

COMMENTARY

Anabolic Interventions for Aging-Associated Sarcopenia

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AGING in humans is associated with a progressive decrease in skeletal muscle mass and strength (sarcopenia) that contributes to frailty and falls. The age-associated changes in body composition result from lower levels of anabolic hormones, neuromuscular alterations, and a general decline in muscle protein turnover (1–3). The frailty of old age has emerged as an important public health problem because it impairs mobility and quality of life and increases the risk of falls and the use of health care resources (4–6). Therefore, recent years have witnessed a growing interest in the use of anabolic interventions for augmenting muscle mass and function in older men.

Pathophysiology of Sarcopenia

Pathophysiology and epidemiology of sarcopenia

The term sarcopenia, originally coined by Rosenberg (4) and recently reviewed by the National Institutes of Aging (5), refers to the involuntary loss of skeletal muscle mass and strength. This is in contrast to wasting, the involuntary loss of weight driven largely by inadequate nutrition, and cachexia, the involuntary loss of fat-free mass (FFM), especially body cell mass, generally resulting from a state of hypermetabolism and hypercatabolism (6). The etiology of sarcopenia is currently unknown. Holloszy (5) identified several possible mechanisms leading to sarcopenia, including loss of α motor neurons in the spinal column, impairment of endogenous growth hormone, androgen and estrogen production, inadequate protein intake, dysregulation of catabolic cytokines, and reduced physical activity.

Mortality in the elderly is primarily associated with atherosclerosis, cancer, and dementia. In an increasing number of the elderly men and women, however, loss of muscle mass and strength is an important determinant of the individual's ability to live an independent life (7). There is no consensus on whether sarcopenia should be viewed as a disease or process of normative aging (4). It has been argued that, because loss of muscle mass occurs even during the course of successful aging, sarcopenia should be considered a disease only when it induces disability (4). There is also no

consensus on what threshold of muscle loss should be used to define sarcopenia.

The magnitude of the public health problem posed by sarcopenia is not known (8). Baumgartner *et al.* (9) examined the prevalence of sarcopenia in Hispanic and non-Hispanic white elderly men and women in New Mexico. Sarcopenia was defined as the relative muscle mass that was two sds below the sex-specific means of the Rosetta Study reference data (10) for young adults, aged 18–40 yr. The study (9) demonstrated that the prevalence of sarcopenia increased from 13% to 24% in persons under 70 years of age. Nearly half of all persons over 80 years of age met this definition of sarcopenia. The study also demonstrated that sarcopenia was associated with a 3- to 4-fold increased likelihood of disability in elderly people, independently of age, sex, obesity, ethnicity, socioeconomic status, chronic morbidity, and health behaviors (9).

Another cross-sectional survey performed by Melton (11) in Olmsted County in Minnesota used slightly different thresholds for defining sarcopenia and reported lower prevalence rates. Based on an age-stratified, random sample of the population of Rochester, Minnesota, this survey verified the findings of Baumgartner *et al.* (9) that lean body mass decreases progressively after the second decade of life in both men and women. Age-related losses in fat-free mass, appendicular muscle mass, and total muscle mass are all linear in both men and women, and there was no significant difference in the slope of the regression line before 50 and after 50 years of age. The prevalence of sarcopenia in individuals over 20 years of age was 2–3% and in those over 65 years of age, approximately 10% (11). Taken together, these two epidemiological studies provide evidence that sarcopenia is an important public health problem.

Aging-associated changes in body composition

In the two-compartment model of body composition, body weight is the combination of fat mass and fat-free mass. Fat-free mass, in turn, is the combination of body cell mass, extracellular fluid, and the extracellular solids such as collagen and bone mineral. Body cell mass can be further divided into the fat-free portion of cells within muscle, viscera, and the immune system. Muscle cell mass is an important determinant of muscle strength, whereas the sum of visceral and muscle body cell mass predicts energy requirements (6). Thus, changes in body composition with aging, especially in

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the FFM component, have important implications for functional status and survival (6, 13).

Weight gain in adults is associated with an increase in absolute and percent fat mass (14). In women, body weight increases between the ages of 40 and 50 yr and remains stable thereafter; percent body fat is also stable until 40 yr of age and increases from 28% to 35% between 40 and 50 yr of age (15). In another cross-sectional study (16) of men and women 18–85 yr of age who used total body potassium, percent fat increased from 18% to 36% and 33% to 44% in men and women, respectively. In addition to an overall increase in adiposity, aging is associated with a more central distribution of fat (14). The composition of lean tissues also changes with advancing age. Men experience a more rapid muscle loss between the ages of 41 and 60 yr, whereas women experience the rapid loss after the age of 60 (17). Total body nitrogen, calcium, water, and bone mineral content also decline with age (18–21). More recent epidemiological surveys suggest that age-associated decrease in skeletal muscle mass starts after the second decade of life in both men and women and is slowly progressive thereafter.

The principal component of the decrease in fat-free mass is the loss of muscle mass; there is little change in nonmuscle lean mass (18, 19). Between 20 and 80 yr of age, the cumulative decline in skeletal muscle mass amounts to 35–40% (22, 23). The depletion of muscle mass does not result in weight loss because of the corresponding accumulation of body fat (24).

Muscle atrophy results from a gradual and selective loss of muscle fibers. The number of fibers in the vastus lateralis muscle from cadavers of older men is 23% lower than in young men (26). There is a preferential atrophy of fast-twitch, type II fibers (24), in part because of their reduced reinnervation capacity than type I fibers (26). There is an increase in intramuscular fat and connective tissue (27). These changes reduce the contractile tissue volume available for locomotive and metabolic functions and the increased amount of connective tissue presumably acts as a friction brake to slow contractile velocity (24, 28).

Most studies of muscle mass and body composition have relied on cross-sectional data. Many of these studies have not taken into account individual variation due to the level of physical activity, nutritional status, and disease. There is also a paucity of data on ethnic differences in body composition.

Changes in muscle function

Sarcopenia has been identified as a contributor to disability in old age (29–30). Walking, stair climbing, rising from a chair, and load carrying represent functional activities that deteriorate with sarcopenia. Loss of muscle mass, particularly the preferential loss of type II fibers (24), results in diminished strength and power-generating capacity (31). There is a significant correlation between strength and leg power and maximal walking speed and stair-climbing height (31–34). Rantanen and Avela (34) have described critical ranges of leg power for different walking speeds, suggesting that below the critical range the probability of walking at a particular speed is low.

Falls are a serious consequence of the loss of muscle

strength and power. Leg weakness and decreased peak torque and power are associated with impaired gait characteristics, such as small steps and slow speeds (35) and a history of falling (36, 37). Because strength is fundamental to the neuromuscular function that supports mobility (37), loss of strength below a critical threshold may be associated with an increased risk of falls. Therefore, interventions that increase muscle mass, strength, and power in the lower extremity may reduce the risk of falling.

The maximal oxygen uptake rate ($\text{VO}_{2\text{max}}$) defines the capacity for endurance exercise (22). Both decreased muscle mass (23) and decreased oxidative capacity of skeletal muscle (38) with aging contribute to the 1% annual decline in maximal aerobic capacity. Resistance training can increase $\text{VO}_{2\text{max}}$ in the elderly (39); this suggests that increasing muscle mass can increase maximal aerobic power. Sarcopenia contributes to the decline of aerobic capacity, thus limiting the extent to which older individuals may participate in a variety of activities and retain their independence. Therefore, interventions that augment muscle mass can help older men maintain or regain their ability to perform daily functional activities and live independently.

Changes in muscle protein dynamics

Approximately 20% of muscle weight is protein; therefore, changes in muscle mass will likely be associated with alterations in muscle protein turnover (which includes muscle protein synthesis and break down) (14, 24). Whole body protein synthesis declines from birth to old age (40). However, when protein turnover rates are normalized to FFM, there is no difference between young and old subjects (41, 42). Because older people lose FFM but not weight, it is possible that the difference observed in whole body protein synthesis in the elderly is due to their increased fat mass (14). Also, the muscle contributes <30% to whole body protein turnover; therefore, small changes in muscle protein synthesis or breakdown are difficult to detect with measurements of whole body protein turnover. Indeed, the fractional synthesis rates of mixed or myofibrillar protein are lower from muscle biopsy samples in old people as compared with young people (42–44). Standardized exercise programs, testosterone, and amino acids can stimulate the synthetic rates of total muscle protein (44), as well as myofibrillar proteins (45). In contrast, high-protein meals do not enhance the stimulation of myofibrillar synthesis induced by resistance exercise (45). Because amino acids alone can stimulate muscle protein anabolism in young and older subjects (46), it is unlikely that alterations of muscle protein metabolism in the elderly are due to a defect in amino acid transport.

There are alterations in the synthesis rates of individual muscle proteins in older individuals. Compared with younger subjects, the middle-aged and older men and women have significantly lower synthetic rates of myosin heavy chain, an important contractile protein (47). The fractional myofibrillar protein synthesis rate (the rate of synthesis per gram of myofibrillar protein already present) is 28% slower in older subjects (42). The reduced myofibrillar protein synthesis in the elderly is not due to a reduction in the

availability of mRNAs encoding actin and myosin (48) and may be the result of posttranslational events.

Protein turnover is important for maintaining the mass of structural and contractile proteins and enzyme function (24). There is a 40% decrease in mitochondrial protein synthesis rates in middle-aged subjects, but no further decrease in older subjects (49). The changes in mitochondrial function may contribute to alterations in muscular endurance and fatigability and contractility (24).

Although it is now possible to measure synthesis and breakdown rates of specific muscle proteins and to study their regulation (14, 47, 49, 50), these methods are invasive and are not clinically applicable to older individuals with sarcopenia. We have little information about the genetic regulation of skeletal muscle protein turnover in humans.

Changes in hormones

Aging is associated with changes in several trophic factors (51), including the male sex hormones and the growth hormone axes (52).

Testosterone. There is an age-associated decrease in serum total and free testosterone levels in healthy men (53). A meta-analysis of 44 studies demonstrated an unequivocal decrease in morning testosterone levels in older men (54). Lower testosterone levels are the result of changes at multiple levels of the hypothalamic-pituitary-gonadal axis (55). Testicular response to gonadotropins is diminished in older men, gonadotrope responsiveness to androgen suppression is attenuated, and the pulsatility of the hypothalamic GnRH pulse generation is altered. Coexisting diseases, malnutrition, and concomitant medications can also affect serum testosterone levels (55).

Although, as a group, serum testosterone levels are statistically lower in older men than those seen in younger men, many older men have normal or low-normal testosterone levels, leading to speculation that older men might be relatively insensitive to the end organ effects of testosterone. The androgen receptor number and affinity are decreased in many organs of the aging rat (56, 57). However, in the human, older men have increased rather than decreased sensitivity to androgen feedback effects on pituitary LH and FSH secretion (58). This issue of androgen insensitivity of muscle and bone to testosterone effects in older men has not been studied.

There is no consensus on the serum testosterone levels that can be used to define androgen deficiency in older men. We do not have a clinically useful biological marker of androgen action. Total testosterone level below 200 ng/dL or bioavailable testosterone levels below 60 ng/dL warrants replacement, especially if associated with symptoms suggestive of androgen deficiency.

GH. There is abundant evidence that GH secretion declines with age. Because GH is an anabolic agent, it has been suggested that some of the changes in body composition with age may be related to decreased GH production. The 24-h integrated secretion of GH and acute GH secretory responses to exercise and GHRH stimulation are decreased in older men and women, as compared with healthy young men (59).

Circulating insulin-like growth factor (IGF-1) levels are lower in older men than young men; the serum IGF-1 levels in older residents of nursing homes are in the lowest tertiles for healthy young men (59). Serum IGF-1 levels correlate positively with maximal aerobic capacity and leisure time physical activity and negatively with adiposity in older men. After reaching a peak in mid-adulthood, GH-binding protein levels decrease after the 6th decade of life (60).

Dehydroepiandrosterone (DHEA). DHEA and its sulfated form, DHEAS, are produced in large quantities by the adrenal glands in humans, nonhuman primates, and some nonprimate species (62–63). DHEA metabolism is substantially different in rodents than it is in humans. The circulating concentrations of DHEA are thousand-fold lower in rodents than humans (62, 63). Also, in rodents, the gonads rather than the adrenal glands are the source of circulating DHEA.

Circulating concentrations of DHEA and DHEAS in humans increase progressively starting at about 5–7 yr. After reaching a peak in the 20s, serum DHEA levels decline, and this rate of decline accelerates after the 8th decade of life. This has led to the hypothesis that the age-related changes in body composition, insulin sensitivity, and diseases of old age may be related to DHEA deficiency (64). The decline in DHEA and DHEAS parallels the decline of the GH/IGF-1 system (64).

DHEA serves as a multifunctional steroid precursor that is converted in the body to testosterone and estrogen. No specific binding site has been described for DHEA in any human organ, and we do not know whether DHEA has physiological effects other than those mediated through its conversion to testosterone and estrogens (64–66).

Anabolic Interventions

Testosterone

There is agreement that replacement doses of testosterone increase FFM, muscle size, and maximal voluntary strength in young, healthy, androgen-deficient men (67–70). Serum testosterone levels correlate inversely with fat mass, particularly visceral fat mass; however, not all studies report a reduction in fat mass after testosterone replacement of hypogonadal men (67–70).

The effects of testosterone supplementation on muscle strength and physical function in older men are unknown. Several short-term studies (52, 69, 71–76) have examined the anabolic effects of testosterone replacement on body composition in older men with low testosterone levels (Table 1). Tenover (53) administered testosterone enanthate, 100 mg per week, or placebo, for 12 weeks to older men with testosterone levels of <400 ng/dL⁻¹. In this double-blind, placebo-controlled, crossover study, FFM increased by 1.8 kg after testosterone replacement. In another study (71), administration of 200 mg testosterone enanthate given every 2 weeks to older men with bioavailable testosterone levels of <70 ng/dL⁻¹ was associated with a modest increase in hand grip strength, but body composition did not change. Haddad *et al.* (73) reported a significant increase in FFM and strength in hypogonadal men treated with a scrotal testosterone patch for 6 months. Urban *et al.* (74) reported increased fractional muscle protein synthesis and muscle IGF-1 messenger RNA expression in the testosterone-treated older men.

TABLE 1. Effects of testosterone supplementation in androgen-deficient young and older men

Study	Subjects	Treatment regimen	Changes in body composition	Changes in muscle function	Comments
Tenover (53)	60–75 yr, serum testosterone <400 ng/dl ⁻¹	Testosterone enanthate 100 mg weekly for 3 months	1.8 kg increase in FFM; no change in fat mass	No change in grip strength	Mild increases in PSA ^a and hematocrit
Morley <i>et al.</i> (71)	69–89 yr, bioavailable testosterone <70 ng/dl ⁻¹	Testosterone enanthate 200 mg every 2 weeks for 3 months	No change in fat mass or body weight	Increase in grip strength	
Sih <i>et al.</i> (72)	Healthy men, 51–79 yr, serum bioavailable testosterone <60 ng/dl ⁻¹	Testosterone cypionate 200 mg every 2 weeks for 12 months	0.9 (+3%) cm increase in mid-arm circumference, no change in fat mass	4–5 kg increase in grip strength	No change in PSA, increase in hematocrit
Katznelson <i>et al.</i> (69)	Hypogonadal men, 22–69 yr, mean testosterone 184 ng/dl ⁻¹	Testosterone enanthate or cypionate 100 mg weekly for 18 months	7 ± 2% increase in FFM; 14 ± 4% decrease in percent body fat	Not measured	
Haddad <i>et al.</i> (73)	Hypogonadal men of various ages	Scrotal patch	FFM increased; fat mass decreased	Unspecified increase in strength	
Urban <i>et al.</i> (74)	Healthy elderly, 67 ± 2 yr, testosterone <480 ng/dl ⁻¹	Testosterone enanthate weekly for 4 weeks to increase testosterone to 500–1000 ng/dl ⁻¹	Body composition not reported	Increase in hamstring and quadriceps work per repetition; no change in endurance	Approximately 2 fold increase in fractional muscle protein synthesis rate
Snyder <i>et al.</i> (76)	Healthy elderly, 73 ± 0.8 yr, mean testosterone 475 ng/dl ⁻¹	Scrotal patch for 36 months	1.9 ± 0.04 kg increase in FFM; 3.0 ± 0.07 kg decrease in fat mass	No change in the extension and flexion strength	
Bhasin <i>et al.</i>	Healthy, young, androgen-deficient men	Testosterone enanthate 100 mg week ⁻¹ for 10 weeks	4.5 kg increase in FFM, no change in fat mass	Increased bench press and squat strength	
Brodsky <i>et al.</i> (68)	Healthy, young, androgen-deficient men	Testosterone enanthate 3 mg/kg/2 weeks for 6 months	15% increase in FFM and muscle mass, 20% increase in muscle mass, 11% decrease in fat mass	Muscle strength not measured	Approximately 56% increase in fractional synthesis rates of mixed skeletal muscle protein
Wang <i>et al.</i> (70)	Healthy, young, androgen-deficient men	Sublingual testosterone 5 mg three times a day for 6 months	Significant increase in FFM, no change in fat mass	Muscle strength increased modestly	Significant increase in serum osteocalcin and decrease in N-telopeptide excretion

^a PSA, prostate-specific antigen.

Three clinical trials have examined the long-term effects of testosterone replacement in older men. Sih *et al.* (72) treated older men over the age of 50 yr with bioavailable testosterone of <60 ng/dl⁻¹ with placebo or testosterone cypionate, 200 mg per 2 weeks, for a period of 1 year. There was a modest improvement in grip strength after testosterone treatment. The FFM did not change significantly.

In another long-term study, Tenover (75) demonstrated significant improvements in FFM, hand grip strength, and bone density in older men with serum testosterone <350 mg/dL⁻¹ who were treated with a replacement dose of testosterone enanthate for 3 years.

Snyder *et al.* (76) examined the effects of testosterone replacement by means of a scrotal testosterone patch (6 mg per day) for 36 months in men over 65 years of age. The investigators randomized 108 older men over the age of 65 to receive either a placebo patch or testosterone scrotal patch designed to nominally deliver 6 mg testosterone daily. Ninety-six of 108 enrolled men completed the protocol. Mean testosterone concentrations increased from 367 ng/dL to 625 ng/dL in men treated with the testosterone patch, but did not change in placebo-treated men.

Testosterone treatment was associated with a significant decrease in fat mass (mean reduction in fat mass, 3 kg) and an increase in lean body mass (mean increase in lean body mass, 1.9 kg) as compared with placebo-treated men. Overall, the change in bone mineral density was not significantly different between the placebo- and testosterone-treated men (76). Further analysis revealed that bone density increased by about 6% in men with baseline testosterone levels of 200 ng/dL, but did not change in those with baseline testosterone levels of 400 ng/dL or greater. This treatment did not significantly increase the strength of knee extension and flexion. Testosterone treatment was well tolerated, and the frequency of prostate events was not significantly different between the placebo and testosterone groups. There were significant increments in hemoglobin levels in testosterone-treated men (76).

Taken together, the landmark studies of Tenover (75) and Snyder *et al.* (76) demonstrate that physiological testosterone replacement in older men with low testosterone levels produces modest increases in lean body mass, bone mineral density, and grip strength. We do not know whether physiological testosterone replacement can induce clinically meaningful changes in muscle function, reduce falls and fractures, or improve quality of life in older men. Also, the effects of testosterone supplementation in frail elderly, particularly the oldest old, the population that is the most at risk for falls, fractures, and debility, have not been examined. The long-term safety of testosterone supplementation of older men, particularly with respect to the risk of cardiovascular disease and prostate cancer remains to be established. Most studies of the androgen effects have used relatively low doses of testosterone. It is conceivable that a higher testosterone dose may yield larger effects. The data on the dose-response relationship between serum testosterone levels and muscle strength are needed to optimize the clinical efficacy and safety of testosterone regimens for use in older men.

GH

Several short-term clinical trials are in agreement that human GH supplementation in older men increases apparent lean body mass and decreases fat mass (Table 2) (77–81). Because most methods of body composition are susceptible to changes in body water, it is possible that apparent increase in lean body mass may partly reflect water accumulation. There are gender differences in GH response to provocative stimuli and in physiological responses to GH replacement therapy (82, 83). In general, premenopausal women experience greater GH secretion in response to pharmacological stimuli than men (82). In contrast, GH-deficient men are more responsive to GH replacement than women (83). During treatment, GH-deficient men have a greater increment in IGF-1 levels, a greater decrease in fat mass and plasma lipids, and a greater change in markers of bone formation and resorption (83) than GH-deficient women.

rhGH treatment does not increase knee flexion or extension and hand grip strength or systemic endurance in older men (78). This is in contrast to the young adults with rhGH deficiency who demonstrate improvements in muscle volume, isometric strength, and exercise capacity (84–86). We do not know the optimum replacement dose of rhGH. At doses in excess of 12.5 ug/kg⁻¹·day⁻¹, rhGH administration to older individuals is associated with significant side effects, including arthralgias, myalgias, edema, and carpal tunnel syndrome. It is possible that lower doses of rhGH may improve submaximal muscle performance without the side effects seen frequently at higher doses. Because of the high cost associated with rhGH treatment and the lack of demonstrable improvement in muscle function, the use of hGH replacement in frail elderly patients remains uncertain.

The response to GH therapy may be modulated by sex steroids. For instance, Ivey *et al.* (87) evaluated the effects of GH administration alone and in combination with testosterone and estrogen replacement in older men and women, 65–88 yr of age. In this study, GH administration alone increased muscle mass and muscle cross-sectional area; combined administration of GH and 100 mg testosterone enanthate every 2 weeks was associated with a greater increase in muscle cross-sectional area and a greater reduction in percent fat than either intervention alone. These data suggest that the effects of rhGH on body composition may be augmented by concomitant administration of low doses of testosterone.

Nutritional supplements

In recent years, several new steroids such as androstenedione, androstanediol, and DHEA and nutritional supplements have become widely available in health food stores.

DHEA. Low DHEAS levels have been correlated with an increased risk of breast cancer in women, higher cardiovascular morbidity in men, and the decline of immunocompetence during aging (64–66). DHEA is widely available in health food stores and over the Internet as a “nutritional supplement” and is advertised as a panacea for many aging-associated ailments including diabetes, obesity, heart disease, Alzheimer’s disease, and muscle weakness. Most of

TABLE 2. Effects of growth hormone supplementation in older men

Study	Subjects	Treatment regimen	Changes in body composition	Changes in muscle function	Comments
Rudman <i>et al.</i> (77)	Healthy men, 61–81 yr, plasma IGF-1 <350 U/L ⁻¹	hGH 0.03 mg/kg ⁻¹ 3 times per week for 6 months	8.8% increase in lean body mass; 14.4% decrease in fat mass; 1.6% increase in lumbar vertebral bone density		Mean plasma IGF-1 rose into youthful range of 500–1500 U/L ⁻¹
Papadakis <i>et al.</i> (78)	Healthy men, 70–85 yr, low baseline levels of IGF-1	hGH 0.03 mg/kg ⁻¹ 3 times per week for 6 months	4.4% increase in lean body mass; 12.8% decrease in fat mass	No change in knee or handgrip strength or systemic endurance	
Taaffe <i>et al.</i> (81)	Healthy men, 65–82 yr, mean plasma IGF-1 106 µg/L ⁻¹ , 14 weeks of pretreatment	rhGH 0.02 mg/kg ⁻¹ for 10 weeks, with resistance training	No change in body weight; lean body mass increased and fat mass decreased	No change in muscle strength	
Burman <i>et al.</i> (83)	Adult onset GH-deficient men, mean age 44.7 yr	Mean rhGH dose 1.3 U/m ⁻² body surface area for 9 months	No change in lean body mass; fat mass decreased 7.4%		
Woodhouse <i>et al.</i> (84)	Adult onset GH deficiency, mean age 43 yr	rhGH replacement	Body composition data not reported		
Jorgensen <i>et al.</i> (85)	GH-deficient adults	hGH 17 µg/kg ⁻¹ for 3 years	Body weight increased 8.4 kg; height increased 1.6 cm	22% increase in ventilation threshold, improved self-paced walking speed	GH-deficient patients required a higher percent of V _{eff} for daily activities
Salomon <i>et al.</i> (86)	GH-deficient adults 21–51 yr, peak plasma GH <3 mU/L ⁻¹	hGH 0.07 U/kg ⁻¹ /d ⁻¹ for 6 months	Lean body mass increased 5.5 kg and fat mass decreased 5.7 kg	Exercise capacity increased; quadriceps muscle strength increased 15 Nm	
Thompson <i>et al.</i> (79)	Obese, postmenopausal women (67 + 5 yr)	Calorically restricted diet, placebo, rhGH, IGF-1, or rhGH plus IGF-1	Greater loss of weight and fat mass in women treated with GH or IGF-1 than with placebo, no change in FFM in rhGH and IGF-1-treated women		RhGH can enhance loss of weight and fat mass

these claims are based on studies performed in rodents in whom the basal DHEA levels are thousand-fold lower than the levels in humans. The doses of DHEA used in the rodent studies have been relatively high and should be viewed as pharmacological. Administration of pharmacological doses of DHEA to rodents is associated with improvements in immune function and memory, reduction of fat mass, and inhibition of the development of diabetes, atherosclerosis, and cancer. In mouse models of obesity, DHEA administration reduces the rate of weight gain. However, these rodent data have yet to be confirmed in human studies.

DHEA administration to postmenopausal women is associated with increments in serum testosterone, androstenedione, estrone, estradiol, and IGF-1 levels (88). However, the human studies of DHEA either show no change or a worsening of insulin sensitivity and plasma high-density lipoprotein levels (89). Although some studies (62) report a significant reduction in fat mass with 1600 mg DHEA (50 times the daily production rates of DHEA in young men) given daily for 4 weeks, others have found no change in body composition.

Yen *et al.* (90) reported that administration of DHEA in older subjects increased DHEA blood levels and increased biologically active IGF-1; however, another study by the same group reported no change in lean body mass. Morales *et al.* (88) demonstrated that 100 mg daily dose of DHEA restored the circulating DHEA, DHEAS and IGF-1 levels in older men and women to those seen in young men and women, and significantly increased lumbar and knee muscle strength in men (88). However, others have found no change in body composition after administration of 100 mg DHEA daily for 6 months (89). Therefore, it remains unclear whether physiological DHEA replacement has beneficial biological effects in humans and claims of its potency remain unsubstantiated.

Androstenedione. Androstenedione is a steroid hormone produced endogenously by the adrenal glands and gonads of both sexes and is an intermediate in the androgen and estrogen biosynthetic pathway. Androstenedione is synthesized from DHEA and is then converted to testosterone by the enzyme 17 β -hydroxysteroid dehydrogenase or to estrone by the aromatase enzyme. Androstenedione is available over-the-counter and is marketed primarily to athletes and people interested in bodybuilding. The number of people taking androstenedione regularly is not known. The prevalence of lifetime use of illegal androgenic steroids in the United States has been estimated to be 0.9% among men and 0.1% among women (92–95). Among 12th grade males, the prevalence of lifetime use of illegal androgenic/anabolic steroids was 3.2% in 1996 (94, 95). It is likely that androstenedione use is even more common. Because supraphysiological levels of testosterone have been shown to increase muscle size and strength (96), many people claim that orally administered androstenedione will have similar anabolic effects.

An uncontrolled study reported that a single 100 mg dose androstenedione increased serum testosterone levels significantly in two women (97). The magnitude of the increase (about 100 ng/dL), however, was small. Two small, unpub-

lished studies (98, 99) have examined the effects of oral androstenedione administration on testosterone levels in men. In one study (98), 100 mg androstenedione was given to six men for 5 days. Plasma androstenedione and estradiol levels increased, but plasma testosterone levels did not change. Moreover, protein synthesis did not increase (98). In another study (99), 100 and 200 mg doses androstenedione were administered to six men for 7 days. Serum androstenedione levels increased slightly, but serum testosterone, estrone, and estradiol levels did not change (99). A third study (100) examined the effects of treating men with 100 mg androstenedione thrice daily for 10 weeks in an intermittent regimen in which 2-week intervals of drug administration were followed by 2-week periods in which the drug was not administered. The total exposure, therefore, was <6 weeks, which may have been insufficient to produce significant changes in body composition. Only 10 men received androstenedione; the sample size may have been too small to detect small, but significant, treatment effects. No significant changes in serum testosterone levels or muscle strength were found (100). The treatment groups in this study included resistance exercise alone and resistance exercise plus androstenedione; the effects of androstenedione alone were not examined. Therefore, we do not know, at present, whether androstenedione has any beneficial effects.

Creatine. Creatine, a natural nutrient found in animal source foods, is purported to have ergogenic effects on exercise performance. It has been argued that phosphorylation of creatine into phosphocreatine (PCr) and the subsequent donation of the phosphate group to adenosine diphosphate to form adenosine triphosphate serves as an important source of chemical energy for muscle contraction (91). The hypothesis is that increased stores of PCr within the muscle can help to rapidly replenish PCr and adenosine triphosphate during exercise. However, data on the effects of creatine on body composition and muscle function are inconclusive because of problems of study design. Some studies report enhancement of body weight and lean body mass with creatine supplementation, others have found no significant change in body composition or muscle performance. In an 8-week, placebo-controlled study conducted by Bermon *et al.* (101), subjects were randomly assigned into one of four groups: creatine but no exercise training; creatine plus training; placebo but no exercise training; and placebo plus training. Oral creatine supplementation, with or without a program of resistance exercise training, failed to demonstrate any increase in strength or endurance. The study also failed to show any significant changes in body composition, as measured by lower limb muscular volume. The beneficial effects of creatine on body composition and muscle function remain to be demonstrated.

Chromium picolinate. The claims that chromium picolinate has ergogenic properties and augments lean body mass, skeletal muscle size, and strength (102–104) lack validity. A well-controlled study by Campbell *et al.* (104) failed to demonstrate any beneficial effects on body composition and muscle function. In this randomized, placebo-controlled study, 18 men were assigned to receive either chromium picolinate or

TABLE 3. Effects of strength training on strength and body composition in older men

Study	Subjects	Treatment regimen	Changes in body composition	Changes in muscle function	Comments
Aniansson and Gustafsson (107)	Healthy men, 69–74 yr	12 weeks, 3 times per week, low-intensity, lower extremity strength training	No change in vastus lateralis muscle fiber cross-sectional area	9–22% increase in peak isometric and isokinetic torques of knee extensors	
Frontera <i>et al.</i> (108)	Healthy men, mean age 64 yr	12 weeks, 3 times per week, knee tension and flexion exercises at 80% of 1RM	Mid-thigh cross-sectional area increased 11%; cross-sectional area of type I and II fibers in vastus lateralis increased 34% and 28% FFM increased and fat mass decreased 5%	Knee extensor strength and knee flexor strength increased 107% and 226%	Urinary 3-methyl-L-histidine increased 41%
Craig <i>et al.</i> (114)	Healthy men, mean age 63 yr	12 weeks, 3 times per week, total body strength training		Leg press strength, leg extensor strength and bench press increased 36%, 32%, and 28%, respectively Muscle strength increased 48%	
Brown <i>et al.</i> (113)	Healthy men, 60–70 yr	12 weeks, 3 times per week, lower body dynamic resistance training at 70–90% of 1RM	Elbow flexor cross-sectional area increased 17%		
Fiatarone <i>et al.</i> (116)	Frail, institutionalized men and women, mean age 90 yr	8 weeks, 3 times per week, knee extension exercises at 80% of 1RM	Mid-thigh cross-sectional area increased 9%	1RM of knee extensors increased 174%	Tandem gait speed increased 48%
Koffler <i>et al.</i> (112)	Healthy men, mean age 60 yr	13 weeks, 3 times per week, total body strength training at 90% of 1RM	Fat mass decreased 7%	Upper body strength increased 41% and lower body strength increased 45%	
Yarasheski <i>et al.</i> (119)	Healthy, old, sedentary men with low IGF-1	16-week progressive resistance exercise at 75–90% of 1RM with placebo or rhGH (12.5–24 ug/kg-day)	FFM and total body water increased more in GH group	Isotonic and isokinetic strength similar in placebo and GH groups	Resistance training alone improved muscle strength and protein synthesis but effects of exercise were not enhanced by GH
Pratley <i>et al.</i> (111)	Healthy men, 50–65 yr	16 weeks, 3 times per week, total body strength training at 90% of 3RM	FFM increased 3% and fat mass decreased 2%	Average strength increased 40%	
Pyka <i>et al.</i> (110)	Healthy men and women, mean age 68.2 yr	30 weeks, 3 times per week, total body strength training at 75% of 1RM	Cross-sectional area of type I and II fibers increased 58% and 67%, respectively	Hip extensor strength increased 30% and hip flexor strength increased 97%	
Fiatarone <i>et al.</i> (115)	Frail, institutionalized men and women, 72–98 yr	10 weeks, 3 times per week, hip and knee extensor exercises at 80% of 1RM	Thigh muscle cross-sectional area increased 2.7%	Muscle strength increased 113%	Gait velocity and stair climbing power increased 11.8% and 28.4%, respectively

placebo in addition to participating in resistance training for 12 weeks. The authors report that chromium picolinate supplementation did not enhance muscle size, strength, or lean body mass accretion in older men during a resistance training program. Data from other studies, on which claims of efficacy are based, are inconclusive.

Strength training

Skeletal muscle mass is very responsive to changes in physical activity. Therefore, the decrease in activity with advancing age may contribute to the multifactorial pathophysiology of sarcopenia (105). The loss of muscle mass may lead to further reduction in the level of physical activity, thus accelerating the downward spiral of skeletal muscle dysfunction (5).

Exercise, specifically strength training, is the only known nonpharmacological intervention that can reverse some of the functional changes seen with aging (105, 106). Strength or resistance training involves a progressive increase in resistance, over time, against which a muscle generates force (106). Muscle strength increases in response to training using resistance that equals or exceeds 60% of the one repetition maximum (1RM; the maximum amount of weight that can be lifted with one contraction) (106). The increase in muscle size with strength training is largely the result of increased accretion of contractile protein (106). The mechanisms by which strength training increases muscle mass are not understood. The effects of strength training on effort-dependent muscle strength and body composition in older men have been examined in several short-term studies (Table 3).

The intensity of strength training determines the magnitude of improvement in muscle strength and outcomes in the elderly. When the intensity of strength training is low, only modest increases in muscle strength are seen. For instance, 12 weeks of low-intensity, lower extremity strength training in a group of older healthy men (107) was associated with a 9–22% increase in peak isometric and isokinetic torques of the knee extensors with no change in muscle cross-sectional area. In contrast, a 12-week, high-intensity, resistance training program (knee tension and flexion exercises three times per week at 80% of the 1RM) in healthy older men (108) led to a 107% and 226% increase in knee extensor and knee flexor strength, respectively. Mid-thigh cross-sectional area, estimated by computerized tomography, increased 11%, and the cross-sectional areas of type I and type II fibers increased by 34% and 28%, respectively. In addition, daily excretion of urinary 3-methyl-L-histidine increased 41%, suggesting an increase rate of myofibrillar protein turnover. Half of the subjects in this study also received a 560 kcal per day mixed-nutrient dietary supplement. The supplement had no effect on strength gains; however, body weight, creatinine excretion, and mid-thigh cross-sectional area were all increased in subjects receiving the nutritional supplement, suggesting that dietary intake may influence the magnitude of changes in body composition as a result of strength training in the elderly (109). Others (110–114) have reported similar data on the effects of strength training on muscle strength and muscle fiber diameter.

Fiatarone *et al.* (115, 116) have demonstrated the beneficial

effects of progressive resistance training in frail, institutionalized elderly individuals. These investigators have reported dramatic gains in muscle strength, muscle cross-sectional area, and tandem walking distance following an 8-week program of resistance exercise training in frail, institutionalized elderly men and women (mean age, 90 years). The maximum voluntary strength of the knee extensors increased 174%, mid-thigh cross-sectional area increased 9%, and tandem gait speed increased 48%. These data demonstrate that even in the oldest old, the capacity of the aging musculoskeletal system to adapt to increased levels of physical activity is preserved. More importantly, strength training can be safely administered to the frail elderly and may restore some of the age-related loss in function (117).

Conclusion

Aging is associated with significant reductions in fat free mass, and an increase in adiposity. The principal component of the decline in fat free mass is a decrease in muscle mass due to a reduction in muscle protein content and synthesis rates. The loss of FFM is associated with loss of muscle strength and function and with increased disability and mortality (6). The body composition changes in old age are multifactorial and may be related to the concomitant changes in hormone production, protein turnover, and disuse atrophy. The evidence to support the use of testosterone or GH supplementation in age-related sarcopenia is only beginning to be presented. Although testosterone and rhGH can augment lean body mass in older men, we do not know whether the body composition changes during these anabolic interventions are associated with improvements in muscle performance, physical function, and health-related outcomes. Also, most of the data have been generated in healthy, older men with good functional status. The effects of these interventions in the frail elderly and the oldest old have not been demonstrated. The long-term safety of pharmacological interventions such as testosterone and GH has not been established; therefore, the risk to benefit ratio remains uncertain. Research into the possible benefits of nonpharmacological supplements in the elderly is still in its infancy. Undoubtedly, the scientific knowledge has lagged far behind the public and media interest in this issue.

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