Published in final edited form as:

Expert Opin Pharmacother. 2014 June ; 15(9): 1247–1264. doi:10.1517/14656566.2014.913022.

An update on male hypogonadism therapy

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Abstract

Introduction—Men who have symptoms associated with persistently low serum total testosterone level should be assessed for testosterone replacement therapy.

Areas covered—Acute and chronic illnesses are associated with low serum testosterone and these should be recognized and treated. Once the diagnosis of male hypogonadism is made, the benefits of testosterone treatment usually outweigh the risks. Without contraindications, the patient should be offered testosterone replacement therapy. The options of testosterone delivery systems (injections, transdermal patches/gels, buccal tablets, capsules and implants) have increased in the last decade. Testosterone improves symptoms and signs of hypogonadism such as sexual function and energy, increases bone density and lean mass and decreases visceral adiposity. In men who desire fertility and who have secondary hypogonadism, testosterone can be withdrawn and the patients can be placed on gonadotropins. New modified designer androgens and selective androgen receptor modulators have been in preclinical and clinical trials for some time. None of these have been assessed for the treatment of male hypogonadism.

Expert opinion—Despite the lack of prospective long-term data from randomized, controlled clinical trials of testosterone treatment on prostate health and cardiovascular disease risk, the available evidence suggests that testosterone therapy should be offered to symptomatic hypogonadal men.

Keywords

alternative methods of treatment; gonadotropin treatment; primary and secondary hypogonadism; testosterone replacement

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Declaration of interest

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

1. Introduction

Male hypogonadism is defined as the failure to produce adequate circulating testosterone and/or spermatozoa in the ejaculate, resulting in signs and symptoms of testosterone deficiency and/or infertility [1]. Male hypogonadism should be diagnosed and treated, because when untreated, hypogonadal men may develop a clinical syndrome of decreased sexual function, infertility, fatigue, impaired sense of well-being, anemia, decreased bone density, decreased lean body mass (LBM) and muscle strength, as well as increased fat mass and visceral adiposity, which may be associated with metabolic dysfunction [1,2]. The decreased functional ability of the testis to produce adequate amounts of testosterone and/or mature spermatozoa can be due to defects in the testis, pituitary and/or hypothalamus, or at multiple levels.

Primary hypogonadism results from disorders of the testes that lead to low testosterone production and impaired spermatogenesis. The more common causes of primary hypogonadism or hypergonadotropic hypogonadism include chromosomal defects (e.g., Klinefelter syndrome), testicular injury (e.g., chemotherapy, radiation, surgery, trauma) and infection. The prevalence of Klinefelter syndrome is thought to be between 0.15 and 0.2% in men [3].

The prevalence of hypogonadism due to genetic or idiopathic abnormalities in the pituitary or hypothalamus is uncommon in clinical practice except in tertiary referral centers. Hypogonadotropic hypogonadism may be due to congenital and/or acquired defects. Congenital hypogonadotropic hypogonadism can occur due to defects in gonadotropin releasing hormone (GnRH) neurons, GnRH regulating neurons, luteinizing hormone (LH) and follicle stimulating hormone (FSH) secreting cells. These can include gene mutations that affect the migration of GnRH neurons (e.g., Kallmann syndrome) and mutations in genes that affect signals regulating GnRH neurons. Isolated hypogonadotropic hypogonadism can also occur due to focal defects in LH and FSH secreting cells. Acquired defects can arise from structural defects or reversible causes. Acquired structural defects can include destruction of GnRH neurons (e.g., meningioma, craniopharyngioma, vascular injury), tumors in the pituitary or suprasellar region that interferes with normal transport of hypothalamic releasing or inhibiting factors reaching the pituitary, damage from trauma or radiation, infections (e.g., abscesses, tuberculosis) and infiltrative disease that affect the hypothalamus and pituitary (e.g., sarcoidosis, hemochromatosis). Potentially reversible causes of hypogonadotropic hypogonadism can include drugs (e.g., metoclopramide, opioids, GnRH agonists and antagonists), acute systemic illness, chronic systemic illness, type 2 diabetes mellitus and obesity. Mixed (combined primary and secondary) hypogonadism can result from dual defects in the testes and in the pituitary-hypothalamic axis, with examples include aging, HIV infection and hemochromatosis.

The effect of aging on the development of hypogonadism remains controversial. Hypogonadism diagnosed based on serum total testosterone levels was estimated to be < 5% in men aged between 20 - 30 years, 12% in men 50 - 60 years, and between 19 and 49% in men aged 60 - 80 years in the Baltimore Longitudinal Study of Aging [4]. The prevalence of

symptomatic hypogonadism in adult men is reported to be 2 - 6 % in US and Europe. Male hypogonadism increases with age and with multiple co-morbid conditions in several epidemiologic studies [5-7]. More recent studies report that age has a lesser impact on serum testosterone levels than associated chronic illness from comorbidities or lifestyle factors [8]. Obesity, in particular visceral obesity, metabolic syndrome and type 2 diabetes are major risk factors for low testosterone concentration [2,6,9-11]. These comorbidities may act independently and others interact with age leading to the observed decline in serum testosterone concentrations. Many of these factors can be modified by lifestyle changes or disease-specific interventions to prevent age-related decline in testosterone [11].

Over the past two decades, significant advances have been made in the development of new delivery systems for testosterone substitution. This has led to more options for physicians to use and newer testosterone delivery methods other than injections. Consumer directed media effort by the pharmaceutical industry has increased the awareness of low testosterone level and its associated symptoms in men. These factors contribute to a marked increase in the number of testosterone prescription in the US, Europe and Australia in the past 10 - 15 years [12-14]. However, only 17% of testosterone prescriptions are filled more than once [15] and discontinuation rates of testosterone treatment have been reported to be high [16]. Testosterone replacement should only be given to men with a diagnosis of hypogonadism based on persistently low serum testosterone concentrations measured reliably and symptoms that are related with low testosterone. These men should have had consideration of correctable causes of their hypogonadism and rational basis for anticipated improvement of symptoms/signs after testosterone treatment.

The goal of testosterone replacement therapy is to raise serum testosterone level into the mid-normal range (e.g., 400 - 700 ng/dl) and resolution or reduction in symptoms of hypogonadism [1]. In this review, we discuss the treatment options for male hypogonadism and the associated benefits and potential short- and long-term risks. The choice for treatment may depend on the cause of hypogonadism (e.g., primary versus secondary) and the desire for maintaining or improving fertility. We also review therapeutic approaches for specific common conditions and mixed hypogonadism that clinicians may encounter frequently.

2. Diagnosis of hypogonadism

2.1 Clinical diagnosis of male hypogonadism

The clinical diagnosis of male hypogonadism is based on signs and symptoms and consistently low morning serum testosterone levels that are below the accepted testosterone reference range in adult men. The more specific symptoms and signs of hypogonadism include incomplete or delayed sexual development, regression of secondary sexual characteristics, reduced libido, decreased spontaneous erections, declining testicular volume, loss of body (facial, axillary and pubic) hair, gynecomastia, decreased muscle mass, hot flushes/sweats, low bone mineral density and low trauma fracture [1]. In addition there are many nonspecific symptoms such as low energy, depressive mood, inability to concentrate and less energy. Hypogonadism is associated with multiple co-morbid conditions such as aging, obesity, metabolic syndrome, type 2 diabetes and cardiovascular and other chronic medical disease [6]. The clinical presentation varies depending on the age of onset of

hypogonadism. In infancy, the presentation may be problems with sexual differentiation; in children delayed puberty; whereas in adulthood sexual symptoms are the commonest. Patients with impaired spermatogenesis such as Klinefelter syndrome usually have very small testes because the seminiferous tubules constitute the majority of the volume of the testes. The symptoms of hypogonadotropic hypogonadism varies with type (congenital vs. acquired), age at onset, duration (functional vs. permanent) and severity (partial vs. complete). Individuals with congenital hypogonadotropic hypogonadism may also present with midline facial defects, hearing loss, visual abnormalities, multiple hormonal abnormalities and neurologic deficits.

2.2 Laboratory diagnosis of male hypogonadism

Because many of the symptoms of hypogonadism are not specific, the diagnosis is usually confirmed with measurement of morning serum testosterone levels. Testosterone levels are lower in the afternoon and evening in adult men because of the diurnal variation in serum testosterone. If the total testosterone is substantially below the reference range (usually reported as between 300 and 1000 ng/dl (10 - 35 nmol/l), then a serum testosterone concentration < 230 ng/ml (8 nmol/l) indicates the patient is most likely hypogonadal and measurement of serum LH and FSH will help to distinguish primary versus secondary hypogonadism. The Endocrine Society recommends that the serum testosterone be measured again to confirm the consistency of the low values [1]. If the serum testosterone is over 370 ng/dl (12 nmol/l), it is unlikely the subject is hypogonadal [6] unless the patient has a very high sex hormone binding globulin (SHBG) resulting in low free or bioavailable testosterone. In recent years it is recognized that serum testosterone levels measured in different laboratories even using similar methodology have large inter-laboratory variations [17-20]. Though liquid chromatography tandem mass spectrometry is regarded as the gold standard, immunoassays are commonly used for measurement of testosterone and may be adequate for the diagnosis of male hypogonadism but not for diagnosis of hypo- or hyper-androgenemia in women and children or when measurement of very low levels of serum T are needed for decision-making in men [18,20]. The Center of Disease Control is establishing a standardization program where testosterone assays are accuracy based and not only precision based (precision-based proficiency testing is commonly used for laboratory certification) [21]. Thus a sample for testosterone measured in a laboratory using any standardized method should be similar to the same sample measured in another laboratory using another method, provided that these assays are accuracy based and referable to a universal standard. Until standardization is implemented the clinician must know the method the laboratory is using and the reference ranges for adult men.

If the patient has symptoms and a serum testosterone level that is borderline, for example, between 230 and 370 ng/dl, The Endocrine Society guidelines suggest measurement of free testosterone by equilibrium dialysis or bioavailable testosterone after precipitation of SHBG bound testosterone, or calculated free or bioavailable testosterone based on SHBG and total testosterone levels [1,20]. It should be noted that SHBG levels are increased with conditions such as old age, hyperthyroidism, elevated estrogen levels and liver cirrhosis and decreased in hypothyroidism, obesity, type 2 diabetes, insulin resistance, nephrotic syndrome and androgen use. Free testosterone should be measured by equilibrium dialysis. Calculated free

testosterone using various formulae will give free testosterone levels depending on the formulae used and accuracy and precision of the assays for total testosterone and SHBG levels [22,23]. Unless the testosterone and SHBG measurements can be standardized and a formula can be devised that can reflect the interaction between free and SHBG-bound testosterone, the calculated free testosterone may not be useful for the diagnosis of male hypogonadism. Direct immunoassay for free testosterone does not provide more information than total testosterone and the levels measured are much lower than free testosterone levels estimated by equilibrium dialysis and should not be used for the diagnosis of hypogonadism [24,25].

3. Benefits and risks of testosterone replacement therapy in hypogonadal males

For all hypogonadal men, replacement of testosterone is indicated except in patients where fertility is desired (Table 1) or when there are contraindications (Table 2). Induction of fertility in hypogonadotropic hypogonadism will be discussed later. The biochemical goal of testosterone therapy is to raise average serum testosterone levels (over days for transdermals and implants or weeks for injectables) into the mid-normal range (e.g., 400 - 700 ng/dl) for male hypogonadism. Studies have shown that testosterone may have a threshold effect on some parameters such as sexual function but there appears to be a dose-related response to testosterone treatment for muscle mass, fat mass and hemoglobin and hematocrit [26,27]. A recent study showed that testosterone increases muscle mass but aromatization to estradiol is necessary for decrease in fat mass and improvement in sexual function [28] suggesting that estradiol in men will be necessary for these functions. This raises some concern about an increasing trend among some practitioners of combining testosterone replacement therapy with aromatase inhibitors.

3.1 Benefits of testosterone therapy in hypogonadal males

In pre-pubertal hypogonadal boys, testosterone replacement therapy will initiate puberty and induce development of secondary sexual characteristics. Androgen therapy for delayed puberty permits more timely secondary sexual development and addresses some of the associated psychosocial problems [29,30]. The starting dose of testosterone in pre-pubertal boys is usually lower than the adult dose such that the boys undergo puberty slowly. As many of the boys have constitutional delayed puberty, after the induction to full puberty, testosterone therapy should be withdrawn and appropriate testing for hypothalamic, pituitary or testicular disorder initiated where long-term testosterone replacement is indicated (Table 1).

Testosterone replacement therapy improves sexual function (libido and erectile function) when testosterone levels are restored to the normal range in younger hypogonadal men [31-33]. There is conflicting information regarding the ability of testosterone to improve erectile dysfunction independent of the effects on libido [31,34-38]. In older men, long-term studies on patient reported outcomes are required to further evaluate the effects of testosterone replacement therapy on erectile function [37].

Testosterone replacement therapy increases bone mineral density in hypogonadal younger and older men [32,39-46]. Meta-analysis studies have also shown testosterone replacement therapy increases bone mineral density and reduces rate of bone loss [39,47]. Testosterone therapy has not been approved by the FDA for treatment of osteoporosis as there are no well-controlled data showing that testosterone replacement therapy reduces fracture rate.

In randomized trials in middle-aged and older men, testosterone administration is associated with increase in LBM, reduction in fat mass and increase in muscle strength when compared with placebo [41,48-50]. The improvements in muscle strength have not been found to result in significant changes in functional ability in older men and this requires further investigation. Recent uncontrolled or non-randomized studies have reported that long-term testosterone replacement therapy in hypogonadal men results in significant decreases in body weight and waist circumference [51,52]. While the significant weight loss requires careful confirmation, randomized controlled trials showed that testosterone replacement therapy reduced body fat mass, regional fat distribution and waist circumference in hypogonadal men with and without obesity [48,53-61]. The decrease in central adiposity and minor improvements in insulin sensitivity and hemoglobin A1C have also been reported in individuals with hypogonadism and metabolic syndrome and/or type 2 diabetes [2,57,58,61-66]. These studies suggest that normalizing testosterone levels may be helpful in improving some of the metabolic dysfunction in men who are obese, have type 2 diabetes and hypogonadism. A number of studies have found that testosterone replacement therapy results in decreases in total cholesterol and LDL cholesterol [53,58,62]. Other studies have observed that testosterone replacement therapy can lower HDL [67-70]. While the observed decrease in LDL may be of some cardiovascular benefit, the associated fall in HDL may counteract this beneficial effect. The decrease in HDL levels are more marked when testosterone is administered orally. Studies of sub-fraction analyses of HDL and efflux of HDL from macrophages are ongoing and the results may clarify the significance of the HDL changes. Small studies have demonstrated that testosterone causes coronary vasodilation, improves performance in cardiac stress tests and heart failure [71-74].

There are reports that testosterone replacement therapy increases mood, energy and vitality in hypogonadal men [33,75-77], but placebo controlled trial with well-defined patient-related outcomes are lacking in particular in older men. There are also reports that testosterone replacement therapy improves depression [77,78]; however the studies are few and controversial.

3.2 Common adverse effects of testosterone replacement in hypogonadal males

Common adverse events of testosterone replacement therapy include development of acne and increased oiliness of skin because of the androgenic effects on sebaceous gland. Crops of acne are usually related to higher serum levels of testosterone and are less common if relatively stable serum testosterone levels are maintained in the mid-adult male range. Gynecomastia may occur with the administration of testosterone because of its conversion to estradiol. If the gynecomastia is severe the dose may be reduced or an aromatase inhibitor can be used concomitantly with testosterone replacement therapy (Table 1).

The most common adverse effect of testosterone replacement therapy is increase in hemoglobin, hematocrit and red cell indices [68]. Testosterone replacement therapy increases hematocrit in anemic hypogonadal men in a dose dependent manner [79-81]. The stimulation of hematopoiesis is influenced by age and appears to be more pronounced in older men [82,83]. Elevation of hematocrit above the reference range may lead to increased blood viscosity, which may increase thrombotic complications such as stroke, myocardial infarction, deep vein thrombosis and pulmonary embolism. It is recommended that hypogonadal men with baseline hematocrit values above 50% undergo a workup prior to testosterone replacement therapy because these men may have an increased chance of developing hematocrit levels above 54% [1]. Testosterone replacement therapy should be withheld or phlebotomy performed if the hematocrit is > 54%, waiting until the hematocrit returns to below 50%; subsequently testosterone replacement therapy should be reinitiated at a reduced dose [1].

Hypogonadal men with moderate to severe obstructive sleep apnea (OSA) are at an increased theoretical risk for exacerbation of OSA with testosterone replacement therapy, particularly if supra-physiologic doses of testosterone are used [1,55,84-86]. However, if serum testosterone levels are maintained within the mid-adult male range, testosterone replacement therapy does not appear to cause OSA [55]. Further large scale longitudinal studies are needed to ascertain the effects of testosterone replacement therapy in men with OSA.

3.3 Testosterone therapy and cardiovascular disease risk in men

Several epidemiological studies showed that men with low testosterone have higher all-cause mortality, which is mainly due to increase in cardiovascular disease [87-91]. In an observational study in US veterans, hypogonadal men treated with testosterone had decreased mortality compared to untreated hypogonadal men [92]. However, in another study in US veterans with low testosterone levels who had undergone coronary angiography, testosterone replacement therapy was associated with an increase in risks of myocardial infarction, ischemic stroke and all-cause mortality [15]. This report generated criticisms on the methods, statistical analyses, and conclusions in letters and responses to the editors and a commentary [93]. A meta-analysis of testosterone replacement therapy clinical trials showed no increase in cardiovascular adverse events [68]. However, a more recent meta-analysis showed that testosterone treatment was associated with an increased risk of cardiovascular adverse event in mainly older men. The increase cardiovascular events risk were higher in non-pharmaceutical supported compared to industry supported studies [94]. Using a large healthcare database and using testosterone prescriptions data, the incidence of myocardial infarction was reported to be twofold higher in men over 65 years and in younger men with preexisting heart disease in the 90 days after filling an initial testosterone prescription compared to a year prior to the initial filling of the prescription [95]. This publication led to the US FDA issuing a Drug Safety Information indicating that the agency is evaluating and monitoring the possible increased cardiovascular disease that may be associated with testosterone replacement therapy in older men.

The above reports are observational studies that do not imply causality; or meta-analyses where the primary data may not be available; or data based on prescriptions where the basis for the diagnosis of hypogonadism and co-treatment medications are not known. In a recent randomized placebo-controlled study in frail older men with significant chronic disease and with limitations with mobility, an increase in cardiovascular adverse events was reported [96]. However, such an increase was not noted in another randomized placebo-controlled study on testosterone treatment in frail older men [50]. In addition these studies were either not designed to investigate the adverse outcome of testosterone on cardiovascular disease or well-controlled, prospective and adequately powered to resolve the controversies on cardiovascular safety or benefit of testosterone replacement therapy. As a result, there is an urgent need of a long-term, large scale, longitudinal, placebo-controlled interventional study in men that will prospectively assess coronary atherosclerotic changes and cardiovascular morbidity to understand whether testosterone replacement therapy has adverse effects on the cardiovascular system in older hypogonadal men. In the meantime until such data are available, clinicians should discuss with and monitor cardiovascular events in older hypogonadal men who will start testosterone treatment.

3.4 Testosterone therapy and prostate disease

The prostate is an androgen dependent tissue. Because intraprostatic levels of 5 α dihydrotestosterone (DHT) are higher than testosterone, DHT is considered the important intraprostatic androgen that regulates growth and proliferation of prostate tissue. Testosterone replacement therapy leads to increase in DHT levels through conversion by 5 α reductase enzymes. Meta-analysis of randomized placebo-controlled clinical trials does not show that testosterone replacement therapy increases the incidence of any prostate disorder including benign prostatic hyperplasia or prostate cancer compared to those treated with placebo [68]. Hypogonadal men treated with testosterone do not have a linear dose response of prostatic specific antigen (PSA) levels, and unless the pre-treatment testosterone levels are extremely low, do not increase intraprostatic testosterone and DHT levels [55,97]. An increase in serum DHT even to very high levels for up to 2 years does not increase intraprostatic androgens, PSA and prostate volume [98-100]. On the other hand, 5 α reductase inhibitors decrease intra-prostatic DHT levels and lead to a relative risk reduction of low grade prostate cancer [101,102]. Currently, there is no evidence to indicate that testosterone replacement therapy will induce prostate cancer or cause a histologic prostate cancer to become clinically significant; however testosterone treatment may unmask latent/histologic prostate cancer. Because PSA, a marker of prostate disease, is androgen dependent and serum PSA levels increase with testosterone administration, testosterone treatment may trigger urological referrals and prostate biopsies. Testosterone replacement in hypogonadal men does not increase the risk of voiding symptoms of benign prostatic hyperplasia [103] but may increase prostate size to that of eugonadal men [104]. A recent long-term study showed no change in symptoms of lower urinary tract obstruction and prostate volume in men administered testosterone [52]. The concomitant use of testosterone and 5 α reductase inhibitors in hypogonadal men older men with or without benign prostatic hyperplasia resulted in lower PSA and smaller prostate volume compared to those who did not received 5 α reductase inhibitor [46,105].

4. Contraindication to testosterone therapy

Guidelines recommend against starting therapy in adult patients with androgen dependent cancer, which includes prostate and male breast (very rare) cancer (Table 2). Testosterone replacement therapy will increase the growth and proliferation of androgen dependent prostate and male breast cancers. High risk patients for prostate cancer including those with a palpable prostate nodule or induration, a PSA level > 4 ng/ml or > 3 ng/ml in men at high risk for prostate cancer (including African-Americans, men with first-degree relatives with prostate cancer) may be referred to a urologist for further assessment and counseling. Patient with severe lower urinary tract symptoms (e.g., International Prostate Symptom Score of > 19) should be assessed and treated before the start of testosterone replacement therapy. Erythrocytosis (defined as a hematocrit > 54%), untreated severe OSA or untreated congestive heart failure should also not be treated with testosterone until these conditions are controlled. Testosterone replacement therapy is not appropriate for men who desire seeking fertility because exogenous testosterone will suppress gonadotropins and endogenous testosterone production with consequent decrease in sperm production.

5. Options for testosterone replacement therapy

Testosterone replacement therapy should be offered to all patients with male hypogonadism provided that there are no contraindications (Table 2) and if fertility is not an immediate concern. In patients with primary hypogonadism, severe testosterone deficiency is usually associated with infertility, which will not respond to medical treatment. Their option would be assisted reproductive technology, adoption or acceptance of childlessness. In secondary hypogonadism, gonadotropin treatment may stimulate or reinitiate spermatogenesis and fertility. Testosterone replacement therapy increases serum testosterone because of negative feedback on the hypothalamus and pituitary leads to lowering of intratesticular testosterone, affecting germ cell maturation and Sertoli cell function and consequent suppression of spermatogenesis. The goal of testosterone replacement therapy is to raise serum testosterone levels into the mid-normal range (400 - 700 ng/dl) and resolution or reduction in signs and symptoms of hypogonadism [1]. Testosterone preparations that are currently available include injections, transdermal patches and gels, oral testosterone, buccal tablets, oral capsules and testosterone implants (Table 3). Currently, testosterone injections and testosterone gel preparations are more commonly used in the US.

5.1 Intramuscular injections

Testosterone intramuscular (IM) injections have been available since the 1940s for hormone replacement in hypogonadal men. They are made up of testosterone with an attached ester including the propionate (TP), enanthate (TE), cypionate (TC) and undecanoate (TU) formulated with an oil plus other excipients to enhance the solubility of the ester. The different formulations TP, TE and TC have been in use for many decades throughout the world. TP with a short three-carbon ester is not used for testosterone replacement therapy because it lasts only for a few days. TE and TC (with an ester side chain with seven carbons for TE and eight carbons for TC) injections have been the most commonly used injectables throughout the world until recently. In adult patients, TE or TC can be administered at 150 - 250 mg once every 2 weeks [106,107]. In older men, a lower dose may be used to achieve

testosterone target levels because the clearance of testosterone may be reduced when compared with younger men [108]. In pre pubertal boys, the starting dose may be 50 mg once every 2 - 4 weeks. After TE or TC injection, serum testosterone levels peaked within 3 days and returned to baseline levels in about 2 weeks. To monitor serum testosterone levels after TE or TC injections some clinicians prefer that a blood sample be drawn midway between injections (e.g., at 7 days) and this should be within the mean serum testosterone seen in normal men. Measurement of the trough level obtained before the next dose is often used to ensure that the testosterone level is near the lower limit of the reference range of adult men to ensure there is no accumulation of testosterone. In some patients, fluctuation in mood and crops of acne may occur with the peaks and troughs of serum testosterone levels attained after TE and TC injections. In such cases, the dose of TE/TC may be reduced to 100 mg and administered every 7 - 10 days. TE/TC formulations have been shown to be effective and relatively inexpensive. There is a greater risk of erythrocytosis with higher maximal peak in testosterone levels with IM injections when compared with transdermal formulations [79]. In a small number of cases, cough has been reported immediately after IM injection and has been speculated to be due to micro-embolism of the vehicle (oil) to the lungs but without histological proof [109].

TU, a long acting testosterone formulation (11 carbon ester side chain) with injection intervals of 10 - 12 weeks markedly reduces the number of required injections. In Europe and many part of the world, the first injection of TU is administered at 1000 mg, followed by another injection of TU 1000 mg at 6 week and subsequently TU is administered at every 12 - 14 weeks [110,111]. The serum testosterone levels rise to supra-physiologic levels for several days and gradually decline over a period of 10 - 14 weeks after administration of TU injection. Studies in the US showed that TU can be administered as a 750 mg initial dose, followed by a second injection at 4 weeks and then every 10 weeks. This regimen provides peak within testosterone levels within the acceptable reference range during the first week after the injection [112,113]. This preparation is available in most countries around the world and has recently been approved in the US; it has wide acceptability in patients and few have the very uncommon adverse events of coughing or fat embolization [114]. When injectable testosterone TU is used, serum testosterone levels should be measured prior to next injection to ensure the levels are at the lower limit of the reference range. TU is formulated as 250 mg/ml in oil and should be administered slowly intramuscularly by experienced personnel. While not an issue in younger men, a potential disadvantage with TU is that testosterone levels cannot be reduced quickly if serum PSA levels begin to rise.

5.2 Transdermal delivery systems

5.2.1 Transdermal patches—The first transdermal preparations are the scrotal patches, which are not currently available because of the need to shave or cut scrotal hair to maintain adequate patch adhesion to the skin [115]. In addition, some individuals complained of scrotal itching or discomfort. Currently non-scrotal testosterone patches are available in the US delivering 2 or 4 mg of testosterone per patch for a 24 h period [79,116,117]. The levels of testosterone peak at 2 - 4 h and last for 24 h. Dose adjustments should be made to achieve testosterone level in the mid-normal range. The drawbacks for patches include skin irritation, which occurs in many patients and results in intolerability of the patches.

Frequently two patches per day may be required to maintain the serum testosterone within the reference range in some men. There are also other newer formulations of patches being currently evaluated in small trials (e.g., modifications of patches with hydrogel, polyurethane matrix patches) [118].

5.2.2 Transdermal gels—Most testosterone gels are hydro-alcoholic-based gels and contain 1 - 2% testosterone. Testosterone is absorbed into the sub-dermal tissue of the skin, which acts as a reservoir to slowly release testosterone into the circulation. It provides a relatively steady level of serum testosterone and is as effective as the patch [119,120]. Long-term safety and efficacy data of testosterone gel are available [32]. Testosterone gel is packaged as sachets, tubes or metered dose pumps. For the 1% testosterone gel the usual starting dose is between 5 and 10 g of gel containing 50 - 100 mg/day of testosterone applied to the skin. About 10% of the testosterone that is applied to the skin is absorbed. It is intended to deliver approximately 5 - 10 mg/day of testosterone to the body, which matches the normal production rate of testosterone in healthy men. In the US, the gel formulations that are currently available are 1, 1.62 and 2% testosterone gel. A 2% hydro-alcoholic testosterone gel that shows similar pharmacokinetics as other gels is available [121] as is another 2% testosterone gel that does not contain alcohol and is applied to the axilla using an applicator. The pharmacokinetics data of the testosterone gel applied to the axillae are comparable to the other testosterone gels [122]. All gel/lotion formulations are able to produce a steady serum testosterone concentration within the physiological range of adult men in most hypogonadal men. The dose adjustment of testosterone gel can be done after a patient has been treated for about 7 - 14 days to allow adequate time for serum testosterone levels to stabilize. For patients using transdermal patches or gels, testosterone levels should be measured 3 - 12 h after application where serum testosterone should be at goal, that is, mid-adult male range. Testosterone gels have minimal skin irritability. However, because this is an open system without a patch, there is potential of transfer of testosterone to others upon close skin contact. Showering and wearing clothing over the gel application areas are required before close skin contact with women and children. Transfer of testosterone can cause clinical virilization in females and children. The transdermal preparations are the favored preparation in the US.

5.3 Testosterone implants (pellets)

Testosterone implants are pellets of testosterone that can be inserted into the subcutaneous tissue of the body, usually in the abdomen. Implants have been available for many decades but earlier larger sized testosterone pellets frequently extruded and were rarely used in the US, until recently. The pharmacokinetics of testosterone implants have been studied and better designed implants has seen greater use in Europe in Australia [123]. Four - six implants of 200 mg of testosterone will maintain serum testosterone in the physiological range for 4 - 6 months. In the US, about 6 - 12 implant of testosterone 75 mg are implanted into the gluteal subcutaneous tissue delivering 450 - 900 mg of testosterone in about 4 - 6 months [124,125]. The problems with pellets include the need of a minor surgical procedure, which may be associated with minor bleeding and pain, and extrusion of the pellet requiring reinsertion. Testosterone levels should be checked before re-implanting pellets.

5.4 Buccal tablets

The buccal testosterone preparation adheres to the surface of the gums as a gel tablet. It provides a controlled- and sustained-release of testosterone over a 12 h dosing period and has to be administered twice a day [126,127]. Gum-related adverse events (e.g., irritation, inflammation, gingivitis) are usually mild and an abnormal taste developed in a number of men. There are men who have not been able to tolerate the feeling of local presence of the buccal testosterone tablet. The tablet can also be dislodged and requires replacement. Another drawback of the buccal preparation is the fixed dose of 30 mg [126,127]. When buccal tablets are used, the testosterone level should be assessed immediately prior to the next application. This delivery system is available but not used by many hypogonadal men.

5.5 Oral testosterone

Testosterone when taken by mouth is poorly absorbed and rapidly metabolized. There are many modified potent androgens that are orally bioavailable including methyl testosterone and the other 17 alkylated androgens (e.g., oxandrolone, fluoxymesterone, stanozolol). Many of these have been utilized for their anabolic effect for performance enhancement in sports and should not be used for androgen replacement [1]. These modified androgens are absorbed through the gastrointestinal tract and undergo a first-pass degradation by the liver. Methyl testosterone has been reported to cause obstructive jaundice and other 17 alkylated androgens may be hepatotoxic [128]. Moreover because of a first-pass effect through the liver and these modified androgens are not aromatized to estrogenic compounds, they cause significant increase in LDL and decrease in HDL cholesterol not observed with testosterone and its esters [70].

Unlike the 17 alkylated androgens, testosterone TU in castor oil capsules do not have a significantly increased risk of adverse liver side-effects. Oral TU has been available for many years in Europe, Australia, Asia and in North and South America except in the US. Oral TU have been able to circumvent the first-pass liver metabolism because testosterone is absorbed into the lymphatic system. Oral TU must be taken with food (fatty meal) to increase absorption to provide levels of testosterone in the physiological range [129]. Oral TU is administered as 40 mg capsules and usually two capsules are administered two or three times a day. The peak levels attained with this formulation occurs at about 4 - 5 h post-administration. There are long-term safety data available for oral TU [130]. While oral TU increases testosterone levels in hypogonadal men, the resultant serum testosterone levels can be variable and may lead to a variable clinical effect. The pre-dose levels in hypogonadal men administered oral TU are frequently in the hypogonadal range [131,132]. Currently there are newer formulations of oral TU that are being developed and evaluated. An oral TU with a proprietary Self Emulsifying Drug Delivery System is being evaluated at higher doses than oral TU in castor oil. Significantly higher serum testosterone levels are attained with the new formulation and food intake improves the absorption [133,134]. Because of the presence of 5 α reductase enzyme in the gut and conversion of the administered TU to DHT TU, serum DHT to testosterone levels may be slightly higher than other testosterone preparations [134]. Pivotal Phase III trials have been completed and if it receives FDA approval, it will be the first oral TU available in the US.

5.6 Other androgens and selective androgen receptor modulators in development

Modifications of testosterone at the seventh position produced androgens that are not 5- α reduced and that have the theoretical advantage that they may not stimulate prostate growth as much as testosterone. They are also not aromatized, which may be an issue for long-term use in view of the effect of estrogens in bone, fat mass and sexual function [28,135]. 7 α -methyl-19-nortestosterone has been formulated as an implant and studied in healthy men as a potential male contraceptive [136] and also investigated for androgen replacement in hypogonadal men [137]. Dimethandrolone (7 α -11 β -dimethyl-19 nortestosterone) is being formulated with the TU ester for oral dosing for male contraceptive development [138]. These modified androgens appear to be more potent than testosterone and do not have liver toxicity.

Selective androgen receptor modulators (SARMs) are nonsteroid compounds that recruits co-activators/co-repressors to bind to the androgen receptor to initiate transcription and activation resulting in enhanced androgen action [139]. Clinical studies of these SARMs are focused on the correction of sarcopenia in elderly, patients with chronic diseases and cancer cachexia [140,141] and not for androgen replacement therapy. Use of these agents for treatment of hypogonadism is not a priority for development for many of these new agents.

6. Monitoring of testosterone treatment

Patients who are started on testosterone replacement therapy should be followed to ensure their symptoms/signs are improved after treatment. The Endocrine Society recommends measuring testosterone at 3 - 6 months after starting therapy, and then annually to assess for improvement in symptoms and development of adverse effects [1]. The time for sampling for testosterone measurements depends on the type of delivery system and is discussed in Section 5 with each preparation. The follow-up visits should focus on evaluating for erythrocytosis, prostate disease (requiring a yearly digital rectal examination per urology practice guidelines), sleep apnea or lower urinary tract symptoms. The International Prostate Symptom scale (IPSS) can be used to monitor for changes by using it at baseline, and subsequent visits to determine if prostate enlargement is leading to worsening of lower urinary tract symptoms, for example, IPSS score increases > 5 from baseline, or IPSS score > 19, these patients should be referred to an urologist. If the PSA increases > 1.4 ng/ml in a 1-year period or digital rectal examination detects a prostate nodule or significant change in prostate size, an evaluation by an urologist is warranted (e.g., a prostate biopsy) [1]. In addition to total testosterone levels, laboratory tests should include measures of hemoglobin, hematocrit and PSA at baseline, 3 months and then yearly. When hematocrit rises above 54%, one should cease testosterone replacement therapy until hematocrit decreases to 50% before reinitiating therapy at a lower dose [1]. The patient with significantly elevated hematocrit should be carefully monitored and evaluated for symptoms of sleep apnea such as daytime somnolence and morning headaches and for cardiovascular events.

7. Treatment options for patients with secondary hypogonadism/hypogonadotropic hypogonadism

Patients with secondary hypogonadism or hypogonadotropic hypogonadism have symptoms and signs of testosterone deficiency, low testosterone and low-to-normal LH and FSH. The serum total testosterone is often very low. If a serum total testosterone is below 150 ng/dl and associated with low or normal LH and FSH, a prolactin level is elevated, or visual field symptoms or signs are present. An MRI of the pituitary and hypothalamus should be obtained to evaluate for a pituitary tumor and other hypothalamic pituitary lesions [1].

Patients with hypogonadotropic hypogonadism may require management of the underlying cause (e.g., pituitary tumors) in addition to treating symptoms of hypogonadism. Functional acquired defects can result in reversible hypogonadotropic hypogonadism. Testosterone replacement therapy should be delayed until it can be determined if the functional defect can be reversed. The treatment of the underlying condition (e.g., nutritional deficiency) or discontinuation of an offending medication (e.g., anabolic steroids, glucocorticoids, opiates) often reverses hypogonadotropic hypogonadism [1]. The treatment of underlying infiltrative disease may also improve gonadotropin secretion. The treatment with dopa-mine antagonists often corrects the hyperprolactinemia and restores GnRH pulsatile secretion. The resection of a pituitary tumor may relieve stalk compression and help restore gonadal function.

7.1 Human gonadotropins therapy

Hypogonadotropic hypogonadism due to congenital and permanent acquired structural defects should be treated with testosterone replacement therapy as described earlier unless the patient desires fertility. Long-term testosterone replacement does not impair future fertility but may require more time for initiation or re-initiation of spermatogenesis to occur [142,143]. If the patient desires fertility, replacement of LH is usually achieved by using human chorionic gonadotropin (hCG). The initial dose of hCG 1000 - 1500 IU (40 - 60 mcg) s.c. is given three times a week. hCG stimulates the Leydig cells in the testis to produce testosterone in hypogonadotropic hypogonadism patients without associated primary testicular disease. The dose of hCG should be adjusted until trough serum testosterone levels are restored to about the lower limit of the adult male range. Many patients with congenital hypogonadotropic hypogonadism require hCG and FSH to complete spermatogenesis while acquired hypogonadotropic hypogonadism may be managed with hCG alone [143,144]. Men using hCG may experience temporary breast enlargement because hCG increases estradiol levels [142-144]. The dose of human recombinant FSH is 75 - 150 IU s.c. administered three times a week. It should be noted that the sperm concentration does not need to be increased to the adult reference range before men with hypogonadotropic hypogonadism become fertile [145]. As the management of infertility in hypogonadotropic hypogonadism requires both skill and patience, we recommend that these patients be referred to experienced endocrinologists. Pulsatile subcutaneous GnRH infusion will also result in pulsatile secretion of both gonadotropins but the administration of gonadotropins injections three times a week is more practical and user friendly [146].

7.2 Other potential agents for secondary hypogonadism

In addition to hCG and testosterone replacement therapy, there are other medications that stimulate the production of endogenous testosterone. These include aromatase inhibitors and selective estrogen receptor modulators that have been studied in men with secondary hypogonadism where there are no organic lesion in the pituitary and hypothalamus and when LH and FSH secretions are not abolished. Clomiphene citrate, a selective estrogen receptor modulator, prevents estrogen binding to its receptors in hypothalamus resulting in gonadotropin release and increases serum testosterone. Clomiphene citrate has been used in men with eu-gonadotropic hypogonadism, for example, aging men [147,148]. Another estrogen partial antagonist Tamoxifen has been used in elevating serum LH and FSH and serum testosterone levels in infertile and hypogonadal men [149]. Aromatase inhibitors (e.g., letrozole and anastrozole) decrease conversion testosterone to estrogen reducing the negative feedback on pituitary LH production. The higher LH levels stimulate the production of endogenous testosterone in men with residual hypothalamic-pituitary function, for example, aging and obesity [150-152]. Neither of these classes of drugs is approved by the FDA for treatment of male hypogonadism. They have been used off-label in men with partial gonadotropin and androgen deficiency. The clinical studies are small and some of them are not placebo-controlled.

8. Hypogonadism associated with obesity, opiate and anabolic steroid abuse, and prostate disease

It is recognized that obesity and type 2 diabetes are associated bi-directionally with low serum testosterone levels [2]. Suppression of the hypothalamic-pituitary-testis axis with chronic opiate use is a common observation in clinical practice. Recently there have been patients who are clinically cured of their prostate disease but have severe symptomatic hypogonadism and who have received testosterone replacement therapy. These special areas of male hypogonadism will be briefly reviewed here.

8.1 Management of hypogonadotropic hypogonadism due to obesity

Men with obesity have lower total testosterone levels and more rapid declines in levels with age. The total testosterone may be low because of decreased SHBG in obese men. This decrease in SHBG levels should not affect the free or bioavailable testosterone levels and hence obese men should be evaluated with free (measured by equilibrium dialysis) or bioavailable testosterone (using ammonium sulfate to precipitate SHBG) particularly when the total testosterone is close to the lower limit of the normal range [1]. However recent studies showed that in obese men, total and free testosterone as well as SHBG levels are all low [54,153]. When obese men present with symptoms of hypogonadism, lifestyle changes (e.g., caloric reduction and exercise) should be advised. A recent meta-analysis study showed that weight loss by lifestyle modification or bariatric surgery is associated with increase in serum testosterone, which is proportional to the amount of weight loss [154]. Obese men who despite weight loss have signs and symptoms of hypogonadism and low testosterone levels should be treated with testosterone replacement therapy. Patients with a normal free or bioavailable testosterone with low or low normal total testosterone and normal LH and FSH do not warrant treatment with testosterone.

8.2 Management of mixed hypogonadism due to opiates

Chronic opiate therapy can result in low testosterone levels because opiates suppress the hypothalamus-pituitary-gonadal axis in a dose dependent manner to reduce testosterone production. Patients with a history of chronic opiate use and who present with symptoms of hypogonadism should be evaluated. Other causes should be excluded and opiate induced hypogonadism may be the diagnosis if there are no other causes of hypogonadism [155,156]. The patient should be referred to a pain clinic and behavioral therapies to help wean the subject off opiates. If this effort is not successful, then the patient may be offered testosterone replacement therapy. If fertility is a concern, then medications that inhibit negative feedback of estrogen (e.g., clomiphene citrate) can be tried even though there are limited data on their effectiveness.

8.3 Management of hypogonadotropic hypogonadism due to anabolic steroids abuse

Anabolic steroid abuse is common in athletes and non-athletes [157]. A man who reports having symptoms of hypogonadism, decreased testicular size, infertility while being athletically fit (e.g., muscular) should be asked about anabolic steroid use. Men with history of anabolic steroid use will present with low testosterone and low gonadotropins because exogenous anabolic steroids suppress gonadotropins and endogenous testosterone and spermatozoa production. These subjects should be advised to stop anabolic steroids, which may be frequently difficult. Because of the pattern of steroid abuse with stacking of several anabolic steroids, the recovery of the hypothalamic-pituitary-testis axis may be prolonged from many months to years. If the patient's testosterone levels do not normalize and he remains symptomatic, we can consider using hCG or clomiphene citrate to attempt to stimulate the testis to respond.

8.4 Management of hypogonadism in individuals with prostate disease

Current guidelines do not recommend testosterone treatment for men with a history of prostate cancer or those with prior prostate cancer who have stable and undetectable PSA levels [1]. Men with prostate cancer with a high Gleason score and metastasis who have been treated with androgen deprivation therapy are not recommended testosterone replacement therapy. In these patients, there is concern that any mild increase in androgen levels may increase the risk of recurrent prostate cancer. In recent years, use of neoadjuvant androgen deprivation therapy before radiation or cryotherapy led to hypogonadism in men with localized higher risk prostate cancer [158-160]. The decrease in bone mineral density associated with low testosterone can be treated with drugs such as bisphosphonates, parathyroid hormone or denosumab. However, small scale clinical studies showed that in men with low grade or localized prostate cancer who had prostatectomy, serum PSA levels that are undetectable, and who had symptomatic hypogonadism, replacement with testosterone did not result in increase in PSA levels or increase in the recurrence of prostate cancer [161-163]. These studies suggest that in low risk patients with significant symptoms of hypogonadism and consistently low testosterone levels, judicious use with careful monitoring of testosterone replacement therapy may be considered after discussion with the patient regarding the risks versus the benefits. In these patients, short acting testosterone delivery systems such as the transdermal gels may be preferred.

9. Conclusion

Male hypogonadism is diagnosed by the presence of symptoms or signs of male hypogonadism and consistent serum testosterone levels that are below the generally accepted adult male range. Once the diagnosis is confirmed, the primary goal of treatment is testosterone substitution to achieve serum testosterone levels that are in the mid-adult range and the symptoms and signs of hypogonadism are relieved. Recent developments led to many delivery systems for testosterone. The most commonly used are testosterone injections or transdermal gels or lotions. For patients with primary hypogonadism testosterone treatment is the method of choice. For patients with secondary hypogonadism who desire fertility, replacement with subcutaneous injection of gonadotropins, hCG or human recombinant FSH can be used to induce testosterone production by the testis and spermatogenesis. For the patients with secondary hypogonadism but with measurable levels of gonadotropins, experimental use of selective estrogen receptor modulators and aromatase inhibitors has reported some success in small clinical trials. For symptomatic patients whose serum testosterone is at the lower limit of the adult reference range, a short therapeutic trial of testosterone can be prescribed to assess the effectiveness of the therapy.

10. Expert opinion

In the recent decade, there has been a re-vitalization with new products for testosterone replacement therapy for male hypogonadism. The availability of long acting testosterone TU injections and the short acting transdermal gels and lotions have increased the options for testosterone replacement therapy. The increase in direct patient advertisement of low testosterone symptoms and the treatment options have led to marked increases in the number of prescriptions for testosterone. It is not clear whether these prescriptions are for symptomatic men with persistently low serum testosterone levels. Thus about 17% of men filled their testosterone prescription only once. For men who have the diagnosis of primary or secondary hypogonadism with symptoms referable to consistently low serum testosterone levels, testosterone replacement should be offered because most studies show that benefits outweigh potential risks. In most studies in hypogonadal men receiving testosterone replacement, improvement in sexual function and lean mass, decrease in fat mass and increase in bone mineral density are more consistent in younger than older men. However data on patient reported outcomes of increased well-being, energy, vitality, cognition and mood have to be confirmed in larger studies. Age-related decline in testosterone has been shown in recent population-based studies to be associated with other co-morbid conditions, the commonest of which is obesity and type 2 diabetes. For these men, treatment of the primary condition by lifestyle modifications and disease-specific medications should be used before testosterone replacement. Injections or transdermal gels are usually the preferred method of testosterone replacement. The clinician should discuss the advantages and disadvantages of each delivery system before a method is chosen by the patient. The availability of a long acting testosterone TU injection will reduce the frequency of injections from about 50 injections per year to about 5. The common adverse effects of testosterone replacement include acne and oiliness of skin. Increase in hematocrit and hemoglobin is dependent on the dose and serum levels of testosterone. The long-term effects of testosterone replacement therapy on cardiovascular disease risks are controversial. Earlier

epidemiological studies showed increased all-cause and cardiovascular disease in men with hypogonadism. Recent case-control studies, meta-analysis, prescription database analyses and intervention studies showed that in some testosterone treatment is associated with increased mortality due to cardiovascular disease and ischemic stroke while others showed no effect or decreased mortality and risks of cardiovascular events. Long-term testosterone replacement studies showed no increase in lower urinary obstruction symptoms or prostate volume. The long-term effect of testosterone treatment on risk of prostate cancer is not known. Long-term prospective, randomized, placebo-controlled studies designed specifically to address the effects of testosterone treatment on cardiovascular and prostate disease are urgently needed. New selective androgen modulators including modified androgens and non-steroidal compounds are being developed for the treatment for sarcopenia rather than hypogonadism. These compounds are not 5 α reduced and may have less stimulatory effect on the prostate. They are also not aromatized to estrogens, which may be cancer-causing in long-term use because of the known effects of estradiol on bone, body composition and possibly sexual function in men. Long-term studies of selective androgen receptor modulations are not available for hypogonadal men. For men with secondary hypogonadism desiring fertility, gonadotropin therapy is used to maintain serum testosterone in the physiological range and stimulate spermatogenesis. There are recent studies indicating agents that stimulate endogenous testosterone production (e.g., partial estrogen antagonists, aromatase inhibitors) in hypogonadal men who have secondary hypogonadism but with residual gonadotropin secretion. The use of such drugs can be considered experimental and deserves more investigation not only in their effects on raising serum testosterone levels but clinical responses of long-term treatment on sexual function, bone and body composition as well as the patient reported outcomes.

Acknowledgments

P Surampudi is supported by the Endocrinology, Metabolism and Nutrition training Grant (T32 DK007571). C Wang is supported by the UCLA Clinical and Translational Science Institute (UL1TR000124) at Harbor-UCLA/LA BioMed and has received research support from Clarus Therapeutics, Lipocine, Besins Health Care and is a speaker for Lilly. RS Swerdloff has received research support from Clarus Therapeutics, Besins Health Care, Abbvie and Novartis and is a consultant for Claus

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Article highlights

- Male hypogonadism is diagnosed by symptoms and signs referable to a persistent low serum testosterone level.
- Serum testosterone level obtained by reliable, accurate and precise assays is the cornerstone for the diagnosis of male hypogonadism.
- Acute and chronic illnesses and co-morbid conditions are associated with low testosterone levels. Treatment should be directed initially to these conditions rather than testosterone replacement.
- The benefits of testosterone treatment in hypogonadal men outweighs the risks provided there is no contraindication to treatment.
- Long acting testosterone injections and the daily transdermal gels increase treatment options.
- Monitoring of symptomatic response and adverse events is necessary for testosterone replacement treatment.
- Long-term effects on cardiovascular disease risk and prostate cancer is not known and available data are controversial. Long-term randomized controlled clinical trials specifically designed to address these questions are needed.

This box summarizes key points contained in the article.

Table 1

Benefits and potential risks of testosterone replacement therapy.

Benefits	Potential risks
Maintains secondary sexual characteristics	Acne, oily skin
Improves libido and erectile dysfunction	Gynecomastia
Increases lean/muscle mass and strength	Weight gain/fluid retention at initiation of treatment
Decreases weight, body fat and visceral obesity	Lipids (decrease in HDL)
Increases bone mass	Prostate (benign prostatic hyperplasia and prostate cancer) *
Improves energy and vitality	Increased hemoglobin, hematocrit and red cell count
Improves mood and depression *	Sleep apnea *
Coronary vasodilatation, reduces cardiovascular disease risk *	Increased cardiovascular adverse effects *

* Controversial, more studies are required.

Table 2

Contraindications to testosterone replacement therapy.

Absolute contraindications
Prostate cancer
Male breast cancer
Uncontrolled or poorly controlled congestive heart failure
Untreated lower urinary obstructive symptoms
Erythrocytosis
Severe untreated obstructive sleep apnea

Table 3

Testosterone delivery systems currently available.

Delivery method	Preparations	Recommended dosage
Injections	Testosterone enanthate/cypionate	Generic preparations available, 150 - 250 mg IM injection once in 2 weeks; can be reduced to 75 - 125 mg once every 7 - 10 days
	Testosterone Undecanoate	First injection 1000 mg, second injection 1000 mg 6 weeks later, then 1000 mg every 12 - 14 weeks In the US, first injection 750 mg, second injection 750 mg 4 weeks later and then 750 mg once every 10 weeks
Transdermal preparations	Testosterone patch	Each patch delivers 2 or 4 mg of testosterone, apply one 4 mg and adjust to 2 or 6 mg as needed
	Testosterone gel	1% gel, start with 5 g gel (either in sachet, tube or pump), which delivers 50 mg testosterone to the skin, apply daily to arms and shoulders. Increase to 10 mg or decrease to 2.5 mg as required 1.62% gel, start with 40.5 mg (two pump actuations, one actuation to each upper arm and shoulder daily). Adjust dose by increasing to 60.75 and 81 mg using three or four actuations or decrease to 20.25 dose using one actuation 2% gel to thighs, start with 40 mg (four pump actuations) once daily. Adjust dose by decreasing or increasing at 10 mg intervals (one pump actuation) 2% testosterone lotion to axillae. Start with 60 mg testosterone by applying 30 mg (one pump actuation) to each axillae daily, no shaving required, axillae should be clean and dry. Dose can be adjusted by decreasing to 30 mg (one pump actuation) or increasing to 90 mg (three pump actuations)
Implants	Testosterone pellets	75 mg pellets (US). 6 - 12 pellets will deliver 450 - 900 mg of testosterone to the body. Implants usually placed in the subcutaneous fat of the abdomen, 100 or 200 mg pellets (Europe, Australia). 6 pellets of 100 mg or 4 - 6 pellets of 200 mg provide serum testosterone levels in adult male range for 3 - 4 months or longer
Buccal delivery system	Testosterone buccal tablet adheres to gums as a gel	30 mg tablets are applied to the gums twice a day.
Oral	Testosterone undecanoate	40 mg capsules. Two capsules, two - three times a day with food (not available in the USA)