Endocrine therapies for sarcopenia in older men

This review looks at new therapeutic developments for the increasingly recognized problem of sarcopenia. Increased adiposity and reduced lean body mass characterize ageing men. The potential therapeutic role of the growth hormone/insulin-like growth factor axis, androgen modulators and myostatin inhibition are discussed.

It is increasingly recognized that an age-related increase in fat mass and decline in muscle mass occur both in men and women. This process is exacerbated by chronic rheumatological or neuromuscular disease and states of immobility. In attempting to understand the pathophysiological processes involved, men have been studied in greater depth. Men show a gradual, but detectable, decline in testosterone levels with age unlike women, in whom more abrupt endocrine changes occur around the menopause. In addition, there is significant controversy in relation to estimating testosterone levels in women. In both men and women it is observed that a reduction in activity the growth hormone (GH)/insulin-like growth factor (IGF-1) system occurs with age. Therefore, overall, the focus of this review is on the older male but many of the underlying principles also have relevance for females.

The process of altered body composition with age places individuals at risk of both developing obesity and the functional consequences of impaired physical strength. It is not known precisely how this occurs, but likely interacting candidates are impaired mechano-transduction and reduced availability of anabolic hormones. Adult skeletal muscle contains satellite cells, located beside muscle fibres, which are able to replicate and fuse with myofibres during regeneration and repair. When this regenerative process exceeds atrophic changes, increased muscle fibre size (hypertrophy) occurs. The endocrine candidates currently under investigation for treating age-related muscle loss would theoretically alter the atrophy-hypertrophy imbalance that is characteristic of ageing (*Figure 1*).

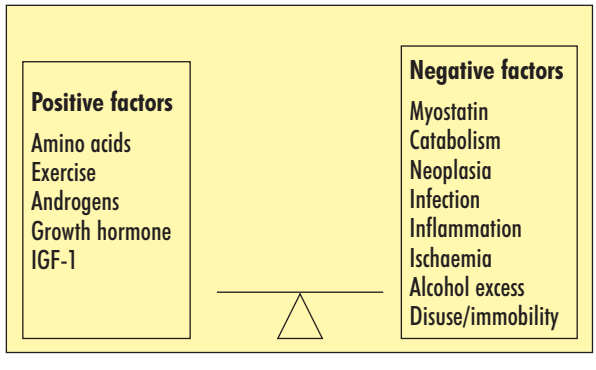
This review assesses several endocrine systems in turn, each of which has the potential to offer therapeutic opportunities. First, the GH/IGF-1 axis is considered. It is known from studies of transgenic mice that circulating IGF-1 is not solely responsible for maintenance of muscle mass and that increased muscle-derived transcription of IGF-1 causes hypertrophy. The indications for use of androgen therapy in older men are a topic of significant debate – ongoing trials assessing changes in body composition will be informative. Recent developments have occurred in attempts to modulate androgen-receptor agonists to create tissue-specific effects – the so-called selective androgen receptor modulators (SARMS). Finally, the muscle-derived protein myostatin is examined. Its physiological role includes negative regulation of muscle accretion – its absence has recently been shown to cause massive muscle hypertrophy. Myostatin inhibition is entering the therapeutic arena.

Endocrine dynamics and sarcopenia

The term sarcopenia is Greek-derived meaning 'lack of flesh'. It is associated with ageing and may coexist with osteopenia or osteoporosis (*Figure 2*). Measurement and clinical definition have not reached international consensus (Lauretani et al, 2003) and clinical trial endpoint data are lacking in comparison with, for example, bone density and fracture risk. In recent years, the condition of sarcopenia has become increasingly recognized. It is clear that reduced muscle strength and the tendency to fall are correlated with reduced muscle mass (Skelton et al, 1994), which may occur at a rate of up to 5–8% per decade after the age of 40 years.

The pathophysiology of sarcopenia is not fully understood. As well as a reduction in muscle mass, efficiency of neuronal activation and the response of muscle

Figure 1. Factors positively or negatively affecting muscle mass in older men. IGF-1 = insulin-like growth factor-1.



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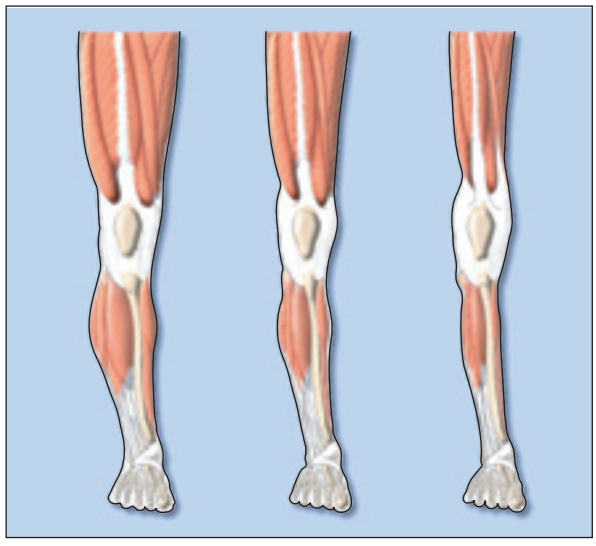
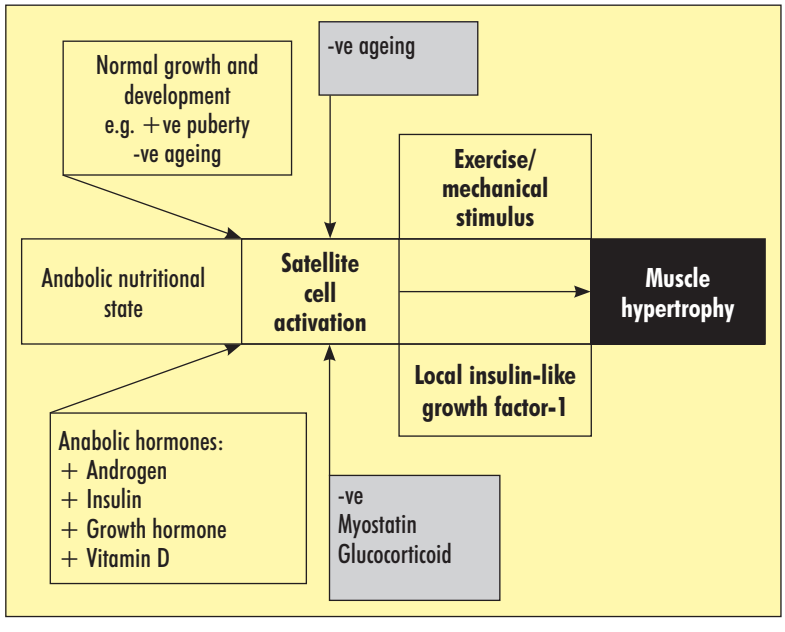


Figure 2. Schematic diagram representing progressive skeletal muscle loss with age.

impaired. In addition, nutrition will affect amino acid availability for muscle protein synthesis. Research efforts have focussed on the potential synergistic effect of exercise and anabolic hormones to kick-start muscle regeneration (Volpi et al, 2004). The key endocrine factors that appear to influence muscle mass directly are GH/IGF-1, androgens, and the negative regulator myostatin. Central to the process of muscle hypertrophy is the generation of locally-derived growth factors such as IGF-1 – the transcription of which is responsive to both mechanical and endocrine stimuli (*Figure 3*).

Measurable reductions in total and bioavailable testosterone occur in older men (Kaufman and Vermeulen, 2005). Factors influencing this include reduced testicular secretory capacity, altered neuroendocrine feedback mechanisms and increased sex hormone-binding globulin (SHBG) binding capacity. In addition, the absolute level and amplitude of diurnal variation is reduced.

Figure 3. Positive factors leading to muscle hypertrophy via activation of satellite cells.



However, although a correlation has been found in older men between androgen status and muscle mass, a causative relationship has not been confirmed. In addition, additional factors must play a role in women.

Developing an endocrine therapy for sarcopenia free of adverse effects, in an age group with often multiple medical problems is clinically challenging. So far several endocrine therapies have been attempted, including androgens, GH, GH-releasing hormone (GHRH), IGF-1, and IGF-1 complexes with binding proteins, with a variable degree of efficacy. Exercise remains a consistently effective means of maintaining functional capacity (Borst, 2004). This article describes the likely developments in the field of endocrine therapies for sarcopenia in older men, including the factors that modulate androgen status.

GH and IGF-1 subtypes

GH is secreted by the pituitary and classically induces IGF-1 generation in the liver. GH is secreted in a pulsatile manner, with serum IGF-1 maintained in a more steady state. GH has positive anabolic effects, both independently and via IGF-1 generated by the liver. In addition, increases occur in systemic GH levels and local IGF-1 generated by muscle following exercise. GH therapy has been shown to have positive effects on lean body mass in the child, young adult or older adult with GH deficiency (Carroll et al, 2004). During the ageing process, GH pulse amplitude and associated systemic IGF-1 levels are reduced. Increased understanding of this process and the availability of recombinant GH have prompted a series of trials of GH or GHRH replacement in the elderly (Borst, 2004). The results of these trials indicate a preferable safety profile for GHRH, but no definite conclusions can be drawn from the data available as yet. It has also been observed that recombinant GH, when administered to young hypogonadal (Hayes et al, 2001) and ageing men (Brill et al, 2002), can increase IGF-1 mRNA in muscle. However, these were short-term studies and data examining the functional effects of this finding in terms of strength and mobility are as yet unavailable.

The effects of recombinant IGF-1 and the fusion of IGF-1 with insulin-like growth factor binding-protein 3 (IGF-BP3) have also been studied, notably in the field of neuromuscular disease (Lynch, 2004). Although well-designed clinical trials have yet to be performed there are expected to be developments in this area.

Variation in IGF-1 gene expression is associated with site specific alternative splicing of the gene. The gene has several splice variants, with one, it is suggested, preferentially transcribed following mechanical stimulation. Termed mechano-growth factor (MGF), this IGF-1 variant may be important in stimulating muscle satellite cells to replicate and therefore trigger regeneration and hypertrophy. The gene has 6 exons, with promoter

regions in exon 1 and 2. The mature peptide is found in exons 3 and 4. Transcripts containing exons 1, 3, 4 and 5 or 1, 3, 4 and 6 are termed class I, and are associated with mechanical stimuli; those including 2, 3, 4 and 6 or 2, 3, 4 and 5 are termed class II, and are associated with endocrine stimuli. The MGF isoform results from a novel splice acceptor site between exons 5 and 6 creating a different C-terminal peptide. There is evidence to suggest that in ageing, MGF upregulation is impaired (Goldspink and Harridge, 2004).

Hameed et al (2003) looked specifically at the differences in gene expression between young and older men following an intense bout of exercise. IGF-1Ea was unchanged in both groups and MGF mRNA increased significantly only in the young men. In a further study (Hameed et al, 2004), IGF-1 subtype expression was examined in muscles of older men receiving either resistance training (RT), GH, or GH plus RT over 12 weeks. In younger subjects a significant difference was seen in MGF expression, with that seen in RT subjects exceeding that seen with subjects receiving GH alone, and that seen in RT plus GH subjects being significantly higher than in either single intervention group. In the RT plus GH group, MGF expression correlated with increased serum IGF-1.

Theoretically, if developed for therapeutic use, an MGF peptide would be able to improve muscle sensitivity to exercise and thus maintain muscle mass in ageing despite reduced levels of activity. There are several further steps required before an IGF-1 variant could be used to treat sarcopenia, including further evaluation of the intracellular target(s) of MGF. In addition, an absence of neoplastic effects will need to be demonstrated. The developments in this field are awaited with interest (*Table 1*).

Modulators of androgens

The androgen status of older men has been a topic of increasing interest (Kaufman and Vermeulen, 2005), for the most part because of the controversy over which individuals should be considered for testosterone therapy. The phrases 'andropause' and 'male menopause' are often quoted but are non-specific. More commonly, the descriptive term, partial androgen deficiency in ageing men (PADAM) is used. It is claimed that in some PADAM may be causally linked with the muscle loss described as sarcopenia, and fat free mass/body composition has been shown to improve favourably following androgen administration in healthy older men (Isidori et al, 2005). From an endocrinological viewpoint, it is relevant that the enzymes aromastase (converting testosterone to oestradiol) and 5-α reductase (converting testosterone to dihydrotestosterone) appear to have only a minor role in skeletal muscle with testosterone being the key androgen involved. However, different androgens have occasionally been used in experimental models. In addition, the efficacy of synthetic anabolic androgenic steroids compared to testosterone has been unequivocally demonstrated at a biological level. Microarray expression profiling was recently used to compare the genomic effects of tetrahydrogestinone (THG), a notorious synthetic anabolic androgen, with dihydrotestosterone in vivo. The affected genes were shown to be remarkably similar (Labrie et al, 2005).

Androgens increase muscle mass in synergy with exercise

In younger subjects, both androgens and exercise have been shown to increase muscle size and strength alone and in combination. In a classical study, Bhasin et al (1996) divided 43 men into four groups receiving weekly injections of testosterone (T) or placebo, and combined with or without resistance exercise (E), over 10 weeks. They showed an additive effect of T plus E in terms of muscle size and strength. Emerging evidence demonstrates dose-dependent anabolic effects in older men including improved fat free mass and strength in a similar manner to younger subjects (Bhasin et al, 2001, 2005).

However, the use of testosterone therapy for sarcopenia in older men is limited by the incidence of adverse effects. Ongoing trials are examining the specific cohort of men over 50 years of age with testosterone levels below the reference range. The lower limit is often quot-

Table 1. Potential endocrine therapies for sarcopenia in older men

	Potential therapy	Advantage	Disadvantage
Modulators of GH/IGF	GH	Used in adult GH deficiency	Unlikely to be effective unless deficient
	IGF-1 +/- IGF-BP3	Positive in-vitro data	Variable clinical data ?Neoplasia risk
	Mechano-growth factor	Potential improved satellite cell function	Clinical data awaited ?adverse effects
Modulators of androgens	Testosterone	Effective hypertrophic effect, inhibition of adipogenesis	Adverse effects
	7 alpha-methyl-19-nortesterone (MENT)	Minimal effects on prostate	No data
	Selective androgen receptor modulators	Specificity; minimal effects on prostate	Clinical data awaited
Modulators of myostatin	Myostatin inhibitors	Specificity of action, inhibition of adipogenesis	?Systemic /adverse effects

GH = growth hormone; IGF = insulin-like growth factor

ed as being 300 ng/dl (10.4 nmol/litre) measured on a morning blood sample – although clinicians should use the reference range provided by their local laboratory.

In 1992, Tenover demonstrated increased muscle mass in older men given 100 mg/week testosterone enanthate for 3 months (Tenover, 1992), and although of variable quality, data in later similar studies have confirmed this trend. A different endocrine approach, using recombinant human chorionic gonadotrophin (r-HCG), was trialled by an Australian group investigating effects on muscle in men with PADAM. HCG can stimulate generation of testosterone, oestradiol and other testicular steroids. Forty men aged over 60 with testosterone levels <15 nmol/litre were randomized to r-HCG or placebo. Lean muscle mass appeared to increase over 3 months in the HCG group but strength was unchanged (Liu et al, 2002).

A promising new androgen therapy is currently being investigated, 7alpha-methyl-19-nortestosterone abbreviated as MENT, also called Trestolone. It may obviate most current difficulties in androgen therapy. It can be delivered by several routes, is non-aromatisable and is not a target of 5-α reductase. A study using MENT in aged (13-month-old) orchidectomized rats showed anabolic effects on muscle and bone (Venken et al, 2005), however, the salutary lesson was a dose-related effect on the prostate. In fact the highest of the doses tested caused both muscle loss and prostate hypertrophy, whereas the low to mid-dose had a dual beneficial effect in the opposite direction. Encouraging findings were reported in an early human trial (n=16) of MENT with no adverse changes to the prostate described (Anderson et al, 2003). Therefore, future, dose-finding prospective randomized placebo-controlled clinical studies will be crucial.

A further therapeutic mechanism in development is the use of SARMS (Rosen and Negro-Vilar, 2002). These novel agents act on the androgen receptor, but have differing efficacy in a tissue-specific manner. This is because minor changes in androgen receptor ligand structure can bring about full agonist, partial agonist or even antagonist activity. An in-vivo study using orchidectomized rats and the compound nominated as S–4 demonstrated improvements in muscle mass, strength and bone density without adverse prostatic effects (Gao et al, 2005). This agent displays full agonist activity in muscle but only partial agonist activity in the prostate. There are as yet no convincing human data using SARMS examining muscle-related outcomes, although phase I/II trials are underway. Overall, the use of androgen therapy in elderly men could therefore be beneficial, but there is a need for large randomized trials in this area.

Myostatin

Myostatin appears to be a muscle-derived hormone of key metabolic importance. It was discovered by McPherron and Lee based at Johns Hopkins University (McPherron et al, 1997) who demonstrated that a phenotype of exaggerated muscle hypertrophy correlated with mutations in the myostatin gene. Such knockout mutations of myostatin in animals – causing the so-called 'double-muscled' phenotype – and in one human child (Schuelke et al, 2004) have been described in detail. The gene is on chromosome 2 in humans, and is highly conserved across species. Polymorphisms of the myostatin gene are increasingly being correlated with measures of muscle mass, strength and, potentially, athletic performance (Seibert et al, 2001).

Myostatin acts as an inhibitor of muscle growth and regeneration and promotes adipogenesis. It is expressed early during embryogenesis. Postnatally, it is classically expressed in skeletal muscle but has been found elsewhere, e.g. cardiac muscle, adipose tissue. It is also more potently expressed in fast glycolytic muscle than in slow twitch fibres.

Myostatin appears to be a physiological gatekeeper maintaining satellite cells in quiescence (McCroskery et al, 2003). Although myostatin's key action appears to be suppression of myoblast differentiation and proliferation, its regulatory mechanism is uncertain and may involve interactions with GH and/or glucocorticoid metabolism. Interestingly, when mice were systemically administered myosatin, cachexia ensued (Zimmers et al, 2002).

Myostatin is likely to be a significant molecular therapeutic target in the future, as its deficiency appears to increase both hypertrophy and hyperplasia in muscle, with concurrent reduction in fat accumulation.

Therefore, manipulating myostatin may be a method for improving insulin sensitivity and could therefore have a role in fighting the obesity epidemic. The principle of myostatin inhibition as a potential therapy for muscle wasting was demonstrated in an animal model of dystrophic muscle (Bogdanovich et al, 2002). The animals showed hypertrophy and increased strength compared to controls. A recombinant human antibody to myostatin (MYO-029) is being tested in phase I/II trials designed to assess safety and efficacy. One prospective, randomized, placebo-controlled trial underway is recruiting 108 subjects with neuromuscular disease including those with Becker muscular dystrophy, facioscapulohumeral dystrophy and limb-girdle muscular dystrophy.

A second therapeutic approach to myostatin is now in development. A soluble activin type IIB receptor (ACVR2B/Fc) that binds to myostatin effectively has been shown to cause reduced myostatin availability. In a study using wild-type mice there was up to a 61% increase in muscle mass observed in 2 weeks at the dose of greatest efficacy (Lee et al, 2005). The increase in muscle weight observed was more impressive than that obtained using other myostatin inhibitors, leading to the suggestion that the receptor may be inhibiting activities of a further ligand. These data are interesting in that normal animals were used, making this a transferable paradigm for sarcopenia research.

It remains to be seen whether myostatin inhibition becomes an effective treatment for sarcopenia. More research into understanding the factors that influence myostatin in models of ageing is required.

Conclusions

In an ageing population, optimizing physical capacity and improving the relationship between muscle and adipose tissue could have important health benefits. Future clinical investigation will require characterization and validation of measures of muscle mass and strength that can be observed in prospective randomized controlled studies. The development of effective yet safe endocrine treatments for sarcopenia is on the horizon, and the areas of IGF-1 variants, androgen modulators and myostatin inhibition are key candidates. The techniques of molecular biology are likely to assist with the design of tissue specific targets therefore minimizing the risk of adverse effects and optimizing treatment success. **BJHM**

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KEY POINTS

- Sarcopenia is the age-associated reduction in muscle mass and strength.
- Improvements in muscle function occur with exercise and anabolic hormones.
- Specific endocrine therapies for sarcopenia are in development.
- New treatments specifically target skeletal muscle while minimizing adverse effects.
- Testosterone therapy in older men is controversial; selective androgen receptor modulators will be increasingly available in the future.