The Evaluation and Management of Testosterone Deficiency: the New Frontier in Urology and Men’s Health

William P. Conners III • Abraham Morgentaler

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Abstract Testosterone deficiency (TD) is a common clinical condition that causes sexual and non-sexual symptoms. Low serum concentrations of testosterone also predict significant health outcomes, such as diabetes, metabolic syndrome, and increased mortality. Treatment with testosterone therapy (TTh) effectively improves symptoms, and also has a positive impact on body composition and bone density. Since there is no serum testosterone value that reliably identifies men who will respond to treatment from those who will not, healthcare providers must exercise clinical judgment in making the diagnosis of TD. Multiple formulations of TTh are available, each with advantages and disadvantages. Overall, TTh is relatively safe but the risks, such as erythrocytosis, makes long-term monitoring mandatory. The evidence does not support concerns regarding cardiovascular and prostate cancer risks.

Keywords Testosterone • Erectile dysfunction • Libido • Sexual dysfunction • Metabolic syndrome • Androgens • Male sexual dysfunction • Prostate cancer

Introduction

Testosterone deficiency (TD) as a clinical entity is gaining substantially increased attention from both patients and physicians, and the use of testosterone therapy (TTh) has been reported to have trebled over the last 10 years [1]. Yet there remain considerable areas of uncertainty among clinicians regarding the evaluation and management of TD in men. The purpose of this article is to provide an evidence-based overview of the evaluation and management of TD, augmented by practical tips gained through extensive clinical experience.

Definition and Terminology

Testosterone deficiency (TD), also termed hypogonadism, refers to the clinical condition in which depressed serum concentrations of testosterone (T) lead to pathophysiological changes in men. The diagnosis of TD requires the combination of characteristic symptoms and/or signs together with abnormally low serum testosterone concentrations. At this point in time neither symptoms alone nor low biochemical T concentrations without symptoms or signs is considered an indication for treatment.

The preferred terminology for the use of testosterone in men is now “testosterone therapy (TTh),” replacing the term “testosterone replacement therapy (TRT),” since treatment augments rather than “replaces” T in men.

Prevalence

Estimates of TD prevalence in adult men vary widely, from 2 % to 38.7 %, due to differing definitions of TD in the literature. Many larger studies have focused primarily on serum T concentrations without regard to symptoms. Studies performed in clinical settings provide a higher prevalence than studies in community-dwelling men.

The Hypogonadism in Males study obtained morning serum T concentrations from men 45 years and older in the waiting room of physicians, the majority of whom were in primary care [2]. The percentage of men with T less than 300 ng/dl, a frequently used threshold for biochemical T deficiency, was 38.7 %. Approximately half of men with obesity and/or diabetes mellitus had T values in this range.
In contrast, the prevalence of TD observed in the European Male Aging Study was only 2.1% in men aged 40–79 years [3]. In that study men were categorized as having TD if they had serum T <11 nmol/L (approx 320 ng/dl) and three sexual symptoms: erectile dysfunction (ED), decreased libido, and reduced morning erections. The 2010 guidelines from the Endocrine Society recommend that clinicians diagnose TD with the presence of suggestive symptoms in combination with serum T concentrations below the lower reference value provided by their laboratory [4•]. This approach arbitrarily sets a rigid prevalence of TD at 2.5%, since laboratory reference values are established by categorizing the upper and lower 2.5% set of values (two standard deviations from the mean) of a reference population as abnormal.

**Physiology and Pathophysiology**

Testosterone is the principal circulating androgen in males [5]. Approximately 90% of testosterone is synthesized from Leydig cells in the testis and roughly 10% of testosterone is produced directly or indirectly from the adrenal glands. Testicular production of T is stimulated by secretion of luteinizing hormone (LH) from the pituitary, which in turn is stimulated by secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Testosterone, as well as its metabolic estradiol, inhibits GnRH and LH secretion via negative feedback at the level of the hypothalamus and pituitary [5].

Androgens are critical to male sexual differentiation beginning during the first trimester of life, inducing differentiation of the Wolffian ducts and development of the testis, penis, scrotum, and prostate. Within the prostate, the primary androgen is 5-alpha dihydrotestosterone (DHT), metabolized intracellularly from T by the 5-alpha reductase enzyme. The androgen receptor (AR) binds both testosterone and DHT, yet has greater affinity for DHT. The androgen-AR complex then enters the nucleus and stimulates transcription of androgen-regulated genes via binding to androgen response elements [6].

The relative importance of testosterone versus DHT appears to be tissue-specific: DHT plays a primary role in prostate, scalp, genital differentiation, and the corpora cavernosa whereas T appears to be the dominant androgen in spermatogenesis, muscle, and bone.

Within the circulation only 1–2% of T is unbound [4•]. Approximately 60% is bound to sex hormone binding globulin (SHBG), and the remainder is bound to albumin and other serum proteins. Free and albumin-bound T are considered bioavailable. The portion bound to SHBG is not biologically available due to tight binding. Testosterone levels demonstrate diurnal variation, with peak levels during the early morning hours of 6–10 a.m. and then a decline to nadir levels in the evening [7]. This diurnal variation is marked in healthy young men, but substantially blunted in men over 40 years [7]. In one cross-sectional study of 3006 men aged 50 years and greater, there was no change in mean serum T from 6 a.m. through 2 p.m., and only a subsequent mild decline of 15% from 2–6 p.m. [8]. Clinical experience suggests men with medical conditions have reduced diurnal variation in serum T concentrations.

Primary hypogonadism refers to failure of the testes to produce normal serum T in response to adequate gonadotropin stimulation. Secondary hypogonadism refers to a central deficiency, hypothalamic or pituitary, resulting in TD. Mixed primary and secondary hypogonadism occurs when there is a subnormal LH response in combination with reduced production of T, such as when TD is associated with normal LH levels. This is the situation most commonly encountered with aging.

As men age, total T declines by approximately 1% per year or 10% per decade following the age of 40 years, whereas free T declines more rapidly. Increases in SHBG with aging are responsible for blunting the decline in total T [7, 9, 10••, 11].

Testosterone deficiency causes pathophysiological changes in tissues that are androgen-dependent, resulting in erectile dysfunction, reduced libido, loss of muscle mass and strength, increased fat, and osteoporosis [12•].

**Medical Conditions Associated with Testosterone Deficiency**

A number of common medical conditions are associated with TD. These include erectile dysfunction, obesity, diabetes, hypertension, chronic obstructive pulmonary disease, renal failure, obstructive sleep apnea, reduced bone mineral density, hypertension, and human immunodeficiency virus (HIV) infection [12•]. There is a strong association with the metabolic syndrome [12•]. A number of medications can also reduce T concentrations, most notably LHRH agonists, ketoconazole, and opioid analgesics [4•]. The latter often produce profoundly reduced serum T concentrations into the near-castrate range via central inhibition [4•].

There is a bidirectional relationship between TD and metabolic syndrome. Men with more than one component of metabolic syndrome have been shown to have testosterone levels 10–15% lower than healthy controls [10••]. Longitudinal studies have demonstrated that low serum T concentrations are associated with increased risk of subsequent development of de novo metabolic syndrome and diabetes 7–11 years later [13, 14]. Physiologic processes that link TD and metabolic syndrome include increased insulin resistance, hyperglycemia, visceral fat accumulation, dyslipidemia, increased inflammatory cytokines, and endothelial dysfunction, leading to vascular disease [15–18].
Making the Diagnosis

Symptoms

The symptoms of TD can be conveniently grouped into sexual and non-sexual categories (Table 1) [12•, 19]. The sexual symptoms include diminished libido, erectile dysfunction, difficulty achieving orgasm, reduced intensity of orgasm, and diminished sense of sexual sensation in the genital region. Non-sexual symptoms include fatigue, lack of energy and vitality, depressed or blunted mood, irritability, reduced motivation, decreased cognitive acuity, decreased strength and stamina, inability to gain muscle with exercise, and increased fat.

In addition, there are several objective signs associated with TD. These include anemia, gynecomastia, and reduced bone mineral density, including osteoporosis [12•].

Blood Tests

The standard test for determining whether a man has TD is total testosterone. Unfortunately, no studies have identified a total T concentration that reliably distinguishes between men who will respond to treatment from those who will not, leading to a lack of consensus as to what serum T concentration signifies TD. The matter is clouded further by diurnal variation, intra- and inter-individual variation, and assay limitations. The interpretation of total T is also confounded by SHBG, since higher SHBG may make total T values appear normal despite low levels of free or bioavailable T [10••]. For these reasons we rely heavily on free T in our practice, together with total T.

Nonetheless, nearly all publications advocate the use of total T for the biochemical diagnosis of TD. The FDA uses a threshold of less than 300 ng/dl. The Endocrine Society recommended the same value in 2006 but amended this in 2010 to state that clinicians should use the lower reference value provided by their laboratory [4•, 20]. The International Committee on Endocrine Aspects of Male Sexual Dysfunctions provided more liberal guidance, observing that men with total testosterone less than 350 ng/dl (12 nmol/l) are candidates for TTh, but recognizing that a trial of TTh may be considered for men with characteristic symptoms and with total T concentrations higher than this threshold [21].

Free or bioavailable testosterone tests are free of the confounding effect of SHBG, and thus may provide a more accurate indication of androgen status [22]. Free testosterone is generally preferred over bioavailable testosterone due to technical issues related to available assays. Free testosterone may be performed as a direct assay by radioimmunoassay (RIA); as a calculation based on known values for total testosterone, SHBG, and albumin; or determined via equilibrium dialysis. Strong correlations between each of these techniques make them roughly equivalent in clinical practice [23, 24], although RIA values are substantially lower, and requires a separate set of reference values. Equilibrium dialysis is labor-intensive and should be reserved for research studies.

In our practice we have used the direct measurement of free T by RIA for over 20 years with excellent clinical correlation [22]. We offer a trial of TTh to men with characteristic symptoms and free T less than 1.5 ng/dl (or 15 µg/ml) by RIA, or with calculated free T <100 pg/ml [12•]. Overall subjective response to TTh in these men has been reported to be fairly similar whether total T was above or below the standard 300 ng/dl threshold for total T [25]. We have not found it necessary to restrict blood testing to the early morning in most cases, with the possible exception of young men less than 40 years.

Additional blood tests that should be obtained in men suspected of TD include LH, prolactin, hematocrit and/or hemoglobin. PSA should be obtained in men over 40 years. There may also be value in obtaining FSH, SHBG, estradiol, and a lipid profile.

Physical Examination

The physical examination is a critical feature of the evaluation of men with suspected TD, and should include assessment for gynecomastia, appearance and palpation of the penis, the size and consistency of the testicles, and prostate examination. Although the examination is usually normal in men with TD, any abnormalities in these areas should be noted. Small or soft testes are consistent with the presentation of TD.

Table 1 Symptoms and signs of testosterone deficiency

<table>
<thead>
<tr>
<th>Sexual</th>
<th>Non-Sexual/Psychological</th>
<th>Physical/Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Diminished libido</td>
<td>• Diminished energy, sense of vitality, or well-being</td>
<td>• Decreased bone mineral density</td>
</tr>
<tr>
<td>• Erectile dysfunction</td>
<td>• Fatigue</td>
<td>• Decreased muscle mass and strength</td>
</tr>
<tr>
<td>• Difficulty achieving orgasm</td>
<td>• Depressed mood</td>
<td>• Increased body fat</td>
</tr>
<tr>
<td>• Decreased spontaneous erections</td>
<td>• Irritability</td>
<td>• Gynecomastia</td>
</tr>
<tr>
<td>• Decreased genital sexual sensation</td>
<td>• Impaired cognition</td>
<td>• Reduced testicular size, firmness</td>
</tr>
<tr>
<td></td>
<td>• Reduced motivation</td>
<td>• Anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insulin resistance</td>
</tr>
</tbody>
</table>
Additional Tests

Pituitary MRI should be obtained in men with TD who have serum prolactin more than twice the upper limit of normal, severe hypogonadism (total T < 150 ng/dl), or men with LH and FSH below the normal range [26]. Consider obtaining karyotype in men with small, firm testes for the possibility of Klinefelter’s or other genetic abnormalities.

Benefits of Testosterone Therapy

Testosterone therapy improves libido in approximately 80% of men [25]. Improved erections are noted in approximately half of men with erectile dysfunction; however, this may not result in adequate rigidity for intercourse. One benefit of TTh versus phosphodiesterase inhibitors such as sildenafil and tadalafil is that TTh offers return of spontaneous adequate erections in responders without the need for planning.

Hwang et al noted that TTh restored adequate erectile function for vaginal penetration in two-thirds of men who had previously failed with 100 mg sildenafil. Half of the responders did not require sildenafil [27].

Testosterone therapy has been shown to increase lean mass, reduce fat mass, increase bone density, and improve hemoglobin A1C [28*, 29–31]. One year of TTh added to diet and exercise significantly increased the number of men with resolution of metabolic syndrome [32]. A 5-year study reported progressive declines in waist circumference and weight over the duration of the study [33*].

Treatment Options

Exogenous Testosterone Formulations

A number of treatment options are available (Table 2). Oral forms of testosterone available in the US are alkylated and are associated with significant hepatotoxicity [34], and for this reason their use is discouraged. No such liver toxicity has been noted for oral testosterone undecanoate, which is absorbed via intestinal lymphatics rather than portal veins, thereby avoiding first-pass hepatic effects. It is available in many countries, but not the US.

Parenteral testosterone formulations in the US consist of testosterone cypionate and enanthate. These are indicated for intramuscular injection, although clinical experience indicates good results may also be obtained via subcutaneous injection. The usual starting dose is 100 mg per week, or 200 mg every 2 weeks, with dose adjustment made based on clinical and biochemical response. Advantages of injections include low cost and reliable absorption. Disadvantages include unpleasant mode of administration and a “roller-coaster” response, as T levels rise and fall over the injection cycle. A long-acting injection, testosterone undecanoate, is available in many countries but not as yet in the US. It is administered every 12 weeks.

Several FDA-approved topical testosterone gels or liquids have become available since 2000 [35]. Concentrations range from 1% to 2%, with dosage varying by formulation. Follow-up monitoring of serum testosterone concentrations is mandatory due to wide variation in individual absorption, and dosage adjustment is frequently required to obtain optimal results. A
specific concern is skin-to-skin transference of T to women and children. Transference is rare, but men must be cautioned about this possibility.

Testosterone patches theoretically provide added convenience over gels without the risk of transference; however, their use has been limited due to a higher rate of skin irritation and less optimal biochemical results.

Testosterone pellets (75 mg) were approved by the FDA in 1972 but only became nationally marketed in 2008. Pellets provide 3–4 months of normalized serum testosterone. The usual initial dosage is 10–12 pellets per treatment [36, 37], placed subcutaneously in the buttock as an office procedure. Benefits include compliance, convenience, and long duration of action. Disadvantages include discomfort at the implantation site and risks of pellet extrusion or infection (1–2 %) [36].

Another testosterone preparation is the buccal patch. This is administered as a non-absorbable buccal patch, applied and changed every 12 hours. A unique side effect of this treatment is irritation of the buccal mucosa which may occur in 15.3 % of individuals [38].

Non-testosterone Treatments To Treat Testosterone Deficiency

Injections of human chorionic gonadotropin (HCG) increase serum T in men. HCG has a chemical structure similar to LH and mimics its actions. Injections are performed three times per week at a starting dose of 1500 IU. Treatment is effective but acceptability is limited due to the frequent rate of injections. Advantages include maintenance of testicular volume and fertility. In our practice we recommend HCG primarily for men with subfertility or younger men for whom testicular volume is important for body image.

Alternative medications used to treat TD include the oral agents clomiphene citrate [39] and aromatase inhibitors. Clomiphene has estrogenic and anti-estrogenic effects. It increases serum T by interfering with the central negative feedback loop, resulting in increased serum LH and FSH. The usual starting dose is 25 mg daily or 50 mg three times weekly. Aromatase inhibitors block the conversion of testosterone to estradiol, thus similarly inhibiting negative feedback. One commonly used formulation is anastrozole 1 mg daily. Advantages of these treatments include the fact that they do not negatively impact spermatogenesis and testicular volume, and the oral route is highly convenient. Curiously, subjective responses to these agents do not appear as positive as with exogenous testosterone formulations presumably due to estrogen antagonism, since central nervous system effects of T are mediated by local aromatization to estradiol [40]. Bone mineral density may decrease with chronic use of aromatase inhibitors. The use of these agents for TD is off-label.

Risks

Overall, testosterone therapy appears to be quite safe in men with TD. However, clinicians should be aware of a number of possible risks. The most commonly seen risk is erythrocytosis, seen in as many as 40 % of men receiving T injections, and at a much lower rate, 5–10 %, in men treated with topical formulations [19]. Although erythrocytosis has been associated with thrombotic events in individuals with polycythemia vera, this may not be a fair comparison since the latter is a malignancy with increases in other blood components such as platelets, whereas the erythrocytosis from TTh uniquely affects erythrocytes. We do not intervene unless the hematocrit exceeds 54 %, consistent with recommendations by the Endocrine Society [4•]. Interventions include decreased T dosage, withholding treatment, and therapeutic phlebotomy.

Pedal edema due to fluid retention may occur occasionally but is rarely of clinical significance. Acne occurs in 1–2 %. Decreased testicular volume and depressed sperm production occur in tandem due to negative inhibition of LH and FSH by exogenous T. Injection therapy has been reported to cause azoospermia in 92 % of men treated for several months [41]. Fertility is restored in nearly all men with cessation of treatment for 6–9 months. Gynecomastia occurs rarely, due to conversion of T to estradiol. All of these resolve with discontinuation of treatment. Sleep apnea in association with TTh has been described; however, a causal relationship seems unlikely [42].

Two concerns regarding TTh merit special comment. One is cardiovascular disease and the other is prostate cancer. Historically, testosterone was believed to contribute to cardiovascular disease because myocardial infarctions were more common in men than women. However, numerous studies have revealed that the relationship between serum T and cardiovascular risk is neutral or beneficial [12•]. Specifically, men with low serum T appear to be at increased risk of atherosclerosis and cardiovascular mortality, and normal serum T appeared to have a protective effect [43, 44]. In the Rancho Bernardo study involving 794 men between 50 and 91 years, total and bioavailable T were found to be inversely related to risk of death. Average follow-up was 11.8 years [45].

All-cause mortality has also been shown to be inversely related to serum T. In one such study 2,314 men aged 40–79 years were followed for a mean of 7 years. This nested case-control study found that every 173 ng/dL increase in serum T was associated with a 21 % lower risk of all-cause mortality even after controlling for multiple variables (age, body mass index, systolic blood pressure, cholesterol, cigarette smoking, diabetes, alcohol intake, physical activity, social class, education, and sex hormone-binding globulin) [46].

A single recent report did raise concerns about T therapy increasing cardiovascular risks [47]. However, this study was designed to investigate the impact of TTh versus placebo on muscle strength in elderly frail men, and not cardiovascular
risk. Although more cardiovascular events were reported in the testosterone group, most of these were not clinically significant, baseline risks were greater in the TTTh group, and there was no formal monitoring for cardiovascular events [47, 48].

A greater concern, particularly for urologists, has been the longstanding belief that higher serum T encourages more rapid growth of prostate cancer (PCa). This belief arose initially from the work of Huggins and Hodges who in 1941 wrote that T injections in men with metastatic PCa caused an increase in serum acid phosphatase, a marker for metastatic PCa [49]. However, it was not appreciated until recently that this conclusion was based on a single hormonally intact individual [50].

Current evidence fails to demonstrate any support for the belief that higher serum T is associated with greater PCa risk. A global pooled analysis of 18 longitudinal studies involving 3,886 men with PCa and 6,438 age-matched controls without PCa found no relationship between PCa risk and serum concentrations of T, DHT, or free testosterone [51]. More recently, Muller et al reported on 3,255 men in the placebo arm of the REDUCE trial who underwent planned prostate biopsies at 2 and 4 years, and found no association between PCa risk and baseline serum T or DHT [52]. A meta-analysis of 19 placebo-controlled TTTh studies reported no difference in the incidences of prostate cancer, PSA elevations over 4 ng/ml, or urinary symptoms [53]. These various studies provide strong evidence that PCa risk is unrelated to serum T concentrations. Indeed, there is growing literature associating low serum T concentrations with worrisome features of PCa, including high Gleason score, advanced stage at presentation, and increased risk of biochemical recurrence after radical prostatectomy [54].

Concepts regarding the relationship between androgens and PCa have undergone a revolutionary change. A number of small to moderate-sized series have now reported the use of TTTh in men previously treated for PCa [55, 56]. In 2011 Morgentaler et al reported that none of 13 men who received TTTh despite untreated PCa while on active surveillance demonstrated cancer progression after a mean of 2.5 years [57]. Although androgen deprivation clearly causes PCa regression and dramatic declines in PSA, the reason TTTh appears to have little impact on PCa growth in most men is due to saturation (Fig. 1) [58••], whereby maximal androgenic stimulation of prostate tissue is achieved at fairly low serum T concentrations. Once saturation is achieved, additional T appears to have little if any stimulatory effect on the prostate. Current data suggests the saturation point is approximately 250 ng/dl.

**Monitoring**

Monitoring is mandatory for men being treated with TTTh. It is recommended that follow-up visits are scheduled at least two or three times during the first year of treatment and at least annually thereafter. Additional visits maybe needed to optimize dosing. Follow-up visits should include physical examination and blood tests. Key elements to document in the physical examination include the development of breast tenderness or enlargement, and any changes on prostate examination. Minimal requirements for follow-up blood tests are total testosterone, hematocrit, and PSA. We find it useful also to measure free testosterone, gonadotropins, and SHBG.

It should be noted that a rise in PSA within the first 3–6 months of TTTh is not uncommon, and is to be expected in men whose baseline serum T was less than 250 ng/dl prior to TTTh. This new PSA value represents the value for the androgen-replete prostate, and is considered the new baseline. Decisions regarding prostate biopsy are made with this new baseline in mind. We perform prostate biopsy for men on TTTh who demonstrate a subsequent rise in PSA of 1.0 ng/ml over the next 2–3 years, and we repeat PSA more frequently in men with a rise of 0.7–0.9 ng/ml [19]. We also discuss biopsy in men with PSA of 2–4 ng/ml, as our own experience has demonstrated a cancer rate of 30% in TD men with PSA in this range [59]. Prostate biopsy is recommended for men with PSA >4.0 ng/ml.

**Conclusions**

Testosterone deficiency is common, and responds well to treatment. Treatment improves sexual and non-sexual symptoms caused by TD. In addition, growing evidence indicates there may be substantial long-term health benefits to men who undergo normalization of serum T, including weight loss, improved body composition and glycemic control, and possibly reduced mortality.
Compliance with ethics Guidelines

Conflict of Interest Dr. William P. Conners, III received consultancies from Auxilliary, Glaxo Smith Klein, Endo Pharmaceuticals, and Eli Lilly Pharmaceuticals.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- Of importance
- Of major importance

4. *Bhasin S et al. Testosterone therapy in adult men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2010;95(6):2356–59. An excellent reference for the field, and one of the most widely cited. It is important to note that the authors acknowledge promoting a conservative approach to treatment.
5. Braunstein G. Testes basic and clinical endocrinology 5th ed 1997 403–33.
sustained weight loss. Obesity (Silver Spring). 2013. First long-term study (5y) of testosterone therapy, provocative showing substantial and progressive weight loss and reduced waist circumference in obese and overweight men with low testosterone concentrations.


