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Review Article: Practical Aspects of Testosterone Deficiency Syndrome in Clinical Urology

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Abstract

In this review we describe the clinical manifestations associated with testosterone deficiency in aging men, termed the testosterone deficiency syndrome (TDS). Since aging men suffer from multiple urological and andrological symptoms, TDS is an important medical condition to be suspected, recognized, clinically and biochemically diagnosed and therefore effectively and successfully treated.

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Introduction

The aim of this review is to shed more light on the importance of recognizing the fairly common testosterone deficiency syndrome (TDS), making the diagnosis and successfully treating patients in a holistic, practical approach. Physiologic or naturally occurring TDS is different from acquired TDS caused by androgen deprivation therapy (ADT) for metastatic prostate cancer. However the effect of testosterone deficiency on body organs may be quite similar. In clinical practice, men over 50 years of age may present with manifestations related to TDS and it is appropriate to recognize,

diagnose and successfully treat it using the currently available pharmacological preparations.

Definitions

TDS is a gradual age-related phenomenon that occurs in a large proportion of the male population [1]. Whether this is due to age-related changes in the testosterone secreting Leydig cells (primary hypogonadism) or changes in the hypothalamic pituitary gonadal axis (secondary hypogonadism), it leads to decline in testosterone production and circulating plasma levels [2]. The clinical manifestations of TDS are usually multiple and involve several body systems [3,4]. This term is essentially equivalent to idiopathic adult or late onset male hypogonadism, a term that is considered a laboratory diagnosis rather than the clinically oriented term TDS. Other terms describing the symptoms associated with decline in serum testosterone levels are now falling out of favor [3,4].

Units of measurements

Total testosterone (TT)

It is useful from a practical point of view to understand what we are measuring and how it is measured before we discuss the clinical

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manifestations of TDS. Great confusion has been created by the non-standardized use of uniform serum testosterone measuring units [5]. In males there is a wide range of total testosterone (TT) levels from 300 to 1000 ng/dL (10.4–35 nmol/L). Symptomatic decline of plasma TT below 300 ng/dL is considered diagnostic for TDS in the United States of America (USA). This value is equivalent to 10.4 nmol/L in SI units. One study showed that in men with clinically manifest decreased libido the plasma level of TT is usually below 8 nmol/L; therefore in Europe TDS is recognized and treated if TT falls below this level [6]. One reason for confusion in understanding laboratory reports is the use of two different systems of measurement, the conventional or English system, expressed in ng/dL and the international system (SI), expressed in nmol/L. The international system is a modernized version of the metric system established by international agreement and is used in most countries. The conventional system is mainly used in the USA [5,6].

Free testosterone (FT) and free testosterone index (FTI)

Free testosterone (FT) is an active, unbound fraction of circulating testosterone. True androgen status can be assessed either by measuring the FT level or by calculating the ratio of TT concentration to the concentration (or binding capacity) of sex hormone binding globulin (SHBG). This ratio, which is a useful indicator of abnormal androgen status, is called the free testosterone index (FTI). It is typically calculated on a molar/molar basis and rescaled by a factor of ten, one hundred or one thousand, as shown below.

$$FTI = \frac{TT \text{ (nmol/L)}}{SHBG \text{ (nmol/L)}}$$

The FTI is often increased in severe acne, male androgenic alopecia (balding), hirsutism, and other conditions in which a normal TT level is found with a low SHBG level. In non-obese, non-hirsute oligomenorrheic women, an elevated FTI during the early follicular phase is reported to be a sensitive and specific indicator for polycystic ovarian disease. Most clinicians use TT measurements in the initial evaluation and subsequent monitoring of treatment, while FT and FTI are used in specialized institutions for specific cases. For practical reasons we recommend the use of TT in the management of TDS [4].

Another reason for confusion is the shortcomings of the current assay methodologies and variation in laboratory calibration, testing and reporting. Therefore it is imperative to use a reliable laboratory and to use the same laboratory for follow-up measurements in the clinical management of patients [4–6].

Related body systems

Although testosterone is the primary androgenic steroid hormone responsible for normal growth and development of male sex organs and maintenance of secondary sex characteristics, it is also responsible for growth and function of many non-sexual organs and tissues [7]. Testosterone is the main drive for libido; it is necessary for erectile function through its role in the synthesis of nitric oxide, and for growth and function of the prostate and seminal vesicles. Therefore the production of adequate amounts of seminal plasma is androgen dependent [8].

Testosterone is an important hormonal stimulus for the cardiovascular and musculo-skeletal systems. Therefore, testosterone deficiency is associated with coronary artery disease, myocardial infarction and sudden cardiac death [9]. Testosterone influences body fat distribution and limits visceral and abdominal wall adiposity; it is vital for the adequate control of blood glucose level, and has recently been linked to the metabolic syndrome. Thus TDS is commonly seen in association with type 2 diabetes mellitus (DM), increased central obesity, dyslipidemia and hypertension. The metabolic syndrome is defined as the presence of central obesity (waist circumference more than 40 in. (105 cm) for males or body mass index (BMI) more than 30 kg/m²) and two of the following criteria: type 2 DM, high blood pressure, high triglycerides and reduced HDL cholesterol [10].

Prevalence

The prevalence of TDS in men older than 45 years is around 40% [11]. The Baltimore longitudinal study of aging has shown that the prevalence of hypogonadism is age-related and when a cut-off level of 325 ng/L for TT was used, the proportion of men who were hypogonadal increased progressively after the age of 50 years [12]. More men are hypogonadal by FTI than by TT after age 50, and there seems to be a progressively greater difference, with increasing age, between the two criteria [12]. This is likely due to the progressive increase in SHBG levels with aging [4,12].

Diagnosis

Clinical picture

Symptoms

The diagnosis of TDS relies on the presence of the clinical manifestations confirmed by the presence of low plasma TT or FT or both. Clinical suspicion is based upon the symptoms and signs listed in Table 1. In the clinic, the urologist often faces a patient with a mixture of sexual complaints in addition to lower urinary tract symptoms (LUTS), such as diminished libido, erectile dysfunction (ED) not responding to phosphodiesterase-5 inhibitor (PDE5-I) therapy and shrinking phallus or testes [13,14].

Table 1 Symptoms and signs suggestive of testosterone deficiency in men [4].

More specific

Reduced libido
Erectile dysfunction (ED)
Reduced intensity of orgasm and genital sensation
Osteoporosis or low bone mineral density
Decreased spontaneous erections
Oligospermia or azoospermia
Very small or shrinking testes
Hot flushes, sweats
Breast discomfort, gynecomastia
Loss of pubic and axillary hair, reduced shaving

Less specific

Decreased energy or vitality, increased fatigue
Depressed mood
Reduced muscle mass and strength
Poor concentration and memory
Sleep disturbance; increased sleepiness
Mild anemia
Increased body fat, body mass index
Diminished physical or work performance

Related conditions

In addition to the urological and sexual history taking, a holistic approach dictates a comprehensive evaluation that includes the cardiovascular system, mainly ischemic heart disease and hypertension [14,15]. DM is common and, if present, must be well controlled [16]. Most clinicians can easily recognize mood changes, in particular depression. General performance, energy and muscle strength should also be assessed. Osteoporosis manifests as bone pain, especially in the hips and vertebrae [17]. Sleep disturbances and snoring [14] are also associated with TDS and metabolic syndrome, and both are frequently associated with central obesity, type 2 DM, hypertension and dyslipidemia [10].

Physical examination

The patient’s weight and height are taken, BMI is calculated, waist circumference is measured, and pulse rate and blood pressure are measured. Testing the hand grip assesses muscle strength in the upper torso and testing for knee flexion/extension evaluates power in the lower half of the body. Abdominal or central obesity is noted and documented.

Genital examination and digital rectal examination (DRE) are mandatory, especially when testosterone replacement therapy (TRT) is intended. Benign prostatic hyperplasia (BPH) or DRE changes suggestive of prostate cancer are looked for. DRE allows the estimation of anal sphincter and pelvic floor muscle power. A patulous anus or weak sphincter is noted if present. Incontinence, especially following prostatic surgery, should be documented. Stress urinary incontinence (SUI) in the male is most commonly seen post-prostatectomy [18,19]. It is always linked to deficient external sphincter muscles; therefore it is reasonable to assume that older men with TDS have a pre-existing internal sphincteric weakness and those undergoing prostatectomy are at risk for SUI [20–23].

Laboratory tests

Coupled with the clinical picture, the diagnosis of TDS is finally confirmed by measuring the morning fasting plasma TT level. FT is reserved for special cases. The diagnosis of hypogonadism and levels to indicate the initiation of treatment are illustrated in Table 2.

Summary of inter-related conditions and syndromes

See Fig. 1.

Treatment

The use of oral testosterone preparations was associated with variability in absorption and liver toxicity; therefore the response was

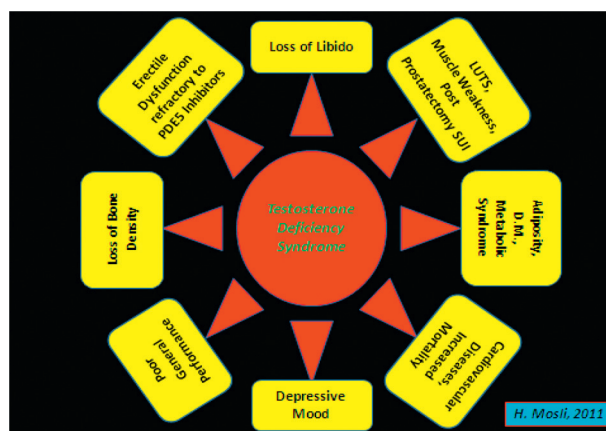


Figure 1 Summary of the TDS-related conditions and syndromes.

suboptimal, unpredictable and has fallen out of favor [24]. Similarly, dermal patches were associated with skin redness, rash and inconvenient skin reactions followed by bouts of itching that limited patches as a treatment modality. Dermal application of gels is a convenient and effective method preferred by men who suffer from needle phobia. The use of gels avoids peaks and troughs in serum levels. However, care must be taken to avoid contact with the female partner, especially if pregnant, since testosterone can be easily and quickly absorbed on contact. Limited experience was reported with the use of buccal pellets which may cause oral irritation.

Testosterones injections are of 2 types: short and long acting [7,13]. The short acting preparations are testosterone cypionate and enanthate oily solutions for depot use that last from 1 to 4 weeks at doses of 100–400 mg per injection and will need frequent monitoring of serum levels since fluctuations in peaks and troughs are expected. The newer long acting preparation testosterone undecanoate at a dose of 1000 mg in 4 ml can last up to 12 weeks and has the advantage of providing a steady serum level over 6–12 weeks. The safety profile of this preparation is high and it has been extensively used. When available, testosterone undecanoate is the drug of choice. The course starts with a loading dose followed by another dose at 6 weeks then every 6–12 weeks according to the serum testosterone level [13].

Progression/regression of TDS and duration of treatment

If left untreated, TDS will gradually and progressively manifest as a group of clinically distinct symptoms [13]. Initially it appears as loss of libido even with the mildest degree of testosterone deficiency. Then there will be decreased vitality, fatigue and mood swings which will be followed by insomnia, anemia, delayed ejaculation and scant ejaculate volume. ED (commonly non-responsive to treatment with PDE5-inhibitors) follows, together with loss of muscle mass, increased visceral body fat, testicular atrophy and general weak-

Table 2 Cut-off levels of TT and FT for diagnosis of hypogonadism and treatment initiation.

	Plasma level			
	Total testosterone		Free testosterone	
	Conventional units	SI units	Conventional units	SI units
Diagnose hypogonadism	≤300 ng/dL	≤10.4 nmol/L	≤50 pg/dL	≤180 pmol/L
Initiate treatment	≤231 ng/dL	≤8 nmo/L	≤0.17 nmol/L	≤72 pg/mL

ness. Osteopenia and osteoporosis/bone pains will follow and finally there will be loss of facial, axillary and pubic hair. Once adequate testosterone treatment is initiated, the body needs about 3 months to adjust its metabolic rate, hence little improvement is expected during the first 3 months of therapy. Following that libido will be enhanced and there will be improved emotional well-being. Within the next 6 months energy will increase, ED becomes reduced, and there is increased strength, enhanced bone mineral density (BMD) and improved cognition. With continued therapy and maintenance of adequate serum testosterone level, it is expected that there will be enhanced cardiovascular health, decreased body fat and improvement in some of the components of the metabolic syndrome. Optimal improvement would be experienced with 12 months of treatment; therefore the course of TRT should last for at least 12 months [7,13].

Monitoring

Clinicians should carefully monitor any man placed on TRT, especially for the development of BPH and prostate cancer. The following tests should be periodically carried out: DRE, serum TT, PSA, hemoglobin, lipid profile, liver function tests, vitamin D3 and serum calcium. Dosage adjustments are made, should any abnormalities such as polycythemia or elevated liver enzymes develop. According to the recently reported saturation model, the pretreatment PSA will initially rise until all the androgen receptors are saturated, then it will become steady [25]. Although androgen deprivation is essential in the management of advanced and metastatic prostate cancer, current evidence supports the theory that the development of prostate cancer is related to low rather than high testosterone levels. In addition, high grade and aggressive prostate cancer is more common in men whose testosterone levels are low [26].

Conclusion

TDS, formerly known as late-onset hypogonadism, is common and deserves to be investigated and treated when associated with a wide range of urological conditions. Clinicians including urologists should be able to manage TDS competently. TDS can be an important component of the metabolic syndrome [10]. Endothelial disease manifesting as ED and muscle weakness due to TDS can be a risk factor for postoperative SUI not responsive to pelvic floor exercises, and should trigger screening for low serum testosterone [27]. TDS is anticipated when ED is not responsive to PDE5-I therapy [28]. Effective therapy is available and can be safely utilized to achieve successful outcomes.

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