INTRODUCTION
Testosterone has now become one of the most widely used medications in the United States. This is partly due to an increasing proportion of the population > 65 years of age and the increasing incidence of medical co-morbidities associated with low testosterone, such as diabetes, metabolic syndrome, and cardiovascular disease. It is well documented that the incidence of testosterone deficiency (TD) increases with age, partly due to a 0.4–2.0% per year decline in testosterone production after age 30. The incidence of TD in healthy, middle-aged men has been reported as high as 6%, with greater increases associated with age beyond 60, medical co-morbidities, and poor health status. In fact, males in the seventh decade have mean plasma testosterone levels 35% lower than young men. Given the nonspecific symptoms and variation in testosterone levels associated with the presentation of this disease, diagnosis and treatment still remain a challenge despite an increasing incidence. This is evidenced by the fact that only 12% of clinically symptomatic, hypogonadal males are successfully treated despite access to care. Therefore, as the usage of testosterone supplementation therapy (TST) continues to increase, clinicians will be challenged to maintain an up-to-date understanding of the diagnosis and management of TD.

PHYSIOLOGY
Testosterone plays a critical role in modulating male sexual development, adult male reproductive health, and sexual function. In addition, it is critical in maintaining lean muscle mass, bone mineral density, and fat metabolism. Testosterone production is regulated by the hypothalamic-pituitary-gonadal (HPG) axis.

Testosterone production through the HPG axis is a tightly controlled, multi-phased biochemical process. Initially, gonadotropin-releasing hormone (GNRH) is secreted from the hypothalamus in a circadian, pulsatile fashion into the portal vascular system. This system provides connection to the anterior pituitary, where GNRH is rapidly internalized, triggering systemic release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). LH targets sertoli cells and spermatogonial membranes that regulate the process of spermatogenesis, whereas LH targets Leydig cells whose role is to produce testosterone.

Once produced, testosterone is released into the systemic circulation where it is either protein bound or unbound. Approximately 30% is tightly protein bound by sex hormone binding globulin (SHBG) and physiologically inactive. SHBG is produced in the liver and circulating levels can be influenced by disease states such as hyperthyroidism, cirrhosis, and HIV, which increase SHBG, whereas hypothyroidism, obesity, and nephrotic syndrome decrease SHBG. Approximately, 68% of serum testosterone is loosely protein bound by albumin and can be coupled with unbound, free testosterone to determine bioavailable testosterone. Physiologically active, unbound testosterone that is free to exert cytologic effects comprises approximately 2% of circulating testosterone. Within non-testicular tissue, testosterone can be converted to the more potent dihydrotestosterone via the 5α-reductase enzyme or to other androgens such as estrogen via the aromatase enzyme. Intratesticular testosterone levels (200–1000 ng ml⁻¹) are 80–100 fold higher than serum levels and are critical for spermatogenesis and maintained by androgen binding protein produced by sertoli cells. In addition to testosterone, estrogen...
aromatized from testosterone, other androgens, and inhibin all provide negative feedback inhibition at the level of the hypothalamus and pituitary glands modulating production.  

Serum testosterone levels can vary over time due to a variety of factors. Diurnal variation, based upon circadian rhythm-driven, pulsatile hypothalamic release of GNRH, results in peak serum testosterone levels during the morning hours. Blunting of the diurnal peak has been shown to occur with aging, however a significant proportion of older men aged 65–80 with low afternoon serum testosterone levels will have normal levels in the morning. Furthermore, 15% of young, healthy men can demonstrate abnormally low levels within a 24 h period. Some of this variation can be explained by assay variation, but a certain amount is due to biologic variation from glucose ingestion, triglyceride levels, diurnal, seasonal variation, and activities performed prior to lab draw.

**ETIOLOGY**

**Classification**

TD can be caused by a failure of the testes to produce testosterone, interruption of one or several layers of the HPG axis, androgen target tissue dysfunction, or environmental factors such as medications or chronic medical illness. TD can be classified as secondary (or hypogonadotropic) hypogonadism when disruption of the HPG axis leads to inadequate FSH and LH production. One important cause of secondary hypogonadism is pituitary dysfunction from hypopituitarism related to radiation, infection, trauma, hyperprolactinemia from hormone-secreting pituitary adenomas, dopaminergic medications, or medical conditions such as chronic renal failure and hypothyroidism. Other causes of secondary hypogonadism are primary GNRH deficiency from Kallmann syndrome, Prader–Willi syndrome, and idiopathic hypogonadotropic hypogonadism. Secondary hypogonadism may also result from GNRH deficiency from medications, radiation, chronic illness or conditions resulting in elevated serum levels of inhibin.

Primary (or hypergonadotropic) hypogonadism refers to testicular failure in production of testosterone and spermatogenesis in presence of elevated gonadotropins. Common intratesticular causes include a history of treatment for testicular tumor, prior infection such as orchitis, chemotherapy, medications with gonadotoxic effects, environmental toxins, idiopathic testicular atrophy, or iatrogenic removal for trauma or malignancy. One of the more common intratesticular genetic causes of primary hypogonadism includes Klinefelter’s syndrome, affecting 0.2% of the male population and representing the most common numerical chromosomal aberration. Klinefelter’s is often diagnosed during a male factor infertility evaluation for severe oligospermia or azoospermia, which can reveal other causes of male factor infertility associated with primary hypogonadism. Some such causes are genetic, including Y-chromosome microdeletions, chromosomal aberration, 47 XYY syndrome, gonadal dysgenesis, or 46 XY disorders of sexual development. Other such causes are anatomic as with varicoceles. Varicoceles cause intratesticular dysfunction secondary to testicular hyperthermia, reflux of venous toxins, and increased reactive oxygen species due to relative hypoxia. Finally, hypogonadism related to defects in androgen target tissue utilization of testosterone such as androgen insensitivity syndrome, which may be partial or complete, and 5α-reductase deficiency are rare.

Mixed gonadal dysfunction, often referred to as late onset hypogonadism (LOH), but also known as androgen deficiency in the aging male, partial androgen deficiency of the aging male, age-associated TD syndrome, male menopause and andropause; has become an increasingly important entity. The age-related symptomatic decrease in serum testosterone has been shown to occur in approximately 3% and 5% of men in the sixth and seventh decades, respectively. Several physiologic changes can account for this phenomenon. SHBG levels have been shown to increase with age, reducing bioavailable and free serum testosterone levels. LH may be variably elevated in response to a decrease in the number and function of the Leydig cell population, which also correlates with the age-related decline in spermatogenesis and fertility. Some have proposed using LH levels in aging men to distinguish compensated hypogonadism from pure primary hypogonadism to understand disease severity and guide treatment decisions. Age-related impairments in the HPG axis are also partly responsible, including reduced LH pulse amplitude, LH pulse frequency and GNRH production. Additionally, the gradual increase in co-morbid medical conditions with age can effect the HPG axis centrally resulting in HPG axis feedback impairment.

**Medications**

Several medications have been associated with TD due to induction of primary hypogonadism, secondary hypogonadism, or both. Glucocorticoids are well-known for their multi-system side-effects such as osteoporosis, but they can also induce mixed primary and secondary hypogonadism and decrease SHBG levels. This process has been found to affect up to 80% of men on long-term glucocorticoid therapy on cross-sectional analysis. Such an effect has been shown to occur regardless of dose and can persist for up to 12 months. Previous exposure to exogenous testosterone or anabolic steroids, at any point in life, has been shown to negatively impact the HPG axis and may cause secondary hypogonadism and infertility, an effect which can endure for up to 2 years and in some cases may be permanent. This effect is more common in younger men as evidenced by the recent observation that hypogonadal men < 50 years of age have a 10-fold higher risk of previous anabolic steroid exposure than men older than 50 years of age.

In addition, GNRH analogs, such as those used for prostate cancer treatment, are potent inhibitors of the HPG axis with effects lasting up to 3–4 months after cessation of therapy. Similarly, isolated reports have shown androgen analogs such as megastrol acetate used for appetite stimulation in cachectic cancer patients can also induce symptomatic male hypogonadism. Commonly used opioid analgesics have been shown to have suppressive effects on the release of gonadotropins centrally and on production of testosterone peripherally by Leydig cells. The onset of action is quick, with duration and severity of opioid effect on the HPG axis appearing to be related to half-life and dose of a particular agent used. The duration of effect, however, appears to be short regardless of duration of therapy. Some studies with selective serotonin reuptake inhibitors have only shown a statistically significant decrease in serum testosterone levels using paroxetine, whereas other studies using fluoxetine have not. Finally, statins have also shown a modest but statistically significant decrease in serum testosterone levels.

**Medical Conditions**

A number of medical conditions have been associated with low serum testosterone levels. Obesity is strongly associated with hypogonadism, with a reported 52% prevalence on large population cross-sectional analysis when controlling for obesity-related declines in SHBG. Proposed mechanisms include decreased amplitude of LH pulsatility, increased plasma leptin levels having central and peripheral inhibitory effects, and peripheral conversion of testosterone to estrogen via...
adipose tissue-dense aromatase enzyme. Often co-morbid with obesity, obstructive sleep apnea has been shown to produce a reversible dysfunction of the HPG axis independent of the effects of obesity. Type 2 diabetes mellitus has also been shown to be highly prevalent in hypogonadal males independent of obesity, with rates nearing 50%. Proposed mechanisms include aforementioned obesity-mediated pathways with addition of increased insulin resistance at the hypothalamic level. In sum, the exact relationship between obesity, insulin resistance, metabolic syndrome, diabetes, and TD has yet to be fully elucidated. Available data promote a spectrum of possibilities ranging from low testosterone and SHBG levels being predictive of development of metabolic syndrome to metabolic syndrome being a risk factor for development of TD.

Other chronic medical conditions such as hypertension, hyperlipidemia, chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease and erectile dysfunction (ED) have all been linked to TD with high prevalence rates. In most cases, the underlying pathways are multifactorial. Alcohol abuse has been shown to effect the HPG axis at all levels resulting in TD. Acute critical illness has long been known to cause decreases in bioavailable testosterone levels. HIV is associated with TD in up to 50% during the preantiretroviral era compared with 20%–25% in the postantiretroviral era. The exact mechanism is unknown, but early recognition is important, as hypogonadism is strongly associated with AIDS wasting syndrome. Adequate treatment with TST demonstrates mitigation of this risk with improvement in several quality of life parameters. Although rare, hemochromatosis can result in TD by causing primary or secondary hypogonadism or both, which is potentially reversible with treatment of the underlying etiology. Finally, men with low testosterone have been found to suffer from some form of depression in up to 90% of cases with 17% having severe depression.

Still somewhat controversial, there is recent evidence that TD may be associated with Peyronie’s disease (PD), and TST may improve its symptoms. A causative role is unclear, although a complex relationship likely exists. TD does lead to the down-regulation of vascular endothelial growth factor and up-regulation of transforming growth factor beta, resulting in corporal fibrosis. Reversal of these findings has been shown with TST in animal models. While two studies have shown a significant association between TD and PD, a large, recent retrospective study found that men presenting with either PD or ED have a similar incidence of TD, suggesting TD has a closer relationship with the ED component of PD.

DIAGNOSIS

Introduction

Despite the recent surge in usage, the diagnosis of TD remains a challenge. This is partly due to the diagnosis being dependent upon establishing presence of clinical symptoms and low serum testosterone levels. However, achieving these two criteria remains difficult due to a lack of standardization regarding the overall evaluation and management of TD. This lack of standardization is due to several factors including wide variation in presenting symptoms, limited clinical correlation between serum androgen levels and symptoms, and various issues with laboratory processing and quantification of serum testosterone levels.

Several specialty societies and expert groups have attempted to standardize the diagnostic process, including the United States Endocrine Society, European Association of Urology, International Consultation on Sexual Medicine (ICSM), and joint guidelines representing numerous international andrology societies (Table 1). Broadly speaking, these guidelines emphasize the importance of diagnosis in men who first demonstrate clinical signs or symptoms of TD, followed by documentation of a low serum testosterone level only in individuals who do not exhibit easily reversible causes of TD such as medications or acute illness as previously discussed. These guidelines provide a good framework within which clinicians can practice. However, they are partly based upon generally low quality data, especially when defining a low serum testosterone level, and there is some individual expert deviation from these in actual clinical practice.

Clinical Diagnosis

The clinical presentation of TD in adult males can be variable, insidious, and often confused with other clinical conditions. Because testosterone is a key regulator in male sexual function pathways, common symptoms of TD include decreased libido, reduced nocturnal erections, ED, and male factor infertility. Additional signs and symptoms less specific to TD are reflective of testosterone’s broad systemic effects and include decreased energy, decreased cognition, reduced muscle mass, reduced strength, increased adiposity, decreased bone mineral density, hot flashes, sleep disturbance, and depressed

| Clinical symptoms | Clinical questionnaire | Serum total testosterone (ng dL⁻¹) | Morning draw on 2 separate occasions | Free testosterone (pg mL⁻¹) |
|-------------------|-----------------------|----------------------------------|-------------------------------------|---------------------------|
| Endocrine society | Yes No                | <300 (10.4 nmol L⁻¹)             | Yes                                 | Calculated method preferred Lab lower limit of normal |
| EAU               | Yes No                | <349 (12.1 nmol L⁻¹)             | Yes                                 | Calculated method preferred<63.5 (220 pmol L⁻¹) |
| ICSM              | Yes No                | <230 230-350 (gray zone) >350 (no treatment) | Yes | Calculated method preferred<65 (225 pmol L⁻¹) |
| Joint society     | Yes No                | <230 230-350 (gray zone) >350 (no treatment) | Yes | Equilibrium dialysis is gold standard Lab lower limit of normal |

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mood. 23,24,30,78 Hypogonadal symptom screening questionnaires can be sensitive, but are poorly specific for diagnosing TD; accordingly, their use is not strongly recommended. Similarly, general population screening for TD is also discouraged. 23,24,30,78

Physical exam is a helpful adjunct to symptom elucidation. Testicular volume < 10 ml is considered a strong predictor of TD, especially with increasing age. However, testicular volume must be interpreted in the context of existing co-morbidities and should prompt questioning as to historical risk factors for primary hypogonadism such as testicular trauma, chemotherapy, or prior surgery. 32,72 Testes volumes < 5 ml in setting of elevated gonadotropins are highly suggestive of Klinefelter’s syndrome and warrant karyotype testing. 72 Other helpful findings during the genital exam include assessment for a testicular asymmetry, varicoceles, or testicular masses. Additional general exam findings of gynecomastia, decreased body hair, visceral obesity, and diminished muscle mass are also helpful findings in the diagnosis of TD. Small, age-adjusted prostate volume has also been implicated as a diagnostic finding but is only corroborated by a few expert clinicians. 77,78,82

Laboratory Diagnosis

Once patients are suspected of TD based upon clinical signs and symptoms, the diagnosis should be confirmed with laboratory testing to determine serum testosterone levels. Most agree this should be done initially by drawing a total serum testosterone level on two separate occasions during morning hours. As previously discussed, there is a diurnal variation in serum testosterone levels, and up to 30% of patients with initially abnormal values have normal levels on repeat testing. 19,20,83 Joint international society guidelines propose an upper limit of normal as 350 ng dl⁻¹, above which treatment is usually not beneficial. 77,78 However, the lower limit of normal, below which all appropriate individuals should undergo treatment, has not clearly been established. These same international society guidelines highlight population-based data from young men with TD undergoing TST that show the greatest benefit from treatment occurs in those with sexual symptoms and total serum testosterone levels < 230 ng dl⁻¹. 77,29 Other population-based data demonstrate variable threshold levels of serum testosterone levels at presentation among different TD symptoms and individuals. Most symptoms correlate to a testosterone threshold level of 300 ng dl⁻¹ at presentation, which corresponds to most laboratories’ lower limit of normal for young men. 77,80 Based on this data, the 2006 U.S. Endocrine Society guidelines recommended a total serum testosterone level of 300 ng dl⁻¹ as the diagnostic threshold for treatment. This is also the same value used by the United States Food and Drug Administration (USFDA) to define hypogonadism for clinical trial purposes. 22 However, in the 2010 Endocrine Society update, clinicians were instead referred to their individual laboratories reference ranges to guide treatment decisions due to several laboratory issues further adding to the difficulty in determining normal levels of serum testosterone. 23,80

One laboratory issue is the preponderance of assays available including radioimmunoassay (RIA), immunoassay (IAs) and liquid chromatography-mass spectrometry (LC-MS). RIA and IA are highly specific but can vary significantly between laboratories based upon antibody type used. 22 LC-MS is accurate and precise but requires strict quality control and calibration. All three are plagued by decreased accuracy at testosterone levels below 300 ng dl⁻¹. In addition, standardized laboratory specimen processing and equipment calibration standards do not yet exist. 22

Regardless of which assay used, most authors agree that those patients who are clinically symptomatic with confirmed total serum testosterone levels < 230 ng dl⁻¹ will benefit the most from treatment. In symptomatic men with confirmed levels > 350 ng dl⁻¹, several guidelines suggest that these patients may not experience benefit from treatment. However, some experts advocate for treatment in clearly symptomatic men regardless of serum testosterone levels, including those with levels > 350 ng dl⁻¹. 77 Within this group, experts attribute benefit of treatment to modulation of the androgen receptor, mediated by genetic polymorphisms in exon one of the androgen receptor gene in the form of increased cysteine adenosine guanine (CAG) repeats. Certain data have shown increased CAG repeats are associated with decreased sensitivity in the receptor to testosterone and manifestation of TD symptoms despite “normal” serum testosterone levels. 65,67

Unfortunately, many patients who experience signs and symptoms of TD fall into the “gray area” of 230–350 ng dl⁻¹. This may be due to altered serum SHBG levels as seen in older or obese patients, and SHBG levels should be checked and serum testosterone levels repeated. For these patients, total testosterone levels may not reflect bioavailable levels. In “gray area” patients, expert and guideline statements support the determination of biologically active testosterone by measuring free testosterone. 23,30,77 Equilibrium dialysis is the gold standard for free testosterone measurement, but it is complex and not available at many laboratories. 23 More commonly available analog assays are not recommended due to lack of sensitivity. 13,89 Therefore, most laboratories utilize calculated free testosterone according to Vermeulen method, which is based upon serum total testosterone, SHBG and albumin levels. This has been shown to correlate well with equilibrium dialysis methods. 13,89 Some experts, including these authors, advocate for use of calculated free testosterone levels in the diagnosis of all patients to avoid the ambiguity of total serum testosterone levels. 77 If clinicians do not have free or bioavailable testosterone levels available at their local laboratory, they can check SHBG and albumin levels and then use an app such as “BioT” or online calculator (www.issam.ch/freetesto.htm) to calculate the levels of free and bioavailable testosterone.

Additional endocrine testing is warranted in those with suspected or confirmed TD. Serum LH levels should be measured to establish primary versus secondary hypogonadism. If LH levels are low and secondary hypogonadotropic hypogonadism is suspected, further testing is important to elucidate the underlying cause. These tests may include serum prolactin levels to rule out hyperprolactinemia, iron saturation studies to rule out the hemochromatosis, and estrogen levels to determine the testosterone to estrogen ratio. 72,23,30,100 Some authors advocate for pituitary magnetic resonance imaging (MRI) if total serum testosterone levels are < 150 ng dl⁻¹ coupled with either severely depressed gonadotropin levels or elevated prolactin levels are present. 23 However, despite the dogma of pituitary MRI and the concern for a prolactinoma, the most common cause of hypogonadotropic hypogonadism with levels < 100 ng dl⁻¹ is prior exposure to exogenous androgens. 46 If primary hypogonadotropic hypogonadism is suspected, consideration should be made to perform karyotype testing for Klinefelter’s syndrome. 23,72,73 TD also increases the risk for decreased bone mineral density and osteoporotic fracture. 93 This effect is reversible in men of all ages on TST, with some experts recommending all osteoporotic men undergo TD evaluation. 94,95,96 Therefore, baseline dual-energy X-ray absorptiometry (DEXA) scanning should be considered in those with severe TD. 23,30

TREATMENT

Treatment Goal

The goal of TST is to alleviate hypogonadal symptoms by restoring physiologic levels of serum testosterone. The exact serum testosterone
level required to achieve maximal efficacy and safety is currently unknown.50 Many authors often cite low-to-mid level range of serum testosterone levels as a reasonable target in otherwise young, asymptomatic men.56 These authors target a mid-to-high range, due to the lower risk of necessary dosing adjustments and a better chance for immediate symptom improvement resulting in improved compliance. However, there can be variation in what these ranges actually mean due to laboratory variation in assay type and processing, as well as individual variation due to CAG repeats mediating changes in androgen receptor sensitivity as previously discussed.28 Periodic observation of serum hormone concentration and its metabolites should be performed to minimize treatment-associated side-effects.97 Sustained supraphysiologic levels should be avoided.96 Improvement in symptoms should become apparent after 3 months of treatment. However, the results vary with the symptom. Energy and libido improve early, while osteoporosis may require as long as 1 year to improve.

**Contraindications**

There are certain clinical scenarios in which several specialty society and expert group guideline statements indicate caution or contraindication to TST.21,24,30,78 Breast cancer in men is rare and universally accepted as a clear contraindication.99,100 Presence of prostate cancer, particularly metastatic prostate cancer,101 has historically been considered a contraindication to TST. Several guideline statements still consider this to be a contraindication,20,24,30 including men at increased risk for developing prostate cancer-based upon the presence of a palpable nodule or elevated prostate specific antigen (PSA).102,103 Emergence of the saturation model104 has initiated a paradigm shift away from withholding TST in men with TD over concern for exogenous testosterone promoting development of prostate cancer.105 The 2010 Endocrine Society guidelines acknowledge that men at risk for prostate cancer may be treated with TST if cleared by a urologist after appropriate referral. A robust body of evidence supports this statement, but such men should still be closely monitored for development of prostate cancer while on TST.106–108 Furthermore, emerging data suggest TST in patients with a history of successfully treated, organ-confined prostate cancer is most likely safe.109–115 The most recent ICSM guidelines emphasize this point, stating that men with TD after successfully treated localized prostate cancer, without evidence of disease after a period of observation, are candidates for TST provided they have a thorough discussion of the potential risks and limited safety data.78

A similar paradigm shift has occurred for TST in men with benign prostate hyperplasia (BPH). The Endocrine Society guidelines recommend urology referral for TST in men with TD and significant lower urinary tract symptoms (LUTS) based upon International Prostate Symptom Score (IPSS) >19. ICSM guidelines acknowledge demonstrated safety of TST in men with IPSS > 21 based upon numerous studies, particularly after successful treatment of lower urinary tract obstruction.78,116 In addition, baseline hematocrit > 50%, uncontrolled or poorly controlled congestive heart failure, and obstructive sleep apnea are also contraindications.116 Finally, TST is clearly contraindicated in men with TD who still desire fertility and alternate therapies should be pursued.78

**Preparations**

Testosterone supplementation therapy exists as several different preparations administered by various routes, thereby requiring the treating physician to have an adequate understanding of the advantages and drawbacks of each preparation (Table 2). This is also important to facilitate the choice of agent by a shared physician-patient decision-making process.116 Due to the possibility of developing an adverse event during treatment requiring discontinuation, an initial trial of a short-acting agent that can be quickly withdrawn may be warranted, particularly in older patients.24,30

Although not available in the United States, oral agents are available internationally and provide TST in the convenience of a pill. Oral testosterone undecanoate is esterified to allow lymphatic absorption and partial avoidance of hepatic first-pass metabolism, but systemic absorption is still variable and at best serum levels reach mid-range.117,118 It is usually prescribed as a 2 or 3-dose regimen (40–80 mg) when using capsules or tablets, respectively.97 Oral 17-alpha-alkylated derivatives of testosterone can be more

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**Table 2: Overview of available testosterone preparations**

| Route          | Formulation | Dose regimen | Pharmacokinetics | Advantages | Disadvantages |
|----------------|-------------|--------------|------------------|------------|---------------|
| Transdermal gels | AndroGel 1%® | Apply daily. For dosing, see Table 3 | Steady state in 48–72 h | Quick onset | Cost |
|                | AndroGel 1.62%® | | | Physiologic pattern | Site irritation |
|                | Axiron® | | | Stable serum levels | Transference |
|                | Testim® | | | | |
|                | Vogelxo® | | | | |
| Oral buccal | Striant® 30 mg tablet | 30 mg BID | Peak serum levels within 30 min | Quick onset | Gum/mouth irritation |
| Injection (short) | Enanthate 200 mg ml⁻¹ injection | 150–200 mg q 2 weeks or 75–100 mg IM q week | Half-life 5–7 days, rapid onset and offset | Easy to discontinue | |
| Injection (long) | Cypionate 100 or 200 mg ml⁻¹ injection | 750 mg IM q 4 week >2, then q 10 weeks thereafter | Normal serum levels maintained for up to 12 weeks | Long duration Stable serum levels | |
| Subcutaneous pellets | Testopel® 75 mg pellet | 600-1050 mg q 3–4 months | Serum level peaks at 1-month, normal levels maintained 3–4 months | Long duration Stable serum levels | |
| Topical patches | Androderm® 2 and 4 mg patches | 2–6 mg (1–3 patches) q day | Maintain physiologic levels for 24 h | Mimics circadian patterns | Skin irritation at application site |
| Nasal | Natesto® 5.5 mg | 11 mg (2 pump actuations) | Peak serum levels within 40 min, short half-life | Easy to use | Intranasal irritation |

IM: intramuscular; TID: three times daily; BID: twice daily

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effective, but have been associated with hepatotoxicity and are no longer used clinically.\textsuperscript{97,118} Buccal and sublingual formulations represent well-tolerated delivery systems with good efficacy due to avoidance of hepatic first-pass metabolism.\textsuperscript{24} Striant\textregistered, available as a 30 mg tablet, is the only buccal formulation available in the United States. The tablet should be applied every 12 h to the gum above the incisor tooth.\textsuperscript{117} Absorption is rapid, reaching peak serum levels in 30 min, which is comparable to topical gel solutions.\textsuperscript{117,119} Commonly reported side effects generally occur in < 10% of patients and include a gum edema, gingivitis, gum blistering and bitter taste. Oral and buccal formulations are rarely used in the current management of TD due to better efficacy and lower side effects of newer formulations.

Intramuscular injections via an oil depot first became available in the 1950's and are considered the most cost-effective form of TST. They are available in short and long-acting preparations. The shortest acting agent is testosterone propionate, which requires frequent doses and has led to infrequent usage due to the inconvenience.\textsuperscript{120} Slightly longer but still relatively short-acting agents testosterone enanthate and testosterone cypionate require injections every 1–2 weeks due to half-lives of 5–7 days, respectively. All of the short-acting agents are plagued by a "roller coaster" effect by achieving supraphysiologic levels within 2–4 days after injection followed by sub-therapeutic levels by 10–14 days.\textsuperscript{31,78,97,120} A rapid decline in serum levels around 10–14 days has been called "testosterone crash" and is associated with sudden recurrence of TD symptoms.\textsuperscript{121} To minimize these effects, more frequent dosing from once to twice weekly has been suggested as is preferred by these authors. An additional drawback of injectable testosterone is an increased susceptibility of patients to develop erythrocytosis.\textsuperscript{122} Longer-acting injectable testosterone undecanoate (Aveded™) recently became USFDA-approved in 2014, with serum levels remaining in mid-normal range for up to 12 weeks after a single injection.

Subcutaneous testosterone pellets represent the longest-acting testosterone preparation, which have been available for decades but were approved as Testopel™ by USFDA in 2008.\textsuperscript{123} The pellets are comprised of testosterone crystals and are inserted in a lateral hip or abdominal location, over time resulting in systemic absorption.\textsuperscript{124} Eight to fourteen, 75 mg pellets are implanted into adipose tissue (600–1050 mg dose), dissolving in 3–4 months, with demonstrated physiologic levels for up to 4 months.\textsuperscript{123,125,126} Traditionally, 5% of patients experience local side-effects including bleeding, infection, bruising, pain and pellet expulsion. More recent reports have described pellet extrusion rate to be < 1%.\textsuperscript{123}

Transdermal testosterone preparations are currently the most commonly utilized forms of TST. Transdermal options include adhesive skin patches, topical gels, or topical solutions, all requiring daily or every other daily use to maintain serum levels within normal range.\textsuperscript{97} Transdermal preparations have a quick onset and a duration < 24–48 h allowing quick discontinuation should an adverse effect be experienced.\textsuperscript{127}

Adhesive patches were initially developed for transcronal application in the 1990’s (Testoderm) but were later discontinued due to significant skin irritation. More recently, nonscratal patches (Androdern) have been developed in 2 or 4 mg formulations, providing consistent testosterone delivery with kinetics mimicking normal circadian rhythms when applied nightly. Some earlier data have suggested better efficacy compared to intramuscular preparations, but patches are still plagued by local skin reactions including induration, vesicle formation, and contact dermatitis occurring in up to 37% of patients, leading to poor compliance.\textsuperscript{127,128} Use of a 0.1% triamcinolone corticosteroid cream at the patch site before patch application has been shown to diminish local skin reactions with minimal impact on testosterone delivery.\textsuperscript{129} Among transdermal preparations, patches have fallen out of favor due to the high rate of dermatitis.

Transdermal gels (AndroGel 1%, AndroGel 1.62%, Testim™, Fortesta™, and Vogelxo™) and solutions (Axiron®) were first introduced in the United States in 2000 as an improvement over transdermal patches (Table 3). Dosing can be titrated individually based upon skin absorption rates related to metabolism across the stratum corneum.\textsuperscript{120} The gels contain ethanol and are mixed with a skin permeation enhancer for application at same skin site daily on the shoulders, upper arms, abdomen or inner thigh during morning hours, with serum steady state levels achieved in 48–72 h.\textsuperscript{130} Application to multiple sites does not appear to effect overall systemic pharmacokinetics of transdermal gels.\textsuperscript{131} Axiron® is a topical alcohol-based testosterone (2%) solution applied in a similar way to axillary skin. In all cases, drying usually occurs within 10–15 min and hand washing is necessary to minimize contact spread to other individuals. This has led to recommendations for mandatory residence time at applications site of up to 2 h to minimize the transference.\textsuperscript{132} The risk of skin-to-skin contact has led to a USFDA black box warning on transdermal gel transference. Similar to patches, gels and solutions provide normal to elevated serum DHT levels due to dernal concentrations of 5-alpha reductase enzyme, which have been associated with hair loss. In general, transdermal gels are very well tolerated by patients with the

| Table 3: Topical testosterone gels and solutions |
|-----------------------------------------------|
| **Starting dose (mg)** | **Approved daily dose (mg)** | **Pump actuation dose (mg)** | **Application site** | **Shower, bathing or swimming** | **Adverse effects (%)** | **Unique characteristics** |
|-------------------------------|-----------------|-----------------|----------------|----------------------|-----------------|------------------|
| AndroGel 1%® | 50 | 50–100 | 12.5 | Upper arm, shoulder, abdomen | Wait 5 h | Acne (5), gynecomastia (<3), headache (<3), hypertension (<3), prostate disorder (5) | Packet or pump available |
| AndroGel 1.62%® | 40.5 | 40.5–81 | 20.25 | Upper arm, shoulder | Wait 2 h | PSA rise (11), emotional lability (2.5), hypertension (2), dermatitis (2) | Packet or pump available |
| Fortesta® | 40 | 10–70 | 10 | Front and inner thighs | Wait 2 h | Skin reaction (16), PSA rise (1), abnormal dreams (1) | Thigh application site minimizes transference |
| Axiron® (solution) | 60 | 30–120 | 30 | Both axilla | Wait 2 h | Skin irritation (8), headache (6), diarrhea (4), vomiting (4), PSA rise (4) | Underarm application |
| Testim® | 50 | 50–100 | NA (1 tube/packet=50 mg) | Shoulder, upper arm | Wait 2 h | Skin reaction (4), hypertension (1), headache (1), bitter taste (1) | Unique scent |
| Vogelxo™ | 50 | 50–100 | 12.5 | Shoulder, upper arm | Wait 2 h | Elevated hemoglobin (2.8), applications site reaction (4) | Packet, pump or tube availability |

NA: not available; PSA: prostate specific antigen
most commonly reported adverse reactions including acne, headache, emotional lability, nervousness, abnormal dreams, gynecomastia, and mastodynia, all occurring in < 8% of patients. Patients in whom the initial clinical response is unsatisfactory may try switching to an alternate gel or solution to improve serum testosterone levels.\textsuperscript{133}

Recently approved by the USFDA on 5/28/2014, intranasal testosterone (Natesto\textsuperscript{1}) represents another alternative route for TST. Recommended dosing is 11 mg 3 times daily, reaching maximum serum levels within 40 min with half-life ranging from 10–100 min.\textsuperscript{144,145} Phase three clinical trials demonstrated 90% effectiveness within 90 days of use with most commonly reported adverse reactions including PSA increase, headache, and local intranasal symptoms. Intranasal route minimizes close contact transference, but minimal data exist to date regarding overall tolerance and effectiveness outside of a clinical trial context.

The aromatase inhibitor anastrozole has demonstrated benefit in men with TD and infertility, and those with LOH, by improving serum androgen levels and testosterone/estradiol ratio.\textsuperscript{156–158} Due to its similarity to LH, human choric gonadotropin (hCG) has been shown to improve the majority of TD symptoms in men with hypogonadotrophic hypogonadism.\textsuperscript{119} In addition, concomitant administration of low dose hCG with TST has been shown to maintain spermatogenesis in hypogonadal men desiring fertility preservation while receiving TST.\textsuperscript{146} Clomiphene citrate, a selective estrogen receptor modulator, is not USFDA approved for TD but has demonstrated improvement in signs and symptoms, with a favorable safety profile and a protective effect on spermatogenesis, suggesting an important role in younger hypogonadal men wishing to preserve fertility.\textsuperscript{131–134} Both clomiphene citrate and its isomer enclomiphene citrate, which is currently being tested in clinical trials, raise gonadotropins to improve hypogonadotrophic hypogonadism. Through a positive LH effect endogenous testosterone production is increased, and a positive FSH effect may protect and potentially improve spermatogenesis.\textsuperscript{144,145} Enclomiphene citrate in phase 3 trials currently and is poised to be a very impactful treatment alternative to exogenous testosterone.

**Monitoring**

Several guideline statements agree\textsuperscript{23,24,30,79} all men diagnosed with TD wishing to undergo TST should be screened for contraindications as described above. All should have a baseline hematocrit, and those at potential risk for prostate cancer development should have a DRE and PSA screening regularly performed according to guideline recommendations.\textsuperscript{146} Those with LUTS associated with BPH should have symptoms evaluated and addressed at baseline, and those suspected of decreased bone mineral density should have a baseline DEXA scan.

Monitoring after initiation of treatment should occur more frequently initially, every 3–6 months for the first year and every 6–12 months thereafter. At each visit, clinicians should specifically monitor for symptomatic improvement, treatment modality-specific adverse effects, serum total and free testosterone levels, serum hematocrit, and in those men identified at increased risk, DRE, PSA testing, and evaluation of LUTS should be performed. Most TD symptoms should be expected to improve by 3–6 months, but a few may require longer.\textsuperscript{147} PSA has been shown to have an initial rise after starting TST,\textsuperscript{148} on average rising 0.3 ng dl\textsuperscript{−1} in young men and 0.44 ng dl\textsuperscript{−1} in older men after 6 months of therapy, with a rise > 1.4 ng dl\textsuperscript{−1} being unusual.\textsuperscript{149} Subsequent rises in PSA may warrant discontinuation of therapy and prostate biopsy. Elevation in hematocrit is one of the most common adverse effects of TD and tends to occur more commonly in older men and with injectable preparations.\textsuperscript{146,150} It can take up to 12 months for hematocrit levels to peak, but should they rise to > 54%, treatment should be attenuated and phlebotomy considered.\textsuperscript{147} Bone mineral density should be monitored every 1–2 years with repeat DEXA scan.

**COMPETING INTERESTS**

The authors declare that they have no competing interests.

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