Pharmacological Treatment of Frailty in the Elderly

Stephen Campbell, Cassandra Szoeke

ABSTRACT

The geriatric frailty syndrome can be characterised by a loss of physiological reserve in a variety of organ systems and an independent association with disability and mortality. The high cost of this condition in terms of decreased quality of life and an increased need for medical and personal care makes it an important focus for the development of effective pharmacological treatments. Several of these treatments have been trialled and have focused on the decreased levels of catabolic hormones seen in advancing age. Despite some improvement in muscle and tissue bulk, most of these treatments have failed to improve physical function in the elderly. In this review we examine the evidence for the pharmacological treatment of frailty in the elderly and provide recommendations for its management.

J Pharm Pract Res 2009; 39: 147-51.

INTRODUCTION

The geriatric frailty syndrome lacks a universal definition but can be characterised by a loss of physiological reserve in a variety of organ systems, with an independent association with both disability and mortality.[1,2] The high cost of this condition in both decreased quality of life and an increased need for medical and personal care makes it an important focus for the development of effective pharmacological treatments. Several of these treatments have been trialled, focusing on the decreased levels of catabolic hormones seen in advancing age. Despite promising initial results and some improvement in muscle and tissue bulk, most of these treatments have failed to improve the physical function of their elderly subjects.

DEFINITION

A major limitation of research in this area is the lack of standardised criteria to define frailty. Studies in geriatric frailty use definitions ranging from description of a physical syndrome (three of the following five attributes – muscle weakness, unintentional weight loss, slow walking speed, exhaustion, low physical activity) to broader definitions of frailty, which include not just the physical functioning of an individual, but also their assets in the form of intellect, medical resources, social support and financial resources.[3,4] This review will focus on physical function, as the broader social parameters are not amenable to pharmacological intervention.

Any useful definition of a syndrome should be supported by research demonstrating an independent correlation with increased risks for hospitalisation and disability – independent of the presence of disease or comorbidity. In a prospective trial, physical frailty as per Fried's definition has been shown to predict falls, fractures and increased mortality.[5] The studies demonstrating a correlation with negative outcomes such as decreases in the quality of life, independence and health in the elderly reinforce the importance of research in this area.[6-8] With the population ageing, the cost to individuals, carers and the community from the sequelae of frailty needs to be addressed.

PATHOPHYSIOLOGY

The focus on muscle strength as a major contributor to frailty stems from research demonstrating strong links between decreased physical capacity and morbidity as well as the potential for treatment. Muscle mass decreases by 3 to 8% per annum after the age of 30 years with an accelerated decline after the age of 60 years.[9] This muscle loss is termed sarcopenia. With ageing, biochemical and structural degenerative changes occur within the muscle fibres, as well as in the neuromuscular junction and motor neurone.[10] These changes contribute to around 30% reduction in exercise capacity seen in the elderly.

Frailty has a significant impact on morbidity in the elderly population and muscle strength plays an important role in its aetiology. Treatment to improve muscle strength has ranged from pharmacological to physical therapy. Targets for therapy of frailty have included anabolic hormones, nutritional factors including vitamin D, and opportunistic discoveries such as the angiotensin converting enzyme inhibitors.

PHARMACOTHERAPY

Angiotensin Converting Enzyme Inhibitors

With the well known positive effects of the angiotensin converting enzyme inhibitors on cardiac muscle, it is perhaps not surprising that they also have positive effects on skeletal muscle. Two isoforms of the angiotensin converting enzyme gene exist – people with the type II genotype have low serum angiotensin converting enzyme levels and an enhanced performance in activities requiring physical endurance.[11] In an observational study of elderly women with hypertension, angiotensin converting enzyme inhibition demonstrated a decrease in the rate of decline in muscle function in women treated with angiotensin converting enzyme inhibitors as compared to other drugs.[12] Following from

Stephen Campbell, MBBS, FRACP, Consultant Geriatrician, Aged and Residential Care Services, Austin Health, Heidelberg, **Cassandra Szoeke,** MBBS, FRACP, Head, Neurosciences Reaserch, Commonwealth Scientific and Industrial Research Organisation, Parkville, Victoria
Address for correspondence: Dr Stephen Campbell, Aged and Residential Care Services, Austin Health, Heidelberg Vic. 3084, Australia.
E-mail: stephen.campbell@austin.org.au

these results, a double-blind randomised trial of 130 subjects aged over 65 years and suffering from decreased mobility or functional impairment, found that a 20-week course of perindopril improved exercise capacity even in the absence of cardiac disease on echocardiography.[13] In this study by Sumkadas et al., 46 of the 52 completing subjects achieved the target dose of perindopril 4 mg daily and six subjects achieved perindopril 2 mg daily.[13] Although the study was not powered for subset analysis, the subjects who benefited the most were under 80 years of age and/or had peripheral vascular disease.

The enhanced effect in this subset of patients might be due to subclinical cardiac dysfunction not detected by echocardiography. In the early stages of cardiac pressure overload, skeletal muscle dysfunction occurs, a process which can be prevented by the use of angiotensin converting enzyme inhibitors. This protective effect has been largely attributed to the prevention of the loss of muscle cross-bridges.[14] It may well be that the excess of angiotensin converting enzyme activity seen in even subclinical cardiac disease is sufficient to decrease muscle strength.

Vitamin D

It has been long known that hypovitaminosis D causes osteomalacia but it was only recently that the beneficial effects of vitamin D on muscle and balance have been recognised. For example, studies such as that of 1271 community-dwelling Dutch individuals over the age of 65 years, have shown an association between low vitamin D levels and physical frailty.[15] An epidemiological study of 4100 subjects over 60 years of age showed that those with a vitamin D level below 60 mmol/L had a slower ability to rise from a chair and walk a set distance (the 'get up and go' test).[16]

Some limited but well-constructed studies have examined the benefits of vitamin D replacement. In elderly subjects with low vitamin D levels, one study showed that a single injection of ergocalciferol 600 000 units reduced postural sway (a known risk factor for falls) during walking.[17] Other tests of neuromuscular function (sum score of the walking test, chair stand and tandem stand) also improved in 1300 elderly subjects given vitamin D supplements.[18,19] With an increase in muscle function and improved neuromuscular function, it is not surprising that the risk of falls can be reduced by vitamin D supplements.[20,21] These benefits are dose-dependent and seen at doses above 700 units but not at 400 units.[21]

Although more research is required on the benefits of vitamin D supplementation in the elderly, given the relative paucity of treatment adverse effects and previously documented benefits on bone strength, it would seem a good choice for both screening and treatment.

Anabolic Hormones

Sex Steroids

Testosterone is one of the most potent human anabolic steroids and is known to increase both muscle mass and strength in the young.[22,23] As such it would seem to be a logical choice for treatment of the reduced muscle mass and strength seen with ageing. Testosterone levels below the normal range are seen in 60% of men over the age of 65 years, a state known as the andropause.[24] A decrease in free testosterone (less than 146 pmol/L) is associated with an increased risk of falls, impaired balance and muscle weakness in older men.[25]

In women, menopause is associated not only with an early loss of bone density but also with loss of muscle strength.[26] This weakness develops earlier than in men, perhaps due to the more abrupt hormonal decreases in the post-menopause and can be prevented with oestrogen replacement therapy.[27] The sex steroids are thus logical candidates for therapy of age-related decreases in muscle strength.

Trials of testosterone replacement and augmentation have produced disappointing results. In hypogonadal men aged 19 to 68 years, testosterone replacement increased muscle mass and strength.[23,28,29] A dose-response study of testosterone replacement in hypo-androgenic younger men showed that testosterone increased muscle bulk but did not improve fatiguability or the power of individual muscle fibres.[30] In younger men with HIV, testosterone supplementation increased muscle bulk but only exercise was able to increase muscle power.[31] Several studies in older men (over 65 years of age), have demonstrated increases in muscle mass but no significant improvement in strength.[32-37] One criticism of these studies is the relatively low dose of testosterone used, with much lower doses used in older subjects than the younger cohorts. The lower doses may have been due to concerns regarding potential adverse effects in older men. Prostatic hypertrophy and prostate cancer are a particular concern, due to the sensitivity of the prostate to testosterone levels, with The Baltimore Study on Aging showing a correlation between prostate cancer and free testosterone levels.[38] Other common adverse effects of testosterone supplementation are oedema, polycythaemia, gynaecomastia and worsening of obstructive sleep apnoea.

In contrast to these results are those from Page et al., where increases in both strength and function were observed when older testosterone-deficient men were given testosterone replacement.[39] The difference in these results may be explained by the use of injectable testosterone by Page et al. rather than testosterone patch used in the other studies. Injectable testosterone achieved higher peak testosterone levels and risk was attenuated by the co-administration of finasteride, which halved the levels of dihydrotestosterone by 50%.[39]

Testosterone therapy is effective in relieving the symptoms of deficiency in younger men but appears to have no clear benefit in the frail elderly. Although muscle mass may increase, strength and physical function will only improve as a result of exercise.

Dehydroepiandrosterone

Dehydroepiandrosterone, an endogenous steroid precursor of testosterone and oestrogen, levels decline with age and there is a correlation between decreasing serum levels, and muscle mass and strength in men aged over 60 years.[40,41] Several trials in the elderly have failed to show any improvement in muscle strength or wellbeing.[42-45] The US Food and Drug Administration, has classified dehydroepiandrosterone as a nutritional supplement thus allowing its use and benefits to be heavily promoted despite the absence of strong evidence for its efficacy.

Growth Hormone

Growth hormone is required for normal growth during childhood and adolescence as well as for the maintenance of normal bone and muscle strength during adulthood. Growth hormone acts by stimulating the liver and other tissues to produce insulin-like growth factor-1 (IGF-1). Skeletal muscle is responsible for the production of approximately a quarter of the total production of IGF-1, with two distinct isoforms produced – one unique to skeletal muscle.[46] This muscle variant of IGF-1 is up-regulated by exercise, growth hormone, testosterone, insulin and vitamin D.[47,48] In the elderly, growth hormone secretion is significantly reduced, a state which theoretically might be expected to result in a decrease in muscle mass.[49] Therefore, growth hormone replacement or supplementation might be expected to improve muscle mass and strength.

When growth hormone is used to treat middle-aged subjects with adult-onset deficiency, an increase in leg strength can be seen in men and women.[50] This response is not replicated in elderly subjects, with several well-constructed prospective trials demonstrating some changes in body composition but minimal improvement in strength. For example, Rudman et al. conducted a six month prospective trial of growth hormone replacement in men aged 61 to 80 years with significantly decreased serum IGF-1 levels.[51] Although there was a 2.4 kg loss of fat mass and a 3.7 kg increase in non-fat mass there was no associated improvement in strength.[51] Papadakis et al. undertook a double-blind, placebo-controlled trial of growth hormone supplementation in healthy elderly men with low serum growth hormone levels with comparable results.[52] In one randomised, controlled trial that combined both growth hormone and sex steroid (transdermal oestrogen in women and intramuscular testosterone in men), small but statistically significant gains in total body strength and VO_2 max (maximum amount of oxygen that can be used in one minute per kilogram of body weight) were seen in men only.[53] These small gains were far outweighed by the significant adverse effects experienced by nearly half of the participants.[53]

As with the sex steroids, the use of growth hormone in older people is associated with significant adverse effects. Hyperglycaemia, gynaecomastia, fluid retention, arthralgia and carpal tunnel syndrome are experienced by many recipients.[53-56] No consistent benefit in strength, mortality or function has been observed with growth hormone supplementation despite many years of research and its use is not recommended in clinical treatment of the frail elderly.

Insulin-Like Growth Factors

Growth hormone acts on skeletal muscle via the production of IGF-1. Several isoforms of IGF-1 exist but only some are produced in response to increased levels of serum growth hormone.[57] At least one of these IGF-1 isoforms is found in skeletal muscle and is produced in response to exercise but not growth hormone. Therefore, it has been postulated that direct IGF-1 supplementation may be able to increase the strength of skeletal muscle where growth hormone has failed. IGF-1 has been administered directly and complexed to its circulating binding protein.[58,59] In a one-year trial of IGF-1 supplementation in healthy women with a mean age of 76 years, despite increasing serum IGF-1 to young-normal values, no increase in bone density or strength was demonstrated.[58]

When given directly, doses of IGF-1 are limited by symptomatic hypoglycaemia. However, Boonen et al. were able to administer higher doses of the IGF-1 complex to their subjects without risking dangerous hypoglycaemia.[59] They studied a small group of women with recent hip fracture in a placebo controlled trial which showed prevention of post-fracture osteoporosis and an increase in grip strength. This study did not demonstrate improvements in overall function and the IGF-1 complex was both expensive and required intravenous administration.

INFLAMMATION

The inflammatory mediators, interleukin-6 and its downstream activity marker C-reactive protein have been associated with the development of the geriatric frailty syndrome.[3,60] Certainly, in those with chronic disease, interleukin-6, C-reactive protein and tumour-necrosis factor alpha have been linked with decreased appetite, osteoporosis and a loss of muscle mass.[61,62] Some commentators have postulated on a possible link between an ageing immune system, an increase in the incidence of autoantibodies and an increase in non-specific inflammation in the frail elderly, as well as the possibility of an identifiable 'immune risk phenotype' among the very old.[63,64]

The association between raised markers of inflammation and outcome have been examined in large epidemiological studies. Barzilay et al. found an association between C-reactive protein levels and the subsequent five year development of frailty in a large cohort of elderly women.[65] Within the 1102 subjects of the Women's Health and Aging Studies I and II, Leng found that raised interleukin-6 levels were associated with an increase in frailty (odds ratio 2.81).[66]

The cause of this association between inflammation and physical function has been debated between those who believe that a dysregulation of the immune system is the primary cause, and those who believe that an accumulation of clinical and subclinical disease results in these outcomes.[60] This might represent a primary disorder of immune regulation or alternatively a loss of the ability to maintain homoeostasis in the face of multiple failing organ systems.

Further prospective studies are required with a focus on health status and the levels of these inflammatory mediators over time. Should a direct association be proven, then immune mediators could be used to reverse these effects. Alternatively, should raised inflammatory mediators be a marker of under-treated medical conditions, then it is possible that future screening could identify a population that could benefit from more intensive medical management.

DISCUSSION

The maintenance of physical strength and independence is a goal shared by most older people. Although some maintain robust good health into an advanced age, others develop increasing frailty, disability and early institutionalisation and death. With the causes of physical frailty still unclear, it is not surprising that attempts to treat pharmacologically have largely failed.

Although levels of anabolic hormones in the form of testosterone, oestrogen, growth hormone and IGF-1 all decline significantly with age, replacement has been largely disappointing. While anabolic drugs are useful in the treatment of hormone deficiencies in the young, the lack of results in the elderly indicate that their decreasing levels are a part of normal ageing rather than a specific cause of functional decline. Although the modest improvements seen with high-dose IGF-1 were encouraging, its use is unlikely to be practical due to cost, adverse effects and means of administration. The lack of positive results is not surprising, as ageing is a complex process of diffuse damage to widespread systems, ranging from the molecular level with genetic damage, changes within subcellular organelles, through to age and disease-related cognitive change. Added to this are social and environmental factors, all of which can affect an older person's independent functioning. As the cause of physical frailty in the elderly is as yet unknown, it is not surprising that specific treatments have been elusive.

In contrast to the disappointing results from pharmacological trials, exercise in combination with protein supplements (but not protein supplements alone) has shown to improve muscle mass and strength in very old nursing home residents.[67] Similar results have been seen for physical therapy in the frail elderly.[68]

Medicines with proven benefit are, surprisingly, not generally thought to have a primary action on muscle. Vitamin D supplements at daily doses of 700 units and over increase muscle strength and neuromuscular function. Angiotensin converting enzyme inhibitors have demonstrated promising results in the improvement of skeletal muscle endurance. Although further study is required, it would seem sensible for angiotensin converting enzyme inhibitors to be chosen as the first-line therapy for hypertension in the elderly, especially in those under 80 years of age with peripheral vascular disease or risk factors for cardiac disease.

Although raised inflammatory mediators are associated with the loss of muscle mass and the development of frailty, it is unclear whether these changes are due to an intrinsic dysfunction within the regulation of the immune system or the presence of an accumulation of underlying disease. It would seem that in the absence of further data, targets for treatment in this condition could be a wide range of potentially under-treated medical conditions with a known inflammatory component, such as peripheral vascular disease, heart failure, osteoarthritis and the metabolic syndrome. Although raised inflammatory cytokines are related to a number of diagnoses and the frailty phenotype, the ability to reduce their levels with successful therapy has yet to be demonstrated. Further research is required into the potential changes in inflammatory cytokines with more intense medical management of these and other conditions as well as any associated improvement in physical function.

CONCLUSION

As enticing as an 'elixir of youth' might be, anabolic hormones are associated with significant adverse effects and no clear evidence of improvements in function. The evidence does support the benefits of vitamin D supplements where levels are low and possibly the use of angiotensin converting enzyme inhibitors. As raised inflammatory cytokines potentially represent underlying untreated pathology, good comprehensive medical care and the optimal treatment of all underlying conditions is important.

Competing interests: None declared

References

1. Barzilay JI, Blaum C, Moore T, Xue QL, Hirsch CH, Walston JL, et al. Insulin resistance and inflammation as precursors of frailty. The Cardiovascular Health Study. Arch Intern Med 2007; 167: 635-41.
2. Borz W. A conceptual framework of frailty: a review. J Gerontol Med Sci 2002; 57: M283-M288.
3. Fried LP, Tangen C, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146-M156.
4. Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hebert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. Lancet 1999; 353: 205-6.
5. Ensrud KE, Ewing SK, Taylor BC, Fink HA, Stone KL, Cauley JA, et al. Frailty and risk of falls, fracture, and mortality in older women: the study of osteoporotic fractures. J Gerontol A Biol Sci Med Sci 2007; 62: 744-51.
6. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in older people. J Gerontol A Biol Sci Med Sci 2007; 62: 738-43.
7. Fried LP, Borhani NO, Enright P, Furberg CD, Gardin JM, Kronmal RA, et al. The Cardiovascular Health Study: design and rationale. Ann Epidemiol 1991; 1: 263-76.
8. Bandeen-Roche K, Xue QL, Ferrucci L, Walston J, Guralnik JM, Chaves P, et al. Phenotype of frailty: characterisation in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 2006; 61: 262-6.
9. Melton LJ, Khosla S, Crowson CS, O'Connor MK, O'Fallon WM, Riggs BL. Epidemiology of sarcopenia. J Am Geriatr Soc 2000; 48: 625-30.
10. Volpi E, Nazemi R, Fujita S. Muscle tissue changes with aging. Curr Opin Clin Nutr Metab Care 2004; 7: 405-10.
11. Montgomery H, Clarkson P, Barnard M, Bell J, Brynes A, Dollery C, et al. Angiotensin-converting-enzyme gene insertion/deletion polymorphism and response to physical training. Lancet 1999; 353: 541-5.
12. Onder G, Penninx BW, Balkrishna R, Fried LP, Chaves PH, Williamson J, et al. Relation between use of angiotensin-converting enzyme inhibitors and muscle strength and physical function in older women: an observational study. Lancet 2002; 359: 926-30.
13. Sumukadas D, Witham M, Struthers AD, McMurdo ME. Effect of perindopril on physical function in elderly people with functional impairment: a randomized controlled trial. CMAJ 2007; 177: 867-74.
14. Coirault C, Langeron O, Lambert F, Blanc FX, Lerebours G, Claude N, et al. Impaired skeletal muscle performance in the early stage of cardiac pressure overload in rabbits: beneficial effects of angiotensin-converting enzyme inhibition. J Pharmacol Exp Ther 1999; 291: 70-5.
15. Puts MT, Visser M, Twisk JW, Deeg DJ, Lips P. Endocrine and inflammatory markers as predictors of frailty. Clin Endocrinol (Oxf) 2005; 63: 403-11.
16. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, et al. Higher 25-hydroxyvitamin D concentrations are associated with better lower extremity function in both active and inactive persons aged ≥ 60 y. Am J Clin Nutr 2004; 80: 752-8.
17. Dhesi JK, Jackson SH, Bearne LM, Moniz C, Hurley MV, Swift CG, et al. Vitamin D supplementation improves neuromuscular function in older people who fall. Age Ageing 2004; 33: 589-95.
18. Wicherts IS, Van Schoor NM, Boeke AJ, Visser M, Deeg DJ, Smit J, et al. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab 2007; 92: 2058-65.
19. Flicker L, MacInnis RJ, Stein MS, Scherer SC, Mead KE, Nowson CA, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomised trial. J Am Geriatr Soc 2005; 53: 1881-8.
20. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of vitamin D on falls: a meta-analysis. JAMA 2004; 291: 1999-2006.
21. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents severe falls in elderly community-dwelling women: a pragmatic population-based 3-year intervention study. Aging Clin Exp Res 2005; 17: 125-32.
22. Urban RJ, Bodenburg YH, Gilkison C, Foxworth J, Coggan AR, Wolfe RR, et al. Testosterone administration to elderly men increases skeletal muscle strength and protein synthesis. Am J Physiol 1995; 269: E820-E826.
23. Bhasin S, Storer TW, Berman N, Yarasheski KE, Clevenger B, Phillips J, et al. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab 1997; 82: 407-13.
24. Lamberts SW, van den Beld AW, van der Lely AJ. The endocrinology of aging. Science 1997; 278: 419-24.
25. Szulc P, Claustrat B, Marchard F, Delmas PD. Increased risk of falls and increased bone resorption in elderly men with partial androgen deficiency: the MINOS study. J Clin Endocrinol Metab 2003; 88: 5240-7.
26. Sipila S, Taafe DR, Cheng S, Puolakka J, Toivanen J, Suominen H. Effects of hormone replacement therapy and high-impact physical exercise on skeletal muscle in post-menopausal women: a randomised placebo-controlled study. Clin Sci (Lond) 2001; 101: 147-57.

27. Phillips SK, Rook KM, Siddle NC, Bruce SA, Woledge RC. Muscle weakness in women occurs at an earlier age than in men, but strength is preserved by hormone replacement therapy. Clin Sci (Lond) 1993; 84: 95-8.
28. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 2000; 85: 2839-53.
29. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men-a clinical research center study. J Clin Endocrinol Metab 1996; 81: 3469-75.
30. Storer TW, Magliano L, Woodhouse L, Lee ML, Dzekov C, Dzekov J, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatiguability or specific tension. J Clin Endocrinol Metab 2003; 88: 1478-85.
31. Bhasin S, Storer TW, Javanbakht M, Berman N, Yarasheski KE, Phillips J, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. JAMA 2000; 283: 763-70.
32. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Endocrinol Metab 1999; 84: 2647-53.
33. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2001; 56: M266-M272.
34. Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. J Clin Endocrinol Metab 2002; 87: 5649-57.
35. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. Int J Androl 1999; 22: 261-5.
36. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. J Gerontol A Biol Sci Med Sci 2003; 58: 618-25.
37. Sih R, Morley JE, Kaiser FE, Perry HM 3rd, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997; 82: 1661-7.
38. Mikuz G. Pathology of prostate cancer. Old problems and new facts. Adv Clin Path 1997; 1: 21-34.
39. Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005; 90: 1502-10.
40. Valenti G, Denti L, Maggio M, Ceda G, Volpatos S, Bandinelli S, et al. Effect of DHEAS on skeletal muscle over the life span: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2004; 59: 466-72.
41. O'Donnell AB, Travison TG, Harris SS, Tenover JL, McKinlay JB. Testosterone, dehydroepiandrosterone, and physical performance in older men: results from the Massachusetts Male Aging Study. J Clin Endocrinol Metab 2006; 91: 425-31.
42. Flynn MA, Weaver-Osterholtz D, Sharpe-Timms KL, Allen S, Krause G. Dehydroepiandrosterone replacement in aging humans. J Clin Endocrinol Metab 1999; 84: 1527-33.
43. Jedrzejuk D, Medras M, Milewicz A, Demissie M. Dehydroepiandrosterone replacement in healthy men with age-related decline of DHEA-S: effects on fat distribution, insulin sensitivity and lipid metabolism. Aging Male 2003; 6: 151-6.
44. Percheron G, Hogrel JY, Denot-Ledunois S, Fayet G, Forette F, Baulieu EE, et al. Effect of 1-year oral administration of dehydroepiandrosterone to 60- to 80-year-old individuals on muscle function and cross-sectional area: a double-blind placebo-controlled trial. Arch Intern Med 2003; 163: 720-7.
45. Nair KS, Rizza RA, O'Brien P, Dhatariva K, Short KR, Nehra A, et al. DHEA in elderly women and DHEA or testosterone in elderly men. N Engl J Med 2006; 355: 1647-59.
46. McKoy G, Ashley W, Mander J, Yang SY, Williams N, Russell B, et al. Expression of insulin growth factor-1 splice variants and structural genes in rabbit skeletal muscle induced by stretch and stimulation. J Physiol 1999; 516: 583-92.
47. DeVol DL, Rotwein P, Sadow JL, Novakofski J, Bechtel PJ. Activation of insulin-like growth factor gene expression during work-induced skeletal muscle growth. Am J Physiol 1990; 259: E89-E95.
48. Grounds MD. Reasons for the degeneration of ageing skeletal muscle: a central role for IGF-1 signalling. Biogerontology 2002; 3: 19-24.
49. Iranmanesh A, Lizzaralde G, Veldhuis JD. Age and relative adiposity are specific negative determinants of the frequency and amplitude of growth (GH) secretory bursts and the half-life of endogenous GH in healthy men. J Clin Endocrinol Metab 1991; 73: 1081-8.
50. Svensson J, Sunnerhagen KS, Johannsson G. Five years of growth hormone replacement therapy in adults: age- and gender-related changes in isometric and isokinetic muscle strength. J Clin Endocrinol Metab 2003; 88: 2061-9.
51. Rudman D, Feller AG, Nagraj HS, Gergans GA, Lalitha PY, Goldberg AF, et al. Effects of human growth hormone in men over 60 years old. N Engl J Med 1990; 323: 1-6.
52. Papadakis MA, Grady D, Black D, Tierney MJ, Gooding GA, Schambelan M, et al. Growth hormone replacement in healthy older men improves body composition but no functional ability. Ann Intern Med 1996; 124: 708-16.
53. Blackman MR, Sorkin JD, Munzer T, Bellantoni MF, Busby-Whitehead J, Stevens TE, et al. Growth hormone and sex steroid administration in healthy aged women and men: a randomized controlled trial. JAMA 2002; 288: 2282-92.
54. Cohn L, Feller AG, Draper MW, Rudman IW, Rudman D. Carpal tunnel syndrome and gynecomastia during growth hormone treatment of elderly men with low circulating IGF-I concentrations. Clin Endocrinol (Oxf) 1993; 39: 417-25.
55. Yarasheski KE, Zachwieja JJ. Growth hormone therapy for the elderly: the fountain of youth proves toxic. JAMA 1993; 270: 1694.
56. Liu H, Bravata D, Olkin I, Nayak S, Roberts B, Garber AM, et al. Systematic review: the safety and efficacy of growth hormone in the healthy elderly. Ann Intern Med 2007; 146: 104-15.
57. Hameed M, Harridge SD, Goldspink G. Sarcopenia and hypertrophy: a role for insulin-like growth factor-1 in aged muscle? Exerc Sport Sci Rev 2002; 30: 15-19.
58. Friedlander AL, Butterfield GE, Moynihan S, Grillo J, Pollack M, Holloway L, et al. One year of insulin like growth factor-I treatment does not affect bone density, body composition, or psychological measures in postmenopausal women. J Clin Endocrinol Metab 2001; 86: 1496-503.
59. Boonen S, Rosen C, Bouillon R, Sommer A, McKay M, Rosen D, et al. Musculoskeletal effects of the recombinant human IGF-I/IGF binding protein-3 complex in osteoporotic patients with proximal femoral fracture: a double blind, placebo-controlled pilot study. J Clin Endocrinol Metab 2002; 87: 1593-9.
60. Walston J, Hadley E, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, et al. Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/ National Institute on Aging Research Conference on Frailty in Older Adults. J Am Geriatr Soc 2006; 54: 991-1001.
61. Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, et al. Inflammatory markers and performance in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2004; 59: 242-8.
62. Bautmans I, Njemini R, Predom H, Lemper JC, Mets T. Muscle endurance in elderly nursing home residents is related to fatigue perception, mobility, and circulating tumour necrosis factor alpha, interleukin-6 and heat shock protein 70. J Am Geriatr Soc 2008; 56: 389-96.
63. Roubenoff R. Physical activity, inflammation, and muscle loss. Nutr Rev 2007; 65: S208-S212.
64. Frederick F, Wikby A, Maxson P, Olsson J, Johansson B. Immune parameters in a longitudinal study of a very old population of Swedish people: a comparison between survivors and nonsurvivors. J Gerontol Bioi Sci 1995, 50A: B378-B382.
65. Barzilay JI, Blaum C, Moore T, Xue Q-L, Hirsch CH, Walston JD, et al. Insulin resistance and inflammation as precursors of frailty. Arch Intern Med 2007; 167: 635-41.
66. Leng SX, Xue Q-L, Tian J, Walston JD, Fried LP. Inflammation and frailty in older women. J Am Geriatr Soc 2007; 55: 864-71.
67. Fiaterone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, et al. Exercise training and nutritional supplementation for physical frailty in very elderly people. N Engl J Med 1994; 330: 1769-75.
68. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons who live at home. N Engl J Med 2002; 347: 1068-74.

Received: 5 May 2009
Revisions requested after external review: 19 June 2009
Revised version received: 24 June 2009
Accepted: 28 June 2009

The material in this article has been accredited by SHPA as suitable for inclusion in a pharmacist's CPD plan as outlined in the **shpacpd** program. A series of questions that can assist you with evaluating your learning outcomes can be found on the SHPA web site <www.shpa.org.au/docs/cpd.html>. Answers to these questions can be lodged until June 2010. In **shpacpd** this is considered an Activity Group 2 activity: improving knowledge and skills with assessment. The number of hours will be dependent on the time taken to read the article, complete the questions and submit the answers.