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SYSTEMATIC REVIEW

Interventions for sarcopenia and muscle weakness in older people

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Abstract

Objective: three major strategies have been tested for combating the losses in muscle mass and strength that accompany ageing. Those strategies are testosterone replacement for men, growth hormone replacement and resistance exercise training. This review will cover the risks and benefits associated with each of these interventions.
Methods: searches of PubMed and Web of Science through May 2004 yielded 85 relevant citations for the following descriptors: sarcopenia, aging/ageing, elderly, testosterone, hormone replacement, growth hormone, resistance training, exercise, muscle mass, nutrition and strength.
Results and conclusions: testosterone replacement in elderly hypogonadal men produces only modest increases in muscle mass and strength, which are observed in some studies and not in others. Higher doses have not been given for fear of accelerating prostate cancer. Growth hormone replacement in elderly subjects produces a high incidence of side-effects, does not increase strength and does not augment strength gains resulting from resistance training. Some alternate strategies for stimulating the growth hormone/insulin-like growth factor (IGF) pathway continue to hold promise. The latter include growth hormone releasing hormone (GHRH) and the complex of IGF-I with its major circulating binding protein (IGF-I/IGFBP-3). Resistance training remains the most effective intervention for increasing muscle mass and strength in older people. Elderly people have reduced food intake and increased protein requirements. As a result, adequate nutrition is sometimes a barrier to obtaining full benefits from resistance training in this population.

Keywords: *sarcopenia, ageing, muscle atrophy, growth hormone, resistance training, testosterone, elderly*

Introduction

The term sarcopenia refers to the loss of muscle mass that occurs with age and is derived from the Greek meaning 'poverty of flesh' [**1**]. Sarcopenia results in a loss of strength and is a major contributing factor to frailty, falls and loss of independence [2]. Hospitalisation following a fall often results in further disuse atrophy and a precipitous physical decline that often results in permanent loss of independence [2, 3]. Complications resulting from falls constitute the sixth leading cause of death in people over 65 [4]. As a part of normal ageing, muscle mass is reduced by approximately one-third between the ages of 50 and 80 [5]. Although there is also a decline in specific force (force per cross-sectional area), reduced muscle mass accounts for most of the loss of strength that occurs with ageing [**1**]. Sarcopenia differs from acute disuse atrophy in several ways: with disuse atrophy, muscle mass is reduced, but fibre number and specific force are maintained and there is a shift toward expression of fast fibre types [6, 7]; with sarcopenia, muscle mass, fibre number and specific force are all reduced and there is a shift toward expression of slow fibre types [7].

Many factors contribute to sarcopenia, including the loss of motoneurons, nutrition, physical inactivity, reduction in levels of sex steroids and impairments in the growth hormone (GH)/ insulin-like growth factor (IGF-I) pathway. Age is accompanied by losses in motoneurons in the anterior horn and ventral root of the spinal column [8], and by losses in the number of functioning motor units in large muscles, such as vastus lateralis [9]. In elderly people, there is a decrease in food intake, despite the increase in adiposity [10]. Reduced food intake has a number of causes, including reduced activity and resting metabolic rate, impaired taste and smell, and rapid satiation due to an impairment of cholecystokinin-mediated dilation of the stomach during a meal [10]. A substantial number of elderly men are hypogonadal. Hypogonadism has been defined as a total testosterone concentration of <9.26 nmol/l (2 SD below the mean for healthy young men [11]). By this definition, 20% of men older than 60 years and 50% of men older than 80 years are hypogonadal [12]. Circulating testosterone is highly bound to sex hormone-binding globulin (SHBG), and because serum SHBG increases with age, bioavailable testosterone (free plus albumin-bound testosterone) declines more markedly with age than does total

testosterone [12]. Loss of testosterone is associated with loss of muscle mass and strength, decreased bone mineral density, lowered libido, lowered haematocrit and increased risk of fracture following falls [12, 13, 14, 15]. Menopause is associated with the well-documented loss of bone mass, but also with loss of strength [16]. Muscle weakness develops earlier in women than in men and muscle strength can be preserved with hormone replacement therapy [17]. The latter finding is especially important because elderly women have greater functional impairment and longer life expectancy than do men. GH stimulates growth during childhood adolescence and is required for maintenance of muscle and bone in adulthood. GH exerts most of its anabolic actions through IGF-I, by stimulating the liver to secrete IGF-I into the circulation and by stimulating tissues, including muscle and bone, to produce IGF-I for local paracrine action. In addition, an important component of exercise-induced muscle hypertrophy is an increase in muscle IGF-I that occurs independently of GH [**18**]. Secretion of GH is impaired in elderly men and women, with the amplitude of night-time GH pulses declining by between 30% [19] and 70% [20].

Based on the known underlying causes of sarcopenia, three main strategies have emerged: testosterone replacement for men, growth hormone replacement and resistance exercise training. This review will cover the progress made to date with each of these strategies.

Methods

Search strategy and selection criteria

Because strength is a better predictor of function than is muscle mass, this review places major emphasis on strength as an outcome. The citations included are the result of PubMed and Web of Science searches using the following descriptors: sarcopenia, aging/ageing, elderly, testosterone, hormone replacement, growth hormone, resistance training, exercise, muscle mass, nutrition and strength.

Results and discussion

Does testosterone replacement increase strength in elderly men?

Interest in testosterone replacement has increased with the advent of transdermal patches, which eliminate the need for repeated injection. The numerous studies of testosterone replacement in elderly men have been recently reviewed by Gruenewald and Matsumoto [**21**]. Some have reported modest increases in lean mass [**22**, **23**]. Some have reported increased grip strength [**24**, 25] and others not [14, **23**, **26**]. Several studies have addressed the question of whether testosterone replacement increases lower body strength [**22**, **23**, **24**, **26**, **27**, **33**], with only two obtaining substantial positive results [**28**, **33**].

The upper panel of Table 1 lists three trials of testosterone administration in mostly younger, but also some older men. These studies demonstrate that testosterone increases muscle mass and strength in this population. Wang *et al.* [**30**] performed a randomized, double-blinded, placebo-controlled study of testosterone administration in hypogonadal men, who were aged 19–68 and were otherwise healthy. Twenty-six weeks of treatment produced substantial increases in lean mass and strength. The two other studies by Bashin *et al.* [**29**] and Brodsky *et al.* [**31**] are longitudinal studies without control groups and report similar increases. The magnitude of strength increases, although substantial, is lower than what can be achieved through resistance exercise training.

Table 1. Trials of testosterone administration in younger versus older hypogonadal men

Reference	Study type	Age (years)	Status	Dose of testosterone	Duration	Effects observed
Bhasin [29]	Longitudinal, no control group	19–47	Hypogonadal	100 mg/week, injection	10 wks	5 kg ↑ lean mass, 22% ↑ strength
Brodsky [31]	Longitudinal, no control group	19–68	Hypogonadal, otherwise healthy	180 mg/day, injection	26 wks	20% ↑ muscle mass, 56% ↑ muscle protein synthesis
Wang [30]	RCT, double-blinded	19–68	Hypogonadal	75 mg/day, transdermal	26 wks	2.7 kg ↑ lean mass, 22% ↑ strength
Brill [27]	RCT, double-blinded	Mean 68	Hypogonadal, otherwise healthy	5 mg/day	4 wks	→ strength, → fat mass, → sexual function
Kenny [22]	RCT, double-blinded	Mean 76	Hypogonadal	5 mg/day, transdermal	12 months	→ strength, ↓ underlying loss of BMD
Clague [26]	RCT, double-blinded	Mean 68	Hypogonadal, community dwelling	200 mg biweekly injection	12 weeks	→ hand grip strength, → leg strength
Snyder [23]	RCT, double-blinded	Over 65	Hypogonadal eugonadal	6 mg/day	36 months	1.9 kg ↑ lean mass, → leg strength, ↑ in lumbar, but not hip BMD in hypogonadal group only
Sih [24]	RCT, double-blinded	Mean 68	Hypogonadal, community dwelling	200 mg biweekly, injection	12 months	10% ↑ hand grip strength
Wittert [32]	RCT, double-blinded	Mean 69	Hypogonadal, community dwelling hypogonadal	80 mg twice daily, oral	12 months	2% ↑ lean mass, 5% ↓ fat mass, → grip and leg strength

RCT = randomized controlled trial, BMD = bone mineral density, LE = leg extension.

The lower panel of Table 1 shows six trials of testosterone replacement in older hypogonadal men, demonstrating that anabolic effects in this population are weaker than those observed with younger hypogonadal men. Most of these studies reported that testosterone treatment improved body composition, with increased lean mass and/or decreased fat mass [14, **22**, **23**, **27**]. However, the changes in body composition have been small and, in most cases, not accompanied by any increase in strength. Reports of randomized, placebo-controlled trials by Brill *et al.* [**27**], Kenny *et al.* [**22**], Clague *et al.* [**26**], Wittert *et al.* [**32**] and Snyder *et al.* [**23**] have all concluded that replacement doses of testosterone fail to increase strength in elderly hypogonadal men. Kenny *et al.* [**22**] found a preservation of bone mineral density, but no change in strength. Wittert *et al.* [**32**] administered an oral twice-daily dose of 80 mg testosterone undecanoate to men aged 60 and older whose circulating testosterone was in the low–normal range. Twelve months of treatment produced a small increase in lean mass, a moderate decrease in adiposity and no change in grip, quadriceps or calf strength. However, doses were not adjusted and the increase in serum testosterone was transient. Three reports have shown testosterone-induced increases in strength [**24**, **27**, 33]. Sih *et al.* [**24**] found a 5-kg increase in grip strength, amounting roughly to a 10% improvement. Urban *et al.* [33] administered testosterone to a group of six elderly men and found an approximate 25% increase in leg strength after 4 weeks of treatment. However, there was no control group in this study and strength increases may have been due to learning. The only other group to find that testosterone increased lower body strength in elderly men is Ferrando *et al.* [**28**]. They gave replacement doses of testosterone to 12 elderly hypogonadal men, adjusting the dose to maintain circulating testosterone within the normal range. Lean mass and biceps, triceps and leg extension strength all increased.

While strength increases obtained with testosterone have not been consistent or impressive, these studies do not necessarily indicate that older men are unresponsive to testosterone. Often, testosterone has been administered to older men at much lower doses than to younger men, particularly in the studies by Kenny *et al.* [**22**], Brill *et al.* [**27**] and Snyder *et al.* [**23**]. A recent abstract by Magliano *et al.* [34] reports the results of a randomized controlled trial in which high doses of testosterone were administered for 20 weeks to younger (aged 18–36 years) and older (aged 60–75 years) men. At doses of 125, 300 and 600 mg testosterone/week, significant increases in muscle mass were observed and were not different in older versus younger men. Safety was not assessed in the latter study and, in general, higher doses of testosterone have not been considered in older men because of the risk of accelerating underlying prostate cancer.

Two groups have studied the effects of dehydroepiandrosterone (DHEA) on strength in elderly people. It has been hypothesized that DHEA might improve or maintain muscle strength by increasing the ratio of circulating testosterone to cortisol. Percheron and co-workers [35] performed a double-blind placebo-controlled trial in which they treated healthy men and women aged 60–80 years for 1 year with 50 mg DHEA/day. No changes were found in a variety of measures of muscle strength. Morales *et al.* [36] performed a randomized, double-blind, placebo-controlled crossover study in which healthy, non-obese men and women aged 50–65 years were treated with a daily dose of 100 mg DHEA for 6 months. Testosterone was markedly elevated in women, but not in men. Small increases in strength were observed in men, but not women. Strength increases may have been due to a surprising increase in serum IGF-I.

Safety of testosterone therapy in elderly men

Risks of testosterone replacement in older men include fluid retention, gynaecomastia, worsening of sleep apnoea, polycythaemia and acceleration of benign or malignant prostatic tumours [14]. Amongst these risks, the potential effects of testosterone on the prostate are of the greatest concern. Initial fears that testosterone replacement would promote prostate cancer have been somewhat lessened by the findings of Hajjar *et al.* [37]. This retrospective, case-controlled study examined 45 hypogonadal men (mean age = 70 years) receiving a replacement dose of testosterone over a 2-year period. Compared to controls, treated individuals had a higher incidence of polycythaemia, but no increase in prostate cancer. However, concerns for the effect of testosterone treatment on the prostate have been rekindled by the recent release of 40-year data from the Baltimore Longitudinal Study on Aging [38] showing a positive correlation between prostate cancer and the blood concentration of free testosterone. To fully answer concerns about prostate cancer will require prospective trials involving greater numbers of subjects and longer periods of treatment. It is estimated that 10% of men will develop clinically manifest prostate cancer in their lifetime and that 3% will die of the disease [39]. However, autopsy data show a 42% prevalence of early-stage prostate cancer in men over 60 [39]. Prostate cancer has a slow progression and concerns remain that it might be accelerated by testosterone replacement.

Does administration of growth hormone increase strength in elderly subjects?

With the advent of recombinant DNA and the increased availability of GH in the 1980s, widespread interest developed in testing the efficacy of GH for a variety of wasting conditions. GH has proved efficacious in treating some conditions. Notably, GH increases muscle mass and strength in young adults with hypopituitarism [40, 41]. Svennson *et al.* [42] recently reported an anabolic effect of growth hormone in middle-aged patients. They administered a low dose of GH for 5 years to 109 men and women (mean age of 50 years) with adult-onset GH deficiency. Increases in leg strength occurred in both men and women. Because this study lacked a control group and because it is expected that some degree of physical decline will occur over 5 years, the effect of GH on strength in middle-aged subjects was probably underestimated.

Because GH is required for maintenance of muscle and bone and because elderly people are GH-deficient, it was hypothesized that GH might be useful in treating sarcopenia. However, most studies have shown that GH does not increase muscle mass and strength in elderly subjects. Initial

excitement followed the 1990 report of Rudman *et al.*, who administered replacement doses of GH for 6 months to men who were aged 60 to 81 years and whose circulating IGF-I levels placed them in the bottom third for their age group [**43**]. GH administration elevated serum IGF-I into the normal youthful range and caused some improvements in body composition; 2.4 kg loss of fat mass and a 3.7 kg increase in non-fat mass as assessed by dual-energy X-ray absorptiometry (DEXA). Papadakis *et al.* conducted a very similar double-blinded, placebo-controlled study, demonstrating conclusively that the increase in fat-free mass was not accompanied by an increase in strength [**44**]. The authors also noted that GH causes fluid retention, an effect that could confound measurement of lean mass.

Because the GH/IGF-I pathway is complex, GH administration may not adequately reproduce the effects of natural, pulsatile GH secretion. For this reason, other strategies have been used to augment the GH/IGF-I pathway in elderly people in the hope of increasing strength. Vittone *et al.* performed a longitudinal study without a control group in which they administered nightly injections of growth hormone releasing hormone (GHRH) for 6 weeks to men aged 64–76 with low circulating IGF-I concentrations [45]. They found a doubling of integrated 12-hour GH secretion, but surprisingly no increase in circulating IGF-I. Strength was moderately increased in some exercises, but not in others. Notably, no significant adverse effects were observed. Khorram *et al.* conducted a single-blind, randomized, placebo-controlled study in which the analogue GHRH (1–29-NH_2) was administered nightly for 5 months to healthy men and women with a mean age of 66 years [46]. They found improved nitrogen balance in both sexes and increased muscle mass in men only. The only adverse effect noted was transient hyperlipidaemia, which was resolved by the end of the study. GHRH may eventually prove useful in treating sarcopenia and is definitely safer than GH (see section below).

Another strategy has been to administer IGF-I, either alone or complexed to its predominant circulating binding protein (IGF-I/IGFBP-3). Freidlander *et al.* performed a 12-month, double-blinded, placebo-controlled trial of IGF-I in women aged 70 years and found no increase in bone density despite normalizing serum IGF-I [47]. However, a 2-month, double-blinded, placebo-controlled study by Boonen *et al.* has shown that IGF-I/IGFBP-3 may be more effective [48]. Use of the complex allows administration of a much higher dose of IGF-I, without the hypoglycaemia that occurs with IGF-I alone. This group administered IGF-I/IGFBP-3 to a small group of elderly women with recent hip fracture and found that, compared to placebo, femoral bone mass was preserved, grip strength was increased and that generally, IGF-I/IGFBP-3 was well tolerated.

Safety of growth hormone therapy in elderly subjects

GH is fairly well tolerated in young subjects [40, 41]. In elderly subjects, not only are the anabolic effects of GH greatly diminished, but also the adverse effects are increased. Yeo *et al.* performed a randomized, double-blind, placebo-controlled study of GH administration in elderly women after surgery for hip fracture [49]. Adverse events were no more common in the treatment group than in controls; however, the lack of serious side-effects may have been due to the short 2-week duration of the study. Most researchers have reported a high incidence of adverse effects when GH is administered to elderly subjects. In a group of elderly men receiving 6 months of GH replacement therapy, Cohn, Rudman and co-workers reported a drop-out rate of 43%, compared with only 9% in the placebo group [**50**]. The most common symptoms were carpal tunnel syndrome, gynaecomastia and hyperglycaemia. Yarasheski *et al.* have reported similar high incidences of carpal tunnel compression, fluid retention and arthralgia [**51**]. The diabetagenic effects of GH are increased in older subjects. Marcus *et al.* reported that following administration of GH to elderly subjects for only 1 week, insulin secretion during glucose tolerance testing was increased three-fold [52]. Other researchers have reported high incidences of adverse effects from GH administration in elderly subjects, including fluid retention, gynaecomastia, orthostatic hypotension, carpal tunnel compression, lower body oedema and general malaise [44, **53**].

Resistance exercise training and nutrition

Resistance exercise is a far more powerful stimulus of muscle hypertrophy than is endurance exercise. It is not surprising that Klitgaard *et al.* have found, in a cross-sectional study of elderly men with different training backgrounds, that elderly master weightlifters maintained youthful muscle mass and strength, while swimmers did not [54]. Compared with younger subjects, resistance training in elderly people produces strength increases that are smaller in absolute terms, but similar in relative terms, that is, similar percentage increases are observed in young and elderly subjects. Latham *et al.* [55] have recently reviewed the literature on progressive resistance training in older adults. Their analysis of 41 randomized controlled trials revealed that moderate to large increases in strength have usually been obtained. The studies listed in Table 2 demonstrate that resistance training produces substantial strength gains in both community-dwelling elders and nursing home residents. Some clinicians have been reluctant to recommend high-intensity resistance training for elderly subjects. However, most studies have shown that resistance training can be performed safely in an elderly population. Sullivan *et al.* [56] performed a 10-week study of lower body resistance training in a group of 19 recuperating nursing home patients whose mean age was 83 years. 1-RM strength increased by 74% and maximum gait speed increased in 53% of subjects without any adverse effects. Similarly, Hauer *et al.* [57] studied 28 elderly subjects (mean age = 81 years) with a history of injurious falls. These subjects performed 12 weeks of lower body resistance training at 70–90% 1-RM and obtained increases of 22–87% in 1-RM strength with no training-related medical problems. However, it has been suggested that patients with congestive heart failure should not engage in resistance training because increased afterload may have a negative impact on left ventricular function [58].

A review of the literature by Fielding demonstrates that a training stimulus of appropriate intensity (70–90% of 1-RM)

Table 2. Increases in leg strength obtained from high-intensity resistance training in the elderly

Reference	Study type	Sex	Age (years)	Type of training	Duration	Effects observed
Bamman [63]	RCT, healthy	M/F	mean 69	3×/week @ 80% 1-RM	25 weeks	82% ↑ in 1-RM leg strength
			mean 66	3×/week @ 80% 1-RM	25 weeks	58% ↑ in 1-RM leg strength
Brose [65]	RCT, healthy, community-dwelling subjects	M/F	mean 69	3×/week @ 80% 1-RM	14 weeks	36% ↑ in 1-RM leg strength
			mean 70	3×/week @ 80% 1-RM	14 weeks	66% ↑ in 1-RM leg strength
Carmeli [87]	RCT, ambulatory nursing home residents	M/F	mean 82	3×/week, 2–5 kg free weights	12 weeks	10–15% ↑in isokinetic leg strength
Charette [66]	RCT, healthy, community-dwelling subjects	F	mean 69	3×/week @ 65–75% 1-RM	12 weeks	28–115% ↑ in 1-RM leg strength, 7% ↑ in area of type I fibres, 20% ↑ in area of type II fibres
Connelly [73]	RCT, healthy, community-dwelling subjects	M/F	mean 76	3×/week concentric/ eccentric isokinetic ankle dorsiflexion @ max effort	2 weeks	15% ↑ in isokinetic ankle strength
Ferri [67]	no control group, healthy, physically active subjects	M	mean 68	3×/week @ 80% 1-RM	16 wk	27% ↑ in 1-RM leg strength 11% ↑ in isokinetic leg strength
Frontera [60]	no control group, healthy, sedentary subjects	M	60–72	3×/week @ 80% 1-RM	12 weeks	107% ↑ in 1-RM leg strength 11–15% ↑ in isokinetic leg strength
Frontera [68]	RCT, healthy, sedentary, community-dwelling subjects	F	mean 74	3×/week @ 85% 1-RM	12 weeks	39% ↑ in 1-RM leg strength 9% ↑ in isokinetic leg strength
Fiatarone [61]	no control group, ambulatory nursing home residents	M/F	mean 90	3×/week @ 80% 1-RM	8 weeks	174% ↑ in 1-RM leg strength
Fiatarone [64]	RCT, ambulatory nursing home residents	M/F	mean 87	3×/week @ 80% 1-RM	10 weeks	37- 178% ↑ in 1-RM leg strength
Lexell [62]	RCT, healthy, community-dwelling subjects	M/F	70–77	3×/week @ 85% 1-RM	11 weeks	163% ↑ in 1-RM leg strength
Roth [69]	RCT, healthy, sedentary community-dwelling subjects	M/F	mean 25	3×/week @ 100% 5-RM	1st 13 weeks	5.9% ↑ in thigh muscle volume
		M/F	mean 69	3×/week @ 100% 15-RM	2nd 13 weeks	5.0% ↑ in thigh muscle volume
Vincent [72]	RCT, healthy, sedentary community-dwelling subjects	M/F	mean 68	3×/week @ 50% 1-RM	24 weeks	16% ↑ in 1-RM leg strength
		M/F	mean 67	3×/week @ 80% 1-RM	24 weeks	20% ↑ in 1-RM leg strength

RCT = randomized controlled trial.

produces gains in muscle size and strength in healthy older individuals that are comparable with gains produced in young individuals [59]. Frontera *et al.* showed that following 12 weeks of progressive resistance training, a group of men aged 60–72 years experienced a two- to three-fold increase in 1-RM leg strength, with an 11% increase in muscle mass [**60**]. However, it should be noted that isokinetic leg strength increased by only 11–15%. Fiatarone *et al.* showed that impressive strength gains could be achieved even in the very old [**61**]. In their study, frail elderly people (average age = 90 years) underwent an 8-week high-intensity resistance training programme. Quadriceps 1-RM strength was increased 175% and thigh muscle area was increased 9%.

Most studies have shown that resistance training in elderly subjects must be conducted at high intensity in order to produce substantial improvements in strength. The studies listed in Table 2 demonstrate that older people can achieve very substantial increases in leg strength through high-intensity resistance training [**62**, **63**, **64**, **65**, **66**, **67**, 68, 69]. In these studies, subjects trained by lifting at least 80% of the maximum that they could lift once (1-RM). In contrast, less intense programmes of resistance exercise have produced smaller strength gains [70] or no strength gains [71]. Somewhat differing results were obtained by Vincent *et al.* [**72**], who conducted a study where elderly subjects participated in a 26-week programme of resistance training, which was performed either at low intensity (50% 1-RM) or at high intensity (80% 1-RM). They reported a modest increase in leg strength that was only slightly greater in the high-intensity group. Most studies of resistance training in the elderly have used standard concentric exercise protocols. Eccentric exercise allows for muscle loads of >1-RM and thus may have potential to produce greater strength gains than are obtained with concentric exercise. Connelly *et al.* performed a carefully controlled study of healthy elderly subjects who performed isokinetic ankle dorsiflexion training with concentric and eccentric phases [73]. Despite the short duration (2 weeks) of the study, a 15% increase in isokinetic strength was observed.

The decline in food intake that occurs even in very healthy older persons has been termed 'anorexia of ageing' and has been recently reviewed by Morley [74]. Elderly people frequently consume less than the recommended daily allowance (RDA) of 0.8 g protein/kg. In addition, elderly people have a higher rate of protein catabolism and probably a higher requirement for dietary protein [75]. Protein requirements for elderly people have been identified in a careful, randomized controlled study by Campbell *et al.*, who administered controlled diets to a group of healthy subjects aged 56–80 years. A diet containing 0.8 g protein/kg/day produced a net negative nitrogen balance and a diet containing 1.6 g/kg/day produced a positive balance [76]. This same group also performed a follow-up study to assess dietary protein requirements in older people performing resistance training, while receiving the RDA for protein [**77**]. Nitrogen balance was positive in the sedentary group and marginally positive in the exercising group, indicating that the RDA may be marginally adequate for exercising subjects. Two points make these studies difficult to interpret. First, there is a discrepancy between the results of the first study, which found negative nitrogen balance in older subjects on a diet containing 0.8 g protein/kg/day, and those of the second, which found positive balance in a similar group of sedentary subjects on a similar diet. Secondly, a marginally positive nitrogen balance in the exercising group did not prevent significant increases in strength from occurring (32–36% increases in isokinetic leg strength). Several other groups have attempted to determine more directly whether nutritional supplementation can augment training-induced strength gains in older people. Meredith *et al.* studied a group of elderly men undergoing 12 weeks of resistance training and found that dietary protein-caloric supplements augmented gains in muscle mass, but not gains in strength [78]. Fiatarone *et al.* performed a randomized, controlled study of nursing home residents undergoing 10 weeks of resistance training. They found that increases in 1-RM strength were augmented by the addition of a nutritional supplement of 360 calories. However, the effect of the supplement was not statistically significant for all exercises [64]. A subsequent, and very similar, study from the same group [79] showed that a nutritional supplement caused a very substantial augmentation of training-induced increases in 1-RM leg strength. Esmarck *et al.* [80] studied 13 elderly men (mean age = 74 years), who underwent a 12-week programme of resistance training and who received an oral protein supplement either immediately after or 2 hours after each training session. Training caused a ~25% increase in quadriceps muscle cross-sectional area if the supplement was taken immediately after the training session, but no increase was observed if the supplement was taken 2 hours after training.

It is not clear whether creatine supplements can enhance strength gains in elderly subjects. Brose *et al.* studied a group of healthy elderly men and women undergoing 14 weeks of resistance training and found that training produced substantial strength gains (Table 2). However, creatine supplementation only marginally enhanced the small increase in lean mass, and only enhanced strength in some exercises [**65**]. One drawback of these studies is that in a short training programme, most of the strength gains are due to neuromuscular adaptation, rather than muscle hypertrophy, and nutritional supplementation is hypothesized to enhance the latter. Despite these questions, it appears that exercising elderly subjects have increased protein requirements and that in some cases under-nutrition may be a barrier to obtaining strength gains from resistance training.

Does hormone replacement therapy in elderly subjects augment strength gains obtained from resistance training?

After it was generally accepted that GH therapy does not produce strength gains in elderly subjects, Taaffe and coworkers were the first to address the question of whether GH might augment strength gains obtained from resistance exercise training [**81**]. In this double-blinded, placebo-controlled study, elderly men (mean age = 70 years) performed 24 weeks of resistance training and had a 27% average increase in 1-RM strength for 10 different exercises. GH supplementation approximately doubled serum IGF-I, elevating it into the low–normal range for young men. However, the addition of GH to the training regimen produced no greater strength gains. As expected, substantial strength increases occurred during the first 12 weeks of training, when neural adaptation might be expected to play the predominant role. However, training also produced strength increases during the second 12 weeks, when hypertrophy might be expected to play the predominant role. Since GH increases strength in younger subjects via muscle hypertrophy, this study is particularly convincing in demonstrating that GH does not augment strength gains obtained from resistance training in elderly people. These findings were confirmed in the double-blinded, placebo-controlled study of Yarasheshki *et al.*, who reported that elderly men participating in a 12-week resistance exercise training programme achieved similar strength gains with or without GH replacement [82].

A study by Brill *et al.* addressed the question of whether co-administration of GH and testosterone might increase muscle mass and strength in healthy elderly men (mean age = 68 years) [**27**]. Serum testosterone and IGF-I were elevated, as was muscle IGF-I. Combined testosterone and GH produced a 2.7 kg increase in lean mass, but no increase in strength. This study is difficult to interpret because of the short, 1-month duration of treatment and because the study lacked a placebo group. However, Blackman *et al.* made similar observations in a randomized, double-blind, placebo-controlled study lasting 26 weeks [83]. Men and women aged 65–88 years were treated with GH and/or testosterone for men and hormone replacement therapy for women. Substantial elevations of serum IGF-I, testosterone and oestradiol were observed. GH reduced fat mass and increased lean mass in men and women. However, little if any increase in strength was observed (6% increase in men receiving GH plus testosterone only).

In young men, supraphysiological doses of up to 600 mg testosterone per week enhance the increases in muscle mass and strength obtained from resistance training [84, **85**]. However, at present, such high doses cannot be considered in elderly subjects and few studies have addressed the question of whether replacement doses can produce similar effects in

young and elderly subjects. Lambert *et al.* [86] examined the combined effects of a 12-week programme of high-intensity resistance training in a randomized, placebo-controlled study of men aged on average 67 years and who also received megestrol. A once-weekly dose of 100 mg testosterone enhanced training-induced muscle hypertrophy, but did not enhance training-induced strength gains despite a two-fold increase in circulating testosterone.

Conclusions and unanswered questions

Administration of testosterone to elderly subjects produces a moderate improvement in body composition (increased lean mass and decreased fat mass), but few studies have reported increases in strength. The risks associated with testosterone replacement are still not clear. Few studies have reported adverse effects, but few have administered to elderly subjects doses high enough to produce substantial anabolic effects. GH has anabolic effects in young and middle-aged subjects with GH deficiency. In contrast, it has been clearly established that GH does not increase strength in elderly people and also produces a high incidence of adverse effects. In addition, GH does not augment strength gains obtained from resistance training. Some question remains as to whether administration of GH is the right way to augment the GH/IGF-I pathway. Several other strategies for augmenting the latter pathway have been developed, the most promising being administration of the complex of IGF-I and its principal circulating binding protein (IGF-I/IGFBP-3). While the subject of this review is too broad to have included every relevant study, it is clear that the greatest and safest strength gains can be obtained by elderly subjects through a programme of high-intensity resistance exercise training. In cases of undernourished or anorectic subjects, nutritional support should be also considered.

Key points

- Testosterone replacement in elderly hypogonadal men produces only modest increases in muscle mass and strength, which are observed in some studies and not in others. Higher doses have not been given for fear of accelerating prostate cancer.
- Growth hormone replacement in elderly subjects produces a high incidence of side-effects, does not increase strength and does not augment strength gains resulting from resistance training.
- Some alternate strategies for stimulating the growth hormone/IGF pathway continue to hold promise. The latter include growth hormone releasing hormone (GHRH) and the complex of IGF-I with its major circulating binding protein (IGF-I/IGFBP-3).
- Resistance training remains the most effective intervention for increasing muscle mass and strength in older people. Elderly people have reduced food intake and increased protein requirements. As a result, adequate nutrition is sometimes a barrier to obtain full benefits from resistance training in this population.

Please note

The very long list of references supporting this review has meant that only the most important are listed here and are represented by bold type throughout the text. The full list of references is available on the journal website (http://www.ageing.oupjournals.org).

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