



Efficacy and Safety of Testosterone Therapy Based on Guideline Recommendations; Re: Clinical Practice Guideline by the American College of Physicians

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A clinical guideline provides physicians with the convenience of applying an appropriate treatment, but it can prevent physicians from alleviating a patients' worst-case scenarios. Therefore, physicians should strive to formulate a treatment policy by interpreting the common and different parts among guidelines. In this sense, we truly appreciate the recent informative work by Dr. Salter and Dr. Mulhall where they summarized the guidelines for 'testosterone therapy for testosterone deficiency (TD)' [1]. Despite the consensus that the effect of testosterone therapy in TD on several symptoms such as sexual function, whether testosterone therapy is advantageous for some areas associated with TD is still inconclusive among guidelines. Very recently, a guideline for testosterone therapy based on a systematic review supported by the American College of Physicians (ACP) was published [2,3] where the authors recommend testosterone therapy only for enhancing sexual function in TD.

When we reviewed the guidelines [3-8], the sources of

statements on the efficacy and safety of testosterone therapy on several clinical statuses were different from one another; the range of sources was from a handful of systematic reviews to a well-designed randomized controlled trial. In the European Association of Urology (EAU) guideline [4], the level of evidence and/or the statement of recommendation was documented for the efficacy of testosterone therapy on the relevant TD-related symptom. In the American Urological Association guideline [5], several systematic reviews were incorporated to make a panel discussion for developing the level of evidence as well as a recommendation grade. In the International Society for Sexual Medicine (ISSM) guideline [6], many previous systematic reviews were employed to determine the level of evidence and recommendation grade where all symptomatic TD was recommended to receive testosterone therapy; evidence of the efficacy of testosterone therapy for relevant symptoms was detailed 3 years later by a systematic review published in the *Journal of Sexual Medicine* [7].

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Table 1. Summarized effect of TTh on specific symptom and on development of unfavorable condition in TD

Symptom/sign	EAU [4]	AUA [5]	ISSM [6] ^a	SR in JSM [7]	ES [8]	ACP [3]
Documentation ^b	Strong/weak R or LE			Mild/moderate/strong effect	+ / + + / + + + + / + + + + +	R
Sexual function						
Libido (desire)	IR	↑ R (Grade B)	↑ R (Grade C)	↑ Strong effect	↑ (+ + +)	Conditional R
Erectile function	In TD, start PDE5I as first line treatment and add T in case of a poor response (Strong R).	↑ R (Grade B)	↑ R (Grade C)	↑ Moderate effect	IR	
Ejaculatory function	IR					
Physical function						
Mood	↑ (LE 3)	↑ R (Grade B)	↑ R (Grade C)	↑ Mild effect		
Cognition	↑ (LE 3)	↔ R (Grade B)	↑ R (Grade C)	↑ Mild effect	IR	
Metabolic syndrome	↑ (LE 3)	↔ R (Grade B)	↑ R (Grade C)	↔ no effect		
DM	↑ (LE 3)	↔ R (Grade B)	↑ R (Grade C)	↑ / ↔ Mild/no effect		
Body composition (muscle/fat ratio)	↑ (LE 3)	↑ R (Grade B)	IR	Not suggested as an alternative Tx for DM or MetS.	↔ Not recommended only for glycemic control (+ +).	
Bone density	IR	↑ R (Grade B)	IR	↑ Mild effect	IR	
Quality of life		↔ R (Grade B)		TTh + LSM > LSM	IR	
Vitality		↔ R (Grade B)		↑ Mild effect	↔	IR
Adverse effects					↔	
Patients with LUTS	Marginal increase in prostate volume		↓	↓ or ↔	↔	
Pca development	↔ (LE1b)	↔ R (Grade B)	↔ R (Grade C)	↔	↔	↔ (insufficient)

Table 1. Continued

	EAU [4]	AUA [5]	ISSM [6] ^a	SR in JSM [7]	ES [8]	ACP [3]
Patients with Pca history (comments)	In treated Pca without evidence of active disease, TTh can be introduced after 1 year follow-up in cases of low risk for recurrence (Weak R).	Inadequate evidence	Possible candidate in successfully treated Pca with symptomatic TD with a prudent interval and without no evidence of residual cancer (Grade C).	IR	Recommended against T supplementation in men with prostate cancer.	
Fertility	↓ (Strong R) Only use hCG treatment	↓ R (Grade A) AI, hCG, SERMS can be used (Grade C)	↓ (Grade A) hCG, hMG, SERMS, AI (short-term) can be used (Grade B/C).	↓	↓ (+++)	
Cardiovascular	↔ (LE1a) Assess for cardiovascular risk factors before commencing TTh (Strong R). In hypogonadal men TTh has been demonstrated to have a positive impact on cardiovascular risks.	↔ R (Grade B) Not recommended until 6 months in pt with CVD.	↔ (Grade B) Possibility of beneficial effect	↔	↔	↔ (low certainty)

TTh: testosterone therapy, TD: testosterone deficiency, EAU: European Association of Urology, AUA: American Urological Association, ISSM: International Society for Sexual Medicine, SR: systematic review, JSM: *Journal of Sexual Medicine*, ES: Endocrine Society, ACP: American College of Physicians, R: recommendation, LE: level of evidence, IR: introducing researches indicating potential effect of TTh without documentation of LE, ↑: increase, PDE5i: phosphodiesterase-5 inhibitors, T: testosterone, ↔: neutral, DM: diabetes mellitus, Tx: treatment, Mets: metabolic syndrome, LSM: life style modification, LUTS: lower urinary tract symptoms, ↓: decrease, Pca: prostate cancer, hCG: human chorionic gonadotropin, AI: aromatase inhibitor, SERMS: selective estrogen receptor modulators, hMG: human menopausal gonadotropin.

^aThe ISSM recommended TTh in TD with symptoms. Symptoms include sexual symptoms (desire, erection, ejaculation), physical symptoms (vigorous activity, muscle strength, bending, fatigue), psychological symptoms (energy, motivation, mood, sadness, irritability, sleep disturbance), and cognitive symptoms (concentration, verbal memory, spatial performance).

^bDocumentations for efficacy were described as degree of recommendation, level of evidence (if degree of recommendation was not documented), or other forms.

A guideline supported by the Endocrine Society used 2 systematic reviews, where evidence or recommendation for testosterone therapy in detailed TD symptoms was seldom documented, but the authors introduced the results from studies implying the potential efficacy of testosterone therapy [8]. Finally, as mentioned before, a clinical guideline from the ACP made from a systemic review recommended testosterone therapy only for sexual function in TD [3].

In Table 1, four of the six studies agreed to the use of testosterone to treat depression in patients with TD. When considering testosterone therapy for mood, we cannot discuss it without mentioning a meta-analysis conducted by Walther et al [9] where 27 randomized controlled trials with 1,890 men found testosterone therapy to be associated with a significant reduction in depressive symptoms, suggesting adjunct testosterone treatment for depressive symptoms in men. With respect to body composition (including fat-to-muscle ratio, lean body mass, or obesity), three of 6 studies focused heavily on testosterone therapy, and 2 of the remaining 3 studies indicated the potential role of testosterone therapy. Similarly, 5 of 6 studies recognized the efficacy of testosterone therapy on bone density. Corona et al [7] concluded that the combination of antiresorptive treatment with TRT should be offered in the presence of TD. Considering a potential linkage between body composition, physical function, and metabolic syndrome, exercise prescription and treatment of the underlying disease may be necessary in patients with metabolic syndrome; however, testosterone therapy combined with the aforementioned treatments is expected to show positive results if TD is confirmed in actual clinical practice. Testosterone therapy should not be an alternative treatment for diabetes or metabolic syndrome, but the therapy could be encouraged as adjunctive therapy in patients with confirmed TD. The effect of testosterone on sexual function in TD is well known; however, with only a specific guideline, physicians may hesitate to prescribe testosterone as an adjunctive treatment, even in TD, unless a patient explicitly states that 'I am losing my sexual function'.

Most of the guidelines in Table 1 share the context in regard to cardiovascular risk, development of prostate cancer, and infertility. The safety of testosterone therapy in patients with treated prostate cancer has been on the rise in recent decades. The relationship between testosterone treatment and the development

of prostate cancer is conclusive in 5 studies in Table 1. In terms of saturation theory [10], prostate cancer (and benign prostate hyperplasia) is suppressed in only the castrated level of testosterone; vice versa, testosterone therapy in TD may neither aggravate prostate cancer (and prostate-related lower urinary tract symptoms) nor cause prostate cancer. For the same reason, the EAU and ISSM guidelines clarified the possibility of testosterone therapy in patients with treated prostate cancer. Most researchers in urology agreed with this concept because all patients scheduled in prostatectomy should undergo bilateral orchiectomies if testosterone is responsible for developing prostate cancer.

Physicians should discuss with their patients on the potential harms of testosterone therapy ahead of initiation of treatment, but at the same time, they should try to maximize the potential benefits of testosterone therapy. Physicians need not be restricted by a guideline in initiating testosterone therapy in symptomatic TD unless an individualized safety recommendation does not permit them to use testosterone.

Conflict of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: DSL, HJP. Data curation: DSL, HJP. Formal analysis: DSL, HJP. Investigation: DSL, HJP. Methodology: DSL, HJP. Project administration: DSL, HJP. Resources: DSL, HJP. Software: DSL, HJP. Supervision: DSL, HJP. Validation: DSL, HJP. Visualization: DSL, HJP. Writing – original draft: DSL, HJP. Writing – review & editing: DSL, HJP.

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