PRIMARY CARE REPORTS

The Practical CME Journal for Primary Care and Family Physicians

January 2017 VOL. 23, NO. 1

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STATEMENT OF FINANCIAL DISCLOSURE

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Wise (editor) reports he is involved with sales for CNS Vital Signs. Dr. Butanis (author), Dr. Beckett (author), Dr. Kabadi (author), Dr. Murdoch (peer reviewer), Ms. Coplin (executive editor), and Ms. Mark (executive editor) report no financial relationships relevant to this field of study.

AHC Media

Male Hypogonadism

Introduction

Testosterone replacement therapy (TRT) is a growing industry, with both risks and benefits, that deserves discussion between patients and their healthcare providers. The concept of testosterone supplementation dates back to 1889, when French-born physician Charles-Edouard Brown-Sequard self-experimented with testicular extract of guinea pigs and dogs and found himself rejuvenated.[1] The scientific interest in the possibility of testosterone supplementation led to the Nobel Prize-winning synthesis of the hormone in the mid-1930s and the reality of medical TRT. Recently, many insights into new formulations, advertising, and potential risks have heightened the controversy surrounding low testosterone syndrome, appropriate diagnosis, and risks and benefits of testosterone supplementation. A plethora of non-regulated supplements termed "testosterone boosters" are being marketed directly to the public without adequate assessment. Therefore, it is important for healthcare providers to be familiar with how to conduct and interpret diagnostic tests as well as with appropriate use of TRT as established by various medical organizations, including the Endocrine Society. This review will discuss the definitions, pathophysiology, causes, clinical manifestations, appropriate diagnostic testing procedures, and the role of testosterone supplementation with currently available formulations, with special attention to efficacy and adverse effects in hypogonadism in men.

Definition

Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiologic levels of testosterone (androgen deficiency and/or a normal count of spermatozoa due to disruption at one or more steps of the hypothalamic-pituitary-testicular [HPT] axis).[2]

Pathophysiology

Normal physiology involves production and secretion of gonadotropin-releasing hormone (GNRH) by the hypothalamus. GNRH stimulates the anterior pituitary to release gonadotropins: follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH promote Sertoli cells and Leydig cells in the testis to produce sperm and testosterone, respectively.[3] Negative feedback loops exist between Leydig cells and LH-producing gonadotrophs via testosterone as well as by inhibin produced by spermatozoa and FSH-secreting gonadotrophs. Multiple other factors may play a role, although minor in nature, in secretion of GNRH and gonadotropin and spermatogenesis. In vitro, testosterone is converted into dihydrotestosterone (DHT) by 5-alpha reductase, which is responsible for development of facial and body hair, acne, scalp hair loss, and

EXECUTIVE SUMMARY

Testosterone replacement therapy has been the focus of intensive scrutiny based on new formulations, extensive advertising, and the controversial risk/benefit analyses.

- Testosterone levels have an average decline of 1-2% per year starting in the fourth decade of life, leading to levels in elderly men low enough to be considered "hypogonadal" as compared to younger counterparts.
- The clinical manifestations vary but typically produce reduced sexual desire or libido, hot flashes, low energy, fatigue, infertility, erectile dysfunction, and low bone mineral density.
- Nonspecific signs and symptoms include depressed mood, sleep disturbance, mild anemia, sleepiness after a meal, reduced muscle mass, and increased body fat.
- Diagnosis is established by documentation of low serum total and free testosterone levels and is determined using at least two blood samples obtained on different mornings.
- Routine screening is not recommended, even in the elderly, in the absence of specific clinical manifestations.
- Replacement therapy formulations improve symptoms and lab abnormalities, but the clinician needs to monitor patients carefully for side effects, especially prostate and cardiovascular risks.

prostate growth. Testosterone also is transformed by aromatase into estradiol, which is responsible for bone formation and breast tissue growth. Testosterone itself is responsible for muscle mass, skeletal growth, spermatogenesis, and sexual function.[4]

Testosterone levels vary during the day, with a peak in the morning hours (7-11 a.m.) followed by a gradual decline of 20-25%, reaching the nadir by 4 p.m. The peak diminishes with age, resulting in approximately 10% difference between the peak and the nadir. Moreover, testosterone levels are apparently the highest in late summer and the lowest in late winter. Testosterone levels also may be affected by a meal, with one study showing a 25% decrease in testosterone levels on ingestion of liquid glucose. About 98% of circulating testosterone is protein bound, with about one-half being bound to albumin and the remaining half being bound to sex hormone-binding globulin (SHBG). Thus, only about 0.5-3% of testosterone circulates in the unbound or "free" form. It is important to note that the testosterone bound to albumin is readily dissociable and, thus, bioavailable. The term "bioavailable testosterone" refers to unbound testosterone plus albumin-bound testosterone. The testosterone bound to SHBG is not dissociable and therefore is not readily available for use by the tissues.[5]

As men age, serum total testosterone levels decline and induce a rise in SHBG concentration, resulting in a greater decrease in free testosterone.[6-9] The average decline in serum total testosterone level is 1-2% per year starting in the fourth decade of life, leading to levels in elderly men low enough to be considered "hypogonadal" as compared to their younger counterparts.[7,8] Moreover, SHBG binds testosterone with a high affinity, leading to further reduction in biologically active testosterone as men age.[6] Finally, the decreases in both serum total and free testosterone levels are greater if accompanied by obesity, an illness, or serious emotional stress.[10]

Etiology

Primary hypogonadism (also called hypergonadotropic hypogonadism) occurs when the testes fail to produce normal concentrations of testosterone and/or promote adequate sperm count, and induce elevated levels of gonadotropins by inhibition of the negative feedback.[2-5] Causes of primary hypogonadism include congenital anomalies such as Klinefelter syndrome (XXY), Noonan syndrome or male Turner's syndrome, cryptorchidism, myotonic dystrophy, varicocele, and others. (*See Table 1.*) Acquired causes include infections, radiation, infiltrative disorders, toxins, certain medications, trauma, and hyperthyroidism.[3,5,12,13] Almost all etiologies cause degeneration of testicular tissue. Hyperthyroidism alone induces primary hypogonadism by lowering free testosterone concentration via enhancing SHBG production with a consequential rise in the bound fraction. Secondary hypogonadism (also termed central or hypogonadotropic hypogonadism) ensues with disorders of the hypothalamus with impaired GNRH secretion or pituitary gland with inhibited gonadotropin release. This results in low or inappropriately normal gonadotropin levels with concurrent subnormal testosterone concentrations and/or decreased sperm count. Secondary hypogonadism can be caused by rare congenital abnormalities, but a majority are acquired causes. They include suppression of gonadotropins by hyperprolactinemia, steroids, illness, diabetes, morbid obesity, inhibition of HPT axis by drugs, toxins, chronic disorders, eating disorders, and damage to gonadotroph cells by tumors, infections, and trauma.[3,12-14] (*See Table 1.*)

Patients also may present with combined primary and secondary hypogonadism, which presents as low testosterone and sperm levels, and variable gonadotropin levels depending on whether primary or secondary hypogonadism predominates. Indeed, the inevitable age-related decline in testosterone levels results from defects in both testicular and hypothalamic-pituitary function.[4,6-9] Autoimmunity recently has been documented as an etiology of central hypogonadism in the elderly by detection of circulating pituitary gonadotroph antibodies.[14]

Clinical Presentation

Symptoms of androgen deficiency have been well documented and vary depending on the age and the type of hypogonadism. Testosterone deficiency in the juvenile period prior to puberty

Table 1. Causes of Male Hypogonadism

Primary Male Hypogonadism		Secondary Male Hypogonadism	
Congenital	**Acquired**	**Congenital**	**Acquired**
• Klinefelter's syndrome • Myotonic dystrophy • Varicocele • Cryptorchidism	• Infections, e.g., mumps, syphilis, tuberculosis, gonorrhea • Autoimmune orchitis, e.g., type 1 diabetes mellitus • Testicular trauma/infarct • Drugs, e.g., chemotherapeutic alkylating agents • Toxins, e.g., alcohol, marijuana, radiation, pesticides • Amyloidosis • Sarcoidosis • Hemochromatosis • Hyperthyroidism • Hepatic cirrhosis	• Kallman syndrome • Prader-Willi syndrome • Thalassemia	• Obesity • Eating disorders, e.g., anorexia nervosa, prolonged starvation • Type 2 diabetes mellitus • Obstructive sleep apnea • Hyperprolactinemia • Medications, e.g., opioids, steroids • Toxins, e.g alcohol • Acute illness • Chronic diseases, e.g., renal failure, congestive heart failure • Hypothyroidism • Hemochromatosis • HIV • Estrogen excess • Amyloidosis • Sarcoidosis • Tumors • Sickle cell disease

results in more specific clinical manifestations of incomplete or delayed sexual development. This includes atrophic testes, underdeveloped phallus, and eunuchoid proportions, expressed by a longer arm span than height and a shorter upper segment from crown to pubis as compared to the lower segment from pubis to soles due to a delay in fusion of the epiphytes of the long bones. Delay in development of other secondary sex characteristics, such as male pattern hair growth and deeper voice, also occur. Onset of post-pubertal testosterone deficiency results in less specific signs and symptoms, including reduced sexual desire or libido, hot flashes, low energy, fatigue, infertility, erectile dysfunction, and low bone mineral density.

Other nonspecific symptoms may include depressed mood, sleep disturbance, mild anemia, sleepiness after a meal, reduced muscle mass, and increased body fat as reported in the Androgen Deficiency in the Aging Male questionnaire.[9,15] Often, primary hypogonadism is manifested by infertility due to a decrease in sperm production much before the decline in serum testosterone level because the damage of Sertoli cells responsible for generation of seminiferous tubules is more prominent and earlier than that of Leydig cells. In contrast, secondary or central hypogonadism is often is characterized by a parallel decline in serum testosterone level and sperm count. Alternatively, gynecomastia occurs more frequently in subjects with primary hypogonadism secondary to increased conversion of testosterone to estradiol by aromatase stimulation induced by elevated FSH and LH levels.[4]

A detailed history and thorough physical examination are crucial in evaluation of patients, especially the elderly, presenting with nonspecific manifestations of fatigue, mood changes, low muscle mass, and decreased libido. Several important disorders other than hypogonadism may be responsible for these clinical features and therefore require appropriate assessment and management. (*See Table 2.*)

Diagnosis

The presence of hypogonadism is suspected in men because of the presence of the aforementioned signs and symptoms. The diagnosis is established by documentation of low serum total and/or free testosterone levels determined using at least two blood samples obtained on two different mornings. The primary reason for determination of serum testosterone levels in the morning is because most laboratories report normal ranges of values using blood samples drawn in the morning. Moreover, serum concentrations vary significantly through the day as a result of circadian and circannual rhythms, episodic secretion, and measurement variation of 10% from one day to another.[2,4,16] Diagnosis is challenging because of nonspecific symptoms that can be modified by age, severity, and duration of androgen deficiency, as well as previous testosterone therapy. A

"low testosterone" threshold level below which TRT has been shown to be beneficial is unknown.

Manifestations of hypogonadism occur at different testosterone levels in different individuals. The discrepancy may be attributed to lack of knowledge about the testosterone level in the individual person at the peak of health or prior to onset of symptoms. The average testosterone threshold at which some of the manifestations become evident corresponds to a lower limit of the normal range for young men, about 300 ng/dL by most laboratories. However, the normal range and the lowest normal testosterone concentration may vary with each individual laboratory and, therefore, the values provided by the individual laboratory must be followed. As stated above, illness, nutritional deficiency, and medications suppressing the HPT axis, such as glucocorticoids and opioids, can lower testosterone levels. Exercise can increase testosterone levels. Because of the circadian rhythm of serum testosterone levels and the fact that normal ranges usually are established using morning blood samples, testosterone measurement for the diagnosis of androgen deficiency should be performed in the morning. Older men may not need determination of morning levels because of the blunting of normal circadian rhythm of testosterone concentrations with aging. However, serum testosterone levels are often subnormal in the afternoon, whereas morning concentrations are frequently normal. Therefore, most endocrine and geriatric organizations recommend determination of morning serum testosterone levels on multiple days to avoid misdiagnosis and maintain consistency, since almost 30% of men with a mildly subnormal testosterone level manifest a normal testosterone concentration on the other. Moreover, 15% of healthy, asymptomatic young men manifest a subnormal testosterone level in a 24-hour period. Therefore, a diagnosis of hypogonadism by a single subnormal serum testosterone level is inappropriate. Confirmation of the diagnosis by a documentation of at least two subnormal testosterone concentrations is crucial since the TRT is often lifelong or over a prolonged duration.[2,4,16,17]

Table 2. Differential Diagnosis of Age-related Male Hypogonadism

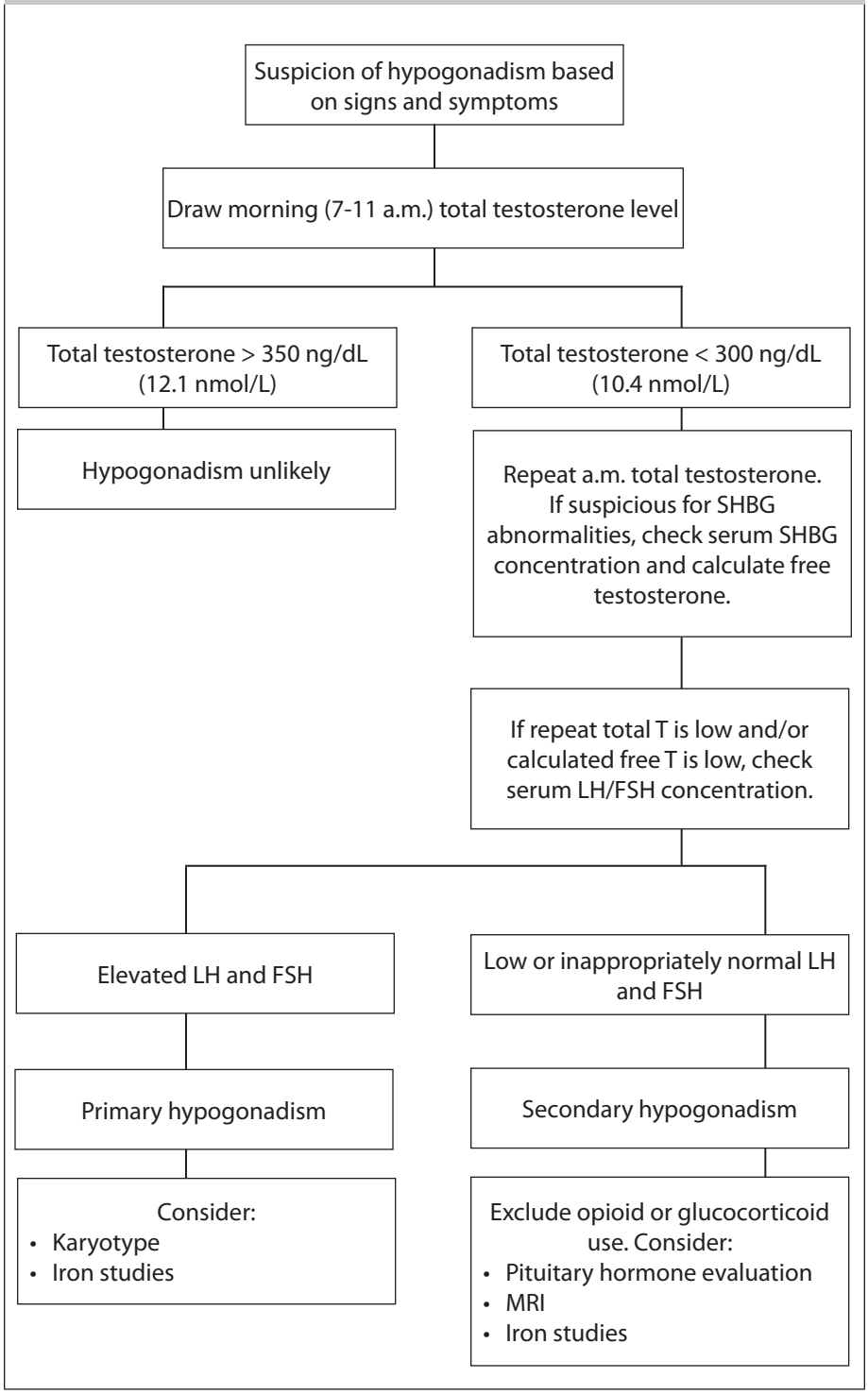
• Depression	• Malignancy
• Obesity/metabolic syndrome	• Substance abuse
• Obstructive sleep apnea	• Steroid use
• Coronary artery disease	• Opioid use
• Congestive heart failure	• Anticonvulsant use
• Peripheral vascular disease	• HIV
• Cirrhosis	• Thyroid disease
• Chronic obstructive pulmonary disease	• Acromegaly
• Anemia	• Hyperprolactinemia

Initial evaluation in diagnosis of male hypogonadism should include determination of total and/or free testosterone level. Total testosterone levels also are influenced by SHBG concentration, and circulating testosterone itself modulates SHBG production. Finally, SHBG-bound testosterone is not bioavailable. Therefore, total testosterone concentration is frequently a poor indicator of the active circulating androgen available to be effective for adequate function of target organs.[17] Disorders associated with increased SHBG concentrations include aging, probably due to age-related decline in circulating active testosterone levels; hepatic cirrhosis and hepatitis; hyperthyroidism; use of estrogens; and HIV or AIDS. Therefore, in the presence of increased circulating SHBG, serum total testosterone may be normal. However, free or bioavailable active testosterone concentration is subnormal, leading to a hypogonadal state. Alternatively, obesity, hypothyroidism, diabetes mellitus, and chronic administration of glucocorticoids, progestins, and testosterone are associated with a decrease in SHBG concentration. Thus, serum total testosterone concentration is often subnormal in these conditions despite bioavailable fractions being normal.[10] Therefore, determination of serum-free testosterone concentration is likely to be a more reliable laboratory test in diagnosis of hypogonadism when compared with total testosterone level as influence of SHBG is eliminated. It is important that free testosterone levels be performed by a laboratory using equilibrium dialysis methodology. Free testosterone measurements by alternative analog methodologies are frequently available in local laboratories, but these measurements are affected by alterations in SHBG and may be unreliable and inaccurate. The normal total and free testosterone ranges in healthy men vary among laboratories and assays. Therefore, clinicians should use the normal range for healthy young men as established in their laboratory.[2,4,5]

Further evaluation of androgen-deficient men is important to distinguish between primary (or hypergonadotropic) and secondary (or hypogonadotropic) hypogonadism. The diagnosis of primary hypogonadism is established in most men by documentation of subnormal testosterone levels with concomitant supernormal concentrations of LH, FSH, or both. Low normal testosterone concentration with simultaneous elevated levels of LH and/or FSH is also consistent with the diagnosis of primary hypogonadism deemed by some as subclinical. The diagnosis of central or secondary hypogonadism is established by subnormal testosterone levels with a low or inappropriately normal LH and/or FSH concentrations. In men with the diagnosis of central hypogonadism, additional diagnostic evaluation must be conducted to exclude many causative disorders. (*See Figure 1.*)

Routine screening for the presence of hypogonadism in men is not recommended, even in the elderly in absence of specific clinical manifestations. Conflicting data regarding definitive benefits of testosterone replacement therapy in aging men have resulted

Figure 1. Diagnosis Algorithm for Male Hypogonadism



in a lack of consensus among providers. However, in populations of men manifesting several chronic disorders with well-established greater relative risk in occurrence of hypogonadism (*see Table 2*), serum testosterone determination definitely is warranted, even without onset of specific symptoms or in presence of subtle nonspecific symptoms.[2,4]

Management of Male Hypogonadism

General Principles of Treatment

Testosterone replacement therapy should be reserved for men in whom the diagnosis of hypogonadism is well established. The presence of primary hypogonadism is easier to establish by documentation with concurrent elevation of LH and/or FSH. Occasionally, even with low normal testosterone concentrations, subclinical primary hypogonadism similar to the well-defined disorder subclinical hypothyroidism is established. In contrast, the diagnosis of central or secondary hypogonadism may require more elaborate laboratory testing, especially in the presence of normal LH and FSH concentrations. Occasionally, the lack of inhibited gonadotropin response to GNRH administration (GNRH stimulation test) may be required to establish the diagnosis. The FDA has warned about administration of testosterone to relieve symptoms in elderly men without a definite confirmation of the diagnosis by appropriate laboratory testing.[18] However, a plethora of "low testosterone" clinics are being operated widely in this country and abroad under the banner of the "anti-aging" objective, despite the lack of proven evidence regarding benefits and safety in this frail population. Various endocrine organizations offer variable guidelines regarding serum testosterone concentrations to be defined as subnormal and, therefore, widely differ in their recommendations in terms of initiation of TRT.[2,4,10,19-24] Primary care physicians should evaluate each patient individually when making the decision to administer testosterone based on symptomatology, physical examination, and the subnormal levels as determined by the laboratory.

Treatment Goals

The goal of treatment is to normalize testosterone levels within the established range as determined by specific laboratories as well as to attain and maintain improvement in symptoms, with the recognition that every symptom may not be improved since frequently many of the symptoms are nonspecific. Debate about targeting the appropriate normal level continues because the normal range is wide and the actual healthy level for an individual is unknown. Fortunately, the guidelines provided by most organizations are consistent in recommending

the mid-normal range as therapeutic for improving symptoms. Nonspecific symptoms, such as fatigue, decreased energy, decline in libido, muscle weakness, and lack of well-being, usually begin to show remission by three months following initiation of treatment.[2,4,19-24] Data regarding objective improvement in clinical manifestations, such as hand grip, strength of other muscle groups, total body fat and muscle mass, and adipose tissue distribution, are available in the literature.[22-24] However, utility of these expensive tests in real-world clinical practice is questioned.

Benefits to Testosterone Replacement

Several clinical benefits of using TRT are documented, although debate continues regarding some of these data because of a lack of firm evidence as a result of the unavailability of long-term prospective, randomized, clinical trials using comparison with placebo in a large population of subjects.

The available data in the literature show that TRT improves libido, sexual thoughts, and erectile function. Secondary sex characteristics, such as increased muscle mass, beard growth, growth of pubic and axillary hair, and phallus growth, improve with testosterone therapy.[5] TRT improves bone mineral density in male hypogonadism patients.[24] Testosterone replacement also is associated with increased fat-free mass, decreased fat mass, and improved muscle strength. Effects of testosterone on quality of life, mood, cognition, and blood sugar remain unclear.[8] The recent Testosterone Trial found that TRT had a moderate benefit in regard to sexual activity, sexual desire, and erectile function in older men; however, the trial did not show significant benefit in walking distance or vitality.[22]

The effect of long-term TRT on cardiovascular outcomes is conflicting. Therefore, two opposing views exist. One group of experts in the field recommends extreme caution prior to initiation of TRT because several studies, including a 2013 meta-analysis, have documented an increase in adverse cardiovascular outcomes, including myocardial infarction (MI) and ischemic stroke events in men receiving testosterone replacement.[24-27] Many of these studies are retrospective in nature and do not report outcomes in individual groups according to the route of administration; in addition, some studies have documented an increased risk of adverse outcomes with intramuscular administration of testosterone and a decreased risk with use of transdermal formulations. The increase in adverse outcomes in terms of rising hematocrit, prostate-specific antigen (PSA), and blood sugars, as well as onset of adverse lipid pattern, fluid retention, and acne, is attributed to supernormal circulating testosterone concentrations during the initial 2-3 days on intramuscular administration of depot testosterone formulations and to subnormal levels noted prior to the next injection at two weeks.

In comparison, application of a daily transdermal preparation has been documented to attain and maintain consistent physiologic concentrations throughout the period of application without a significant diurnal variation. These consistent physiologic circulating testosterone levels are apparently responsible for reducing the risk of the same adverse outcomes in subjects receiving testosterone via transdermal route. Moreover, in most of these studies, post-treatment serum testosterone concentrations were not reported irrespective of the route of administration, thus raising questions about compliance on the part of subjects and also the conclusion. Finally, in one study, subjects receiving even a lone testosterone prescription without confirming actual administration were included in the final analyses, raising doubts about the reliability of the accuracy of the results.[28-33]

Unfortunately, despite lack of resolution of these issues with appropriate prospective, randomized, clinical trials, the FDA published a safety communication in 2015 acknowledging a possible increased cardiovascular risk associated with TRT and required label changes reflecting the possibility of increased risk. Manufacturers also are required to conduct prospective, randomized, clinical trials with testosterone replacement therapy to address the cardiovascular risks, especially in elderly men with subnormal testosterone concentrations.[17] However, several recent studies have challenged this notion by reporting either no increase in all-cause or cardiovascular mortality and MI or a modest decrease in overall mortality in men following testosterone replacement, especially with transdermal formulations.[34-40] Therefore, it is apparent that there is no consensus regarding cardiovascular benefits or safety of testosterone replacement therapy in men with low testosterone, especially the elderly.

The American Association of Clinical Endocrinologists recommends evaluating each patient by obtaining a detailed history regarding previous occurrence of cardiovascular events, a thorough physical examination, and appropriate laboratory testing (including extensive cardiac assessment, if indicated) prior to prescribing TRT. Initiation of TRT equivocally is not recommended for men with decompensated congestive heart failure and chronic pulmonary disorders requiring recurrent hospitalization. TRT must be deferred for at least six months after occurrence of a major vascular event including MI or stroke.[4] Finally, a thorough dialogue and a frank and open discussion between the patient and the physician about the risks and benefits of TRT is crucial prior to its initiation. The decision regarding TRT must be individualized and initiated only on confirmation of the diagnosis of hypogonadism and after exclusion of contraindications.

Contraindications to Testosterone Replacement Therapy

It has been well established by several expert panels that testosterone replacement is absolutely contraindicated in patients with active prostate cancer, a history of or currently active breast cancer, patients desiring fertility, uncontrolled heart failure, and patients with hematocrits > 55%. Relative contraindications include men with untreated

obstruction sleep apnea (OSA), severe lower urinary tract symptoms, symptoms defined as an International Prostate Symptom Score > 19, hematocrit > 50%, men with a PSA > 4.0, and men with a history of prostate cancer in a first-degree relative. All African-American men should be evaluated by urology prior to any TRT.[4,41]

Testosterone Replacement Methods

Testosterone replacement is available in multiple preparations with various routes of administration. (*See Table 3.*) Each preparation has advantages and disadvantages, and it is important to consider each individual patient's preference when choosing testosterone supplementation.

Intramuscular

Intramuscular injection has been a popular form of testosterone replacement because of its cost-effectiveness and the eliminated risk of possible person-to-person transmission. It has the most variable pharmacokinetics, causing peaks and troughs in testosterone levels, leading to fluctuations in mood, energy, and sexual desire. Gynecomastia is also seen during the supratherapeutic phase, which occurs within 24-48 hours of injection. The short-acting formulations include testosterone cypionate and testosterone enanthate, which are administered once every 1-2 weeks up to once every four weeks at a higher dose. Although administration once every 2-4 weeks is more convenient, it is known to cause greater fluctuations in testosterone levels and, therefore, symptoms.[42] Because of fluctuating testosterone levels, monitoring should be performed at the midpoint of injections, usually 1-2 weeks after the dose.

In 2014, a longer formulation of intramuscular replacement, testosterone undecanoate, was approved in the United States. A loading dose is given four weeks after the first dose, and then it is administered every 10 weeks. This preparation does not reach supratherapeutic levels, which decreases the fluctuation in patient symptoms. In addition, compliance is improved with the less-frequent dosing regimen. Testosterone undecanoate is a restricted medication; it requires administration in the clinic, and patients must to be monitored for 30 minutes after administration because of the low risk of pulmonary oil microembolism.[43] Up to 33% of men reported injection site tenderness with intramuscular injections.[44]

Transdermal

Transdermal gel administration has become a popular form of testosterone replacement because of its convenience. The most popular preparation is a daily application of a clear, colorless gel that contains 1% testosterone (AndroGel®). Dosing starts at 5 g of 1% testosterone daily and is titrated up to 7.5 g or 10 g as needed to achieve free testosterone levels within the normal range. There is also a pump version that contains 1.62% testosterone. The gel is applied in the morning to the shoulders, upper arms, or abdomen, and patients should be instructed to wash their hands immediately after application. There is risk of transmission to close contacts, so the application site should be covered after the gel has dried for 3-5 minutes. Other formulations include Axiron for axillary application, Fortesta for thigh application, and Testim, which is a sustained-release 1% gel. The most commonly reported adverse effect with use of the transdermal gel is localized skin reactions. Rare cases of headache, hot flashes, and insomnia also have been reported. Testosterone levels usually are monitored 2-4 weeks after initiation.

Testosterone patches also are available. The patches are applied nightly and are available in 2 mg or 4 mg doses. Patches typically are applied to the abdomen, back, thigh, or upper arm. Localized dermatitis has been reported in up to 30% of men using the patch, but this can be relieved with application of an over-the-counter hydrocortisone cream after patch removal.[4,45] Another common complaint is issues with adhesion of the patch due to sweating or showering.

Both the transdermal gels and patches provide more physiologic administration of testosterone when compared to the intramuscular injections. Monitoring for adequate testosterone response should be performed 3-12 hours after the application of a patch and two weeks after initiation.[44,46,47]

Intranasal

Intranasal testosterone gel was approved for use in the United States in 2014 under the trade name Natesto®. It is administered three times daily via a pump dispenser and nasal applicator. Patients should refrain from blowing their nose or sniffing for one hour after administration. In an early clinical trial, Natesto did not show an increase in DHT or PSA levels. Small incidences of nasopharyngitis, rhinorrhea, and epistaxis were reported. Monitoring of testosterone levels starts one month after initiation.[48]

Buccal

The buccal preparation is a 30 mg tablet that is placed on the upper gum line every 12 hours. The tablets are well-tolerated with low incidence of gum irritation, gingivitis, and dysgeusia.[49] Testosterone response is measured 4-12 weeks after initiation prior to a morning dose.[44]

Intradermal Pellets

Intradermal pellets are the longest acting form of testosterone replacement, providing stable testosterone levels for 4-6 months. They are implanted in the lower abdomen, proximal thigh, deltoid, or buttock as an in-office procedure. Reported adverse effects include insertion site pain, tenderness, swelling, infection, and extrusion of the pellets.[44] Pellet therapy offers a very convenient option for testosterone replacement; however, cost is the primary deterrent for many patients.

Adverse Effects of TRT and Management

Erythropoiesis

Testosterone induces erythropoiesis, a known side effect of TRT. Injectable testosterone has been shown to increase hematocrit levels more than transdermal and pellet applications.[42] A 2010 meta-analysis showed that men taking testosterone were at a significantly

Table 3. Testosterone Preparations[43-51]

Route	Forumlations	Dosing	Monitoring of Serum Testosterone Level	Advantages	Disadvantages	Approximate Cost per Month◊
Transdermal gel	Androgel 1% Androgel 1.62% Fortesta 2% Testim 1% Vogelxo 1% Axiron (axillary)	Apply daily	2-4 weeks after initiation of treatment, any time of day	Convenient Quick onset Physiologic pattern Stable serum levels	Site irritation Transference Need to cover application site	Androgel $625 (pump) $645 (packets) Fortesta $500 Testim $600 Vogelxo $540 Axiron $690
Transdermal Patch	Androderm 2 mg and 4 mg patches	2-6 mg (1-3 patches) daily	2 weeks after initiation; 3-12 hours after application	Convenient Easy to use Physiologic pattern	Application site irritation Adherence problems with sweating	$300-900
Intramuscular Injection	Enanthate 200 mg/mL Cypionate 100 or 200 mg/mL Undecanoate (Aveed) 750 mg/3 mL	150-400 mg every 2 -4 weeks or 75-100 mg every week 750 mg every 4 weeks x 2, then every 10 weeks	Midway between injections Before each injection	Inexpensive Easy to discontinue No transference	Supraphysiologic levels Office injection (undecanoate only) Pain at injection site	Enanthate $30 Cypionate $20 Undecanoate (Aveed) $1,065
Subcutaneous pellets	Testopel 75 mg pellet	150-450 mg every 4-6 months	Prior to insertion of new pellets	Long duration Stable serum levels No transference	Procedural insertion Pellet extrusion Fibrosis at insertion site	$200-600 every 4-6 months*
Nasal	Natesto 5.5 mg	2 sprays (11 mg) in each nostril TID	1 month after initiation, before a spray	Quick onset Easy to use Minimal transference	Nasal irritation	$780
Buccal	Striant 30 mg	30 mg BID	4-12 weeks after initiation, before application of tablet	Quick onset Physiologic pattern Easy to use	Mouth irritation Dysgeusia	$720

*Dependent on the number of pellets inserted
◊Costs are estimated and will vary based on insurance coverage and formularies

higher risk of developing erythrocytosis, defined as hematocrit > 52%, with hemoglobin levels rising 0.86 g/dL on average.[35] Hemoconcentration causes increased blood viscosity, which has been hypothesized to contribute to adverse cardiac events; however, studies have shown no increase in stroke or venous thromboembolic events in men taking testosterone replacement.[52,53] The pathophysiology of testosterone therapy-induced erythropoiesis is unclear. Current guidelines recommend checking hemoglobin and hematocrit prior to initiation of TRT and then every 3-6 months, with discontinuation of TRT if hematocrit levels exceed 54%.[4] Moreover, a thorough evaluation should be performed to identify a precipitating cause of erythrocytosis, such as obstructive sleep apnea and hypoxia. If documented, these disorders must be treated appropriately and TRT then may be reinitiated at a lower dose. TRT is to be avoided in patients with presence of thrombophilia.[54]

Effects on the Prostate

Many prostate-related effects of TRT have been studied, including potential increased risk of prostate cancer and an increase in lower urinary tract symptoms. It was thought for some time that testosterone promoted prostate tumor growth. No studies have shown an increase in the diagnosis of prostate cancer in men on TRT, although no trial has been large enough or long enough to detect a difference. TRT has been shown to cause an increase in serum PSA levels by approximately 0.3 ng/dL in some studies; however, a recent systematic review showed no significant increase in PSA.[55-58]

Although the link between TRT and prostate cancer is unclear, it is suggested that clinicians perform a rectal examination and obtain a PSA concentration prior to initiation of TRT as well as at 3, 6, and 12 months after initiation in men older than 40 years of age. Men should be monitored annually for prostate cancer. A urology consult is warranted if the serum PSA level increases > 0.4 ng/mL/year, if there is a rise > 1.4 ng/mL in the first 3-6 months of starting therapy, or if there is a suspicion of prostatic abnormality on rectal examination.[4] Benign prostatic hypertrophy also has been documented to ensue or progress in men administered TRT. Therefore, a calculation of an International Prostate Symptom Score is recommended prior to initiating TRT. Discontinuation of TRT is recommended if clinical manifestations of lower urinary tract involvement, such as polyuria, nocturia, dysuria, hesitancy and precipitancy of urination, or urinary retention, occur with an International Prostate Symptom Score > 19.[59]

Sleep Apnea

Although not well established, worsening of obstructive sleep apnea has been reported in men on TRT, probably secondary to suppression of the central respiratory center. Therefore, it is advised not to administer TRT to men with untreated obstructive sleep apnea unless they are using respiratory assistance such as continuous positive airway pressure or bilevel positive airway pressure.[60]

Overview of Clinical Monitoring

Prior to initiation of TRT, a detailed history, a thorough physical examination, and appropriate laboratory testing must be conducted in all men with hypogonadism. Prostate evaluation by a rectal examination and determination of serum PSA must be performed. Cardiovascular risk factors, such as hypertension, dyslipidemia, and diabetes, must be assessed periodically, especially with onset of symptoms of these disorders. Complete blood count, including hemoglobin and hematocrit levels, and serum chemistries, including glucose, lipids, and liver enzymes, should be obtained. These parameters must be determined again 3-6 months after initiation of TRT and then annually as long as they remain stable. A thorough evaluation is in order at any time on documentation of adverse alteration of any of these monitoring parameters following a prompt discontinuation of TRT. Finally, men with osteoporosis or low trauma fracture should be evaluated with bone mineral density scan after 1-2 years on TRT.[4,24]

Conclusion

Male hypogonadism is a disorder with a rising prevalence due to an increased life expectancy in men. Almost always, the initial presentation is encountered by primary care physicians. Therefore, it is important for primary care physicians to be knowledgeable about the clinical manifestations, diagnostic testing, and appropriate management. Moreover, it is imperative for primary care providers to have a thorough discussion with patients regarding the pros and cons of the diagnostic laboratory tests, and the benefits and pitfalls of TRT, with a special attention to the various formulations as well as the side effects.

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CME Questions

1. Which of the following statements is *true* regarding diagnosis of male hypogonadism?
   a. The low testosterone threshold level is well defined.
   b. Testosterone levels should be drawn in the afternoon.
   c. Guidelines discourage obtaining more than one testosterone level to diagnose hypogonadism.
   d. Older men exhibit blunting of peak testosterone levels.
2. Which of the following is *not* an absolute or relative contraindication to testosterone supplementation?
   a. Diabetes
   b. Prostate cancer
   c. Hematocrit > 55%
   d. Untreated sleep apnea
3. Which disorder is associated with decreased circulating sex hormone binding globulin, leading to a low total testosterone level but normal free testosterone level?
   a. Hepatic cirrhosis
   b. Hyperthyroidism
   c. Obesity
   d. Use of estrogens
4. Which of the following is a monitoring parameter for the testosterone patch?
   a. Hematocrit
   b. Testosterone levels
   c. Signs of skin irritation at application site
   d. All of the above
5. Hemoglobin and hematocrit levels, serum chemistries, lipids, and liver enzymes should be obtained on initiation of testosterone replacement therapy. At what time should they be rechecked?
   a. 1 year
   b. 4-6 weeks
   c. 3-6 months
   d. No need to recheck

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Executive Editor: Leslie Coplin
Continuing Education and Editorial Director: Lee Landenberger

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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