

CONSENSUS STATEMENT

Investigation, treatment and monitoring of late-onset hypogonadism in males**ISA, ISSAM, EAU, EAA and ASA recommendations**

C Wang, E Nieschlag¹, R Swerdloff, H M Behre², W J Hellstrom³, L J Gooren⁴, J M Kaufman⁵, J-J Legros⁶, B Lunenfeld⁷, A Morales⁸, J E Morley⁹, C Schulman¹⁰, I M Thompson¹¹, W Weidner¹² and F C W Wu¹³

Division of Endocrinology, Department of Medicine, Harbor-UCLA Medical Center and Los Angeles BioMedical Research Institute, General Clinical Research Center, 1000 W. Carson Street, Torrance, California 90509, USA, ¹Centre for Reproductive Medicine and Andrology, University of Muenster, Muenster, Germany, ²Center for Reproductive Medicine and Andrology, University Hospital Halle, Martin-Luther-University Halle-Wittenberg, Halle, Germany, ³Department of Urology, Tulane University, New Orleans, Los Angeles, USA, ⁴Department of Endocrinology, VU University Medical Center, Amsterdam, The Netherlands, ⁵Department of Endocrinology, Academisch Ziekenhuis, Gent, Belgium, ⁶Centre Hospitalier Universitaire, Sart-Tilman, Liège, Belgium, ⁷Faculty Life Science, Bar-Ilan University, Ramat-Gan, Israel, ⁸Centre for Applied Urological Research, Queen's University, Kingston, Canada, ⁹Division of Geriatric Medicine, St Louis VA Medical Center, St Louis University, and GRECC, St Louis, Missouri, USA, ¹⁰Department of Urology, Erasme Hospital, University Clinics Brussels, Brussels, Belgium, ¹¹Department of Urology, University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA, ¹²Department of Urology and Pediatric Urology, University Hospitals, Justus-Liebig-University, Giessen, Germany and ¹³Department of Endocrinology, University of Manchester, Manchester Royal Infirmary, Manchester, UK

(Correspondence should be addressed to C Wang; Email: wang@labiomed.org)

Introduction

Demographic data clearly demonstrate that the percentage of the population in the older age group is increasing. Androgen deficiency in the aging male has become a topic of increasing interest and debate throughout the world. Cross-sectional and longitudinal data indicate that the testosterone falls progressively with age and that a significant percentage of men over the age of 60 years have serum testosterone levels that are below the lower limits of young adult (age 20–30 years) men (1–4). The principal questions raised by these observations are whether older hypogonadal men will benefit from testosterone treatment and what will be the risks associated with such intervention.

The past decade has brought evidence of benefit of androgen treatment of hypogonadal men on multiple target organs and the recent studies show short-term beneficial effects of testosterone in older men that are similar to those in younger men. This has been comprehensively reviewed and summarized by the Institute of Medicine in 'Testosterone and Aging: Clinical Research Directions' (5). Long-term data on the effects of testosterone treatment in the older population are limited mainly to effects on body composition and bone mass (6–11). Key questions of the effects of testosterone on patient reported outcomes and functional benefits that may retard physical or mental frailty of the elderly or improve the quality of life are not yet available. Specific risk data on the prostate and cardiovascular systems are needed.

(12–14). Recommendations on the diagnosis, treatment, and monitoring of late-onset hypogonadism (LOH) were published by International Society for the Study of Aging Male (ISSAM) in 2002 (15). In 2005, a writing committee formed by the International Society of Andrology (ISA), the ISSAM, and the European Association of Urology (EAU) prepared a set of recommendations specifically on the 'Investigation, treatment and monitoring of LOH'. In order to reach a large audience, these recommendations were published in the International Journal of Andrology, the Journal of Andrology, the Aging Male, and European Urology (16–19). In view of the growing interest from practitioners on the treatment of older men with testosterone, the ISA, ISSAM, EAU, European Academy of Andrology, and American Society of Andrology convened meetings of the writing group with expert representatives from each of the societies. The writing group membership from 2005 was expanded to include additional urologists. Members of the writing group met in Berlin 2007, Toronto 2007, and Tampa 2008 to revise these recommendations. There was no corporate funding or support for the development of these recommendations. The revised recommendations are supported by a selection of appropriate references and categorized by the level of evidence and grade of recommendation according to the US Department of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research (1992; Table 1).

To ensure broad outreach to multidisciplinary audiences, these recommendations are published in several journals simultaneously.

Process for development of recommendations

Recent guidelines for the testosterone treatment of younger hypogonadal men are available from professional societies

Recommendation 1: definition

LOH, also referred to as age-associated testosterone-deficiency syndrome (TDS), is a clinical and biochemical

Table 1 Level of evidence and grade of recommendation utilized in the recommendations.

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomized trials
1b	Evidence obtained from at least one randomized trial
2a	Evidence obtained from one well-designed controlled study without randomization
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies, and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial
B	Based on well-conducted clinical studies, but without randomized clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range) (16–20). This condition may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

Recommendation 2: clinical diagnosis and questionnaires

2.1. At present, the diagnosis of treatable hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency (Level 3, Grade A) (12, 16–19). The symptom most associated with hypogonadism is low libido (Level 3, Grade A) (21, 22). Other manifestations of hypogonadism include: erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, and decreased vitality and depressed mood. None of these symptoms are specific to the low androgen state but may raise suspicion of testosterone deficiency. One or more of these symptoms must be corroborated with a low serum testosterone level (Level 3, Grade A) (1, 23–25).

2.2. Questionnaires such as Aging Male Symptom Score (AMS) (26, 27) and Androgen Deficiency in Aging Men (ADAM) (28) are not recommended for the diagnosis of hypogonadism because of low specificity (Level 3, Grade B) (24, 29, 30).

Recommendation 3: laboratory diagnosis

3.1. In patients at risk or suspected of hypogonadism, a thorough physical and biochemical work-up is necessary (Level 4, Grade A). Transient decreases of serum testosterone levels such as those due to acute illnesses should be excluded by careful clinical evaluations and repeated hormone measurement. Hypogonadism (primary or secondary) can occur at all ages including elderly men. Risk factors for hypogonadism in older men

may include chronic illnesses (including diabetes mellitus, chronic obstructive lung disease, inflammatory arthritic disease, renal disease, and HIV-related disease), obesity, metabolic syndrome, and hemochromatosis (12). Such chronic diseases should be investigated and treated (Level 4, Grade A).

3.2. A serum sample for total testosterone determination should be obtained between 0700 and 1100 h (Level 2a, A) (31). The most widely accepted parameters to establish the presence of hypogonadism is the measurement of serum total testosterone. There are no generally accepted lower limits of normal. There is, however, general agreement that the total testosterone level above 12 nmol/l (350 ng/dl) does not require substitution. Similarly, based on the data of younger men, there is consensus that patients with serum total testosterone levels below 8 nmol/l (230 ng/dl) will usually benefit from testosterone treatment. If the serum total testosterone level is between 8 and 12 nmol/l, repeating the measurement of total testosterone with sex hormone-binding globulin (SHBG) to calculate free testosterone or free testosterone by equilibrium dialysis may be helpful (see 3.5 and 3.7 below) (Level 2b, Grade A).

3.3. Measurements of serum luteinizing hormone will assist in differentiating between primary and secondary hypogonadism and serum prolactin is indicated when the serum testosterone is lower than 5.2 nmol/l (150 ng/dl) (32–35) or when secondary hypogonadism is suspected (12, 36, 37) (Level 3, Grade B).

3.4. Since there are known variations between assay methods, it is imperative that the practitioners utilize reliable laboratories and are acquainted with the reference ranges for testosterone from their local laboratory (38–41) (Level 2b, Grade A).

3.5. Current immunometric methods for the measurement of testosterone can distinguish between hypogonadism and normal adult men. However, the methods based on mass spectrometry are more accurate and precise (39–41) (Level 2b, Grade A) and are increasingly recognized as the method of choice for serum testosterone measurement.

3.6. The measurement of free or bioavailable testosterone should be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. There are no generally accepted lower limits of normal for free testosterone for the diagnosis of hypogonadism. However, a free testosterone level below 225 pmol/l (65 pg/ml) can provide supportive evidence for testosterone treatment (37, 38, 42) (Level 3, Grade C). Threshold values for bioavailable testosterone depend on the method used and are not generally available (38).

3.7. Equilibrium dialysis is the gold standard for free testosterone measurement. Free testosterone assays based on analog displacement immunoassays are widely available but do not give an accurate measurement of free testosterone; thus they should not be used (43, 44). Alternately, measuring serum SHBG levels together with reliable serum total testosterone levels provides the data necessary for calculating free testosterone levels (Level 2b, Grade A). Calculated free testosterone correlates well with free testosterone by equilibrium dialysis (38, 42).

Efforts to create standardization of testosterone assays, agreement on standards for testosterone measurement and accurate reference ranges for testosterone by liquid chromatography mass spectrometry (LC-MS)/MS are being developed. International reference standards, characterization of methodology, and population-based reference ranges for free testosterone by equilibrium dialysis are needed. Consensus on the equilibrium constants for testosterone binding to SHBG and albumin will allow improved calculation of free testosterone (38).

3.8. Salivary testosterone has also been shown to be a reliable substitute for free testosterone measurements but cannot be recommended for general use at this time, since the methodology has not been standardized and adult male ranges are not available in most hospital or reference laboratories (45) (Level 3, Grade B).

3.9. Alterations in other endocrine systems occur in association with aging (i.e., estradiol, growth hormone (GH), and DHEA) but the significance of these changes is not well understood. Determinations of estradiol, thyroid hormones, cortisol, DHEA, DHEA-S, melatonin, GH, and insulin-like growth factor-I are not indicated unless other endocrine disorders are suspected based on the clinical signs and symptoms of the patient (12) (Level 2, Grade A).

Recommendation 4: assessment of treatment outcome and decisions on continued therapy

Improvement in signs and symptoms of testosterone deficiency should be sought. Failure to benefit clinical manifestations within a reasonable time interval (3–6 months) is adequate for libido and sexual function, muscle function, and improved body fat; improvement

in bone mineral density requires a longer interval to show improvement) should result in discontinuation of treatment. Further investigation for other causes of symptoms is then mandatory (Level 1b, Grade A).

Recommendation 5: body composition

In men with hypogonadal values of testosterone, testosterone administration improves body composition (decrease of fat mass, increase of lean body mass (5, 7, 9, 10, 46) (Level 1b, Grade A). Secondary benefits of these changes of body composition on strength, muscle function, and metabolic and cardiovascular dysfunction are suggested by available data but require confirmation by large-scale studies.

Recommendation 6: bone density and fracture rate

Osteopenia, osteoporosis, and fracture prevalence rates are greater in hypogonadal younger and older men (47). Bone density in hypogonadal men of all ages increases under testosterone substitution (8, 11, 48) (Level 1b, Grade A). Fracture data are not yet available and thus the long-term benefit of testosterone requires further investigation. Assessment of bone density at 2-year intervals is advisable in hypogonadal men and serum testosterone measurements should be obtained in all men with osteopenia (49, 50).

Recommendation 7: testosterone and sexual function

7.1. The initial assessment of all men with erectile dysfunction and/or diminished libido should include determination of serum testosterone. These dysfunctions, with or without a testosterone deficiency, might be related to co-morbidities (i.e., diabetes mellitus, hyperprolactinemia, the metabolic syndrome, bladder outlet obstruction, peripheral vascular disease, or medications (51)) (Level 2a, Grade A).

7.2. Men with erectile dysfunction and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy (Level 2a, Grade A). An inadequate response to testosterone treatment requires reassessment of the causal mechanisms responsible for the erectile dysfunction (see 7.4 below).

7.3. In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short (e.g., 3 months) therapeutic trial may be justified. An absence of response calls for discontinuation of testosterone administration. A satisfactory response might be placebo generated, so that continued assessment is advisable before long-term treatment is recommended (52) (Level 2a, Grade B).

7.4. There is evidence suggesting therapeutic synergism with combined use of testosterone and phosphodiesterase-5 inhibitors in hypogonadal or borderline eugonadal men (53, 54) (Level 1b, Grade B). These observations are still preliminary and require additional study. However, the combination treatment should be considered in hypogonadal patients with erectile dysfunction failing to respond to either treatment alone. It is unclear whether men with hypogonadism and erectile dysfunction should be treated initially with phosphodiesterase-5 inhibitor (PDE-5-I), testosterone, or the combination of the two.

Recommendation 8: testosterone and obesity, metabolic syndrome and type 2 diabetes

8.1. Many of the components of the metabolic syndrome (obesity, hypertension, dyslipidemia, impaired glucose regulation, and insulin resistance) are also present in hypogonadal men. Numerous epidemiological studies have established a close relationship between obesity and low serum testosterone levels in healthy men (55). Obese men of 20–64% have a low serum total or free testosterone levels (56). The metabolic syndrome and type 2 diabetes mellitus are associated with low plasma testosterone (25, 55, 57–62). Serum testosterone should be measured in men with type 2 diabetes mellitus with symptoms suggestive of testosterone deficiency (Level 2b, Grade A).

8.2. The effects of testosterone administration on glycemic control of men with diabetes mellitus are much less certain (63–65). It is premature to recommend testosterone treatment for the metabolic syndrome or diabetes mellitus in the absence of laboratory and other clinical evidence of hypogonadism. In men with hypogonadism and diabetes and/or the metabolic syndrome, the testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status (Level 2a, Grade B).

Recommendation 9: prostate cancer and benign prostatic hyperplasia (BPH)

9.1. At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or BPH (66, 67). There is also no evidence that testosterone treatment will convert subclinical prostate cancer to clinically detectable prostate cancer (Level 4, Grade C). However, there is unequivocal evidence that testosterone can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer (68, 69) (Level 2a, Grade A). Currently, adequately powered and optimally designed long-term prostate disease data are not available to determine whether there is any additional risk from testosterone

replacement. Hypogonadal older (>45 years) men should be counseled on the potential risks and benefits of testosterone replacement before treatment and carefully monitored for prostate safety during treatment (Level 3, Grade A).

9.2. Prior to therapy with testosterone, a man's risk of prostate cancer must be assessed using, as a minimum, digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA). However, the pretreatment assessment can be improved by incorporating other risk predictors such as age, family history, and ethnicity/race. Several tools have been developed to assist the clinician in assessing prostate cancer risk (e.g., on-line prostate cancer risk calculator) (70, 71). These tools have not been validated for patients with LOH TDS. If the patient and physician feel that the risk is sufficiently high, further assessment may be desirable (71, 72) (Level 2a, Grade B). However, pretreatment prostate ultrasound examinations or biopsies are not recommended as routine requirements.

9.3. After initiation of testosterone treatment, patients should be monitored for prostate disease at 3–6 months, 12 months, and at least annually thereafter (Level 3, Grade C). Should the patient's prostate cancer risk be sufficiently high (suspicious finding on DRE; increased PSA or as calculated using a combination of risk factors as noted above) transrectal ultrasound-guided biopsies of the prostate are indicated (73–76) (Level 2b, Grade A).

9.4. Severe symptoms of lower urinary tract symptoms (LUTS) evident by a high (>21) International Prostate Symptom Score due to benign prostatic hyperplasia represents a relative contraindication (although there are no compelling data to suggest that testosterone treatment causes exacerbation of LUTS or promotes acute urinary retention) (Level 3, Grade C). After successful treatment of lower urinary tract obstruction, this contraindication is no longer applicable (Level 4, Grade C).

9.5. Men successfully treated for prostate cancer and suffering from confirmed symptomatic hypogonadism are potential candidates for testosterone substitution after a prudent interval, if there is no clinical or laboratory evidence of residual cancer (77–80). As long-term outcome data are not available, clinicians must exercise good clinical judgment together with adequate knowledge of advantages and drawbacks of testosterone therapy in this situation (81, 82) (Level 2b, Grade C). The risk and benefits must be clearly discussed with and understood by the patient and the follow-up must be particularly careful.

Recommendation 10: treatment and delivery systems

10.1. Preparations of natural testosterone should be used for substitution therapy. Currently available i.m.,

subdermal, transdermal, oral, and buccal preparations of testosterone are safe and effective (Level 1b, Grade A). The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics as well as of the advantages and drawbacks of each preparation. The selection of the preparation should be a joint decision of an informed patient and physician (83).

10.2. Since the possible development of an adverse event during treatment (especially elevated hematocrit or prostate carcinoma) (84) requires rapid discontinuation of testosterone substitution, short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with LOH (Level 4, Grade C).

10.3. Inadequate data are available to determine the optimal serum testosterone level for efficacy and safety. For the present time, mid to lower young adult male serum testosterone levels seem appropriate as the therapeutic goal (85). Sustained supraphysiological levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels (Level 3, Grade B).

10.4. Obese men are more likely to develop adverse effects (83, 85) (Level 2b, Grade B).

10.5. 17- α -alkylated androgen preparations such as 17 α -methyl testosterone are obsolete because of their potential liver toxicity and should no longer be prescribed (Level 2b, Grade A).

10.6. There is not enough evidence to recommend substitution of DHT in aging men; other non-testosterone androgen precursor preparations such as DHEA, DHEA-S, androstenediol, or androstenedione are not recommended (Level 1b, Grade A).

10.7. Human chorionic gonadotropin (hCG) stimulates testosterone production of Leydig cells, albeit at a lower rate in older than in younger men. Since insufficient information exists about the therapeutic and adverse effects of hCG treatment in older men and its higher cost, this treatment cannot be recommended in LOH except when fertility is an issue (Level 1b, Grade B).

10.8. Anti-estrogens and aromatase inhibitors have been shown to increase endogenous testosterone levels (Level 2b, Grade B). Adequate evidence does not exist to recommend their use. Selective androgen receptor modulators are under development, but not yet clinically available. Many of these compounds are non-aromatizable and the risks of long-term use are unclear.

Recommendation 11: adverse effects and monitoring

11.1. Testosterone treatment is contraindicated in men with prostate or breast cancer (Level 3, Grade A). Testosterone treatment is relatively contraindicated in men at the high risk of developing prostate cancer. It is unclear whether localized low-grade (Gleason score < 7) prostate cancer represents a relative or absolute

contraindication for treatment. (See Section 9 for more details; Level 4, Grade, C) (83, 86, 87).

11.2. Men with significant erythrocytosis (hematocrit > 52%; Level 3, Grade A), untreated obstructive sleep apnea (Level 3, Grade B), untreated severe congestive heart failure (Level 3, Grade B) should not be started on treatment with testosterone without prior resolution of the co-morbid condition (83, 88).

11.3. Erythrocytosis can develop during testosterone treatment, especially in older men treated by injectable testosterone preparations. Periodic hematological assessment is indicated, i.e., before treatment, then 3–4 and 12 months in the first year of treatment and annually thereafter. While it is not yet clear what critical threshold is desirable, dose adjustments and/or periodic phlebotomy may be necessary to keep hematocrit below 52–55% (12, 82, 83) (Level 3, Grade A).

Recommendation 12: summary

Age is not a contraindication to initiate testosterone treatment. Individual assessment of co-morbidities (as possible causes of symptoms) and potential risks versus benefits of testosterone treatment is particularly important in elderly men (Level 2a, Grade A).

Conclusion

The diagnosis of late-onset testosterone deficiency is based on the presence of symptoms or signs and persistent low serum testosterone levels. The benefits and risks of testosterone therapy must be clearly discussed with the patient and assessment of prostate and other risk factors considered before commencing testosterone treatment. Response to testosterone treatment should be assessed. If there is no improvement of symptoms and signs, treatment should be withdrawn and the patient investigated for other possible causes of the clinical presentations.

Declaration of interest

R S Swerdloff received consulting fees, grants, research materials, and speaker fees from the following: Acrux, Ardana, Auxillium, Clarus, GlaxoSmithKline, Indevus, Organon, Pierre Fabre, Solvay Pharmaceuticals, and Repros. H Behre and E Nieschlag have received honoraria for lectures on testosterone. J J Legros received lecture fees from Organon. A Morales received research grants from Solvay Pharmaceuticals. C Wang received consulting fees from Indevus and research materials or grants from Acrux, Indevus, Met et P, Clarus Therapeutics, and Besins Health Care.

References

- 1 Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV & McKinlay JB. Prevalence of symptomatic androgen deficiency in men. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 4241–4247.

- 2 Gray A, Feldman HA, McKinlay JB & Longcope C. Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *Journal of Clinical Endocrinology and Metabolism* 1991 **73** 1016–1025.
- 3 Harman SM, Metter EJ, Tobin JD, Pearson J & Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 724–731.
- 4 Wu FC, Tajar A, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva F, Forti G, Giwercman A, Huhtaniemi IT, Kula K, Punab M, Boonen S & Vanderschueren D. Hypothalamic–pituitary–testicular axis disruptions in older men are differentially linked to age and modifiable risk factors. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 2737–2745.
- 5 Liverman CT & Blazer DG. *Testosterone and Aging: Clinical Research Directions* Washington, DC: National Academies Press, 2004.
- 6 Isidori AM, Giannetta E, Gianfrilli D, Greco EA, Bonifacio V, Aversa A, Isidori A, Fabbri A & Lenzi A. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clinical Endocrinology* 2005 **63** 381–394.
- 7 Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, Lenzi A & Fabbri A. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clinical Endocrinology* 2005 **63** 280–293.
- 8 Amory JK, Watts NB, Easley KA, Sutton PR, Anawalt BD, Matsumoto AM, Bremner WJ & Tenover JL. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 503–510.
- 9 Page ST, Amory JK, Bowman FD, Anawalt BD, Matsumoto AM, Bremner WJ & Tenover JL. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 1502–1510.
- 10 Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, Holmes JH, Dlewati A, Santanna J, Rosen CJ & Strom BL. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 2647–2653.
- 11 Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, Dlewati A, Staley J, Santanna J, Kapoor SC, Attie MF, Haddad JG Jr & Strom BL. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 1966–1972.
- 12 Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS & Montori VM. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 1995–2010.
- 13 The Practice Committee of the American Society for Reproductive Medicine. Treatment of androgen deficiency in the aging male. *Fertility and Sterility* 2004 **81** 1437–1440.
- 14 AACE Hypogonadism Task Force. American Association of Clinical Endocrinologist Medical Guidelines for Clinical Practice for the Evaluation and Treatment of Hypogonadism in Adult Male Patients-Update 2002. <http://www.aace.com/pub/pdf/guidelines/hypogonadism.pdf> 2002.
- 15 Morales A & Lunenfeld B. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official recommendations of ISSAM. International Society for the Study of the Aging Male. *Aging Male* 2002 **5** 74–86.
- 16 Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W & Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males ISA, ISSAM, and EAU recommendations. *European Urology* 2005 **48** 1–4.
- 17 Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W & Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males. *Aging Male* 2005 **8** 56–58.
- 18 Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W & Wu FC. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *International Journal of Andrology* 2005 **28** 125–127.
- 19 Nieschlag E, Swerdloff R, Behre HM, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morley JE, Schulman C, Wang C, Weidner W & Wu FC. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. *Journal of Andrology* 2006 **27** 135–137.
- 20 Morales A, Schulman CC, Tostain J & Wu CW. Testosterone deficiency syndrome (TDS) needs to be named appropriately – the importance of accurate terminology. *European Urology* 2006 **50** 407–409.
- 21 Schiavi RC, Schreiner-Engel P, White D & Mandeli J. The relationship between pituitary–gonadal function and sexual behavior in healthy aging men. *Psychosomatic Medicine* 1991 **53** 363–374.
- 22 Travison TG, Morley JE, Araujo AB, O'Donnell AB & McKinlay JB. The relationship between libido and testosterone levels in aging men. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 2509–2513.
- 23 Kelleher S, Conway AJ & Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 3813–3817.
- 24 Morales A, Spevack M, Emerson L, Kuzmarov I, Casey R, Black A & Tremblay R. Adding to the controversy: pitfalls in the diagnosis of testosterone deficiency syndromes with questionnaires and biochemistry. *Aging Male* 2007 **10** 57–65.
- 25 Zitzmann M, Faber S & Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 4335–4343.
- 26 Heinemann LA, Saad F, Heinemann K & Thai DM. Can results of the Aging Males' Symptoms (AMS) scale predict those of screening scales for androgen deficiency? *Aging Male* 2004 **7** 211–218.
- 27 Moore C, Huebler D, Zimmermann T, Heinemann LA, Saad F & Thai DM. The Aging males' Symptoms Scale (AMS) as outcome measure for treatment of androgen deficiency. *European Urology* 2004 **46** 80–87.
- 28 Morley JE, Charlton E, Patrick P, Kaiser FE, Cadeau P, McCready D & Perry HM III. Validation of a screening questionnaire for androgen deficiency in aging males. *Metabolism* 2000 **49** 1239–1242.
- 29 Tancredi A, Reginster JY, Schleich F, Pire G, Maassen P, Luyckx F & Legros JJ. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. *European Journal of Endocrinology* 2004 **151** 355–360.
- 30 Beutel ME, Wiltink J, Hauck EW, Auch D, Behre HM, Brahler E & Weidner W. Correlations between hormones, physical, and affective parameters in aging urologic outpatients. *European Urology* 2005 **47** 749–755.
- 31 Diver MJ, Imtiaz KE, Ahmad AM, Vora JP & Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. *Clinical Endocrinology* 2003 **58** 710–717.
- 32 Citron JT, Ettinger B, Rubino H, Ettinger VM, Minkoff J, Hom F, Kan P & Alloo R. Prevalence of hypothalamic–pituitary imaging abnormalities in impotent men with secondary hypogonadism. *Journal of Urology* 1996 **155** 529–533.
- 33 Bunch TJ, Abraham D, Wang S & Meikle AW. Pituitary radiographic abnormalities and clinical correlates of hypogonadism in elderly males presenting with erectile dysfunction. *Aging Male* 2002 **5** 38–46.
- 34 Rhoden EL, Estrada C, Levine L & Morgentaler A. The value of pituitary magnetic resonance imaging in men with hypogonadism. *Journal of Urology* 2003 **170** 795–798.

- 35 Buvat J & Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. *Journal of Urology* 1997 **158** 1764–1767.
- 36 Araujo AB, O'Donnell A, Brambilla DJ, Simpson WB, Longcope C, Matsumoto AM & McKinlay JB. Prevalence and incidence of androgen deficiency in middle-aged and older men: estimates from the Massachusetts male aging study. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 5920–5926.
- 37 Vermeulen A. Hormonal cut-offs of partial androgen deficiency: a survey of androgen assays. *Journal of Endocrinological Investigation* 2005 **28** 28–31.
- 38 Rosner W, Auchus RJ, Azziz R, Sluss PM & Raff H. Utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society Position Statement. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 405–413.
- 39 Sikaris K, McLachlan RI, Kazlauskas R, de Kretser D, Holden CA & Handelsman DJ. Reproductive hormone reference intervals for healthy fertile young men: evaluation of automated platform assays. *Journal of Clinical Endocrinology and Metabolism* 2005 **90** 5928–5936.
- 40 Taieb J, Mathian B, Millot F, Patricot MC, Mathieu E, Queyrel N, Lacroix I, Somma-Delpero C & Boudou P. Testosterone measured by 10 immunoassays and by isotope-dilution gas chromatography–mass spectrometry in sera from 116 men, women, and children. *Clinical Chemistry* 2003 **49** 1381–1395.
- 41 Wang C, Catlin DH, Demers LM, Starcevic B & Swerdloff RS. Measurement of total serum testosterone in adult men: comparison of current laboratory methods versus liquid chromatography–tandem mass spectrometry. *Journal of Clinical Endocrinology and Metabolism* 2004 **89** 534–543.
- 42 Vermeulen A, Verdonck L & Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 3666–3672.
- 43 Swerdloff RS & Wang C. Free testosterone measurement by the analog displacement direct assay: old concerns and new evidence. *Clinical Chemistry* 2008 **54** 458–460.
- 44 Rosner W. Errors in the measurement of plasma free testosterone. *Journal of Clinical Endocrinology and Metabolism* 1997 **82** 2014–2015.
- 45 Wang C, Plymate S, Nieschlag E & Paulsen CA. Salivary testosterone in men: further evidence of a direct correlation with free serum testosterone. *Journal of Clinical Endocrinology and Metabolism* 1981 **53** 1021–1024.
- 46 Allan CA, Strauss BJ, Burger HG, Forbes EA & McLachlan RI. Testosterone therapy prevents gain in visceral adipose tissue and loss of skeletal muscle in nonobese aging men. *Journal of Clinical Endocrinology and Metabolism* 2008 **93** 139–146.
- 47 Meier C, Nguyen TV, Handelsman DJ, Schindler C, Kushnir MM, Rockwood AL, Meikle AW, Center JR, Eisman JA & Seibel MJ. Endogenous sex hormones and incident fracture risk in older men: the Dubbo Osteoporosis Epidemiology Study. *Archives of Internal Medicine* 2008 **168** 47–54.
- 48 Kenny AM, Prestwood KM & Raisz LG. Short-term effects of intramuscular and transdermal testosterone on bone turnover, prostate symptoms, cholesterol, and hematocrit in men over age 70 with low testosterone levels. *Endocrine Research* 2000 **26** 153–168.
- 49 Freitas SS, Barrett-Connor E, Ensrud KE, Fink HA, Bauer DC, Cawthon PM, Lambert LC & Orwoll ES. Rate and circumstances of clinical vertebral fractures in older men. *Osteoporosis International* 2007 **19** 615–623.
- 50 Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES, Melton LJ III, Bauer DC & Ensrud KE. Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. *Journal of the American Medical Association* 2007 **298** 629–637.
- 51 Morales A, Buvat J, Gooren LJ, Guay AT, Kaufman JM, Tan HM & Torres LO. Endocrine aspects of sexual dysfunction in men. *Journal of Sexual Medicine* 2004 **1** 69–81.
- 52 Black AM, Day AG & Morales A. The reliability of clinical and biochemical assessment in symptomatic late-onset hypogonadism: can a case be made for a 3-month therapeutic trial? *BJU International* 2004 **94** 1066–1070.
- 53 Shabsigh R, Kaufman JM, Steidle C & Padma-Nathan H. Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone. *Journal of Urology* 2004 **172** 658–663.
- 54 Greenstein A, Mabjeesh NJ, Sofer M, Kaver I, Matzkin H & Chen J. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? *Journal of Urology* 2005 **173** 530–532.
- 55 Allen NE, Appleby PN, Davey GK & Key TJ. Lifestyle and nutritional determinants of bioavailable androgens and related hormones in British men. *Cancer Causes and Control* 2002 **13** 353–363.
- 56 Kalyani RR & Dobs AS. Androgen deficiency, diabetes, and the metabolic syndrome in men. *Current Opinion in Endocrinology, Diabetes and Obesity* 2007 **14** 226–234.
- 57 Selvin E, Feinleib M, Zhang L, Rohrmann S, Rifai N, Nelson WG, Dobs A, Basaria S, Golden SH & Platz EA. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2007 **30** 234–238.
- 58 Rodriguez A, Muller DC, Metter EJ, Maggio M, Harman SM, Blackman MR & Andres R. Aging, androgens, and the metabolic syndrome in a longitudinal study of aging. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3568–3572.
- 59 Derby CA, Zilber S, Brambilla D, Morales KH & McKinlay JB. Body mass index, waist circumference and waist to hip ratio and change in sex steroid hormones: the Massachusetts Male Ageing Study. *Clinical Endocrinology* 2006 **65** 125–131.
- 60 Kapoor D, Aldred H, Clark S, Channer KS & Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care* 2007 **30** 911–917.
- 61 Kupelian V, Page ST, Araujo AB, Travison TG, Bremner WJ & McKinlay JB. Low sex hormone-binding globulin, total testosterone, and symptomatic androgen deficiency are associated with development of the metabolic syndrome in nonobese men. *Journal of Clinical Endocrinology and Metabolism* 2006 **91** 843–850.
- 62 Laaksonen DE, Niskanen L, Punnonen K, Nyyssönen K, Tuomainen TP, Valkonen VP, Salonen R & Salonen JT. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004 **27** 1036–1041.
- 63 Kapoor D, Goodwin E, Channer KS & Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *European Journal of Endocrinology* 2006 **154** 899–906.
- 64 Corrales JJ, Burgo RM, Garca-Berrocal B, Almeida M, Alberca I, Gonzalez-Buitrago JM, Orfao A & Miralles JM. Partial androgen deficiency in aging type 2 diabetic men and its relationship to glycaemic control. *Metabolism* 2004 **53** 666–672.
- 65 Basu R, Dalla MC, Campioni M, Basu A, Nair KS, Jensen MD, Khosla S, Klee G, Toffolo G, Cobelli C & Rizza RA. Effect of 2 years of testosterone replacement on insulin secretion, insulin action, glucose effectiveness, hepatic insulin clearance, and postprandial glucose turnover in elderly men. *Diabetes Care* 2007 **30** 1972–1978.
- 66 Roddam AW, Allen NE, Appleby P & Key TJ. Endogenous sex hormones and prostate cancer: a collaborative analysis of 18 prospective studies. *Journal of the National Cancer Institute* 2008 **100** 170–183.
- 67 Carpenter WR, Robinson WR & Godley PA. Getting over testosterone: postulating a fresh start for etiologic studies of prostate cancer. *Journal of the National Cancer Institute* 2008 **100** 158–159.

- 68 Fowler JE Jr & Whitmore WF Jr. Considerations for the use of testosterone with systemic chemotherapy in prostatic cancer. *Cancer* 1982 **49** 1373–1377.
- 69 McConnell JD. Prostatic growth: new insights into hormonal regulation. *British Journal of Urology* 1995 **76** (Suppl 1) 5–10.
- 70 Parekh DJ, Ankerst DP, Higgins BA, Hernandez J, Canby-Hagino E, Brand T, Troyer DA, Leach RJ & Thompson IM. External validation of the Prostate Cancer Prevention Trial risk calculator in a screened population. *Urology* 2006 **68** 1152–1155.
- 71 Thompson IM, Ankerst DP, Chi C, Goodman PJ, Tangen CM, Lucia MS, Feng Z, Parnes HL & Coltman CA Jr. Assessing prostate cancer risk: results from the Prostate Cancer Prevention Trial. *Journal of the National Cancer Institute* 2006 **98** 529–534.
- 72 Thompson IM, Carroll PR & Carducci MA. Recommendations for defining and treating high risk localized prostate cancer. *Journal of Urology* 2006 **176** S6–S10.
- 73 Marks LS, Mazer NA, Mostaghel E, Hess DL, Dorey FJ, Epstein JI, Veltri RW, Makarov DV, Partin AW, Bostwick DG, Macairan ML & Nelson PS. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *Journal of the American Medical Association* 2006 **296** 2351–2361.
- 74 Meikle AW, Arver S, Dobs AS, Adolfsson J, Sanders SW, Middleton RG, Stephenson RA, Hoover DR, Rajaram L & Mazer NA. Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. *Urology* 1997 **49** 191–196.
- 75 Bhasin S, Singh AB, Mac RP, Carter B, Lee MI & Cunningham GR. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. *Journal of Andrology* 2003 **24** 299–311.
- 76 Rhoden EL & Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *New England Journal of Medicine* 2004 **350** 482–492.
- 77 Agarwal PK & Oefelein MG. Testosterone replacement therapy after primary treatment for prostate cancer. *Journal of Urology* 2005 **173** 533–536.
- 78 Kaufman JM & Graydon RJ. Androgen replacement after curative radical prostatectomy for prostate cancer in hypogonadal men. *Journal of Urology* 2004 **172** 920–922.
- 79 Khera M & Lipshultz LI. The role of testosterone replacement therapy following radical prostatectomy. *Urologic Clinics of North America* 2007 **34** 549–553 (vi).
- 80 Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer* 2007 **109** 536–541.
- 81 Nieschlag E & Behre HM. *Testosterone: Action, Deficiency, Substitution*. edn. 3. Cambridge: Cambridge University Press, 2004.
- 82 Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. *Clinical Endocrinology* 2006 **65** 275–281.
- 83 Calof OM, Singh AB, Lee ML, Kenny AM, Urban RJ, Tenover JL & Bhasin S. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences* 2005 **60** 1451–1457.
- 84 Parsons JK, Carter HB, Platz EA, Wright EJ, Landis P & Metter EJ. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiology, Biomarkers and Prevention* 2005 **14** 2257–2260.
- 85 Zitzmann M & Nieschlag E. Androgen receptor gene CAG repeat length and body mass index modulate the safety of long-term intramuscular testosterone undecanoate therapy in hypogonadal men. *Journal of Clinical Endocrinology and Metabolism* 2007 **92** 3844–3853.
- 86 Malkin CJ, Pugh PJ, West JN, van Beek EJ, Jones TH & Channer KS. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *European Heart Journal* 2006 **27** 57–64.
- 87 Hanafy HM. Testosterone therapy and obstructive sleep apnea: is there a real connection? *Journal of Sexual Medicine* 2007 **4** 1241–1246.
- 88 Drinka PJ, Jochen AL, Cuisinier M, Bloom R, Rudman I & Rudman D. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. *Journal of the American Geriatrics Society* 1995 **43** 899–901.

Received 4 August 2008

Accepted 14 August 2008