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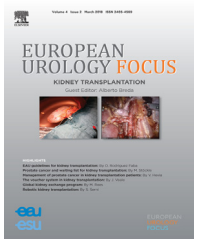

Guidelines

Late-onset Hypogonadism and Testosterone Therapy – A Summary of Guidelines from the American Urological Association and the European Association of Urology

Mikkel Fode[a,*], *Andrea Salonia*[b,c], *Suks Minhas*[d], *Arthur L. Burnett*[e], *Alan W. Shindel*[f]

[a] *Department of Urology, Herlev and Gentofte Hospital, Herlev, Denmark;* [b] *Division of Experimental Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [c] *Università Vita-Salute San Raffaele, Milan, Italy;* [d] *Imperial College Healthcare, NHS Trust, London, UK;* [e] *The James Buchanan Brady Urological Institute and Department of Urology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA;* [f] *Department of Urology, University of California-San Francisco, San Francisco, CA, USA*

Article info

Article history:
Accepted February 25, 2019

Associate Editor: Dr. Malte Rieken

Keywords:
Androgens
Erectile dysfunction
Hypogonadism
Libido
Lifestyle
Major cardiac adverse event
Prostate cancer
Sexual desire
Testosterone
Testosterone deficiency
Testosterone replacement therapy

Abstract

Men with low serum testosterone and symptoms of androgen deficiency may be diagnosed with testosterone deficiency. This condition is associated with metabolic syndrome and cardiovascular disease. The benefits (eg, improvement in sexual function) and risks (eg, prostate cancer and cardiovascular disease) of testosterone therapy are controversial. The American Urological Association and European Association of Urology guidelines on testosterone therapy differ on several points of management, likely reflecting the ambiguities surrounding testosterone therapy in practice. This paper summarizes both guidelines with a focus on the differences between the two sets of guidelines.

Patient summary: The benefits and risks of testosterone therapy are controversial, as reflected in the European Association of Urology and American Urological Association guidelines that differ on several points of management.

* Corresponding author at: Department of Urology, Herlev and Gentofte Hospital, Herlev Ringvej 75, 2730 Herlev, Denmark.
E-mail address: mikkel.mejlgaard.fode@regionh.dk (M. Fode).

1. Introduction

Testosterone (T) decreases on average by 0.8–2% per year after the age of 40 yr [1–3]. Adult men with low serum T and symptoms of androgen deficiency may be diagnosed with late-onset hypogonadism (LOH). LOH has implications for general and cardiovascular health, and has attracted considerable attention as an increasingly

https://doi.org/10.1016/j.euf.2019.02.021
2405-4569/

Table 1 – Summary of the main differences between the EAU and AUA guidelines.

EAU guidelines	AUA guidelines
Recommends measurement of free T in men with total T levels close to the lower normal range (8–12 nmol/l) or abnormal sex hormone-binding globulin levels	Does not recommend routine use of free T measurements
Defines the total T threshold of 12.1 nmol/l (349 ng/dl)	Defines the total T threshold of 10.4 nmol/l (300 ng/dl)
State that TT can improve sexual desire	Offers no definitive conclusion on the effects of TT on sexual desire
Does not directly state that TT can improve erections and recommends TT as an adjunctive ED in hypogonadal men with a poor response to PDE 5 inhibitors	States that TT may improve ED in hypogonadal men and considers TT as a first-line treatment
Recommends routine PSA monitoring in all patients on TT	Recommends only baseline DRE and PSA before treatment
Recommends that TT be "cautiously considered" at a minimum of 1 yr following curative treatment of low-risk PCA with no signs of recurrence	Recommends risk stratification of patients after curative PCA treatment and states that patients should be informed that there is inadequate evidence to quantify the risk-benefit ratio
States that TT may confer beneficial cardiac effects	States that the evidence on TT and cardiovascular risk is inconclusive

AUA = American Urological Association; DRE = digital rectal examination; EAU = European Association of Urology; ED = erectile dysfunction; PCA = prostate cancer; PDE 5 = phosphodiesterase type 5; PSA = prostate-specific antigen; T = testosterone; TT = testosterone therapy.

important area within urology [4]. Herein, we summarize the current European Association of Urology (EAU) and American Urological Association (AUA) T guidelines relating to LOH with special emphasis on the differences between the two guidelines (Table 1) [5,6].

2. Scope and definitions

The EAU guideline deals broadly with hypogonadism, and in addition to its attention to LOH, it describes primary and secondary forms of androgen deficiency attributable to specific diseases. This includes how the conditions may manifest in prenatal, prepubertal, and postpubertal forms. The AUA guideline specifically defines their index patient as an adult male with T deficiency (equivalent to LOH) and only sporadically mentions other conditions. The AUA has chosen to use the term "testosterone deficiency" rather than hypogonadism, as this is deemed to be more scientifically accurate because hypogonadism was historically associated with impaired semen parameters. The terminology regarding treatment has been subject to disagreement as some prefer to call it "testosterone replacement therapy" signifying that it constitutes replacement of a specific hormonal deficiency. However, both guidelines use the term "testosterone therapy/treatment" as they consider amelioration of symptoms as the main aim of treatment. In this review, we will use the terms LOH and testosterone therapy (TT).

3. Diagnosis of LOH

Assessment for LOH should include a detailed medical and sexual history along with a physical examination, with particular focus on virilization, body mass index, waist circumference, presence of gynecomastia, and testicular size/consistency. Total T testing is indicated in the presence of symptoms and/or conditions known to be associated with LOH (Table 2) [7], but not in routine screening [7]. Serum total T should be drawn before 11:00 hours, preferably in the fasting state. Confirmatory (repeat) testing should be performed before T supplementation is initiated to confirm biochemical evidence of low T [7–9]. The EAU guidelines also recommend that luteinizing hormone (LH) be assessed at least twice within 30 d, since the levels of this hormone may show considerable intraindividual variation [10]; prolactin is noted, but no specific guidance is provided on prolactin testing [4]. The AUA guidelines recommend that LH be assessed after an initial low serum T level and that prolactin be assessed if both LH and T are low/low-normal, while follicle stimulating hormone and estradiol are mentioned as optional assays [5]. Both guidelines recommend a baseline hemoglobin/hematocrit measurement, as these may increase with T treatment.

There remains a controversy regarding what constitutes a "low" level of T. The EAU guidelines have defined a total T threshold of 12.1 nmol/l (349 ng/dl), as this constitutes the

Table 2 – Clinical symptoms and signs suggestive of LOH (adapted from the EAU and AUA guidelines).

General symptoms
Reduced energy and endurance
Diminished physical performance
Hot flushes
Physical changes
Reduced testis volume
Loss of body hair
Gynecomastia
Decrease in lean body mass and muscle strength
Visceral obesity
Sexual symptoms
Reduced sexual desire and sexual activity
Erectile dysfunction
Fewer and diminished nocturnal erections
Cognitive, mood, and quality-of-life–related symptoms
Changes in mood
Sleep disturbances
Depression
Diminished cognitive function
Associated conditions
Male-factor infertility
Metabolic syndrome
Insulin resistance and type 2 diabetes mellitus
Decrease in bone mineral density (osteoporosis) with low trauma fractures
Anemia

AUA = American Urological Association; EAU = European Association of Urology; LOH = late-onset hypogonadism.

Please cite this article in press as: Fode M, et al. Late-onset Hypogonadism and Testosterone Therapy – A Summary of Guidelines from the American Urological Association and the European Association of Urology. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.02.021

lower end of the 2.5 percentile of population norms [11]. The AUA guideline focuses on total T values below which men are likely to benefit from TT and sets a threshold of 10.4 nmol/l (300 ng/dl) based on randomized controlled trials (RCTs) in which TT has been shown to have clinically significant effects compared with placebo.

The EAU guidelines recommend calculation of free T in men with (1) symptoms of LOH and normal T, (2) borderline total T (between 8 and 12 nmol/l [231–346 ng/dl]), and (3) elevated sex hormone–binding globulin levels [4]. The AUA guideline does not endorse the measurement of free T in clinical decision making; leeway is granted for providers to use this metric in select patients at their discretion [5].

4. Treatment of T deficiency

Men with LOH should be counseled about lifestyle modifications as they may increase endogenous T levels and improve general health [12–15]. TT is an alternative, with the aim of ameliorating symptoms by restoring T levels to the mid-normal range [16]. Briefly, TT formulations consist of oral preparations, intramuscular injections, and transdermal gels. The EAU guidelines recommend using short-acting preparations when initiating TT, to be able to adjust quickly if side effects arise. However, they caution against short-acting injections due to fluctuations in serum T. The AUA guidelines caution against the use of alkylated oral T and recommend commercially manufactured products over compounded T. Both guidelines note that TT has adverse effects on spermatogenesis and that the treatment should therefore not be prescribed to men who wish to father children. In such patients, human chorionic gonadotropin aromatase inhibitors and/or selective estrogen receptor modulators may be used.

In patients receiving TT, follow-up with serum testing of T should be offered at 3, 6, and 12 mo after the onset of treatment, and every 6–12 mo thereafter to assure appropriate serum levels of T and to monitor effects [5,6]. Both guidelines also recommend monitoring hematocrit and performing a digital rectal examination, and prostate-specific antigen (PSA) monitoring is recommended by the EAU.

5. Effects of TT

TT may cause clinically meaningful increases in hemoglobin/hematocrit. This may be beneficial in men with anemia, but problematic in men with normal or elevated baseline hemoglobin/hematocrit [17,18]. Bone mineral density and lean body mass are also increased with TT. However, there are no high-quality studies demonstrating reduced fracture risk from TT [19–22].

The EAU guidelines state that TT can improve sexual desire [23–25], while the AUA guideline references several contradictory studies, offering no definitive conclusion [23,26–29]. The discrepancies between the guidelines stem in part from the inclusion of different studies. The EAU guidelines focus on trials designed specifically for evaluating sexual function, while the AUA guidelines has considered studies with sexual desire as a secondary outcome, indicating that some study participants were not bothered by this prior to treatment. Both guidelines reference meta-analyses, which conclude that TT may improve sexual desire [25,29].

The EAU guideline does not state that improvements in erectile function can be expected with TT. It rather recommends TT as an adjunctive option in men with erectile dysfunction (ED) who have concomitant LOH, particularly in the setting of a poor clinical response to phosphodiesterase type 5 inhibitors [24,26,30,31]. The AUA guideline states that TT may improve ED in hypogonadal men based on pooled results of a series of RCTs [23,26–28,32–36]. However, the mean 1.32 (confidence interval: 0.38, 2.26) point improvement in International Index of Erectile Function score derived from this analysis is below the threshold for minimal clinically meaningful improvement [37]. In this respect, individual trials are contradictory and the guideline states that it is not possible to predict which men with ED are most likely to benefit from therapy.

In summary, men with low sexual desire and ED may benefit from TT. Men with ED only should initially be offered ED-specific therapy. Given the complexity of human sexual responses, clinician judgment is of primary importance when instituting therapy. However, men with sexual dysfunction and normal T levels should not be offered TT [29].

There is no high-quality evidence of cognitive improvements with TT [38,39]. Data from RCTs have shown that TT may confer mild improvements in depressive symptoms and mood [33,40]. Evidence on TT effects on energy levels and QOL is conflicting [23,26,33,34,38,41].

6. Major controversies in TT

6.1. *Prostate cancer*

TT has historically been associated with the risk of prostate cancer (PCA) [42]. However, neither observational studies nor RCTs on TT have identified changes in PCA risk [43–45]. TT does not increase intraprostatic T levels [46,47]. The EAU guidelines advocate routine PSA monitoring in all patients on TT. The AUA guideline makes a strong recommendation to inform patients of the absence of evidence linking TT and PCA; furthermore, the AUA guideline does not recommend alteration of routine PSA screening practices aside from a single PSA measurement in men over 40 yr of age prior to the commencement of TT, a recommendation informed by the guidance on PSA testing provided by the AUA guidelines on early detection of PCA. Both guidelines acknowledge important limitations in available studies on TT and PCA, including a lack of long-term follow-up data.

For patients who have previously undergone PCA treatment with curative intent, available series do not demonstrate an increased risk of recurrence with TT [48–54]. The EAU guidelines recommend that TT be “cautiously

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considered" at a minimum of 1 yr following treatment of low-risk PCA with no signs of recurrence. The AUA guideline recommends that all patients are candidates for TT following successful surgery or radiation therapy, subject to risk stratification. Data on TT for men on active surveillance for PCA are very limited [54–57]. Very few data exist on TT in the context of focal therapy for PCA (eg, high-intensity focused ultrasound and cryotherapy). Neither guideline makes any specific recommendations on TT in these contexts. TT is contraindicated in men with locally advanced or metastatic cancer.

It should be highlighted that the statements on PCA in both guidelines are based on poor-quality evidence, and that no strong recommendations are given in relation to patients with previous or current cancer. In our opinion, TT should not be withheld solely due to the fear of PCA development, but patients should be informed of the controversy. Treatment of hypogonadism in men with PCA should be commenced only in well-informed and carefully selected patients, under close clinician supervision.

6.2. *Testosterone and cardiovascular disease*

There is an epidemiological association between low T and diabetes, obesity, hypertension, and dyslipidemia [58–60]. However, the link between LOH and metabolic disease is less clear, and the effect of TT on general cardiovascular risk is controversial. Most studies have found no change or a reduced risk of cardiovascular disease with TT, although an increased cardiac risk after TT has also been reported [61–63]. In this context, the EAU guidelines state that TT may confer beneficial cardiac effects, whereas the AUA guidelines state that the evidence is inconclusive. Overall, the literature on the topic is of low quality, and most of our knowledge is derived from short-term RCTs that were not designed to detect cardiovascular issues and from retrospective cohort studies. Interestingly, the disparate conclusions in the two guidelines are based on an analysis of the same studies. The main difference is that the EAU guideline limits methodological critiques almost exclusively to studies linking cardiac risk to TT while citing the results of several retrospective trials, all showing a potential benefit of TT. The AUA guideline is more generally critical of the existing literature on TT and cardiac risk, and highlights several different studies with protective, detrimental, and neutral results of TT on cardiovascular risk. Interestingly, the EAU guideline states that the level of evidence for TT's protective role is strong, while the AUA gives a moderate recommendation to inform patients that it cannot be stated definitively whether TT increases or decreases the risk of cardiovascular events. There is general agreement that men with pre-existing cardiovascular disease should carefully be counseled on the unknown effects of TT [64].

Overall, the literature points to a positive effect of TT on cardiovascular health, but the evidence is not strong enough to recommend TT specifically for cardiac benefit. Men at risk of cardiac disease may consider TT; consultation with a cardiologist may be warranted prior to TT in men with existing moderate to severe cardiac disease. Positive lifestyle changes and medical optimization of the cardiovascular risk profile should accompany TT [65].

7. Goals for future research

Discrepancies between the guidelines reflect limited and conflicting evidence throughout the literature. Future studies should be designed with the intent of defining biochemical thresholds and elucidating the true clinical relevance of free T. Exploration of the effects of TT on overall QOL and identification of men with sexual dysfunction who will benefit from TT are other priorities. Further data on (1) the overall long-term effects of TT, and (2) long-term effects on cardiovascular health and PCA risk are required, with particular emphasis on high-quality prospective/randomized clinical studies.

Author contributions: Mikkel Fode had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Fode, Salonia, Minhas, Burnett, Shindel.
Acquisition of data: Fode.
Analysis and interpretation of data: Fode, Salonia, Minhas, Burnett, Shindel.
Drafting of the manuscript: Fode.
Critical revision of the manuscript for important intellectual content: Fode, Salonia, Minhas, Burnett, Shindel.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: None.
Other: None.

Financial disclosures: Mikkel Fode certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Mikkel Fode is a speaker and consultant for Astellas Pharma and Ferring Pharmaceuticals. Arthur L. Burnett has received research grants for clinical fellow training from Boston Scientific and Endo Pharmaceuticals. Andrea Salonia, Suks Minhas, and Alan W. Shindel have no conflicts of interest to declare.

Funding/Support and role of the sponsor: None.

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Please cite this article in press as: Fode M, et al. Late-onset Hypogonadism and Testosterone Therapy – A Summary of Guidelines from the American Urological Association and the European Association of Urology. Eur Urol Focus (2019), https://doi.org/10.1016/j.euf.2019.02.021