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Platinum Opinion

European Association of Urology Position Statement on the Role of the Urologist in the Management of Male Hypogonadism and Testosterone Therapy

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Testosterone is a crucial sex hormone important for the health and development of men of all ages. Low androgen levels in utero can lead to genital abnormalities, and disruption during childhood alters pubertal development. Low androgen levels after puberty and throughout adulthood can affect quality of life (eg, reduced libido, sexual dysfunction, and mood and cognitive function [1]), alter physiology (eg, infertility, lower muscle mass and bone mineralization [osteopenia or osteoporosis]), and adversely affect metabolism (changed fat metabolism, muscle strength, physical activity, and function). These effects relate to every man and are therefore of strong urological interest. While late-onset hypogonadism may be treated by testosterone therapy (TTH), the indications and risks for TTH are yet to be fully defined [2–10]. To define the role and responsibilities of the urologist, the EAU has considered all the available data and formulated this position statement. Issues encountered in urological daily practice include erectile dysfunction (ED), lower urinary tract symptoms (LUTS), prostate cancer (PCa), male fertility, and potential risks related to TTH. Urologists should have the skills to recognize, diagnose, and treat disorders associated with male hypogonadism. They should be aware of the indications and contraindications for TTH.

1. Libido and ED

Sexual dysfunction symptoms are the most predictive determinant sign of potential male hypogonadism: 23–36% of men with sexual dysfunction are hypogonadal [11]. In hypogonadal men, TTH increases sexual desire [12]. Likewise, testosterone plays an important role in the physiology of erection and ED [1,2]. Androgen ablation results in impaired relaxation of the smooth muscle of the corpora cavernosa, and adequate levels of circulating testosterone are necessary for restoring penile erections in hypogonadal men. The reported effects on erectile function and male sexual behavior are positive overall; however, a certain degree of discrepancy exists in randomized trials [2,12].

Testosterone plays a role in sexual function via multiple molecular processes. (1) Testosterone stimulates nitric oxide synthase to facilitate NO production, leading to smooth muscle relaxation (via the nitric oxide/cyclic guanosine monophosphate signaling pathway). (2) Testosterone establishes and maintains the structural and functional integrity of the penis. (3) Testosterone has a major role in the development, maintenance, function, and plasticity of the cavernous nerve and pelvic ganglia [13]. TTH also has beneficial effects on ED because of the

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vasodilatory actions of testosterone (ie, regulation of the autonomic vascular nervous system) and the restoration of normal vascular function [14]. Testosterone may help to preserve sexual function via protection against tissue damage from aging and diabetes. Furthermore, testosterone exerts a facilitating action on phosphodiesterase type 5 (PDE5) inhibition, thus keeping plasma PDE5 levels within the normal range [2,13,15]. Testosterone may also have role in sexual desire.

Overall, data suggest that TTH has positive effects on male sexual function in hypogonadal subjects [16]; the role of TTH in men who are not clearly hypogonadal is uncertain. Randomized controlled trials (RCTs) have shown that TTH improves sexual arousal, interest, and drive [17]. In two large RCTs, TTH only improved erectile function in hypogonadal men with ED [18,19].

2. LUTS

LUTS have represented a relative contraindication for TT because of the assumed belief that testosterone may exacerbate symptoms by increasing prostatic growth [7,8]. A recent systematic review analyzed data from patients with mild LUTS who were randomized to TTH or no treatment in 14 trials (n = 2029) [7]. The findings showed no significant difference in International Prostate Symptom Score (IPSS) change from baseline over average follow-up of 34.4 mo. Moreover, observational studies have found that long-term TTH may decrease the IPSS with only a marginal increase in prostate volume [20]. No data are available on TTH in men with severe LUTS (IPSS >19).

3. Prostate cancer

Historically, TTH in the presence of previous or current PCa was contraindicated [20]. However the relationship between PCa and TTH is not clear. Recent literature does not link high intrinsic testosterone levels with PCa [9,10] and low testosterone is associated with higher Gleason score cancers and poor prognosis [9,10,21]. Recent data from observational or controlled studies among hypogonadal men without PCa and treated with TTH found no evidence of a higher risk of PCa development [9,10]. The same lack of higher PCa risk is found in studies among men receiving TTH after curative treatment for low-risk PCa [10,21]. The major criticism is the still short follow-up for these trials, which limits the possibility of detecting new-onset or recurrent PCa at a later stage. No trials have evaluated patients treated for high-risk PCa. Reports on TTH in men on active surveillance are too scarce to draw meaningful conclusions.

4. Male fertility

TTH reduces endogenous testosterone production via negative feedback on the hypothalamic-pituitary-gonadal axis and leads to hypospermatogenesis and even azoospermia [1]. In addition, reduction/suppression of intratesticular testosterone due to TTH leads to an inability of round spermatids to complete the elongation process, with the overall result of detachment of round spermatids from the seminiferous epithelium [22]. The overall rate of spermatogenesis recovery with TTH will often be satisfactory, but depends on ethnicity and pretreatment or treatment parameters. All men recover to pretreatment values within 24 mo [2,5]. Higher rates of recovery may be seen with older age, shorter treatment duration, short-acting testosterone preparations, higher sperm concentrations at baseline, faster suppression of spermatogenesis, and lower blood concentrations of luteinizing hormone at baseline [2,23]. Men with a desire for fatherhood or an unfulfilled wish for children should either not be treated with testosterone or be counseled regarding sperm recovery after 6–24 mo.

5. Risks of TTH

There are several risks or considerations to be aware of. (1) A possible link between TTH and cardiovascular disease (CVD) is controversial [2–4,24]. On the basis of five cohort studies and two meta-analyses, the US Food and Drug Administration required testosterone products to carry a warning about a possible increase in the risk of CVD [25]. Meanwhile, the European Medicines Agency concluded that there is no consistent evidence of a higher risk of CVD with TTH [26]. Some studies even indicate that TTH has a protective effect. Large-scale, long-term RCTs are needed to definitively define the CVD effects of TTH. (2) As androgens stimulate erythropoiesis, hemoglobin and hematocrit should be measured before and throughout TTH to avoid overstimulation and the risk of thrombosis. (3) Mammary carcinoma represents an absolute contraindication, as androgens are aromatized to estrogens and may stimulate estrogen receptor–positive cancers.

6. Conclusions

With the increasing interest in men's health, the EAU has formulated the following statements:

- Testosterone is a crucial sex hormone linked to the physiological development of the male gender across all stages of growth. It leads the integrity and maintains functioning of several systems and organs (including the male sexual and reproductive system, erythropoiesis, and bone, lipid, and glucose metabolism).
- Obesity and poor general health are the main causes of late-onset male hypogonadism. Losing weight and improving lifestyle are important advice points for men with hypogonadism, since these will result in normalization of testosterone and reduce associated health risks.
- Testosterone deficiency is linked to a number of signs and symptoms potentially affecting every man in his complexity and masculinity, and is therefore of close urological interest. For this reason, the urologist should attach importance to the need for knowledge, vocational education, and training in this specific area.
- TTH should be given only to symptomatic men in whom the deficiency has been confirmed by laboratory tests. Testosterone levels should be monitored regularly during

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