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REVIEWS

British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice

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ABSTRACT

Background: Testosterone deficiency (TD) is an increasingly common problem with significant health implications, but its diagnosis and management can be challenging.

Aim: To review the available literature on TD and provide evidence-based statements for UK clinical practice.

Methods: Evidence was derived from Medline, EMBASE, and Cochrane searches on hypogonadism, testosterone (T) therapy, and cardiovascular safety from May 2005 to May 2015. Further searches continued until May 2017.

Outcomes: To provide a guideline on diagnosing and managing TD, with levels of evidence and grades of recommendation, based on a critical review of the literature and consensus of the British Society of Sexual Medicine panel.

Results: 25 statements are provided, relating to 5 key areas: screening, diagnosis, initiating T therapy, benefits and risks of T therapy, and follow-up. 7 statements are supported by level 1, 8 by level 2, 5 by level 3, and 5 by level 4 evidence.

Clinical Implications: To help guide UK practitioners on effectively diagnosing and managing primary and age-related TD.

Strengths and Limitations: A large amount of literature was carefully sourced and reviewed, presenting the best evidence available at the time. However, some statements provided are based on poor-quality evidence. This is a rapidly evolving area of research and recommendations are subject to change. Guidelines can never replace clinical expertise when making treatment decisions for individual patients, but rather help to focus decisions and take personal values and preferences and individual circumstances into account. Many issues remain controversial, but in the meantime, clinicians need to manage patient needs and clinical expectations armed with the best clinical evidence and the multidisciplinary expert opinion available.

Conclusion: Improving the diagnosis and management of TD in adult men should provide somatic, sexual, and psychological benefits and subsequent improvements in quality of life. **Hackett G, Kirby M, Edwards D, et al. British Society for Sexual Medicine Guidelines on Adult Testosterone Deficiency, With Statements for UK Practice. J Sex Med 2017;14:1504–1523.**

Key Words: Hypogonadism; Testosterone Deficiency; Testosterone Therapy; Type 2 Diabetes; Erectile Dysfunction

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PANEL COMPOSITION

The British Society of Sexual Medicine (BSSM) panel consists of a group of experts in urology, andrology, cardiology, psychiatry, and sexual medicine.

SOURCES OF INFORMATION

The BSSM UK policy statements on testosterone deficiency (TD), published in 2016,[1] were based on evidence derived from Medline, EMBASE, and Cochrane searches on hypogonadism, testosterone (T) therapy, and cardiovascular (CV) safety from May 2005 to May 2015, which yielded 1,714 articles, including 52 clinical trials and 32 placebo-controlled randomized controlled trials (RCTs). Further searches continued until May 2017. Levels of evidence (LoEs) and grades of recommendation were based on the Oxford Criteria for Evidence-Based Medicine.[2]

INTRODUCTION

T is the principal androgen in men. It is essential for the development and maintenance of secondary male characteristics.[3] When T levels decrease, patients can experience physical and psychological effects, which can compromise their general well-being, sexuality, and fertility.[4,5]

These statements have been developed for UK practice and aim to address the widespread media and scientific concerns over the appropriate treatment of TD with T therapy.

They apply to adult men only. Women are not included, because there is currently no consensus for using T in women and the T products available are not licensed for use in women.

DEFINITION

TD is a well-established and significant medical condition.[1] It is defined as a clinical and biochemical syndrome associated with advancing age and comorbidities (LoE = 2, Grade = B)[6] and is characterized by a deficiency in serum androgen levels (with or without decreased genomic sensitivity to androgens[1]) and relevant signs and symptoms.[6,7]

TD can adversely affect multiple organ systems and result in significant decreases in quality of life, including changes in sexual function[4,6,7] (LoE = 2, Grade = B).[6]

EPIDEMIOLOGY

Estimates regarding the prevalence of TD vary widely. The European Male Aging Study (EMAS) evaluated more than 3,000 men 40 to 79 years old according to biochemistry and symptoms. Results showed an overall prevalence of 2.1% in men 40 to 79 years old and rates of 0.1% in men 40 to 49 years old, 0.6% in men 50 to 59 years old, 3.2% in men 60 to 69 years old, and 5.1% in men 70 to 79 years old (in which the syndrome of TD included $\geq$3 sexual symptoms associated with a total T [TT] level $<$ 11 nmol/L and a free T [FT] level $<$ 220 pmol/L [$<$0.22 nmol/L]).[8] However, 75% of men maintained normal T levels into old age, suggesting that TD is not merely a function of aging. The prevalence of secondary TD was 11.8%, with 2% having primary TD and 9.5% having compensated (subclinical) TD, worthy of observation but not treatment with T.[9]

TD is more common in older men and those with obesity, comorbidities, and poor health status.[4]

BASIC PHYSIOLOGY

In eugonadal men, the regulation of T production is controlled by the hypothalamic-pituitary-gonadal axis.[3] In the brain, the hypothalamus secretes gonadotropin-releasing hormone, which stimulates the anterior pituitary gland to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH). In the testes, LH stimulates the Leydig cells to produce T, and FSH stimulates the seminiferous tubules for sperm maturation. Through a negative feedback mechanism, T inhibits gonadotropin-releasing hormone and LH secretion, and the hormone inhibin B, secreted by Sertoli cells, inhibits the release of FSH.[3,10]

Androgen receptors (ARs) are present in many body tissues. They allow the body to respond appropriately to T by attaching (binding) to it. The resulting AR complex binds to DNA, regulating the activity of androgen-responsive genes. The *AR* gene contains a DNA segment known as CAG, which is repeated multiple times. In most people, the number of CAG repeats ranges from less than 10 to approximately 36.[11] The length of these repeats in the *AR* gene can influence androgen sensitivity,[12] androgen action,[13] and androgenic phenotypical effects, even in the presence of normal T levels.[14]

T has multiple effects on the body. In the brain, it stimulates libido and aggression and aids cognition, memory, and feelings. In the kidneys, it promotes erythropoiesis. In the skin, it supports collagen production and stimulates hair growth and sebum production. In the heart, it affects cardiac output and coronary and peripheral blood flow, decreases the corrected QT interval, and decreases reperfusion injury. T also affects muscle mass and strength, bone growth, density and erythropoiesis, growth of the sex organs, spermatogenesis, and erectile function.[1,15–18]

ETIOLOGY

TD occurs when the body cannot produce sufficient T to function normally. This can result from disruption of at least 1 level of the hypothalamic-pituitary-gonadal axis (LoE = 1, Grade = A)[6]:

- Testes (primary TD, Figure 1)
- Hypothalamus and pituitary gland (secondary TD)
- Hypothalamus,[19,20] pituitary, and testes (combined primary and secondary TD; adapted from Grossman and Matsumoto[19])