Decrease in type 2 fiber size with no change in type I fiber size
4. Decrease in type 2 fiber number
5. Decrease in type 1 fiber number
6. Accumulation of internal nuclei, ring fibers, and ragged fibers
7. Disarrangement of myofilaments and Z-lines
8. Proliferation of the sarcoplasmic reticulum and t-tubular system
9. Accumulation of lipofuscin and nemaline rod structures
10. Decreased number of motor units

phy and found 25 to 35% reduction in the cross-sectional area of the quadriceps muscle in older men[11] and women[12] compared with their younger counterparts. The computed tomography scanning technique has shown similar age-related reductions in cross-sectional area of the psoas major and sacrospinalis muscles,[13] the quadriceps muscle,[14] and the plantar flexors.[15] Several studies also documented increases in fat and connective tissue in aging muscle.[13,15] This may indicate that the reduction in muscle contractile tissue is greater than the actual reduction in muscle volume.

Multiple attempts have been made to assess the microscopic anatomy of aging muscle using muscle biopsies. In the majority of these studies, the vastus lateralis of the quadriceps muscle has been examined; the overall conclusion is rather consistent: type 2 (fast-twitch) fiber size is reduced with increasing age, whereas the size of type 1 (slow-twitch) fibers is much less affected.[16–18] Later, when techniques that allowed analyses of whole-limb muscle tissue became available, investigators found that the total number of muscle fibers is significantly reduced with increasing age.[19] The numbers of type 1 and type 2 fibers are affected to a similar extent, which maintains the proportions of muscle fiber types.[19] Various morphologic abnormalities have also been observed using light microscopy, including internal nuclei, ring fibers, and ragged red fibers.[20] Electron microscopic studies of muscle biopsy samples have revealed a variety of alterations including disarrangement of myofilaments and Z-lines, proliferation of the sarcoplasmic reticulum and t-tubular system, and accumulation of lipofuscin and nemaline rod structures.[20]

There is evidence to indicate a loss of motor units as muscles age. Studies using quantitative electromyography have reported a reduction in the number of functioning motor units in aging human muscle.[21] This loss appears to be greatest among the largest and fastest motor units, type 2 motor fibers. Morphologic studies have shown that the number of motor neurons in the lumbosacral cord is reduced after age 60, that some individuals exhibit counts 50% of those in younger persons, and that the loss of motor neurons in the lumbar spinal cord is accompanied by a reduction in the numbers of large and intermediate ventral root fibers.[22] It appears that with increasing age, therefore, muscle fibers undergo continuous denervation and reinnervation owing to accelerated loss of motor neurons in the spinal cord. It is highly likely that such a process is one of the main contributors to the reduction in muscle volume accompanying advancing age. What causes this progressive loss of motor units with advancing age is a question that remains to be answered.

Biochemical Changes in the Aging Muscle

Several biochemical changes have been noted in the aging muscle. Both animal and human studies have demonstrated a progressive decline in muscle protein synthesis with age. Welle et al.[23] measured the synthesis rate of mixed muscle proteins (average of all muscle proteins) and found a 28% decrease in the synthesis rate in the elderly. Balagopal et al.[24] studied 24 subjects (aged 20–92 years) and noted a decline in synthesis rate of mixed muscle protein from young to middle age with no further change with advancing age. More recently, however, Volpi et al.[25] studied basal muscle acid kinetics and protein synthesis in 26 healthy younger and 22 older men and concluded that there is no age-related change in the fractional synthetic rate of skeletal muscle. Myosin heavy-chain synthesis rate was shown to decline progressively with advancing age, but sarcoplasmic protein synthesis did not decline with age. Myosin heavy-chain synthesis rate was correlated with measures of muscle strength, circulating insulin-like growth factor I, and dehydroepiandrosterone sulfate in men and women and free testosterone levels in men. A decline in the rate of myosin heavy-chain synthesis implies decreased ability to remodel this important muscle contractile protein, which likely contributes to declining muscle mass and contractile function in the elderly.[26]

Using biopsy sampling to assess the effects of aging on muscle enzyme activities, researchers have demonstrated little or no change in the activities of enzymes of the glycolytic pathway with aging.[27] On the other hand, mitochondrial marker enzyme activities have been found to be lower in older subjects in most[28] but not all studies.[29] A reduction in muscle respiratory capacity with aging is consistent with the observation that mitochondrial volume is decreased in older individuals.[30] This finding is also supported by studies using ^{31}P magnetic resonance spectroscopy (^{31}P-MRS) to assess muscle metabolism in vivo.[28] These changes likely con-

tribute to the reduction in aerobic endurance noted with aging.[31]

Changes in muscle protein expression also occur with aging. Klitgaard et al.[32] found that myosin heavy-chain and myosin light-chain expression was altered with aging, and that there was an increase in the slow-type isoforms. Investigators also identified increased incidence of fibers expressing both fast- and slow-myosin heavy chains. Marked alterations occurred in the concentrations of proteins of the sarcoplasmic reticulum. The concentration of the Ca-ATPase protein was reduced by 35% in older subjects, whereas the concentration of the Ca-channel release protein was actually increased. These age-related alterations in protein expression may explain the slowing of muscle contraction with age in the absence of detectable changes in histochemically defined fiber type distribution.[33]

Changes in Muscle Strength with Aging

Most of the data describing changes in muscle strength with age come from cross-sectional studies. Such data indicate that muscular strength tends to peak between the second and third decade of life and remains the same until about 45 to 50 years of age in men. Losses then begin to occur at the rate of approximately 12 to 15% per decade until the eighth decade.[33,34] Isometric strength levels in the quadriceps of young men (age range 20–35 years) are approximately 30 to 47% greater than those reported in older men.[35] When comparing isometric strength levels of the same muscle group in women, declines begin sooner than in men, but appear to occur at a slower rate from cross-sectional analysis.[36] Moreover, on a percentage basis, there is less total strength loss with age in women compared with in men.[35,37] A 30 to 39% strength loss has been reported when comparing women in their 60s and 70s with those in their 20s.[37] Similar findings were reported by other investigators.[38]

The few longitudinal studies available on this topic show a higher rate of loss of muscle strength in the elderly.[39–42] Strength losses ranging from 9 to 27% after five years,[40] 10 to 22% after seven years,[41] and 25 to 35% after approximately 11 years were observed in elderly men and women.[42] The 7-year strength losses were accompanied by a 14% reduction in area of type 2a fibers, a 25% reduction in area of type 2b fibers, and no significant change in area of type 1 fibers.[41] This indicates a possible relationship between age-related changes in muscle fiber type and peak torque changes,[37] as well as changes in the force/velocity relationship with increasing age.[43]

Pathophysiology of Sarcopenia

Age-related loss of muscle mass and strength cannot be explained entirely by age-associated reduced physical activity. Rather, it is most likely the result of many interacting factors (Figure 1). Presently, possible mechanisms include increased oxidative stress, dysregulation of catabolic cytokines, loss of endogenous growth hormone production, loss of estrogen and androgen production, inadequate protein intake, and reduced physical activity.[44]

There are reasons to believe that oxidative stress in skeletal muscle or in the upper and lower neurons, which innervate the muscle, may contribute to the development of sarcopenia. This belief stems from the free radical theory of aging, which was first proposed by Harman in 1956.[45] Free radicals are molecules derived from O_2 as it is reduced to H_2O during oxidative metabolism; they are believed to create a state of "oxidative stress," which produces changes in DNA, lipids, and proteins (including collagen and elastin) that may result in significant biologic damage.[46] Certain biochemical indicators of oxidative stress have been found to increase with aging. The "age pigment," lipofuscin, which is believed to be formed by the oxidative polymerization of lipids, is found in increased amounts in muscles from old rats. Further, levels of the antioxidant enzyme, glutathione, were found to increase with age in muscle obtained from rats and mice, which may reflect increased oxidative stress with age.[47] Together, these observations indicate a possible role of free radicals in the pathogenesis of sarcopenia.

There are many observations that support a possible role for cytokines in the pathogenesis of sarcopenia. During infection, a catabolic state develops that comprises a loss of skeletal muscle mass and increased urinary excretion of 3-methylhistidine, a breakdown product of muscle contractile protein. Interleukin-1 (IL-1) and tumor necrosis factor (TNF) have been im-

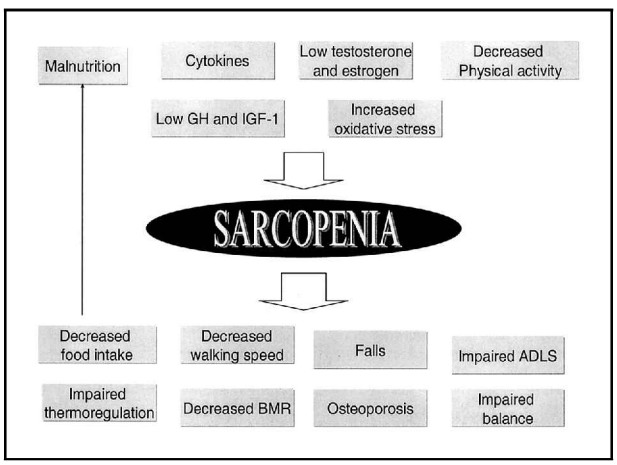

Figure 1. The pathogenesis and functional and metabolic consequences of sarcopenia. IGF-1 = insulin-like growth factor-1, GH = growth hormone, ADLS = activities of daily living, BMR = basal metabolic rate.

plicated in this process.[48] In addition, treatment of animals with a natural inhibitor of IL-, IL-1 receptor antagonist, reduced muscle proteolysis during endotoxemia[49] and restored normal muscle protein synthesis rates during sepsis.[50] In humans, urinary excretion of 3-methylhistidine has been correlated with IL-1 secretion following damaging exercise.[51] Moreover, IL-1 and TNF production have been related to resting energy expenditure and body cell mass in rheumatoid arthritis, supporting the concept that inappropriate production of these cytokines leads to loss of body cell mass.[52] Cellular production and urinary excretion of IL-1 are higher in older subjects.[52] Whether these increases are sufficient to cause age-associated reduction of muscle mass is yet to be determined.

Normal menopausal transition is associated with changes in body composition and muscle strength. Poehlman et al.[53] examined longitudinal changes in resting energy expenditure and body composition in a cohort of 35 women, and showed a 3 kg loss of fat-free mass, a 2.5 kg increase in fat mass, a 100 kcal/day decline in resting metabolic rate, and an increased waist-to-hip ratio in those who experienced natural menopause compared with age-matched volunteers who remained premenopausal. Whether the effect of menopausal transition on muscle acts via hormonal changes and/or lifestyle modifications deserves further study.

The observation that inadequate energy intake causes negative nitrogen balance[54] indicates that malnutrition may be an important cause of sarcopenia in the elderly. Roberts et al.[55] studied the effects of age on both energy requirements and the control of food intake in 17 younger men (age 22.7 $\pm$ 0.6 years) and 18 older subjects (age 68 $\pm$ 1.5 years) and concluded that healthy older men may have increased energy needs relative to those expected based on current Recommended Dietary Allowances; the authors also concluded that these individuals appear to exhibit a profound loss of the ability to control energy intake. Furthermore, nationwide studies have suggested that low dietary energy intake is common among healthy elderly adults.[56] Factors such as reduction in the sensation of taste and smell, poor dentition, and depression, as well as the physiologic age-related decrease in food intake, also known as "anorexia of aging," are thought to promote inadequate energy intake and weight loss in older persons.[57] Low serum albumin levels, indicating protein-energy undernutrition, were found to be associated with low muscle mass in 275 older subjects participating in the New Mexico Aging Process Study.[58]

There is evidence to support that age-related decline in growth hormone (GH) and serum insulin-like growth factor-1 (IGF-1) may contribute to the development of sarcopenia. Studies of GH-deficient adults have revealed important similarities with the changes in body composition frequently observed in older adults. Individuals deficient in GH have more adipose tissue and less fat-free mass when compared with age-matched controls.[59] In addition, GH-deficient adults have a more central distribution of adiposity as measured by circumferences. This decline in GH and IGF-1 levels with aging is attributed to changes in the effect of the hypothalamic factors, somatostatin (SRIF) and growth hormone–releasing hormone (GHRH), on the pituitary gland.[60] With advancing age, there is a reduction in the response to GH to GHRH and a simultaneous increase in the inhibitory SRIF tone. These observations have resulted in several attempts to replace the GH axis in the elderly.

Testosterone is associated with muscle strength in both animals and humans. Baumgartner et al.[58] studied 121 male participants in the New Mexico Aging Process Study, and found that free testosterone index, IGF-1, and physical activity were strong predictors of muscle mass and strength. The mechanisms by which testosterone increases muscle strength are not yet clear. One likely hypothesis is that testosterone mediates its effects on muscle through IGF-1; there is an association between testosterone and IGF-1 levels.[61] In addition, evidence from in vitro studies suggests that testosterone increases both IGF-1 and its binding protein.[62] A decline in testosterone levels with aging has been observed by both cross-sectional[63] and longitudinal studies.[64] Although there is great inter-individual variability in testosterone and bioavailable testosterone levels with advancing age, half of healthy men between the ages of 50 and 70 years will have bioavailable testosterone levels below the lowest levels seen in healthy men between the ages of 20 and 40.[65] This age-related decline in testosterone is due to a combination of hypothalamic-pituitary and testicular failure.[65]

Functional and Metabolic Consequences of Sarcopenia

Presently, there is only limited understanding of the functional and metabolic consequences of sarcopenia (Figure 1). The well recognized consequences are those related to the effect on function, including gait and balance problems, increased fall risk, and loss of physical functional independence. Sarcopenia may also contribute to increased risk of chronic diseases such as diabetes and osteoporosis.

The effects of sarcopenia on function in older adults have been extensively studied. Bendall et al.[66] reported a significant association between calf strength and walking speed, both of which decreased with age. Other investigators demonstrated a significant relationship between leg extensor power and rising from a chair, climbing stairs, and walking speed.[67] Older women with lower

extremity weakness had difficulty rising from a chair.[68] Sarcopenia was also linked to increased fall risk in older adults. Whipple et al.[69] compared the strength of knee extensors, knee flexors, ankle extensors, and ankle flexors of a group of nursing home residents with a history of falls with age-matched controls. The strength of the four muscle groups was significantly lower in subjects with a history of falls compared with subjects with no such history. Ankle dorsoflexors were the most affected of the four muscle groups in the group with a history of falls. In addition, reduced lower extremity strength has been implicated as a factor contributing to nursing home placement.[70]

There is evidence to indicate a possible relationship between muscle mass and bone density. Results from cross-sectional comparisons of athletes and sedentary controls indicate a delay or slowing of bone loss in "athletic" versus "sedentary" cohorts.[71] In non-athletic populations, muscle strength was an independent predictor of bone mass.[72] Some of all of the noted effects of muscle mass on bone density, however, may be due to the effect of exercise, rather than the effect of muscle mass, on bone. Regardless of the extent sarcopenia's role in bone loss, muscle weakness indirectly exerts a powerful influence on hip fracture incidence because it is associated with increased incidence of falls.

Another consequence of sarcopenia is the effect on body temperature and thermoregulatory processes. Evidence from published data suggests that loss of muscle mass has the potential to profoundly influence body temperature in both cold and warm environments.[73] In a hot environment, decreased muscle mass is associated with a greater temperature increase per kcal per kg weight.[74] In addition, low muscle mass is associated with decreased blood volume, which influences cardiovascular responses to exercise and heat stress.[75] In a cold environment, low muscle mass is associated with impaired peripheral insulation[73] and decreased capacity for shivering thermoregulation.[74]

Based on the observation that skeletal muscle is the major site of glucose uptake following an oral glucose tolerance test,[76] some have postulated that sarcopenia may contribute to age-related decline in glucose tolerance.[77] However, the lack of association between glucose tolerance, as assessed by a standard 75-g oral glucose tolerance test, and muscle mass does not support this concept.[78] Rather, there is evidence that the accumulation of abdominal visceral fat plays an important and possibly primary role in the age-related development of insulin resistance and glucose intolerance.[78]

Therapeutic Interventions

Several interventions have been tried to slow or reverse age-related decline in muscle mass and quality. These can be divided into three groups: hormonal interventions, exercise, and nutritional supplements.

Hormonal Interventions

GH is one of the earliest and most extensively studied hormones in relation to sarcopenia. The landmark study in this regard was reported by Rudman et al. in 1990.[79] This randomized controlled trial assessed changes in parameters of body composition and lean body mass in relation to GH supplementation over a 6-month period in 21 healthy older men (61–81 years) with relatively low IGF-I levels (<0.24 U/mL). Subjects were randomized to receive either recombinant human GH supplementation (0.03 mg/kg 3 times a week) or placebo subcutaneously for 6 months. The GH-treated group had a 2.5- to 3-fold increase in plasma IGF-I levels (to the mid-normal range for young healthy males) at the end of the study. GH treatment resulted in an 8.8% increase in lean body mass. Both plasma glucose and systolic blood pressure increased by 7% but none of the subjects became frankly diabetic or hypertensive. Subsequently, the same group of investigators carried out a larger study for a total of 12 months of intervention.[80] In this study, 44% of the GH-treated group had dropped out by 6 months of treatment compared with 10% in the placebo group. After 12 months of intervention, of the remaining 35 GH-treated subjects, 29% developed carpal tunnel syndrome, 11% developed gynecomastia, and 9% developed hyperglycemia. More recently, Blackman et al.[81] randomized 57 female and 74 male community-dwelling elderly to receive GH (starting dose, 30 μg/kg, reduced to 20 μg/kg, subcutaneously 3 times/week) plus sex steroids (women received transdermal estradiol, 100 μg/d, plus oral medroxyprogesterone acetate, 10 mg/day, during the last 10 days of each 28-day cycle; men received testosterone enanthate, biweekly intramuscular injections of 100 mg), GH plus placebo sex steroids, sex steroid plus placebo GH, or placebo GH plus placebo sex steroids using a 2×2 factorial design for a period of 26 weeks. GH administration (with or without sex steroids) significantly increased lean body mass and decreased fat mass in both men and women. Adverse events were frequent in this study and included carpal tunnel symptoms, arthralgias, diabetes, and glucose intolerance. Findings from these studies, as well as from other studies,[82,83] indicate that GH therapy reverses age-associated sarcopenia. However, the high incidence of side effects combined with the very high cost is a major limitation of its clinical utility.

Investigators have recently begun to assess a different approach to enhance the GH/IGF-I axis in older individuals. Iovino et al.[84] demonstrated that repetitive intravenous dosing with GHRH could restore the suppressed GH response to GHRH usually observed with aging. Corpas et al.[85] noted that twice-daily subcutane-

ous doses of GHRH for 14 days increased GH and IGF-I levels in older men. The potential advantage to using GHRH is the maintenance of the major counter-regulatory mechanisms that could modulate the adverse effects of treatment.[86]

Several studies tested the effect of testosterone supplementation on muscle mass and strength. Tenover[87] treated 13 healthy older men with weekly injections of testosterone or placebo for 3 months using a randomized crossover design. Testosterone therapy was associated with a 3% increase in fat-free mass, but no changes were noted in grip strength, body fat, or fat distribution. Both hematocrit and prostate specific antigen (PSA) increased, but plasma lipid levels remained unchanged except for a 12% decline in total cholesterol. In another study, Morley et al.[88] administered testosterone (200 mg every 2 weeks) to eight older men (mean age 78 years) and a placebo to six control subjects (mean age 76 years) for a period of 3 months; he found that testosterone therapy was associated with increased grip strength and hematocrit, as well as a small decline in low-density lipoprotein cholesterol. No significant changes in weight, body fat, or lean body mass were detected. In another study[89] using a prospective placebo-controlled design, the same group of investigators administered testosterone cypionate 200 mg biweekly for 12 months to 15 hypogonadal men (mean age 68 years) and placebo to 17 hypogonadal men (mean age 65 years); the result was a significant increase in bilateral grip strength in the treated group. No measures of body composition were used in this study. Snyder et al.[90] tested the effect of the testosterone patch; the authors randomized 108 men over age 65 (who had serum testosterone concentrations that were 1 SD or more below the mean for normal young men) to wear either a testosterone patch or a placebo patch in a double-blind randomized controlled trial for 36 months. They measured body composition using DXA and measured lower body muscle strength by dynamometer before and during treatment. The intervention group showed significant decreases in fat mass and increases in lean body mass compared with the control group. No significant change in lower limb muscular strength was noted between both groups. More recently, Wang and colleagues[91] reported the effects of 180 days of treatment with 1% testosterone gel preparation (50 or 100 mg/day) compared with the effects of a permeation-enhanced testosterone patch (5 mg/day) on muscle mass and strength in 227 hypogonadal men (aged 16–68 years). Body composition was determined by DEXA and muscle strength was measured by the repetitive maximum technique on bench and leg press exercise. Mean muscle strength in the leg press exercise increased by 11 to 13 kg in all treatment groups after 90 days and did not improve further after 180 days of treatment. Moderate increases were also observed in arm/chest muscle strength. After 90 days of treatment, lean body mass increased more in the group receiving 100 mg/day testosterone gel (2.74 $\pm$ 0.3 kg, $P < 0.01$) than in the groups receiving 50 mg/day testosterone gel (1.28 $\pm$ 0.3 kg) and the testosterone patch (1.2 $\pm$ 0.3 kg). Fat mass and percent body fat were not significantly affected in the testosterone patch group, but decreased in the testosterone gel groups. Both the increase in lean body mass and the decrease in fat mass were correlated with the changes in average serum testosterone levels attained after transdermal testosterone replacement. These studies indicate that the response to testosterone supplementation in older males is quite variable, with improvement in lean mass, muscle strength, fat mass, and fat distribution noted in some but not all studies. This variability is most probably due to the degree of hypogonadism of the subjects at baseline. The most consistent side effect of testosterone therapy has been an increase in hematocrit levels.

The direct biologic activity of adrenal androgens (androstenedione, dydroepiandrosterone [DHEA], and dehydroepiandrosterone sulfate [DHEAS]) is minimal; they function primarily as precursors for peripheral conversion to the active androgenic hormones testosterone and dihydrotestosterone. With the exception of DHEA and DHEAS, other anabolic hormones such as androstenedione and nandrolone deconate have not been studied in elderly subjects. In a study of 144 male and 118 female independent, community-dwelling elderly, DHEAS levels were found to be significantly correlated to percent body fat ($r = -0.3$) and percent lean body mass ($r = -0.3$) in men but not in women.[92] Baulieu et al.[93] randomized 280 healthy older men and women (aged 60 to 79) to receive 50 mg DHEA orally or placebo daily for a year. DHEA supplementation increased serum DHEAS levels to that of younger individuals. In addition, there was a small increase in the serum levels of testosterone and estradiol, particularly in women. Bone density as assessed by DEXA increased selectively in women who were more than 70 years of age. This group of women also showed a significant increase in most libido parameters. Significant improvement was noted in skin status, particularly in women. The administration of this dose of DHEA for a year did not result in significant side effects. Flynn et al.,[94] on the other hand, found no change in body composition after the administration of 100 mg DHEA daily for a period of 6 months. Longer and larger-scale randomized controlled trials are needed before drawing valid conclusions as to the clinical utility of DHEA supplementation in the management of sarcopenia.

There is little information documenting the effects of estrogen replacement therapy on muscle mass and strength in postmenopausal women. Baumgartner et

al.,[58] using a cross-sectional design, compared a group of elderly women who were on estrogen replacement therapy with an age-matched control group not receiving estrogen and found no association between estrogen replacement therapy and muscle mass or strength. Similarly, the results from a 2-year, prospective, randomized, placebo-controlled trial of 62 early postmenopausal women showed no effect on lean body mass. Estrogen replacement therapy, however, prevented postmenopausal accumulation of central fat.[95] In a cross-sectional study of 70 postmenopausal women (aged 45 to 55), Gower and Nyman[96] showed that estrogen use resulted in higher serum levels of sex hormone–binding globulin and lower concentrations of free testosterone. Total testosterone concentrations were not affected by estrogen use. In this study, total lean body mass and leg lean mass, but not arm lean mass, were related to free testosterone levels. Sorensen et al.,[97] using a placebo-controlled, crossover design, randomized 16 postmenopausal women (mean age of 55) to receive 17β-estradiol plus cyclic norethisterone acetate or placebo in two 12-week periods separated by a 3-month washout period and showed that hormone replacement therapy was associated with a significant increase in lean body mass and decrease in total fat mass.

Exercise and Nutritional Supplements

Strength training results in an increase in muscle size, which is largely the result of an increase in contractile protein content.[98] Strength training may be defined as exercise in which the muscles are challenged to generate progressively increasing force over time. Muscle strength has been shown to increase in response to training between 60 and 100% of the one repetition maximum. A number of studies have demonstrated that older men and women show similar or greater strength gains compared with young individuals as a result of resistance training. Frontera et al.[98,99] demonstrated that older men responded to a 12-week progressive resistance training program (80% of the 1 repetition maximum, 3 sets of 8 repetitions of the knee extensor and flexors, 3 days per week) by more than doubling extensor strength and a more than tripling flexor strength. The increases in strength averaged approximately 5% per training session, similar to strength gains observed by younger men. Total muscle area estimated by computerized tomography increased by 11.4%. Biopsies of the vastus lateralis muscle revealed similar increases in type 1 (33.5%) and type 2 (27.6%) fiber area. Daily excretion of urinary 3-methyl-L-histidine increased with training by an average of 41%, indicating that the increased muscle size and strength resulting from progressive resistance training is associated with an increased rate of myofibrillar protein turnover. Other investigators[100] demonstrated a beneficial effect of high intensity, progressive resistance training on quadriceps muscle strength in a group of institutionalized elderly men and women (ages 87–96). In this study, the absolute amount of weight lifted by the subjects during the training increased from 8 to 21 kg. The average increase in strength after 8 weeks of resistance training was 174%, and mean increase in muscle cross-sectional area via computerized tomography was 10%. The increases in muscle size and strength were accompanied by improvements in tandem gait speed and index of functional mobility.

Suominen et al.[100,101] observed increases in enzyme activities of energy metabolism with progressive resistance training in 55- to 70-year-old subjects. Orlander and Aniansson[102] studied the effects of a 12-week program of physical training on vastus lateralis characteristics in five elderly men. Their findings indicate that heart rate decreased during submaximal bicycle exercise after training, indicating improved cardiovascular performance. The anaerobic capacity and the mitochondrial oxidative capacity were also increased, indicating metabolic adaptation with training.

Fiatarone et al.,[103] using a randomized, placebo-controlled design, studied the effect of progressive resistance exercise training, nutritional supplementation, both interventions, and neither intervention on muscle strength and function in 100 frail nursing home residents over a 10-week period. Muscle strength increased by 113%, gait velocity by 12%, and stair-climbing power by 28% in the group that received exercise training. No significant changes were noted in subjects who did not receive resistance exercise training. The nutritional supplementation had no effect on any of the outcomes measured.

The limited data available on the effects of caloric multinutrient supplements on muscle mass and strength indicate no apparent beneficial effect.[102,103] Oral creatine monohydrate is a nutritional supplements often used by young athletes and is thought to enhance exercise performance.[104,105] These effects, however, need to be confirmed by research studies, and the safety of the prolonged administration of creatine supplementation need to be established.

Conclusion

Sarcopenia, or age-related decline in muscle mass and function, is a recently recognized epidemic that constitutes a great threat to the functional independence and quality of life of older adults. This condition has been linked to functional disability, falls, decreased bone density, glucose intolerance, and decreased heat and cold tolerance in older adults. The occurrence of sarcopenia has been linked to decreased physical activity, malnutrition, increased cytokine activity, oxidative stress, and abnormalities in growth hormone and sex steroid axes.

Options currently available for the management of sarcopenia are limited because the mechanisms involved in its development and progression are poorly understood. At the present time, progressive resistance training is the best intervention to slow down or reverse the age-related decline in muscle mass or strength. Preliminary studies show that the use of several trophic factors, notably testosterone and DHEA, may have positive effects on muscle mass and/or muscle strength in the elderly. Long-term trials are needed, however, to define the risk-benefit ratio of such therapies before they can be recommended.

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