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REVIEW

Male hypogonadism. Part II: etiology, pathophysiology, and diagnosis

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Male hypogonadism has a multifactorial etiology that includes genetic conditions, anatomic abnormalities, infection, tumor, and injury. Defects in the hypothalamic-pituitary-gonadal axis may also result from type II diabetes mellitus and treatment with a range of medications. Circulating testosterone levels have been associated with sexual function, cognitive function, and body composition. Apart from reduced levels of testosterone, clinical hallmarks of hypogonadism include absence or regression of secondary sex characteristics, reduced fertility (oligospermia, azoospermia), anemia, muscle wasting, reduced bone mass (and bone mineral density), and/or abdominal adiposity. Some patients, particularly those with partial androgen deficiency of the aging male, also experience sexual dysfunction, reduced sense of vitality, depressed mood, increased irritability, difficulty concentrating, and/or hot flushes in certain cases of acute onset. As many patients with male hypogonadism—like patients with erectile dysfunction—do not seek medical attention, it is important for clinicians to be acquainted with the signs and symptoms of hypogonadism, and to conduct appropriate laboratory testing and other assessments to determine the causes and inform the treatment of this condition.
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Etiology

Hypogonadism is characterized by low serum testosterone (T) levels (<300 ng/dl) together with ⩾1 clinical symptom or sign. Symptoms of postpubertal hypogonadism include[1–3] (1) sexual dysfunction, such as reduced libido, erectile dysfunction (ED), diminished penile sensation, difficulty attaining orgasm, as well as reduced ejaculate with orgasm; (2) reduced energy, vitality, or stamina; (3) depressed mood or diminished sense of well-being; (4) increased irritability; (5) difficulty concentrating and other cognitive problems; and/or (6) hot flushes in some cases of acute onset.

Signs of hypogonadism include (1) anemia; (2) muscle wasting (sarcopenia); (3) reduced bone mass or bone mineral density (BMD); (4) absence or regression of secondary sex characteristics; (5) abdominal adiposity (i.e. 'pot belly' obesity); and/or (6) oligospermia or azoospermia.

A number of hypothalamic-pituitary-gonadal (HPG) axis defects may induce hypogonadism (Table 1).[2,4] The term *primary* (*hypergonadotropic*) *hypogonadism* refers to testicular disorders and is characterized by low serum T despite high levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Causes of primary hypogonadism include (1) genetic conditions (e.g. Klinefelter syndrome, gonadal dysgenesis); (2) anatomic defects; (3) infection; (4) tumor; (5) injury; (6) iatrogenic causes (surgery or certain medications); and/or (7) alcohol abuse.[3]

The term *secondary* (*hypogonadotropic*) *hypogonadism* denotes deficient release of gonadotropin-releasing hormone (GnRH) and is characterized by low–normal or low levels of FSH, LH, and T. Causes or manifestations of secondary hypogonadism include (1) hyperprolactinemia (often secondary to pituitary adenoma); (2) GnRH deficiency with anosmia (Kallmann syndrome); (3) hypothalamic lesions or disorders; and (4) pituitary lesions or disorders. The term *normogonadotropic hypogonadism* denotes symptoms or signs of hypogonadism together with low serum T and normal LH levels.

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Table 1 Differential diagnosis of male hypogonadism

Primary (hypergonadotropic) hypogonadism
- Testicular disorders (primary gonadal failure)
  - Undescended testes
  - Acquired bilateral torsion of testes
  - Orchitis (e.g. mumps orchitis)/cryptorchidism
  - Vanishing-testes syndrome (congenital anorchism or prepubertal functional castrate)
  - Seminiferous tubule dysgenesis (Klinefelter syndrome)
  - Pure gonadal dysgenesis (46XX and 46XY)
  - Sweyer syndrome (phenotypic female with gonads and genitalia identical to gonadal dysgenesis)
  - Noonan (Boonevie–Ullrich) syndrome
  - Hemochromatosis
  - Impaired Leydig cell activity
    - Inborn errors of testosterone biosynthesis
  - Leydig cell hypoplasia
  - Testicular unresponsiveness (LH receptor failure?)
  - Androgen-resistant states and enzyme defects
    - Testicular feminization (absence of androgen receptors)
    - Incomplete androgen insensitivity (Reiffenstein syndrome)
    - 5α-Reductase deficiency
- External testicular insults
  - Trauma
  - Radiation treatment
  - Chemotherapy
- Autoimmune syndromes (e.g. anti-Leydig cell antibody-associated disorders)
- Sertoli-cell only syndrome

Secondary (hypogonadotropic) hypogonadism
- GnRH deficiency
  - Hypothalamic lesions
    - Tumors
    - Encephalitis
    - Granuloma
    - Abscess
    - Craniopharyngioma
  - Isolated GnRH deficiency
    - Idiopathic (Kallmann syndrome or fertile-eunuch syndrome)
  - Prader–Willi syndrome
  - Lawrence–Moon–Bardet–Biedl syndrome
  - Alström syndrome
  - Fertile-eunuch syndrome
  - Familial cerebellar syndrome
- Hyperprolactinemia
  - Prolactinoma
  - Certain drugs
  - Hemochromatosis
  - Neurosarcoid
  - Myotonic dystrophy
- Pituitary disorders (gonadotrophin deficiency)
  - Isolated LH deficiency
    - Pasqualini syndrome
    - Eunuchoidism
    - Absent secondary sexual characteristics
    - Oligospermia
  - Tumors
  - Pituitary infarction, apoplexy
  - Empty sella syndrome
  - Hemochromatosis
  - Cranial trauma with or without pituitary-stalk transection
  - Irradiation
  - Hypophysitis

FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LH, luteinizing hormone.
Sources: AACE guidelines[2] and Rehman *et al*.[4]

Conditions that may be associated with hypogonadism include type II diabetes mellitus (DM); cancer; acquired immune deficiency syndrome; cirrhosis of the liver; renal failure; hyperthyroidism or hypothyroidism; Cushing syndrome; protein-calorie malnutrition (and anorexia nervosa); morbid

Table 2 Agents that may cause low circulating testosterone

Cytotoxic agents
Spironolactone
Corticosteroids, ketoconazole, aminoglutethimide, ethanol
Decrease Leydig-cell testosterone production
Anticonvulsants, hepatic microsomal liver enzyme inducers
Augment testosterone metabolism
Gonadotropin-releasing hormone agonists, estrogens, anabolic steroids, psychotropic medications, post-transplant immunosuppressants, corticosteroids, ethanol
Reduce gonadotropin secretion

Adapted with permission from Hameed *et al.*[3]

obesity; hemochromatosis or sickle-cell anemia; paraplegia and myotonia dystrophica; as well as certain psychiatric disorders, including depressive disorders.[5] In addition, several agents are associated with low circulating testosterone[3] (Table 2).

Pathophysiology

Effects of testosterone on sexual function

It has been suggested that normal or low–normal T levels are necessary to maintain normal sexual function, whereas increases in fat-free and lean-tissue mass rise in a dose-dependent manner over the normal range of circulating T.[6,7]

In a recent study of androgen-deficient patients undergoing subdermal T implantation (T pellets), Handelsman's group determined thresholds for T and free T (FT) below which symptoms of androgen deficiency returned as T levels declined.[8] Reduced libido and lack of motivation and/or energy recurred when T reached approximately 280 ng/dl in patients with secondary (hypogonadotropic) hypogonadism and 337 ng/dl in patients with primary (hypergonadotropic) hypogonadism.

Testosterone appears to play a role in maintaining sexual function, especially libido, although androgen deficiency *per se* is infrequently the sole cause of ED in hypogonadal males, particularly elderly men.[9] Preclinical evidence suggests that T promotes erectile responses via both the central and peripheral nervous systems.[10–12] For instance, T modulates α-adrenergic (antierectile) sensitivity of cavernosal smooth muscle.[13]

Preclinical work in DM-prone rats also suggests that decreases in penile nitric oxide synthase (NOS) expression or activity associated with low serum androgens contribute to the pathophysiology of diabetic ED.[14] Other investigations have suggested that androgen deprivation blunts erectile responses via structural changes in the corpora that culminate in decreased blood storage (i.e. veno-occlusive dysfunction) without influencing NOS activity.[15]

In man, it is believed that androgens mediate nocturnal penile tumescence, whereas erectile responses to visual stimuli are androgen independent.[9,16] It has also been suggested that the influence of T on erectile function may be mediated partly via effects on genital sensitivity and that the T metabolite 5α-dihydrotestosterone may also play a role in maintaining erections.[17,18]

T levels in the corpora cavernosa and peripheral blood during transitions from penile flaccidity to tumescence and rigidity, and then detumescence were compared in healthy subjects and ED patients.[19] In healthy volunteers, T levels increased significantly in corporal blood during the transition from flaccidity (2.9 ng/ml) to tumescence (4.3 ng/ml; $P<0.001$) and rigidity (4.4 ng/ml), followed by a return to 3.5 ng/ml during detumescence. In ED patients, the rise in cavernous T was of lower magnitude: from 2.6 to 3.0 ng/ml during tumescence ($P<0.05$). Similar patterns were observed with respect to T concentrations in peripheral blood.

The rise in cavernous T levels from flaccidity to tumescence was also somewhat more marked in patients with psychogenic rather than organic ED.[19] The investigators suggested that the difference between peripheral and cavernous T concentrations during the flaccid phase might serve as a useful marker of bioavailable T (BT) and T receptor density in corporal smooth muscle.[19]

Effects of testosterone on cognitive function and affect

Cognitive performance, including mental-rotation tasks, is related to androgen levels across the normal range in healthy volunteers.[20,21] In addition, certain studies have shown that androgen replacement enhances cognitive and language functions (but not memory).[22–24]

In vivo studies have also suggested that endogenous androgens confer potentially beneficial neuroprotective effects within the hippocampus and limit accumulation of β-amyloid protein—a central pathophysiologic defect in Alzheimer's disease.[25,26] In addition, a study of nondemented patients with Parkinson's disease demonstrated that the degrees of patient- and informant-reported apathy were inversely related to FT levels.[27]

On the other hand, Kenny and co-workers recently determined that intramuscular T (i.m. T) injections did not significantly affect a wide range of cognitive indices in elderly hypogonadal men with early cognitive impairment and BT < 128 ng/dl.[28] I.m. T also did not affect activities of daily living or depression ratings.

In the Rancho Bernardo Study, depression rating scales were inversely related to BT levels ($P=0.0007$) irrespective of age, physical activity, or alterations in body weight.[29] Although certain elderly dysthymic men and patients with treatment-refractory depression have low T levels, there

is no strong evidence that reduced T levels play a pivotal pathophysiologic role in major depression.

At the time of writing, there is insufficient evidence to recommend testosterone replacement therapy (TRT) as first-line therapy for major depressive disorder in men with hypogonadism, although adjunctive T treatment may enhance clinical outcomes in patients with treatment-refractory depression.[30–33] Moreover, certain elderly men report an enhanced sense of well-being on TRT,[34,35] although this may be an indirect effect of other physiologic changes.

Effects of testosterone on body composition

Androgens may promote bone formation. In two recent studies of young healthy men, serum sex hormone binding globulin (SHBG) emerged as an independent positive predictor of bone turnover or BMD.[36,37] The decrease in bone mass with advancing age may be associated with declining insulin-like growth factor (IGF-1) levels as well as T concentrations.[38]

Partly by facilitating commitment of pluripotent mesenchymal cells, androgens may also foster skeletal-muscle hypertrophy and hence promote lean body mass.[39] Exogenous T increases satellite-cell populations within muscles, with attendant rises in numbers of myoblasts and large-myofiber myonuclei, as well as formation of larger motoneurons. On the other hand, data suggesting that reduced muscle strength in elderly men relates to reversible declines in androgen levels are conflicting.[38,40–42]

Androgens also attenuate adipogenesis in man. The effects of TRT on adipogenesis may differ in different anatomic regions. In a recent study of men randomized to a GnRH agonist together with i.m. testosterone enanthate (TE) injections at five doses over the range of 25–600 mg weekly,[7] lowering T levels was associated with increases in adipose-tissue stores, with particularly marked rises in subcutaneous depots. However, increasing T levels above baseline via i.m. T injections preferentially mobilized smaller, deeper i.m. adipose-tissue deposits. Overall fat mass was inversely correlated with TE doses across all sites.[7]

Diagnosis

In addition to recognizing presenting symptoms, conducting appropriate laboratory testing is central to diagnosing male hypogonadism.[3] According to the Second International Consultation on Erectile Dysfunction of the World Health Organization (WHO),[43] a blood sample for serum T determination should be obtained between 0800 and 1100 hours, when T levels typically peak in healthy young men. This circadian rhythmicity may be abolished or blunted in men with advancing age[44] or during certain forms of TRT.

A morning T level $\leqslant 300$ ng/dl should be confirmed and if there is a need to differentiate primary from secondary hypogonadism, levels of LH and FSH should be evaluated.[43] According to the guidelines of the American Association of Clinical Endocrinologists (AACE), exceedingly low T levels ($\leqslant 150$ ng/dl) warrant pituitary imaging even in the absence of other signs or symptoms.[2] Some authorities recommend sellar magnetic resonance imaging with thyroxine, cortisol, and prolactin assessments when secondary hypogonadism is considered likely.[45] According to Australian consensus guidelines:[46]

- primary (hypergonadotropic) hypogonadism is indicated by serum T < 231 ng/dl with LH > 1.5 times the upper limit of normal (1.5 × ULN);
- secondary (hypogonadotropic) hypogonadism is indicated by T < 231 ng/dl without LH elevations;
- Leydig-cell failure is indicated by T = 231–432 ng/dl with LH > 1.5 × ULN; and
- androgen resistance is indicated by T > 864 ng/dl with LH > 1.5 × ULN.

Total T assays may not indicate true androgenic status, particularly in elderly men. According to the most recent WHO guidelines,[43] BT (normal range = 92–420 ng/dl) and FT (normal = 5–21 ng/dl) are the most reliable assays to establish male hypogonadism. As serum T may be normal in patients with primary testicular disorders (e.g. Klinefelter syndrome) or increased SHBG, obtaining FT or BT may also be useful.[2] However, the validity and accessibility of a number of diagnostic tests (e.g. equilibrium dialysis) and other, dynamic assessments are matters of ongoing debate.

Recent data from the Massachusetts Male Ageing Study (MMAS) provide perspectives on normal androgen ranges.[47] In the MMAS, the threshold for abnormally low total T as established by the 2.5th percentile was 251 ng/dl for healthy men aged 40–49 years, 216 ng/dl for ages 50–59, 196 ng/dl for ages 60–69, and 156 ng/dl for ages 70–79. Corresponding 2.5th-percentile values for FT were 5.3, 4.2, 3.7, and 2.2 ng/dl, while corresponding values for BT were 99.7, 79.8, 69.7, and 41.8 ng/dl.

In the MMAS, the mean FT in men aged 40–49 years was 14.3 ng/dl, with a range of 3.7 ng/dl (mean−2 standard deviations (s.d.)), to 24.9 ng/dl (mean + 2 s.d.). The mean FT in men aged 70–79 was 7.6 ng/dl (0.8–14.4 ng/dl). The mean BT in men aged 40–49 years was 270.9 ng/dl (69.2–469.7 ng/dl) and the mean BT in men aged 70–79 was 144.1 ng/dl (14.4–270.9 ng/dl).[47]

As with ED, signs and symptoms of hypogonadism often go unreported to physicians. Therefore, it is important to maintain a proactive dialogue with the patient about possible symptoms such as low

libido, ED, impaired concentration, and fatigue to uncover hypogonadism. It is also often important to inquire about *increased* fatigue during TRT because this may be a manifestation of treatment-related sleep apnea.

Conclusions

In summary, male hypogonadism has a multifactorial etiology that includes congenital abnormalities, injury, infection, cancer, diabetes, treatment with certain medications, and alcohol abuse. In addition to obtaining androgen and other hormone levels, it is important to be familiar with the signs (e.g. anemia, oligospermia/azoospermia, muscle wasting) and symptoms (e.g. sexual dysfunction, mood disturbances, cognitive problems) because many patients do not report these manifestations. Assessment of presenting signs and symptoms, in concert with evaluations of the HPG axis, enables diagnosis of primary (hypergonadotropic) or secondary (hypogonadotropic) hypogonadism, which may prompt further work-ups and treatment.

References

1 Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med* 2004; **350**: 482–492.
2 American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients: 2002 update. *Endocr Pract* 2002; **8**: 440–456.
3 Hameed A, Brothwood T, Bouloux P. Delivery of testosterone replacement therapy. *Curr Opin Invest Drugs* 2003; **4**: 1213–1219.
4 Rehman J, Melman A. Pathophysiology of erectile dysfunction. In: Lue TF, Goldstein M, Vaughan Jr ED, Perlmutter AP, (eds.), *Impotence and Infertility. Atlas of Clinical Urology* vol. 1, Philadelphia, PA: Current Medicine, Inc., 1999, pp. 1.1–1.16.
5 Morley JE, Melmed S. Gonadal dysfunction in systemic disorders. *Metabolism* 1979; **28**: 1051–1073.
6 Bhasin S, Woodhouse L, Casaburi R, Singh AB, Bhasin D, Berman N *et al.* Testosterone dose–response relationships in healthy young men. *Am J Physiol Endocrinol Metab* 2001; **281**: E1172–E1181.
7 Woodhouse LJ, Gupta N, Bhasin M, Singh AB, Ross R, Phillips J *et al.* Dose-dependent effects of testosterone on regional adipose tissue distribution in healthy young men. *J Clin Endocrinol Metab* 2004; **89**: 718–726.
8 Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. *J Clin Endocrinol Metab* 2004; **89**: 3813–3817.
9 Vermeulen A. Androgen replacement therapy in the aging male: a critical evaluation. *J Clin Endocrinol Metab* 2001; **86**: 2380–2390.
10 King BE, Packard MG, Alexander GM. Affective properties of intra-medial preoptic area injections of testosterone in male rats. *Neurosci Lett* 1999; **269**: 149–152.
11 Mills TM, Reilly CM, Lewis RW. Androgens and penile erection: a review. *J Androl* 1996; **17**: 633–638.
12 Baba K, Yajima M, Carrier S, Morgan DM, Nunes L, Lue TF *et al.* Delayed testosterone replacement restores nitric oxide synthase-containing nerve fibres and the erectile response in rat penis. *BJU Int* 2000; **85**: 953–958.
13 Reilly CM, Stopper VS, Mills TM. Androgens modulate the α-adrenergic responsiveness of vascular smooth muscle in the corpus cavernosum. *J Androl* 1997; **18**: 26–31.
14 Vernet D, Cai L, Garban H, Babbitt ML, Murray FT, Rajfer J *et al.* Reduction of penile nitric oxide synthase in diabetic BB/WORdp (type I) and BBZ/WORdp (type II) rats with erectile dysfunction. *Endocrinology* 1995; **136**: 5709–5717.
15 Traish AM, Munarriz R, O'Connell L, Choi S, Kim SW, Kim NN *et al.* Effects of medical or surgical castration on erectile function in an animal model. *J Androl* 2003; **24**: 381–387.
16 Carani C, Scuteri A, Marrama P, Bancroft J. The effects of testosterone administration and visual erotic stimuli on nocturnal penile tumescence in normal men. *Horm Behav* 1990; **24**: 435–441.
17 Lugg JA, Rajfer J, Gonzalez-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. *Endocrinology* 1995; **136**: 1495–1501.
18 Davidson JM, Kwan M, Greenleaf WJ. Hormonal replacement and sexuality in men. *Clin Endocrinol Metab* 1982; **11**: 599–623.
19 Becker AJ, Uckert S, Stief CG, Scheller F, Knapp WH, Hartmann U *et al.* Cavernous and systemic testosterone plasma levels during different penile conditions in healthy males and patients with erectile dysfunction. *Urology* 2001; **58**: 435–440.
20 Hooven CK, Chabris CF, Ellison PT, Kosslyn SM. The relationship of male testosterone to components of mental rotation. *Neuropsychologia* 2004; **42**: 782–790.
21 Christiansen K, Knussmann R. Sex hormones and cognitive functioning in men. *Neuropsychobiology* 1987; **18**: 27–36.
22 Alexander GM, Swerdloff RS, Wang C, Davidson T, McDonald V, Steiner B *et al.* Androgen–behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Horm Behav* 1998; **33**: 85–94.
23 Sih R, Morley JE, Kaiser FE, Perry III HM, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. *J Clin Endocrinol Metab* 1997; **82**: 1661–1667.
24 Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. *Behav Neurosci* 1994; **108**: 325–332.
25 Ramsden M, Nyborg AC, Murphy MP, Chang L, Stanczyk FZ, Golde TE *et al.* Androgens modulate β-amyloid levels in male rat brain. *J Neurochem* 2003; **87**: 1052–1055.
26 Ramsden M, Shin TM, Pike CJ. Androgens modulate neuronal vulnerability to kainate lesion. *Neuroscience* 2003; **122**: 573–578.
27 Ready RE, Friedman J, Grace J, Fernandez H. Testosterone deficiency and apathy in Parkinson's disease: a pilot study. *J Neurol Neurosurg Psychiatry* 2004; **75**: 1323–1326.
28 Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci* 2004; **59**: 75–78.
29 Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab* 1999; **84**: 573–577.
30 Rabkin JG, Wagner GJ, McElhiney MC, Rabkin R, Lin SH. Testosterone versus fluoxetine for depression and fatigue in HIV/AIDS: a placebo-controlled trial. *J Clin Psychopharmacol* 2004; **24**: 379–385.
31 Seidman SN, Spatz E, Rizzo C, Roose SP. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry* 2001; **62**: 406–412.
32 Pope Jr HG, Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003; **160**: 105–111.

33 Carnahan RM, Perry PJ. Depression in aging men: the role of testosterone. *Drugs Aging* 2004; **21**: 361–376.
34 Morley JE, Perry III HM, Kaiser FE, Kraenzle D, Jensen J, Houston K *et al.* Effects of testosterone replacement therapy in old hypogonadal males: a preliminary study. *J Am Geriatr Soc* 1993; **41**: 149–152.
35 Buena F, Swerdloff RS, Steiner BS, Lutchmansingh P, Peterson MA, Pandian MR *et al.* Sexual function does not change when serum testosterone levels are pharmacologically varied within the normal male range. *Fertil Steril* 1993; **59**: 1118–1123.
36 Valimaki VV, Alfthan H, Ivaska KK, Loyttyniemi E, Pettersson K, Stenman UH *et al.* Serum estradiol, testosterone, and sex hormone-binding globulin as regulators of peak bone mass and bone turnover rate in young Finnish men. *J Clin Endocrinol Metab* 2004; **89**: 3785–3789.
37 Rucker D, Ezzat S, Diamandi A, Khosravi J, Hanley DA. IGF-I and testosterone levels as predictors of bone mineral density in healthy, community-dwelling men. *Clin Endocrinol (Oxford)* 2004; **60**: 491–499.
38 Abbasi AA, Drinka PJ, Mattson DE, Rudman D. Low circulating levels of insulin-like growth factors and testosterone in chronically institutionalized elderly men. *J Am Geriatr Soc* 1993; **41**: 975–982.
39 Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care* 2004; **7**: 271–277.
40 van den Beld AW, de Jong FH, Grobbee DE, Pols HA, Lamberts SW. Measures of bioavailable serum testosterone and estradiol and their relationships with muscle strength, bone density, and body composition in elderly men. *J Clin Endocrinol Metab* 2000; **85**: 3276–3282.
41 Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev* 1999; **107**: 123–136.
42 Verhaar HJJ, Samson MM, Aleman A, de Vries WR, de Vreede PL. The relationship between indices of muscle function and circulating anabolic hormones in healthy men. *Aging Male* 2000; **3**: 75–80.
43 Lue TF, Giuliano F, Montorsi F, Rosen RC, Andersson K-E, Althof S *et al.* Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2004; **1**: 6–23.
44 Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab* 1983; **56**: 1278–1281.
45 Snyder PJ. Hypogonadism in elderly men: what to do until the evidence comes. *N Engl J Med* 2004; **350**: 440–442.
46 Conway AJ, Handelsman DJ, Lording DW, Stuckey B, Zajac JD. Use, misuse and abuse of androgens: The Endocrine Society of Australia consensus guidelines for androgen prescribing. *Med J Aust* 2000; **172**: 220–224.
47 Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol* 2005; **62**: 64–73.