EDITORIAL

Recommendations on the diagnosis, treatment and monitoring of late-onset hypogonadism in men – a suggested update

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Abstract
Recommendations on the diagnosis, treatment and monitoring of late-onset hypogonadism (LOH) in men were first published by ISSAM in 2002. In 2005, and, in 2008, updated recommendations were published in the International Journal of Andrology, the Journal of Andrology, the Aging Male and European Urology. Towards discussions at the next ISSAM/ESSAM meeting in Moscow, 29 November 2013, we suggest the following update.

Keywords
Late-onset hypogonadism, men, testosterone.

Recommendation 1: late onset hypogonadism definition
Late onset hypogonadism (LOH; also referred to as age-related testosterone deficiency syndrome [TDS]) is a clinical and biochemical syndrome in men with advancing age (who have had normal pubertal development and normal male secondary characteristics) associated with low testosterone (T), age-related comorbidities, and deterioration in general health status. Prevention of obesity, disease and frailty, and maintenance of a healthy lifestyle (adequate physical and mental activity, and healthy food intake) may delay or prevent the occurrence of LOH [1].

LOH is characterized by hypo-gonadal symptoms and either deficiency in total serum testosterone (TT) levels or low calculated free testosterone levels (below the young healthy adult male reference range). An elevated LH level with TT below 15 nmol/l would also suggest LOH. This condition may result in a significant deterioration in quality of life and may adversely affect the function of multiple organ systems.

Though the clinical significance of LOH is becoming increasingly apparent, the extent of its prevalence in the general population is underappreciated. There are a large number of men with LOH who remain undiagnosed and untreated [2].

Recommendation 2: clinical diagnosis
At present, the diagnosis of treatable LOH requires the presence of symptoms and signs suggestive of testosterone deficiency (TD) (Level 2, Grade A). Clinicians should ask specifically about issues such as low libido, impotence, fatigue, impaired concentration, depression, sexual dysfunction and diminished frequency of morning erections [3].

Screening questionnaires on male symptomatic hypogonadism, although sensitive, have low specificity. Morley et al. compared the most commonly used questionnaires in 148 men using bioavailable testosterone (BT) as the biochemical “gold standard” for the diagnosis of hypogonadism, and found the sensitivity to be 97% for the ADAM, 83% for the AMS and 60% for the MMAS. Specificity was 30% for the ADAM, 59% for the MMAS and 39% for the AMS [4] (now validated in many languages [5,6]). Despite having low specificity, the AMS and other male hypogonadism questionnaires may be useful for monitoring the clinical response to testosterone replacement therapy (TRT) [7–10]. The AMS and other questionnaire may be useful to monitor results of testosterone therapy as well as to assess the presence and severity of symptoms as a prerequisite for initiating TRT [11].

Physical examination of patients with suspected LOH should include an assessment of the amount and distribution of body hair (including beard growth, and axillary and pubic hair); presence of acanthosis nigricans, associated with insulin resistance [12–15]; presence and degree of breast enlargement; size and consistency of the testes; abnormalities in the scrotum; and size of the penis. The prostate should be examined; it should be noted that the prostate may be enlarged in older men, despite a low TT level [16]. Weight, height, BMI and waist circumference should also be...
measured, since symptoms and signs potentially indicative of TD in men include height loss, reduced muscle bulk and strength and increased body fat, in particular, abdominal fat accumulation and BMI [17].

The clinical symptoms most commonly associated with LOH are low libido [18,19] and poor morning erections [20]. Other clinical symptoms of LOH include: erectile dysfunction, decreased vigor and muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, decreased vitality, depressed mood and fatigue [21,22]. None of these symptoms are specific to the testosterone (T)-deficient state. One or more of these symptoms may raise suspicion of symptomatic LOH. There is also a high prevalence of symptomatic LOH in aging, obese men with benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS) [23,24].

One or more of these symptoms must be corroborated with a decreased serum T level in order to support a diagnosis of symptomatic LOH (Level 2, Grade A).

Various prospective studies have reported the occurrence of hypo-gonadal symptoms as side effects of androgen-deprivation therapy, including hot flashes, decreased libido and erectile dysfunction [25,26]. Other complications of androgen-deprivation therapy include osteoporosis, with increased risk of fractures, and worsening of comorbidities such as diabetes, cardiovascular disease and metabolic syndrome, as well as physical, functional and cognitive impairment [27–30].

TD may influence not only quality of life in men, but also life span. Some observational studies including meta-analysis show that low endogenous testosterone levels are associated with increased risk of all-cause and cardiovascular disease-related mortality [31–33]. But these studies have several limitations [34,35] and there is not enough convincing data concerning the effect of testosterone therapy on mortality.

Based on the above and below mentioned data, we recommend the screening of LOH in men with the following conditions:
- Low libido
- Poor morning erections
- Erectile dysfunction
- Depressed mood and fatigue
- Cognitive impairment
- Insulin resistance, including acanthosis nigricans
- Obesity
- Metabolic syndrome
- Diabetes mellitus type 2
- Decreased muscle mass and strength
- Decreased bone mineral density and osteoporosis
- Decreased vitality
- Vitamin D deficiency
- Glucocorticoids, opioids

### Recommendation 3: laboratory diagnosis

In patients at risk or suspected of LOH, a thorough physical and biochemical work-up is recommended (Level 2, Grade A).

Transient decreases of serum T levels, such as those due to acute illnesses [36], should be excluded by careful clinical evaluation and repeated hormone measurement. TD has a strong association with cardiovascular disease risk [37,38] (Level 1, Grade A).

Risk factors for LOH in aging men may include chronic illnesses, including type 2 diabetes mellitus (T2DM), impaired thyroid gland function, hyperprolactinemia, chronic obstructive lung disease, rheumatoid arthritis, renal and HIV-related diseases, obesity, metabolic syndrome [39], stress and hemachromatosis. Such chronic diseases should be investigated and treated (Level 2, Grade A).

Vitamin D deficiency may also play a vital role in hypogonadism pathogenesis [40–42].

There is still a controversy in defining normal TSH levels in the elderly. Several observational studies claim TSH distribution progressively shifts toward higher concentrations with age [43–46], meanwhile there is data showing serum TSH concentrations decrease in healthy elderly subjects due to an age-related decrease in TSH secretion by the pituitary [47]. Thyroid gland function impairment should be excluded in patients with hypogonadism.

TT levels have been reported to be lower in depressed men compared with non-depressed men. TT is particularly low in men with severe, treatment-resistant depression [48]. TRT has been shown to reduce depression symptoms in hypo-gonadal men, including middle-aged men with LOH and those using antidepressants [49].

Drugs such as glucocorticoids, opioids induce TD. Glucocorticoids are the most widely used anti-inflammatory drugs in the world. However, prolonged use of glucocorticoids results in undesirable side effects, including hypogonadism [50].

Aloisi and colleagues [51] were the first to show that morphine induces a dramatic and long-lasting decrease in TT. This finding has now been corroborated by numerous subsequent studies [52]. It has also been reported that statins may reduce TT [53].

A serum sample for TT determination should be obtained between 07.00 and 11.00 h [54] (Level 2a, Grade A).

The most widely accepted parameter to establish the presence of hypogonadism is the measurement of TT. Unfortunately, no consensus has been reached regarding the lower TT threshold defining TD, and there are no generally accepted lower limits of normal TT [55]. TT values above 15 nmol/L usually rule out a diagnosis of hypogonadism. Measurements of serum LH will assist in differentiating between primary and secondary hypogonadism and serum prolactin is indicated when TT is <5.2 nmol/L (150 ng/dL) [56,57] or when secondary hypogonadism due to a pituitary tumor (like prolactinoma) is suspected [58–60] (Level 2, Grade A).

In aging men presenting with hypo-gonadal symptoms, measurement of free or bioavailable T should be considered when the TT concentration is not definitively diagnostic of LOH, particularly in obese men. Equilibrium dialysis is the gold standard for free T measurement. Free T assays based on analog displacement immunoassays are widely available but do not give an accurate measurement of free T; thus they should not be used [61]. Alternatively, measurement of serum SHBG together with a reliable measurement of TT allows for the determination of the calculated free T level [62].
(Level 2b, Grade A). A calculated free T level below 225 pmol/L (65 pg/mL) together with the presence of one or more LOH symptoms can provide supportive evidence for TRT [63] (Level 2, Grade B).

Since testosterone sensitivity may vary in different individuals it has also been argued that the magnitude of the decrease in serum T concentrations might be a better predictor of LOH than the actual concentrations of TT and BT [64].

The prevalence of LOH symptoms increases with TT levels below 12.1 nmol/L (350 ng/dL) [65] (Level 2b, Grade A). However, Zitzmann et al. have shown that LOH symptoms may also be seen with TT levels as high as around 15 nmol/L. This study showed that the prevalence of loss of libido or vigor increased at testosterone concentrations below 15 nmol/L (p < 0.001), whereas depression and T2DM (also in non-obese men) were significantly more prevalent in men with TT concentrations below 10 nmol/L (p < 0.001). Erectile dysfunction has been identified as a composite pathology of metabolic risk factors, smoking and depression, whereas only TT concentrations below 8 nmol/L contributed to that symptom (p = 0.003). Behre [66] demonstrated that 6 months of TRT improved body composition and HRQoL in men aged 50–80 years with TT < 15 nmol/L and LOH symptoms; these men showed further improvements in body composition and HRQoL over the following 12 months of TRT. Lower TT levels have also been shown to be associated with sub-threshold symptoms of anxiety and depression [67].

The other recommended laboratory parameters should include: LH, TSH, SHBG, prolactin and vitamin D.

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

Improvement in signs and symptoms of LOH occur at different times for different organ systems [68].

Reduction in fat mass and increased lean body mass and muscle strength occur within 12 to 16 weeks of starting TRT and stabilize at 6 to 12 months, but can marginally continue to improve over years.

Significant improvement in libido starts within 3 weeks of commencing TRT, with maximum improvement occurring at 6 weeks. Up to 6 months of TRT may be required before significant improvement in erectile and ejaculatory function is observed. Significant improvement in quality of life (QoL) usually occurs within 3 to 4 weeks of starting TRT; longer-term TRT is required to achieve maximum QoL benefit. Effects on depressive mood become detectable after 3 to 6 weeks of starting TRT, with maximum improvement occurring after 18 to 30 weeks. Improvements in bone are detectable after 6 months of TRT, while the full beneficial effect of TRT on bone mineral density may take 24 months [69] or 36 months as suggested by Aversa [70]. Effects of TRT on lipids appear after 4 weeks, with maximal effects being seen after 6 to 12 months of treatment. Insulin sensitivity may improve within a few days of starting TRT, but effects on glycemic control become evident only after 3 to 12 months. Failure to improve clinical symptoms within a reasonable period of time should result in discontinuation of TRT and further investigation should be undertaken to determine other causes of the symptoms (Level 1b, Grade A).

**Recommendation 5: body composition**

In hypo-gonadal men, TRT improves body composition (decrease of fat mass, increase of lean body mass). Meta-analyses of randomized trials in middle-aged and older men have demonstrated the beneficial effects of TRT in reducing fat mass [71,72] (Level 1a, Grade A) with a significant increase in lean body mass and grip strength.

Secondary benefits of TRT on body composition include improvement of surrogate parameters of cardiometabolic risk [73], such as significant reductions in fasting plasma glucose, homeostasis model assessment index (HOMA), triglycerides and waist circumference. There is also some initial evidence that long-term T may result in substantial and sustained weight loss in obese hypo-gonadal men [74–76].

Higher free testosterone concentration is positively associated with lower risk of developing mobility limitation and progression of mobility limitations [77].

**Recommendation 6: Bone density and fracture rate**

Osteopenia, osteoporosis and fracture prevalence rates are greater in younger and older hypo-gonadal men [78]. In a recent meta-analysis and in the FRAX algorithm hypogonadism was identified as a known disorder strongly associated with secondary osteoporosis [79,80]. According to the latest Endocrine Society’s guidelines on osteoporosis total testosterone measurement is suggested in all men evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents [81].

Bone density in hypo-gonadal men of all ages is increased with TRT (Level 1b, Grade A).

In older men low testosterone levels are associated with increased fall risk [82]. TRT has beneficial effects on muscle mass and strength that may reduce propensity to fall and therefore decrease fracture risk. Physical exercise, including stretching and equilibrium exercises are mandatory.

Assessment of bone density at 2-year intervals is recommended in aging, hypo-gonadal men.

**Recommendation 7: testosterone and sexual function**

The initial assessment of all men with erectile dysfunction and/or diminished libido should include determination of TT levels. These symptoms, with or without a testosterone deficiency, might be related to co-morbidities (i.e. T2DM, hyperprolactinemia, the metabolic syndrome, bladder outlet obstruction, peripheral vascular disease or medications) (Level 2a, Grade A).

Men with poor morning erections, erectile dysfunction and/or diminished libido and documented TD, are candidates for TRT. Meta-analyses of randomized, placebo-controlled trials of TRT in men with sexual dysfunction and varying TT levels demonstrated benefits in some aspects of sexual desire, erectile function and performance [83] (Level 2a, Grade A).

In sildenafil non-responders with T2DM, a combination of oral T undecanoate and sildenafil was associated with improvement in erections, a significant increase in IIEF scale
and increased sexual contacts [84]. In hypo-gonadal men with an inadequate response to phosphodiesterase type-5 inhibitors, TRT has been shown to be of benefit.

In the international, multicenter, prospective study IPASS with a sample of 1493 men, TRT showed a significant improvement in libido, erectile function and response to PDE-5 inhibitors therapy [85].

In aging men presenting with one or more sexual dysfunction symptoms and low-normal TT levels, a short (e.g. 6-month) trial of TRT may be justified. An absence of clinical response calls for discontinuation of TRT. A satisfactory clinical response might be placebo-generated, therefore, continued monitoring is advisable before long-term treatment is recommended (Level 2a, Grade B).

An inadequate response to TRT requires reassessment of the causal mechanisms responsible for the sexual dysfunction.

**Recommendation 8: Testosterone and obesity, metabolic syndrome and type 2 diabetes mellitus**

Many of the components of the metabolic syndrome (MetS) such as obesity, hypertension, dyslipidemia, impaired glucose regulation and insulin resistance, are also present in hypo-gonadal men [86]. The MetS and T2DM are associated with low TT levels and the majority of patients with these conditions display symptoms of hypogonadism [87]. TT levels should be measured in men with T2DM with symptoms suggestive of LOH (Level 2b, Grade A).

In a big epidemiologic study, including more than 1150 healthy middle-aged Japanese men, it was shown that probability of MetS was associated with lower levels of serum TT [88].

TRT in hypo-gonadal men with the MetS improved some MetS components as well as a number of inflammatory markers [89,90]. TRT is potentially an effective treatment in aging, obese men with TD [91]. In an uncontrolled, observational cohort, normalization of serum T with TRT led to significant reductions in body weight, waist circumference and BMI in aging, hypo-gonadal, obese men. These improvements were progressive over 5-year study period [74,92]. This has been confirmed in a controlled study.

Rodriguez-Tolra et al. demonstrated clearly that Testosterone supplementation therapy in men with TDS decreased fat mass overall, and to the greatest extent in the android and gynoid regions and caused improvements in body composition, increasing lean mass, primarily in arms and legs [93].

TRT improved significantly glycemic control (HbA1c), insulin levels and sensitivity, and C-reactive protein levels [94,95].

In addition to improving LOH symptoms, TRT may have other benefits on metabolic status in aging men with LOH and diabetes and or the metabolic syndrome (Level 2a, Grade B). It has been demonstrated that low- to intermediate-dose TRT may be safely utilized to ameliorate somatic and psychological frailty symptoms in association with improved anthropometric and glycometabolic parameters in aging, overweight men with LOH and impaired fasting glucose [96].

Numerous correlations have also been found between T levels and markers of atherosclerosis. Cross-sectional studies associated a low T level in men with endothelial dysfunction [97] and carotid intima-media thickness (IMT) independent of other cardiovascular risk factors [98]. Prospective studies in TRT-treated men with coronary artery disease (CAD) showed that TRT improved endothelial function [99] and reduced carotid IMT, with these effects being independent of BMI [100,101].

**Recommendation 9: depression and cognitive function**

Recent meta-analysis showed a significant positive effect of TRT in depressed patients, assessed by the Hamilton Rating Scale for Depression when compared with placebo [102] (Level 1a, Grade A). TRT has been shown to reduce depression symptoms in hypo-gonadal men, including middle-aged men with MetS [103], LOH and those using antidepressants [104].

Though the effect of TRT on cognitive function in men with hypogonadism remains controversial [105,106], it can be considered after exclusion of other causes of cognitive impairment [107,108].

**Recommendation 10: benign prostatic hyperplasia (BPH) and lower urinary tract symptoms (LUTS)**

Approximately one in five men with BPH has low TT. There is a well-established relationship between LUTS/BPH and increased BMI and low TT.

At present, there is no conclusive evidence that TRT either increases the risk of BPH or contributes to worsening of LUTS [109].

There is evidence that TRT improves LUTS in hypo-gonadal men with mild BPH [110].

**Recommendation 11: prostate cancer (PCa)**

There is no evidence that TRT will convert sub-clinical prostatic lesions to clinically detectable PCa (Level 2, Grade B).

Analysis of worldwide data from 18 prospective studies (more than 3000 cases and 6000 controls) found no association between serum testosterone concentrations and prostate cancer (PC) risk [111]. Another meta-analysis showed no significant association between TRT and the incidence of PCa or the need for prostate biopsy when compared with the placebo/non-intervention group [112].

In the multicenter, prospective study IPASS with a sample of 1493 men, the prevalence of such adverse effects like increase of the hematocrit and increase of the PSA was <1%, no cases of prostate cancer were observed [113].

However, there is unequivocal evidence that T can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer (Level 2a, Grade A).

Prior to starting TRT, a patient’s risk of PCa must be assessed using, at a minimum, digital rectal examination (DRE) and measurement of serum prostate-specific antigen (PSA). Prostate ultra-sound examinations or biopsies are not recommended as routine screening requirements.
However, the pre-treatment assessment can be improved by assessing for other PCa risk predictors such as age, family history of PCa and ethnicity/race. If the patient and physician decide that the PCa risk is unacceptable, further assessment may be desirable (Level 2a, Grade B).

After initiation of TRT, patients should be monitored for prostate disease at 3 to 6 months, 12 months and at least annually thereafter (Level 2, Grade B).

An initial increase of PSA and prostate volume (PV) with TRT are expected because the prostate is an androgen-dependent organ. T plays an important role in the maintenance of normal prostatic structure and function. If a prostate has been deprived of androgens for an unknown period of time, it is underdeveloped. Upon commencing TRT, its structure will normalize, i.e. it will grow back to normal and PSA will increase. To avoid potential misdiagnosis of the initial TRT-induced PSA and PV normalization, it could be argued that the PSA level occurring 6 months after initiation of TRT should be used as the baseline for PSA velocity (PSAV) assessments [114].

Should a patient’s PCa risk be sufficiently high (suspicious finding on DRE; increased PSA), transrectal ultrasound-guided biopsies of the prostate are recommended and the patient should be referred to a urologist for further clinical examination (Level 2b, Grade A).

In all cases in which PSA level is >4 ng/mL, PSAV could be still considered useful to identify men with high-risk PCa when they might otherwise be categorized as low- or intermediate-risk by absolute PSA level. This could minimize over-diagnosis of clinically insignificant cancers and improve timely detection of clinically significant cancers.

Data from the Baltimore Longitudinal Study on Aging reported by Carter and collaborators suggested that a PSAV >0.35 ng/mL per year might be used to identify life-threatening PCa in men with PSA levels <4 ng/mL. In men with PSA levels >4 ng/mL, a PSAV of 0.75 ng/mL per year has been suggested to identify those patients with slow-growing cancers or BPH and who therefore may not need treatment [115].

Punglia and collaborators [116] stated that the PSAV threshold necessary to minimize over-diagnosis of clinically insignificant PCa should be at least 1.25 ng/mL per year. In this case, reduced sensitivity in terms of the detection of Gleason 7 to 10 cancers was observed while also reducing the number of biopsies in which no cancer or Gleason 6 cancer was found.

Recommendation 12: treatment and delivery systems

Preparations of natural T should be used for TRT. Currently available intramuscular, subdermal, transdermal, oral and buccal T preparations 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 TRT preparation. The selection of the TRT preparation should be a joint decision of an informed patient and physician.

Because the possible development of an adverse event during treatment (especially elevated hematocrit or PCa) requires rapid discontinuation of TRT, short-acting TRT preparations may be preferred over the older long-acting depot preparations in the initial treatment of patients with LOH. However, it must be noted that elevated hematocrit is typically only associated with high serum T concentrations and rarely occurs with modern long- and short-acting TRT preparations, which have been formulated to maintain maximal serum T levels well within the normal range.

The Endocrine Society Guidelines 2010 recommend that TRT be discontinued if hematocrit is >54%, which may be reasonable [117]. However, this recommendation is based on assumptions – the clinical significance of a hematocrit >54% is unknown. The meta-analysis by Fernández-Balsells [118] showed that, despite a higher incidence of elevated hematocrit, no clinical adverse affects were reported. Results of earlier studies (MEDLINE database search from 1966 to 2004) showed that, despite TRT-treated men being nearly four times as likely to have hematocrit >50% compared with placebo-treated men (OR = 3.69, 95% CI, 1.82–7.51), the frequency of cardiovascular events, sleep apnea or death was not significantly different between the two groups. Abnormal hematocrit elevations were reported in 43.8% of patients administered intramuscular T enanthate injections and in 15.4% of patients administered transdermal T treatment [119].

The lack of increase in cardiovascular events with elevated hematocrit may be due to the fact that T has vasodilator and anti-atherosclerotic effects [120]. Isolated hematocrit elevations can be the result of insufficient fluid intake on a hot day. Only repeated measures of hematocrit >54% should be followed by concomitant administration of aspirin, bleeding and/or reduction of TRT dose. Periodic hematological assessment is, however, indicated, i.e. before TRT, then 3 to 4 months and 12 months in the first year of treatment, and annually thereafter. Although it is not yet clear what upper limit of hematocrit level is clinically desirable, dose adjustments may be necessary to keep hematocrit below 52 to 55%.

Inadequate data are available to determine the optimal target serum T level for men with LOH. For the present time, the treatment goal with TRT is to maintain serum T levels in the normal range. Sustained supra-physiological serum T levels should be avoided. No evidence exists for or against the need to maintain the physiological circadian rhythm of serum T levels (Level 2, Grade B).

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

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

References


64. Holm AC, Fredrikson MG, Theodorsson E, et al. Change in testosterone concentrations over time is a better predictor than the actual concentrations for symptoms of late onset hypogonadism. Aging Male 2011;14:249–56.


