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ISA, ISSAM, EAU, EAA and ASA recommendations

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

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ISA, International Society of Andrology
ISSAM, International Society for the Study of Aging Male
EAU, European Association of Urology
EAA, European Academy of Andrology
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INTRODUCTION

Demographic data clearly demonstrate that the percent of 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 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 (Araujo *et al.* 2007; Gray *et al.* 1991; Harman *et al.* 2001; Wu *et al.* 2008). 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. This has been comprehensively reviewed and summarized by the Institute of Medicine in "Testosterone and Aging: Clinical Research Directions" (Liverman *et al.* 2004). Long term data on the effects of testosterone treatment in the older population are limited mainly to effects on body composition and bone mass (Isidori *et al.* 2005a; Isidori *et al.* 2005b; Amory *et al.* 2004; Page *et al.* 2005; Snyder *et al.* 1999b; Snyder *et al.* 1999a), 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.

PROCESS FOR DEVELOPMENT OF RECOMMENDATIONS

Recent guidelines for the testosterone treatment of younger hypogonadal men are available from professional societies (Bhasin *et al.* 2006; The Practice Committee of the American Society for Reproductive Medicine, 2004; AACE Hypogonadism Task Force, 2002). Recommendations on the diagnosis, treatment and monitoring of late onset hypogonadism was published by ISSAM in 2002 (Morales *et al.* 2002). In 2005, a writing committee formed by the International Society of Andrology (ISA), the International Society for the Study of Aging Male (ISSAM) and the European Association of Urology (EAU) prepared a set of recommendations specifically on the "Investigation, treatment and monitoring of late onset hypogonadism". 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 in European Urology (Nieschlag *et al.* 2005b; Nieschlag *et al.* 2005a; Nieschlag *et al.* 2005c; Nieschlag *et al.* 2006). In view of the growing interest from practitioners on the treatment of older men with testosterone, the ISA, ISSAM, EAU, European Academy of Andrology (EAA) and American Society of Andrology (ASA) 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).

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 randomisation
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

To assure broad outreach to multidisciplinary audiences, these recommendations are published in *European Journal of Endocrinology, European Urology, International Journal of Andrology, International Journal of Impotence Research, Journal of Andrology*, and *The Aging Male.*

RECOMMENDATION 1. Definition

Late-onset hypogonadism (LOH, also referred to as age associated testosterone deficiency syndrome, TDS) is a clinical *and* biochemical syndrome associated with advancing age and characterized by symptoms and a deficiency in serum testosterone levels (below the young healthy adult male reference range) (Nieschlag *et al.* 2005c; Morales *et al.* 2006; Nieschlag *et al.* 2005b; Nieschlag *et al.* 2005a; Nieschlag *et al.* 2006). 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) (Bhasin *et al.* 2006; Nieschlag *et al.* 2005c; Nieschlag *et al.* 2005b; Nieschlag *et al.* 2005a; Nieschlag *et al.* 2006). The symptom most associated with hypogonadism is low libido (Level 3, Grade A) (Schiavi *et al.* 1991; Travison *et al.* 2006). Other manifestations of hypogonadism include: erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, 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) (Araujo *et al.* 2007; Kelleher *et al.* 2004; Morales *et al.* 2007; Zitzmann *et al.* 2006).

2.2. Questionnaires such as Aging Male Symptom Score (AMS) (Heinemann *et al.* 2004; Moore *et al.* 2004) and Androgen Deficiency in Aging Men (ADAM) (Morley *et al.* 2000) are not recommended for the diagnosis of hypogonadism because of low specificity (Level 3, Grade B) (Morales *et al.* 2007; Tancredi *et al.* 2004; Beutel *et al.* 2005).

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 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, renal and HIV-related diseases), obesity, metabolic syndrome, and hemachromatosis (Bhasin *et al.* 2006). 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 07.00 and 11.00 hours (Level 2 a, A)(Diver *et al.* 2003). 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 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 to 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 LH 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) (Citron *et al.* 1996; Bunch *et al.* 2002; Rhoden *et al.* 2003; Buvat *et al.* 1997) or when secondary hypogonadism is suspected (Bhasin *et al.* 2006; Araujo *et al.* 2004; Vermeulen, 2005) (Level 3, Grade B).

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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 (Rosner *et al.* 2007; Sikaris *et al.* 2005; Taieb *et al.* 2003; Wang *et al.* 2004) (Level 2b, Grade A).

3.5. Current immunometric methods for measurement of testosterone can distinguish between hypogonadism and normal adult men. However, methods based on mass spectrometry are more accurate and precise (Taieb *et al.* 2003; Wang *et al.* 2004; Sikaris *et al.* 2005) (Level 2b, Grade A) and are increasingly recognized as the method of choice for serum testosterone measurement.

3.6. 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 T treatment (Vermeulen *et al.* 1999; Vermeulen, 2005; Rosner *et al.* 2007) (Level 3, Grade C). Threshold values for bioavailable testosterone depend on the method used and are not generally available (Rosner *et al.* 2007).

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 (Swerdloff *et al.* 2008; Rosner, 1997). Alternately, measuring serum SHBG levels together with a 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 (Rosner *et al.* 2007; Vermeulen *et al.* 1999).

Efforts to create standardization of testosterone assays, agreement on standards for testosterone measurement and accurate reference ranges for testosterone by 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 T binding to SHBG and albumin will allow improved calculation of free T (Rosner *et al.* 2007).

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 (Wang *et al.* 1981) (Level 3, Grade B).

3.9. Alterations in other endocrine systems occur in association with aging (i.e. estradiol, 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 IGF-I are not indicated unless other endocrine disorders are suspected based on the clinical signs and symptoms of the patient (Bhasin *et al.* 2006) (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 to 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 (Isidori *et al.* 2005b; Liverman *et al.* 2004; Allan *et al.* 2008; Page *et al.* 2005; Snyder *et al.* 1999b) (Level 1b, Grade A). Secondary benefits of these changes of body composition on strength, muscle function, 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 (Meier *et al.* 2008). Bone density in hypogonadal men of all ages increases under testosterone substitution (Snyder *et al.* 1999a; Kenny *et al.* 2000; Amory *et al.* 2004) (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 two-year intervals is advisable in hypogonadal men and serum testosterone measurements should be obtained in all men with osteopenia (Schousboe *et al.* 2007; Freitas *et al.* 2008).

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 (Morales *et al.* 2004) (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 (Black *et al.* 2004) (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(Greenstein *et al.* 2005; Shabsigh *et al.* 2004) (Level 1b, Grade B).These observations are still preliminary and require additional study. However, the combination treatment should be considered in hypogonadal patients with ED failing to respond to either treatment alone. It is unclear whether men with hypogonadism and ED should be treated initially with 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
(Allen *et al.* 2002). 20%-64% of obese men have a low serum total or free testosterone levels (Kalyani *et al.* 2007). The metabolic syndrome and type 2 diabetes mellitus are associated with low plasma testosterone (Selvin *et al.* 2007; Rodriguez *et al.* 2007; Allen *et al.* 2002; Derby *et al.* 2006; Kapoor *et al.* 2007; Kupelian *et al.* 2006; Laaksonen *et al.* 2004; Zitzmann *et al.* 2006). 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 (Kapoor *et al.* 2006; Corrales *et al.* 2004; Basu *et al.* 2007). 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, testosterone treatment for traditional hypogonadal symptoms may have other unproven benefits on their metabolic status (Level 2a, Grade B).

RECOMMENDATION 9- Prostate Cancer and BPH

9.1. At the present time, there is no conclusive evidence that testosterone therapy Increases the risk of prostate cancer or BPH (Roddam *et al.* 2008; Carpenter *et al.* 2008). There is also no evidence that testosterone treatment will convert sub-clinical 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 (Fowler, Jr. *et al.* 1982; McConnell, 1995) (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 yr) men should be counselled 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 pre-treatment 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 (Parekh *et al.* 2006; Thompson *et al.* 2006a). 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 (Thompson *et al.* 2006a; Thompson *et al.* 2006b) (Level 2a, grade B). However, pre-treatment prostate ultra-sound 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 to 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 (Marks *et al.* 2006; Meikle *et al.* 1997; Bhasin *et al.* 2003; Rhoden *et al.* 2004) (Level 2b, Grade A).

9.4. Severe symptoms of lower urinary tract symptoms (LUTS) evident by a high (>21) International Prostate Symptom Score (IPSS) due to benign prostate hyperplasia represents a relative contraindication (although there are no compelling data to suggest that testosterone treatment causes exacerbation of LUTS or promote 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 (Agarwal *et al.* 2005; Kaufman *et al.* 2004; Khera *et al.* 2007; Sarosdy, 2007) . 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 (Nieschlag *et al.* 2004; Nieschlag, 2006) (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 intramuscular, 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 (Calof *et al.* 2005).

10.2. Since the possible development of an adverse event during treatment (especially elevated hematocrit or prostate carcinoma) (Parsons *et al.* 2005) 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 (Zitzmann *et al.* 2007). 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 (Calof *et al.* 2005; Zitzmann *et al.* 2007) (Level 2b, grade B).

10.5. 17-alpha-alkylated androgen preparations such as 17α-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 1 b, 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 [SARMs] 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 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) (Malkin *et al.* 2006; Hanafy, 2007; Calof *et al.* 2005).

11.2. Men with significant erythrocytosis (hematocrit > 52%) (Level 3, Grade A), untreated obstructive sleep apnoea (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 (Calof *et al.* 2005; Drinka *et al.* 1995).

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 to 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 to 55% (Bhasin *et al.* 2006; Nieschlag, 2006; Calof *et al.* 2005) (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 vs. 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.

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