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Therapeutic Options

MANAGEMENT OF TESTOSTERONE DEFICIENCY IN MEN: A FOCUS ON PRACTICAL IMPLEMENTATION OF THERAPY

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Testosterone deficiency (TD) is a clinical and biochemical syndrome that may occur in men, often associated with advancing age. However, it's essential to recognize that younger men with specific conditions can also be affected. The hallmark of TD lies in deficient testicular production of testosterone, accompanied by changes in receptor sensitivity to androgens.[1]

TD is surprisingly common, affecting a significant proportion of the male population. Men experiencing TD may present with a diverse range of symptoms, including fatigue, reduced libido, mood disturbances, and diminished muscle strength. These symptoms can significantly impact quality of life, affecting daily functioning, relationships, and overall well-being.

In 2015, the Canadian Urological Association (CUA) recognized the importance of addressing TD. Their commitment to education and best practice standards led to the creation of clinical practice guidelines dedicated to TD management. These guidelines, recognized as a "living document," serve as an educational tool, bridging existing knowledge gaps and offering contemporary insights into this complex condition.[1,2]

This article will focus on updating practical points of testosterone replacement, clarifying the management of specific scenarios and providing an overview of the therapeutic options currently available based on the most recent 2021 update of the guideline.

OVERVIEW OF TESTOSTERONE DEFICIENCY

Testosterone deficiency (TD) syndrome occurs due to either a failure of the testes to produce testosterone (primary hypogonadism) or a signalling problem within the hypothalamic-pituitary-gonadal axis that regulates its production (secondary hypogonadism).[1,2,3] Both causal pathways can result in low levels of testosterone but varying levels of gonadotropins (LH, FSH) and a combination of the two routes is common. TD often occurs in men with advancing age (hence, referred to as late-onset hypogonadism), but can occur in younger men with certain medical conditions.[2] Serum total testosterone is thought to normally start to decline in men in their mid-30s and gradually continue at a rate of 1.6% per year.[4] Actual figures of TD prevalence are not well defined, due to variability in reporting measures and more specifically, in biochemical testosterone thresholds. Recent international guidelines and studies have estimated prevalence rates of TD to be in the following ranges: 4-12% in men 50-59 years of age, 9-23% in men 60-69 years of age, and 28-49% in men over 70 years of age.[2]

Signs and symptoms of TD tend to be non-specific and vary based on age, comorbidities, and duration of TD.[2,5] Table 1 provides an overview of potential signs and symptoms, but not all need to be present for a diagnosis of TD. Sexual symptoms and fatigue are the most common presentations and tend to occur the earliest.[1]

Given the ambiguity that can be associated with the clinical presentation of TD, a diagnosis often requires a correlation between signs/symptoms and the presence of low or equivocal serum testosterone levels.[2] Serum *total testosterone* (free plus protein-bound) is considered the preferred initial screening test to diagnose TD as it is considered an accurate reflection of testosterone secretion.[1,2,6] The Canadian TD guideline recommends this sample be collected between 7 AM and 11 AM, or within 3 hours of waking for shift workers.[1,2] The rationale for this is the natural diurnal fluctuation that occurs with testosterone, reaching a maximum level at approximately 8 AM. Since food or glucose can suppress testosterone, a patient should be fasting prior to this measurement. The normal range of serum total testosterone will depend on the specific assay and reference population used, but the range is usually 10.4-31.2 nmol/L.[6] The Canadian TD guideline suggests a total testosterone level <10 nmol/L is a *reasonable diagnostic threshold consistent for TD*.[2] Typically, if a level is low or borderline low, the level should be repeated once or twice to confirm the diagnosis of TD. The measure of *free testosterone* is only recommended if an abnormality in sex-hormone binding globulin (SHBG) is suspected (commonly in obesity), or if the initial total level is near the lower end of normal; however, only specific methods of analysis are reliable and should be chosen carefully.[6] Further testing of other serum entities may be useful in evaluating whether the TD is primary or secondary and for ruling out other potential causes. Although several validated screening questionnaires for TD are available, these tools are not recommended for diagnostic purposes due

to a lack of specificity but may be used for initial screening purposes instead.[2]

TREATMENT OF TESTOSTERONE DEFICIENCY

Nonpharmacologic Treatment

Treatment of sleep apnea, weight reduction, lifestyle modification, and discontinuation of opioid medication may result in increased testosterone synthesis. Unless the clinician has good reason to believe that their patient will be compliant in the long term with a diet and exercise regimen for weight loss, drug treatment should be considered.[7]

Who to Treat?

The decision to treat TD is made on an individual basis, as symptoms vary in degree and intensity. The primary goal of treatment is to mitigate the negative effects of low testosterone. Diagnosis is often confirmed by serum testosterone level and the choice to treat may also be impacted by this result. A symptomatic patient with low serum testosterone is an obvious candidate for treatment but other scenarios are not as straightforward. In the case of a patient with symptoms characteristic of TD but with a normal testosterone level, other conditions with similar symptoms (e.g., depression, hypothyroidism) need to be ruled out first. Due to difficulties in the measurement of serum testosterone (e.g., lack of consistent reference ranges between labs, variability in sensitivity of androgen receptors, testosterone neutralizing effects of SHBG), this is a situation where other markers, such as SHBG or free or bioavailable testosterone, may need to be measured to better interpret the total testosterone levels and direct treatment. Finally, in the case of a patient who has a low serum testosterone level but is otherwise asymptomatic, the recommendation is *not* to treat with testosterone replacement unless symptoms develop.[2] The benefits and safety of using testosterone replacement in asymptomatic patients remain unclear.[5]

Use of testosterone replacement in the absence of identifiable pituitary or hypothalamic disease among aging men with a decline in serum testosterone levels has been controversial, as previous studies have not demonstrated consistent benefit in this particular population.[8,9] The Testosterone Trials were a series of seven randomized placebo-controlled studies evaluating the efficacy of testosterone on several symptoms including sexual, physical, and cognitive function, specifically in older men with symptoms of hypogonadism and low testosterone levels.[8,10] The study included 790 men over the age of 65 years who received testosterone or placebo gel for a period of one year. Benefits of testosterone therapy seen in the trials included a marked increase in bone mineral density, an increase in sexual interest and activity, increased hemoglobin, a small but significant improvement in mood, and only slight improvements in walking.[2,8,9] Symptoms of energy and cognition did not improve compared to placebo.[8] Similar to the Canadian TD guideline, the findings of the Testosterone Trials suggest testosterone replacement could be used in older men who have both specific clinical symptoms and a low serum testosterone level.[2,8] A clinical practice guideline from the American College of Physicians on testosterone treatment in adult men with age-related low testosterone has recommended testosterone be used in older men with low serum testosterone levels who are experiencing sexual dysfunction.[4]

Table 1. Signs and symptoms associated with testosterone deficiency[1,2,3,5]

Sexual	Reduced libido
	Erectile dysfunction
	Decreased frequency of morning erections
	Decreased performance
	Delayed ejaculation, reduced ejaculate volume
	Decreased intensity of orgasm
	Infertility
Cognitive / Psychological	Depression
	Mood changes
	Irritability
	Anxiety
	Poor concentration and memory
	Decreased motivation, initiative, and self-confidence
	Insomnia / Sleep disturbances
Physical / Structural	Increased body fat
	Decreased lean muscle mass/strength
	Testicular atrophy
	Fatigue / Loss of energy
	Low bone mineral density / Low-trauma fracture
	Anemia
	Loss of facial, axillary, and pubic hair
	Gynecomastia
	Hot flushes, sweats

Therapeutic Choices

Testosterone is the natural consideration for treatment of TD. Choice of testosterone preparation is dependent on personal preference, safety, tolerability and cost. Table 2 provides an overview of testosterone products that are available in Canada. Transdermal products, especially gel formulations, are commonly chosen based on their convenience, ease of use and ability to produce stable serum testosterone levels.[7] Although compounded products are often a consideration, the Canadian TD guideline suggests caution as published data has indicated significant variability in the concentration of testosterone in these products, which can impact both effectiveness and safety.[2,11] With respect to herbal or "natural" forms of testosterone (known as "T-boosters"), current evidence does not demonstrate consistent efficacy. Of the limited studies done in humans, 68% of the products had no effect on testosterone levels. Also of concern was the number of case studies demonstrating severe adverse events with these products, often due to the presence of banned substances including steroids. For these reasons, the Canadian TD guideline only recommends evidence-based treatments. In addition to providing exogenous testosterone, lifestyle modifications in the form of weight loss, dietary restriction, bariatric surgery, exercise, and better sleep patterns have also demonstrated some benefit in improving testosterone levels.[2]

DHEA (dehydroepiandrosterone) and Testosterone: Unraveling the Connection

DHEA, a steroid hormone produced by the adrenal glands, is a precursor for testosterone synthesis. While not directly testosterone, DHEA supplementation has been linked to preventing testosterone decline during high-intensity exercise, as shown in studies published in the

European Journal of Applied Physiology and Urology.[12] Other studies confirmed that DHEA administration was associated with an increase in testosterone levels. Potential benefits of DHEA include enhanced immune function, mood and memory improvement, reduced fat mass, better sexual function, and skin health, with some controversial evidence suggesting improved athletic performance. Hence, DHEA is banned by the National Collegiate Athletics Association (NCAA) and the World Anti-Doping Agency (WADA). Further, the National Institutes of Health does not endorse it for athletic enhancement. It's important to consult a healthcare professional before starting DHEA supplementation due to ongoing research and safety considerations.

Response to Therapy

The response to testosterone replacement therapy can vary depending on formulation and dose, as well as baseline testosterone level and symptoms. The current recommendation is to target improvement in serum level to a mid-normal range (total testosterone, 14-17 nmol/L).[2] The majority of men (>90%) will see a normalization of serum levels with therapy, which occurs earlier than symptom improvement.[2,10] The common sexual symptoms of TD tend to improve after 3 months of treatment while the physical/structural symptoms may require 6 or more months of therapy before improvement is seen.[2] One study treating hypogonadal men with transdermal testosterone reported these same timelines for symptom improvement, however, the full effect on bone mineral density was not seen until 24 months of therapy.[7] These timelines are important for both healthcare providers and patients to be aware of as they affect monitoring times and patient follow-up.[2]

Using these timeframe parameters, patients who have symptom improvement or resolution, combined with *at-target* or *lower-than-target* serum testosterone levels, can continue at the same dose with retesting of levels every 6-12 months.[2,10] Patients who achieve symptom resolution with an increase in testosterone levels *above* the normal range should be considered for dose reduction. If the serum testosterone level increases to within the recommended range but symptoms do not improve, a dose increase is suggested, targeting a higher serum level in the upper range of normal. If symptoms continue despite improvement in serum level and a trial of at least 3 months therapy, an alternate diagnosis and management plan should be considered.[2]

Duration of Therapy

There is no defined duration of therapy. Since initiation of testosterone therapy is based on the presence of intolerable symptoms and/or decreased quality of life, continuation can occur if the therapy is helping and is tolerated. If significant adverse effects occur and/or there is a cessation of clinical improvement, therapy should be stopped. Testosterone therapy does not require tapering of doses upon discontinuation.[2]

Safety and Tolerability

Before starting any testosterone product, safety concerns should be assessed. Besides allergy or a hypersensitivity to testosterone products, contraindications to use may include known or suspected male breast cancer, metastatic or high-risk prostate cancer requiring androgen-deprivation therapy or the presence of unstable cardiovascular disease.[2] Several areas of concern are discussed below; in each situation, potential risks and benefits should be discussed with the patient.[1]

Prostate Cancer Concerns

A perceived increased risk of developing prostate cancer secondary to testosterone use has been an ongoing concern when prescribing these products. There is now consistent evidence to suggest otherwise. In the aforementioned large randomized controlled trial (RCT; the Testosterone Trials) of 790 men treated with either testosterone or placebo gel, only one man developed prostate cancer over a period of 12 months. Similarly, a meta-analysis evaluating 2351 men found no greater risk of prostate cancer among patients treated with testosterone therapy versus those in the placebo group. Higher testosterone levels were not associated with significantly higher prostate specific antigen (PSA) levels or a greater risk of developing prostate cancer. The Canadian TD guideline makes the recommendation that men with localized prostate cancer that have been treated and have no evidence of active disease may be *considered for a medically supervised trial of testosterone therapy.*[2] However, due to the role of androgen receptor signaling in the process of prostate cancer, patients with metastatic or high-risk prostate cancer, especially cases likely to require androgen-deprivation treatment, should avoid testosterone therapy.[1,2,5] All candidates being considered for testosterone use should ideally be screened for prostate cancer prior to initiation.[5]

Benign Prostatic Hyperplasia (BPH) and Lower Urinary Tract Symptoms (LUTS)

The impact of testosterone on progression of BPH or development of LUTS has also been reviewed. In the Testosterone Trials of one-year placebo-controlled therapy in 790 men, worsening of urinary symptoms suggestive of BPH was monitored and occurred at the same rate in both treatment arms. A review of 16 RCTs of a total of 1030 men found that testosterone therapy did not affect prostate volume. Other testosterone studies have reported improvement in urinary symptoms, peak urinary flow rates, and voided volumes, potentially due to testosterone's effect on bladder detrusor function.[2]

Cardiovascular Risks

The association between testosterone levels and cardiovascular risk has been conflicting. The data indicates that untreated testosterone-deficient men are at greater risk of obesity, diabetes, dyslipidemia, and metabolic syndrome, all of which can increase their risk of cardiovascular events. The majority of studies found that hypogonadal men given testosterone demonstrated cardiovascular benefits.[1,2] Conversely, more recent studies have reported increased cardiovascular risk with the use of exogenous testosterone; however, these studies were thought to contain significant methodological flaws.[2] The United States Food and Drug Administration has conducted a review of the data and found the evidence for a causal effect was weak, but still mandated precautionary labelling on testosterone products.[5] Similar action was taken due to a concern about a possible association between testosterone therapy and increased incidence of venous thromboembolic events; however, these cases were considered anecdotal, and no definitive evidence of this has been found.[10] A large, long-term RCT is needed to clarify these effects.[2] Currently, a meta-analysis accruing data from 20,000 men in North America, Europe and Australia is looking to clarify the effect of exogenous testosterone on the incidence of cardiovascular events and other outcomes.[14] In the meantime, the Canadian TD guideline makes the recommendation that men with stable cardiovascular disease who meet the criteria for testosterone therapy are candidates for use but should be monitored accordingly.[2]

Fertility Preservation

In addition to risk assessment, one of the concerns to be aware of when considering testosterone use is the patient's desire for fertility preservation as the use of exogenous testosterone can ultimately cause male infertility. Administration of testosterone results in negative feedback to the pituitary gland, which suppresses production of sperm and testosterone at the testicular level.[2] Patients who want to maintain fertility should avoid isolated use of exogenous testosterone and opt for measures that increase their endogenous serum testosterone

production instead, such as human chorionic gonadotropin (hCG), selective estrogen receptor modulators (SERMs; e.g., clomiphene, tamoxifen) and/or aromatase inhibitors (e.g., anastrozole, letrozole).[2,10] Consultation with a fertility specialist is recommended, especially since many clinicians have unknowingly prescribed testosterone products in the past to help with fertility.[2]

CONCLUSIONS

Testosterone deficiency has the potential to negatively impact multiple facets of a man's well-being. By being aware of who may best benefit from therapy and what therapeutic options are currently available, pharmacists can ensure therapy is tailored to the individual patient and that monitoring of response is timely and appropriate.

Table 2. Testosterone deficiency treatment options[2,4,5,7,15,16,17,18,19,20,21,22,23,24,25,26,27]

Formulation	Drug (brand/generic) Strength / Dosage Form / Availability	Usual Dose	Comments
Oral	Testosterone undecanoate (generics only) 40 mg capsule	120-160 mg PO per day in 2 divided doses for 2-3 weeks then 40-120 mg PO per day, based on serum level* and clinical effect	**Advantages** • ease of administration • immediate discontinuation is possible **Disadvantages‡** • gastrointestinal AEs • must be taken with a meal as fat enhances absorption; from day to day, bioavailability can be variable
Injectable	Testosterone cypionate (Depo-testosterone®, generics) 100 mg/mL; 2 mL single dose ampoules or 10 mL vial	200 mg IM every 2 weeks	**Advantages** • long-lasting formulations allow for biweekly or monthly administration • injectable testosterone may be more cost-effective than transdermal and intranasal formulations **Disadvantages‡** • a longer time frame between doses can be associated with greater fluctuation in testosterone levels, producing variations in symptoms, especially in energy, mood, and libido • injection site pain/reactions • higher risk for erythrocytosis (increased hemoglobin and hematocrit) than with transdermal preparations • rarely, cough immediately after administration • IM injection usually requires clinic visit
Transdermal	Testosterone gel (Androgel®, Testim®, generics) 1% w/w Available as 2.5 g (=25 mg testosterone) or 5 g (=50 mg testosterone) unit dose packets; Androgel® also available as a metered-dose pump of 60 actuations (1.25 g per actuation)	5 g applied topically once daily in the morning Apply to clean, dry, intact skin of the upper arms, shoulders, and/or abdomen, according to specific product recommendations[β] (ideally an area that can be covered by a short-sleeved shirt)	**Advantages** • less fluctuation of testosterone levels than with injectable formulations • serum testosterone levels remain steady over a 24-hour period • better skin tolerability than with patches • ease of administration **Disadvantages‡** • testosterone concentrations may vary depending on application technique • skin irritation (erythema, induration, or burning) are the most frequently reported AEs • strict adherence to application precautions is necessary to prevent transfer of testosterone to women or children via skin-to-skin contact or contact with clothing/towels/sheets that have been in direct contact with application site; virilization has been reported in children as a result of secondary exposure and is listed as a black box warning • Testim® may be associated with musk-like odour • washing or swimming after application of gel should ideally be spaced by 5-6 hours • can be slow-drying, sticky and messy to apply
Intranasal	Testosterone nasal gel (Natesto®) 4.5% w/w Available as a metered-dose pump of 60 actuations; (5.5 mg testosterone per actuation)	11 mg (=1 actuation IEN) intranasally twice daily Based on serum testosterone level* and clinical response, dose may be increased to a maximum dose of 11 mg three times daily	**Advantages** • may be the preferred option in cases where fertility preservation is desired as it potentially results in less suppression of spermatogenesis • reduced risk of person-to-person transfer of testosterone • ease of administration **Disadvantages‡** • not recommended for use in patients with chronic nasal conditions or alterations in nasal anatomy (including sinus disease or nasal mucosal inflammatory disorders such as Sjögren's syndrome); should not be used during episodes of severe rhinitis • AEs include nasopharyngitis, rhinorrhea, sinusitis, scabbing and epistaxis, typically mild to moderate in severity • frequent dosing can be inconvenient • approved by Health Canada but currently not available due to supply issues

AE=adverse effect; IEN=into each nostril; IM=intramuscularly; PO=orally

* Preferred serum testosterone level is total (free plus protein-bound) testosterone.[1,2,6]

‡ All testosterone products share similar adverse effects and potential for drug interactions; only formulation-specific details have been listed.

β Androgel® and Taro (generic) administration instructions specify application to the upper arms, shoulders, and/or abdomen whereas Testim® application instructions specify only the upper arms and shoulders.[20,22]

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