

Investigation, treatment and monitoring of late-onset hypogonadism in males

ISA*, ISSAM**, and EAU recommendations

E. Nieschlag, Institute of Reproductive Medicine, University of Münster, Germany and
R. Swerdloff, Division of Endocrinology, Harbor-UCLA Medical Center, and Los Angeles BioMedical Research
Institute, Torrance, CA/USA

H.M. Behre, Andrology Unit, Department of Urology, Martin-Luther-University, Halle, Germany

L.J. Gooren, Department of Endocrinology/Andrology, Free University Hospital, Amsterdam, The Netherlands

J. M. Kaufman, Department of Endocrinology, Academisch Ziekenhuis, Gent, Belgium

J.J. Legros, Centre Hospitalier Universitaire, Sart-Tilman, Liège, Belgium

B. Lunenfeld, Faculty Life Science Bar-Ilan University, Israel

J.E. Morley, Div. of Geriatric Medicine, St. Louis University, St. Louis, MO/USA

C. Schulman, Department of Urology, University Clinic of Brussels, Erasme Hospital, Belgium

C. Wang, General Clinical Research Center, Harbor-UCLA Medical Center, and Los Angeles BioMedical Research
Institute, Torrance, CA/USA

W. Weidner, Department of Urology, Justus-Liebig-University, Giessen, Germany

F.C.W. Wu, Central Manchester Healthcare NHS Trust, Manchester, UK

*ISA: International Society of Andrology

**ISSAM International Society for the Study of the Aging Male

EAU

European
Association
of Urology

Androgen deficiency in the ageing male has become a topic of increasing interest and debate throughout the world. Demographic data demonstrates the increasing percentage of the population that is found in the older age groups. The data also support the concept that 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 men (age 20-30 years). 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 recent studies show short-term beneficial effects of testosterone in older men that are similar to those in younger men. Long-term data on the effects of testosterone treatment in the older population are limited and specific risk data on the prostate and cardiovascular systems are needed. Key questions of functional benefits that may retard frailty in the elderly are not yet available.

The recommendations described below were prepared for the International Society of Andrology (ISA) and the International Society for the Study of the Aging Male (ISSAM) following a panel discussion with active participation from the audience sponsored by the ISA on the topic at the 4th ISSAM Congress in Prague in February 2004. The ISA Member Societies were requested to comment on the draft guidelines. Representatives of the European Association of Urology participated in the final draft of this document. This document is not intended to provide evidence for each recommendation as a review of pertinent studies has recently been comprehensively summarized in the Clinical Research Directions on "Testosterone and Aging" by the Institute of Medicine (Washington 2004). The recommendations will be subject to revision as larger-scale and longer-term data become available.

In order to reach a large audience these recommendations are published in the *International Journal of Andrology*, the *Journal of Andrology*, *The Aging Male* and in *European Urology*.

RECOMMENDATION 1

Definition of late-onset hypogonadism (LOH): A clinical *and* biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.

RECOMMENDATION 2

LOH is a syndrome characterized primarily by:

- (1) The easily recognized features of diminished sexual desire (libido) and erectile quality and frequency, particularly nocturnal erections.
- (2) Changes in mood with concomitant decreases in intellectual activity, cognitive functions, spatial orientation ability, fatigue, depressed mood and irritability.
- (3) Sleep disturbances.
- (4) Decrease in lean body mass with associated diminution in muscle volume and strength.
- (5) Increase in visceral fat.
- (6) Decrease in body hair and skin alterations.
- (7) Decreased bone mineral density resulting in osteopenia, osteoporosis and increased risk of bone fractures.

RECOMMENDATION 3

In patients at risk or suspected of hypogonadism in general and LOH in particular, a thorough physical and biochemical work-up is mandatory and, especially, the following biochemical investigations should be done:

- (1) A serum sample for total testosterone determination and sex hormone binding globulin (SHBG) should be obtained between 07.00 and 11.00 hours. The most widely accepted parameters used to establish the presence of hypogonadism are the measurement of total testosterone and free testosterone calculated from measured total testosterone and SHBG or measured by a reliable free testosterone by dialysis method.
- (2) There are no generally accepted lower limits of normal and it is unclear whether geographically different thresholds depend on ethnic differences or on the physician's perception. There is however general agreement that total testosterone levels above 12 nmol/L (346 ng/dL) or free testosterone levels above 250 pmol/L (72 pg/mL) do not require testosterone substitution. Similarly, based on the data of younger men, there is consensus that serum total testosterone levels below 8 nmol/L (231 ng/dL) or free testosterone below 180 pmol/L (52 pg/mL) require substitution. Since symptoms of testosterone deficiency become manifest between 12 and 8 nmol/L, trials of treatment can be considered in those in whom alternative causes of these symptoms have been excluded. (Since there are variations in the reagents and normal ranges between different laboratories, the cutoff values given for serum

testosterone and free testosterone may have to be adjusted depending on the reference values given by each laboratory).

- (3) Salivary testosterone has been shown to be a reliable substitute for free testosterone measurements, but cannot be recommended at this time since the methodology has not been standardized and adult male ranges are not available in most hospital or reference laboratories.
- (4) If testosterone levels are below or at the lower limit of the accepted normal adult male values, it is recommended that a second determination is performed together with assessment of serum luteinizing hormone (LH) and prolactin.

RECOMMENDATION 4

- (1) It is recognized that significant alterations in other endocrine systems occur in association with ageing but the significance of these changes is not well understood. In general terms, determinations of thyroid hormones, cortisol, DHEA, DHEA-S, melatonin, GH and IGF-I are not indicated in the uncomplicated evaluation of late-onset hypogonadism. If endocrine disorders are suspected, assessment of these and other hormones may be warranted.
- (2) Diabetes mellitus type 2 is a frequent disorder of ageing men. It is unclear at the present time what effect testosterone has on blood sugar and insulin sensitivity; thus, until positive effects of testosterone on blood sugar control are definitively demonstrated, diabetes should be evaluated and treated before or simultaneously with testosterone substitution.
- (3) In ageing men with the major complaint of erectile dysfunction, lipids and cardiovascular status should be assessed.

RECOMMENDATION 5

A clear indication based on a clinical picture together with biochemical evidence of low serum testosterone should exist prior to the initiation of testosterone substitution.

RECOMMENDATION 6

- (1) Testosterone administration is absolutely contraindicated in men suspected or having carcinoma of the prostate or breast.
- (2) Men with significant polycythaemia, untreated sleep apnoea, severe heart failure, severe symptoms of lower urinary tract obstruction evident from high scores in the IPSS (International Prostate Symptom Score) or clinical findings of bladder outflow obstruction (increased post-micturition residual volume, decreased peakflow, pathological pressure flow-studies) due to an enlarged, clinically benign prostate should not be treated. Moderate obstruction represents a partial contraindication. After successful treatment of the obstruction, the contraindication is lifted.
- (3) In the absence of definite contraindications, age as such is not a contraindication to initiating testosterone substitution.

RECOMMENDATION 7

- (1) Preparations of natural testosterone should be used for substitution therapy. Currently available intramuscular, subdermal, transdermal, oral and buccal preparations of testosterone are safe and effective. The treating physician should have sufficient knowledge and adequate understanding of the pharmacokinetics, as well as the advantages and drawbacks, of each preparation. The selection of the preparation should be a joint decision by the patient and the physician.
- (2) Since the possible development of a contraindication during treatment (especially prostate carcinoma) requires rapid discontinuation of testosterone substitution, short-acting (transdermal, oral, buccal) preparations should be preferred over long-acting (intramuscular, subdermal) depot-preparations in patients with LOH.
- (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 and should be the therapeutic goal. Supraphysiological levels must be avoided. Although it may appear desirable, no evidence exists for or against the need to maintain the physiological circadian rhythm of serum testosterone levels.

RECOMMENDATION 8

- (1) Alkylated androgen preparations such as 17 α -methyl testosterone are obsolete because of their potential liver toxicity and should no longer be prescribed.
- (2) There is not enough evidence to recommend substitution with DHT in ageing men and there is no evidence to recommend other androgen preparations such as DHEA, DHEA-S, androstenediol or androstenedione for treatment.

- (3) hCG stimulates testosterone production of Leydig cells, albeit at a lower rate in older than in younger men. Since insufficient information exists about the effects and side effects of hCG treatment in older men this treatment cannot be recommended in LOH.

RECOMMENDATION 9

Improvement in signs and symptoms of testosterone deficiency should be sought and failure to benefit clinical manifestations should result in discontinuation of treatment. Further investigation for other causes is then mandatory.

RECOMMENDATION 10

Digital rectal examination (DRE) and determination of serum prostate-specific antigen (PSA) are mandatory in men over the age of 45 years as baseline measurements of prostate health prior to therapy with testosterone, at quarterly intervals for the first 12 months and yearly thereafter. Transrectal ultrasound-guided biopsies of the prostate are indicated only if the DRE or the serum PSA levels are abnormal.

RECOMMENDATION 11

Testosterone normally results in improvements in mood and well-being. The development of negative behavioural patterns during treatment calls for dose modifications or discontinuation of therapy.

RECOMMENDATION 12

Polycythaemia occasionally develops during testosterone treatment. Periodic haematological assessment is indicated, i.e. before treatment, 3 monthly for one year and then annually. Dose adjustments may be necessary.

RECOMMENDATION 13

Bone density increases under testosterone substitution and fracture rates may be reduced. Therefore assessment of bone density at two-year intervals may be advisable, if available and affordable.

RECOMMENDATION 14

Some men with erectile dysfunction and low serum testosterone may not respond adequately under testosterone treatment alone. In these cases addition of phosphodiesterase-5 inhibitors may be indicated. Similarly, men with erectile dysfunction not responding to phosphodiesterase-5 inhibitors may have low serum testosterone and require testosterone substitution.

RECOMMENDATION 15

Men successfully treated for prostate cancer and suffering from confirmed symptomatic hypogonadism are candidates for testosterone substitution after a prudent interval if there is no evidence of residual cancer. The risk and benefits must be clearly understood by the patient and the follow-up must be particularly careful. No reliable evidence exists in favour or against this recommendation. The clinicians must exercise good clinical judgement together with adequate knowledge of the advantages and drawback of testosterone therapy in this situation.