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Testosterone Replacement Therapy in Hypogonadal Men

Christina Wang, MD [Site Director],

Clinical and Translational Science Institute at The Lundquist Institute at Harbor-UCLA Medical Center and Division of Endocrinology, Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA

Ronald S. Swerdloff, MD [Chief]

Division of Endocrinology, The Lundquist Institute and Harbor-UCLA Medical Center, 1124 W. Carson Street, Torrance, CA 90502, USA

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Introduction

Testosterone replacement is indicated in men with symptoms or signs of testosterone insufficiency and persistently low circulating testosterone concentrations.[1] The diagnosis, indication, benefits versus risks, and monitoring of testosterone replacement for hypogonadal men are described in other chapters. This chapter focuses on the different formulations and routes of administration of testosterone used to achieve physiological testosterone concentration and alleviate symptoms of testosterone insufficiency. We also discuss how to adjust the dose of testosterone replacement depending on the method used for testosterone replacement, goals of testosterone replacement, and patient preferences.

The decision on which formulation and route to replace testosterone depends on the patient's choice, his acceptance of different modalities, the pharmacokinetics of testosterone that best suit the patient, and the goals of treatment. This decision is made by the patient with information provided by the physician. Because long-acting androgens remain in the body for a longer time and there is lack of a placebo controlled long term safety study to ascertain possible cardiovascular and prostate adverse events, long-acting testosterone replacement is usually reserved for younger men with hypogonadism. This recommendation may be revised when additional safety data are available. Shorter acting injections, gels and oral testosterone are frequently used in initiation of therapy in hypogonadal older men and those where a therapeutic trial of testosterone may be indicated. Testosterone gels and creams may be available from compounding pharmacies and from many internet sites, but these

Corresponding author: Christina Wang, MD, wang@lundquist.org.

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compounded preparations are not recommended for testosterone replacement because their composition and the pharmacokinetics have not been verified.

There was an increase in testosterone prescriptions reported from 2000 to 2011 throughout the world but the increase was most marked (more than threefold) in the United States.[2-4] Topical gel is the most used method of testosterone replacement in the Unites States; globally injections are the most prescribed testosterone formulation. Interestingly, long-term adherence with the prescribed testosterone treatment is relatively low; in one study, about 18% of the men only filled one prescription. The increase in testosterone prescriptions was the highest in men over 60 years.[2] The striking increase in prescribed testosterone usage in the first decade of the 21st century may be related to the introduction of new testosterone gels in 2003; continued medical education for general physicians on recognition of testosterone deficiency; rising prevalence of blood testosterone testing, and direct marketing of testosterone products to the public. In the United States, there was substantial use of testosterone without testing of testosterone levels and for the treatment of men with symptoms despite normal testosterone levels.[3] The increase in prescribed testosterone has been viewed because of direct-to-consumer marketing of testosterone products to the public. Many men, who were prescribed testosterone may not have hypogonadism with persistently low serum testosterone.[5] More recent data indicate that testosterone use in the United States declined by 48% from 2013 to 2016[6]; similar trends were observed in Canada.[7] This decline in testosterone prescription and use may be related to reports of possible adverse effects of testosterone therapy on cardiovascular disease and the change in the labeling of testosterone products to include possible but debatable increased risk of myocardial infarction and stroke.[8-12] In addition, the Food and Drug Administration (FDA) in the United States provided guidance that testosterone therapy should be used only in men with low testosterone concentration due to defined causes (testicular or hypothalamic-pituitary dysfunction) of hypogonadism.[8] Low testosterone in aging men is not regarded by the FDA as an indication for testosterone replacement. Physicians should discuss all the benefits and risks of testosterone replacement including possible increased risk of cardiovascular events before starting testosterone replacement therapy. Each patient needs to be aware of the possible risks to himself and balance that against the proven beneficial effects of testosterone treatment.

Testosterone Replacement Therapy

Table 1 shows the available testosterone replacement options in the United States (US) which includes topical patch and gels; nasal gel and buccal tablets; oral pills and capsules; injections and implants. The goal of testosterone replacement therapy is to relieve the symptoms and signs of testosterone insufficiency and maintain serum testosterone concentrations in the physiological range. While reference ranges differ according to assay methodology,[13] the population used to determine the reference range, the lower reference range from published data is commonly between 250 and 300 ng/dL (8.7—10.4 nmol/L) and the upper reference levels between 950 −1000 ng/dL (33.0-34.7 nmol/L).[14] In most hypogonadal patients receiving testosterone the optimal average concentrations are in the mid reference range (approximately 400 to 800 ng/dL; 13.9 to 27.8 nmol/L) although the

exact ideal levels within the normal range are not known and may differ based on symptom relief and adverse effects in an individual.

Testosterone binds and activates the androgen receptors to exert its actions on the target tissues. It is converted by the 5 alpha reductase enzymes to 5 alpha-dihydrotestosterone (Fig. 1) which also exerts its effect through the androgen receptor predominantly in the skin, hair follicles, and the male reproductive tract including the external genitalia, Wolffian duct derived structures including the epididymis, vas deference, ejaculatory ducts and seminal vesicle as well as the prostate.[15] Mutations of the 5 alpha reductase gene cause underdevelopment of the external genitalia.[16,17] Testosterone is also aromatized to estradiol (Fig. 1) and absence of the aromatase enzyme results in low bone mass.[18] Placebo controlled clinical investigations in adult healthy men with induced hypogonadism demonstrate that after testosterone replacement the increase in concentrations of testosterone are related to increased hematocrit/hemoglobin; lean body mass; bone mineral density and decreased fat mass in both young and older men.[19-23] In experimental studies, when an aromatase inhibitor was co-administered with testosterone to men with suppressed testosterone concentrations, the increase in bone mass and decrease in fat mass were lessened compared to testosterone treatment alone; these studies suggest that aromatization of testosterone to estradiol may be required for greatest testosterone effects on bone density and reduction of fat mass.[22] Sexual desire and activity but not erectile function have been more recently shown to be related to increases in serum total and free testosterone as well as estradiol concentrations achieved after testosterone replacement in older hypogonadal men.[24] Taken together, these studies suggest that aromatizable androgens such as testosterone may be preferred over non-aromatizable modified androgens for androgen replacement in hypogonadal men.[25]

Some modified androgens are available in the US, such as methyltestosterone, mesterolone, oxandrolone oral tablets and stanozolol injections, but are not recommended for testosterone replacement in hypogonadal men (Fig. 1). One reason for this reservation for their use in treating hypogonadal adult men is that they are not aromatizable and may result in greater increase in LDL cholesterol and decrease in HDL cholesterol levels.[26] In addition, the 17 alpha-alkylated androgenic steroids (methyltestosterone, oxymetholone, and stanozolol) are hepatotoxic, whereas testosterone, testosterone esters and 19-nortestosterone showed no toxic effects on the liver.[27-30] Thus these modified 17 alpha-alkylated androgens are not recommended for testosterone replacement therapy. There are many designer synthetic androgens that are marketed over the internet as nutritional supplements. Little is known about the pharmacological effects of these unapproved androgens, and they should not be used as testosterone replacement, athletic or bodybuilding, nor for performance enhancement.[31,32]

Topical (Transdermal) Testosterone

Transdermal testosterone patches became available in the late 1990s and early 2000s. Testosterone is slowly released from transdermal patches providing a state level of testosterone over 24 hours. The transdermal patch was introduced first as a scrotal patch[33] which requires shaving or clipping of the scrotal hair. Because of higher 5-alpha reductase

activity in the scrotal skin, the scrotal patch produced higher serum dihydrotestosterone levels.[33,34] This scrotal patch was then replaced by a large skin patch (Testoderm®) which has the problem of adhesiveness to the skin. Both the scrotal and the body patch are no longer available. The only available testosterone patch is Androderm®; which can be applied to the body and is available as a 2 or 4 mg testosterone patch. [35-37] The application to the skin has to be rotated and application to the same area should be avoided for at least 7 days. However, the permeation enhanced patches are a closed system with an enhancer; mild irritation at the application site occurs in over two thirds of patients and up to 10 to 15% of men discontinue treatment because of skin irritation. The localized skin irritation can be partially mitigated by topical glucocorticoids.[38,39]

The Food and Drug Administration (FDA) approved the first testosterone gel (AndroGel®) in 2003 as a new method of delivering testosterone. After application of the hydro-alcoholic gel, about 10 percent of the testosterone is absorbed in the subdermal area forming a reservoir where the testosterone is released slowly into the blood stream providing a relatively steady serum testosterone concentration. The 1% AndroGel contains 50 mg testosterone in 5 g gel and nominally delivers about 5 mg of testosterone to the body. The gel was applied over a large area of skin over the shoulders and upper arms and over the abdomen. Steady state levels were reached in about a week. Serum testosterone levels increase in proportion to the applied dose of the gel in hypogonadal men.[40]

The surface area of the skin to which the gel was applied had a modest effect on the bioavailability of the testosterone gel. Application to four different sites (shoulders and two sides of the abdomen) compared to one site (four application on one shoulder) increased mean serum testosterone levels by 23%.[41] Since both absorption through the skin and clearance of testosterone may vary from patient to patient, periodic assessment of blood levels of testosterone is recommended. It should be noted that substantial day to day variations of serum testosterone concentration is often seen in the same man as well as among different men after testosterone gel application. This variation was tested in a sub-study of The Testosterone Trials, where hypogonadal older men administered 1 % AndroGel daily for 12 months. Dose adjustment, based on a 2-hour post-application testosterone measurement, was utilized to maintain serum testosterone concentrations within the adult male range.[42] In the sub study, ambulatory 2-hour post-application testosterone concentrations were measured in random order at two ambulatory clinic visits and during a 24-hour in clinic pharmacokinetics study. The ambulatory clinic 2-hour post-gel applications serum testosterone concentration did not correlate with the 2-hour nor the average concentration of serum testosterone during a 24-hour in clinic pharmacokinetics study after the same dose of testosterone gel application. Despite these variations in post-gel application testosterone concentrations, over 80 % of men had their 24-hour average serum testosterone concentration within the adult male reference range (300 to 1000 ng/dL; 10.4 to 34.7nmol/L).[43] As dose adjustments may be required to keep serum testosterone in the desired range, the physician should not make major dosage decisions on a single measurements as short term variability in blood testosterone levels may occur for unknown reasons. Testosterone gel relieves the symptoms of low testosterone, restores sexual function and mood, increases lean mass and bone mineral density, and decreases fat mass in testosterone deficient men.[44-46] In contrast to the testosterone patches, testosterone gel causes minimal skin

irritation (5.6% of patients) but has the anticipated adverse effects of androgens including acne, oiliness of skin, urinary symptoms. [44] A 1.62% AndroGel® is supplied as a pump where one actuation delivers 20.25 mg of testosterone.[47,48] The pharmacokinetic profile and safety profile is similar to the 1% gel but the recommended starting dose is 40.5 mg or two actuations which is less than 50 mg recommended for the 1 % gel.

Several other testosterone gel preparations are available in the US including Testim® (1 % testosterone gel)[49]; Fortesta (2% testosterone gel)[50] and the generic Vogelxo (1% testosterone gel) and Testosterone gel (1.62%). They have similar pharmacokinetics and safety profile as AndroGel. A 2% testosterone lotion (Axiron, not hydroalcoholic) was developed to be applied to the axilla. The starting dose is 60 mg/day, but the product has been discontinued because of market competition.[51]

These testosterone gel products dry rapidly within a few minutes after application. Because only about 10 percent of testosterone is absorbed into the subdermal tissues, the rest remains on the skin until it is washed off. Upon close skin contact, there may be skin-to-skin transfer of testosterone to another person, which could increase serum testosterone concentrations in women and children.[52-54] Before coming into close skin contact with another person, the area of testosterone gel application should be washed with soap and water or covered by clothing. This warning is in the prescription information for all gels (Warning: Secondary Exposure to Testosterone).

Serum testosterone concentrations reach steady state after a few days.[41] Dose adjustment can be made based on serum levels 2 to 8 hours after application. Most testosterone gels maintain serum testosterone concentrations within the adult male range for about 24 hours. The dose adjustment should aim at testosterone ranges usually within the mid adult male reference range.

Buccal/ Nasal Testosterone

Buccal testosterone tablets are applied twice a day to the gums where the tablets adhered to the gums and testosterone was absorbed into the venous system. The tablets can produce physiological testosterone levels in hypogonadal men. Mild gum irritation is reported in about 16 percent of men; about 4.7% of men have dislodgement of the buccal system.[55] This product is no longer available in the United States. Testosterone gel delivered through the nose three times a day can achieve average serum testosterone concentrations over 24-hour within the adult male range in 73% of men. Nasal testosterone improves sexual function, body composition and bone mineral density in hypogonadal men.[56] The medication is well tolerated and severely hypogonadal men had similar improvement compared to those with less severe testosterone insufficiency.[57] The dose titration from a total of 22 mg to 33 mg per day nasal testosterone can be based on the relief of symptoms of the patients.[58] Nasal administration of testosterone may have benefits on symptoms of hypogonadism while maintaining LH, FSH within the reference range in about 70 to 80% and sperm concentration over 5 million/ml in about 90% of the treated men in a 6-month uncontrolled study suggesting that there may be less suppression of spermatogenesis with nasal testosterone.[59] Further studies may be required to be certain of this benefit in men with symptomatic low testosterone wishing to father children.

Oral Testosterone Capsules

As discussed above, the currently available 17 alpha-alkylated modified testosterone tablets should not be used for testosterone replacement because of possible liver toxicity[29,30] and more marked effects on lowering FIDL cholesterol and increasing LDL cholesterol concentrations.[26] Testosterone undecanoate has been available as 40 mg capsules (Andriol Testocaps) for many decades outside of the United States.[60,61] One or two capsules ingested two or three times per day with food result in increased blood testosterone levels.[62,63] The medication is well tolerated and has an acceptable long term safety profile.[64] However, serum testosterone levels are frequently low before the administration of the next dose.[65]

A new oral formulation of testosterone undecanoate in self-emulsifying drug delivery system (Jatenzo®) was able to increase serum testosterone concentration to the adult male range when administered with food twice a day[66,67]. This testosterone delivery system was approved in 2019 by the Food and Drug Administration based on a study that showed that the orally administered testosterone undecanoate in the self-emulsifying system was able to maintain average testosterone concentration within the adult male range in 87% of hypogonadal men comparable to transdermal testosterone lotion/gel.[68] Because of the presence of intestinal 5 alpha reductase, serum dihydrotestosterone to testosterone ratio is increased; the clinical significance of the increased DHT levels is not known.[69] There was improvement in the sexual symptoms of hypogonadism and safety profile of this new testosterone undecanoate preparation is similar to the transdermal gels except that oral testosterone appeared to have greater increase in hematocrit, blood pressure and greater decrease in HDL-cholesterol than the transdermal gel.[68] Ambulatory blood pressure monitoring showed that the small increase in blood pressure is most likely a class effect as it was also shown with testosterone injections. Dose adjustment is based on a serum testosterone concentration drawn 4 to 6 hours after dosing.

Another oral testosterone undecanoate absorbed also via intestinal lymphatics is administered twice a day with meals without dose adjustment (Tlando®). This oral testosterone undecanoate provides adult male range levels in 72 to 88% of hypogonadal men, and has been tentatively approved by the FDA.[70]

Testosterone Ester Injections

Testosterone was isolated in 1935 and chemical synthesis was completed shortly afterwards. The short acting testosterone propionate was available in 1939 and the medium longer acting testosterone enanthate in 1954. Testosterone enanthate injection was the main testosterone preparation for therapeutic use in hypogonadal men for over 50 years.[71] Testosterone enanthate (Delatestryl®) and testosterone cypionate (Depo-Testosterone®) formulated in sesame or cotton seed oil, respectively, have similar pharmacokinetics. After a single intramuscular injection of 200 to 250 mg of testosterone enanthate or cypionate, serum concentration of testosterone rise to above the physiological level and then gradually decrease remaining in the adult reference range for about two weeks.[72,73] These testosterone esters are rapidly converted to testosterone in the body and are not hepatotoxic. Injectable testosterone produces higher levels about 2 days after injection and this peak may cause higher hemoglobin levels compared to transdermal preparations.[37]

The injections are administered slowly as a deep intramuscular injection into the gluteal muscle. The patients can be trained to administer their injections, but some prefer to have the injections administered by a health professional. The starting dose of testosterone enanthate or cypionate is 200 (or 250) mg intramuscularly every two weeks in adult men. Dose adjustment is either based usually on the trough level of serum testosterone that should be at the lower limit of the adult male range (300 ng/dL or 10.4 nmol/L) or in the mid normal range one week after injection. Recent studies demonstrate that administration of testosterone enanthate/cypionate as a weekly subcutaneous injection into the abdominal fat produced concentrations of serum testosterone within the adult male range while minimizing the peaks and troughs observed after intramuscular injections.[74] Testosterone enanthate can also be administered by a single-use autoinjector designed to eject high viscosity solution (oil) through a short 27-guage needle (Xyosted®). The autoinjector system enables patients to self-inject testosterone more easily and with less pain. The autoinjector is filled with 50, 75 or 100 mg of testosterone in sesame oil and the recommended starting dose is 75 mg every week. Steady state pharmacokinetics of serum testosterone concentrations were attained by week 4. The injection site adverse events included erythema and induration that were transient and mild.[75] A one-year study showed that 92.7% of hypogonadal men achieved average testosterone concentration between 300 to 1000 ng/dL (10.4 to 34.7 nmol/L). Dose adjustment was based on the trough testosterone level (at the lower reference range) before the next injection. Most patients reported no pain, but the common adverse events were elevated hematocrit and hemoglobin, increased in blood pressure and prostate specific antigen levels. Testosterone enanthate administered weekly by an autoinjector may provide a viable option for some men with hypogonadism.[76] Testosterone undecanoate in castor oil is also available as a 250 mg/mL deep intramuscular injection (Aveed®) in the United States. The recommended starting dose is 750 mg (3 mL) as the initial injection, followed by a second injection 4 weeks later and subsequent injections are administered every 10 weeks. The second injection administered 4 weeks reduces the chances of a sub-normal serum testosterone levels after the first injection.[77,78] This recommended treatment schedule is different from that in other countries, where testosterone undecanoate is administered as a 1000 mg in 4 ml injection as the first dose, followed by 1000 mg in 6 weeks and thereafter as 12 weekly injections. The use of 750 mg intramuscular injections eliminates some of the high serum testosterone levels observed with the higher dose and generates serum testosterone concentrations in the adult male range for 10 weeks.[79,80] Steady state testosterone concentration is achieved after the third injection in hypogonadal men. The serum testosterone concentrations were inversely proportional to body weight with higher levels in men with BMI< 30 Kg/m^2 or body weight <100 Kg.[81] Dose adjustment is usually based on the trough level before the next injection that should be in the lower adult male range.

The prescription information of Aveed includes warning for pulmonary oil microembolism reaction characterized by cough, dyspnea, hyperhidrosis, throat tightening, chest pain, dizziness and syncope which occurred rarely (0.1%) in patients administered testosterone undecanoate in castor oil. Most of the adverse events resolved within 30 minutes.[82] To reduce the risks of intravascular injection of testosterone undecanoate, the injection should be administered slowly deep into the gluteal muscle ensuring that the needle is not in a blood

vessel. It is required that the patient remains under observation in a healthcare setting for at least 30 minutes after injection. Proper administration technique of the 3 mL oil injection may reduce the incidence of this side effect.

Testosterone implants

Fused crystalline testosterone pellets for subcutaneous implantation require a small skin incision and insertion of the pellet through a trocar. There are problems associated with extrusion of the implants, but the frequency of extrusions decreases as the experience of operators increases. The pellets are available as 100 or 200 mg pellets inserted into the abdomen; four to six pellets provide steady serum testosterone levels in the mid adult male range for 4 to 6 months.[83] The most common adverse event is extrusion in about 8% of men that is related to physical activity. Continuation rate of use of testosterone pellets is > 90 percent.[84] In the United States, Testopel® pellets contain 75 mg of testosterone and are inserted in fat in the gluteal region. The prescription instructions indicate 2 to 6 implants will last 3 to 4 months; however, clinical studies showed that 6 to 12 pellets increased serum testosterone concentration in hypogonadal men to the adult male range within a month. Higher number of testosterone pellets produced more consistent and longer maintenance of serum testosterone concentrations for 4 to 6 months. There is low frequency of extrusion and hematoma formation that may be related to the number of pellets inserted. They are often favored by clinicians comfortable with the insertion process.[85,86] Increased hematocrit and hemoglobin have been reported with testosterone pellets, which is directly related to dose.[87,88] Monitoring of symptoms and serum testosterone concentrations will determine when and how many pellets should be implanted to maintain testosterone within the adult male range.

Treatment of Testosterone Deficiency in Men Using Methods Other Than Testosterone

We describe here the use of agents other than testosterone for the treatment of hypogonadism. These include non-hepatotoxic androgens and compounds that stimulate the production of testosterone by the Leydig cells in the testis.[89,90]

Modified Androgens

Although 17alpha-alkylated androgens are not recommended for androgen replacement for hypogonadal men, there are modified androgens with higher potency then testosterone that have been tested in men. Clinical studies of dihydrotestosterone formulated as a gel have been performed in hypogonadal men.[91-93] This formulation is only marketed in a few countries in Europe and has not underdone further development. Nandrolone, 19-nortestosterone (Fig. 1), and its derivatives are not hepatotoxic.[28] Modified 19-nortestosterone derivatives with methyl groups at the 7 or 11 position of the steroid ring have been studied (Figure 1). Esters of these compounds have been investigated in hypogonadal men for androgen replacement and eugonadal men as a potential male contraceptive (7α-methyl-19-norestosterone, MENT[94,95]; 7α-methyl-11 β-methyl-19-norestosterone, Dimethandrolone DMA[96-98]; and 11β-methyl-19-norestosterone, 11 β MNT[98,99]). These modified androgens did not exhibit hepatotoxicity in early phase clinical

studies and are being formulated as oral capsules (to be taken with food), injections and implants. Because these modified androgens may not aromatize to estrogenic compounds, longer-term studies are required to demonstrate lack of adverse effects on bone health.[93,100]

Selective Androgen Receptor Modulators (SARMS)

Non-steroidal, orally bioavailable, selective androgen receptor modulators (SARMs) with tissue specific action that promote muscle and bone health without affecting prostate growth have also been tested (see Chapter 12). Non-steroidal SARMS have been tested for safety and tolerability. Certain SARMs suppressed endogenous production of testosterone with increase in lean mass, no change in fat mas, and decreased HDL-cholesterol and triglycerides.[101] SARMs are being developed for prevention and treatment of frailty in older men and women with impaired ability to do their daily activity and or those with cancer cachexia.[102-104] Clinical studies showed that treatment with a SARM of men and post-menopausal women with frailty or cancer cachexia for 12 weeks significantly increased lean mass and physical function.[105,106,107] Other studies are in progress where a SARM is used to treat cancer cachexia associated with non-small cell lung cancer.[108] The Food and Drug Administration has not yet approved a SARM for treatment of cachexia.[109] This may be related to concern about the potential abuse of anabolic agents for enhancement of athletic performance and bodybuilding. Recreational users of SARMs can obtain these compounds without quality control via the internet; there is a risk that inappropriate off-label use could result in deleterious effects.[110]

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG, Pregnyl®) and recombinant human luteinizing hormone (Lutropin alfa, Luveris®) are administered as intramuscular or subcutaneous injections in men to stimulate Leydig cells in the testis to produce endogenous testosterone. Because these hormones rely on relatively normal Leydig cells to produce testosterone, they are effective in treatment of men with hypogonadotropic hypogonadism but not in men with primary testicular dysfunction. Human recombinant LH is available only for ovulation induction in females. The dose of hCG for off label use in hypogonadotropic men is between 500 to 2000 IU two or three times a week.[111] Serum testosterone after hCG administration should be in the mid adult male range and dose can be adjusted to keep testosterone within this range. In males with delayed puberty, hCG is used to induce puberty and to assess the testicular responsiveness to this gonadotropin.[112] In males with post-pubertal hypogonadotropic hypogonadism, hCG alone is usually adequate for stimulating Leydig cells to produce testosterone and maintaining adequate intra-testicular testosterone concentrations to stimulate spermatogenesis.[113,114] Chronic administration of hCG may increase serum levels of estradiol; it is thought that this is due to increased serum levels of testosterone and increased aromatization of testosterone and androstenedione in the testes.[115] Because of cost and the frequency of injections, men with hypogonadotropic hypogonadism are usually treated with testosterone until the patient and his partner desire fertility. Then hCG with or without recombinant hFSH can be used to initiate or re-initiate spermatogenesis.[111,116,117] Studies have shown that prior testosterone treatment of hypogonadal men does not adversely affect responsiveness to hCG although the recovery of spermatogenesis may take longer time.[118-120] In contrast, others have reported that

testosterone replacement in hypogonadal men may adversely affect spermatogenesis after testosterone is withdrawn.[121] Recovery of spermatogenesis after testosterone treatment in healthy adult men has been documented in male hormonal contraceptive studies[122] and in men after androgen abuse.[123,124] Measurement of intratesticular testosterone showed that hCG treatment at relatively low doses was able to maintain intratesticular testosterone concentration when gonadotropins were suppressed by exogenous testosterone injections.[111] Based on this observation, hCG has been proposed to be used with testosterone injections for more rapid recovery of spermatogenesis[125] as well as preventing the suppression of spermatogenesis[126] induced by exogenous testosterone administration. These studies should be verified in multicenter, larger, controlled studies. Fertility induction in hypogonadal men is described in greater detail in Chapter 14.

Estrogen Antagonists and Aromatase Inhibitors

Partial estrogen antagonists (e.g., clomiphene) and selective estrogen receptor modulators (SERMs, e.g., tamoxifen) bind to the estrogen receptors and decrease the effects of estrogens on target tissues. Aromatase inhibitors (e.g., Anastrozole, Letrozole) decrease estrogen concentrations by preventing the conversion of androgens to estrogens. These agents remove the negative feedback of estrogens on the hypothalamus and pituitary and stimulate the secretion of both gonadotropins LH and FSH. LH stimulates testosterone production by the Leydig cells in the testis and together with FSH stimulates spermatogenesis. These agents have no effect in patients with complete deficiency of LH and FSH or those with primary testicular failure causing testosterone deficiency. Estrogen antagonists such as clomiphene have been used in men with testosterone insufficiency with symptomatic improvement and increased bone mineral density.[127,128] Aromatase inhibitors have been used to stimulate endogenous testosterone production.[129,130] For these agents, the increase in LH and FSH and serum testosterone can be monitored and dose adjusted to attain serum testosterone levels in the mid adult range. Adverse effects with bone health occur when aromatase inhibitors are administered for months because of decreased bone mineral density associated with decreased estradiol concentrations.[119] Aromatase inhibitors are also used in uncontrolled studies in hypogonadal infertile men with and without concomitant testosterone therapy to improve testicular sperm retrieval for intracytoplasmic sperm injection.[131,132]

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- The decision on which testosterone preparation for replacement therapy resides with the patient after information on the differences between different modalities is provided by the health professional.

- Testosterone prescriptions soared from 2000 to 2011 with the introduction of transdermal testosterone gels.
- About 18% of the men only filled testosterone prescription once.
- From 2013 to 2016, the prescriptions for testosterone replacement decreased following FDA and professional society recommendations to use testosterone therapy only for symptomatic men with consistently low testosterone.

- The goal of testosterone replacement is to maintain serum testosterone concentration in the mid reference range of adult men (about 400 to 800 ng/dL; 13.9 to 27.8 nmol/L)
- Serum testosterone levels achieved with testosterone replacement are related to increases in lean and bone mass, sexual activity and desire, and hemoglobin and hematocrit, and decrease in fat mass
- Modified non-aromatizable androgens, in particular the 17alpha-alkylated androgens, are not recommended for testosterone replacement therapy.

Transdermal testosterone

- Delivery of testosterone on the skin results in a relatively steady release of testosterone from a reservoir in the subdermal reservoir.
- Transdermal patches are a closed system and produce skin irritation that necessitates stopping application in about 10 percent of men.
- Transdermal testosterone gels and solutions have less skin irritation/rash but can be transferred upon close skin contact resulting in secondary exposure of another person to testosterone.
- Skin transfer can be prevented by washing the application area or covering the skin with clothing.
- Dose adjustment can be accomplished by measuring testosterone concentration about 2 to 8 hours after gel application.

Buccal/ Nasal Testosterone

- Buccal tablets dislodge from the gums and may cause gum irritation. The product has been discontinued.
- Nasal testosterone must be applied three times a day to maintain serum testosterone within the adult male range.

Oral testosterone capsules

- Oral testosterone undecanoate capsules had been used throughout the world except United States with proven long-term safety.
- New testosterone undecanoate delivery systems administered twice a day with food are available and provide acceptable adult male concentrations in most hypogonadal men. Safety profile is like transdermal testosterone.

Testosterone Ester Injections

- Intramuscular testosterone enanthate and cypionate have been used since the 1950s with long- term safety data. The pharmacokinetics profile showed that there were peaks and troughs of serum testosterone after each injection.
- Weekly subcutaneous injections of testosterone enanthate provide more steady concentrations of testosterone. The patients can self-administer the injections with less pain than intramuscular injection.
- Testosterone undecanoate injections are long acting. Once steady state is reached after the third injection, the patient can administer his own injections every 10 weeks. Dose adjustment can be accomplished based on the 7-day mid-range or trough serum testosterone level prior to the next injection when every two-week regimen is used.
- Pulmonary oil micro embolism presenting usually with cough is a rare occurrence after testosterone ester injection. Injection should be administered slowly with a small gauge needle.

- Testosterone pellets are available in the United States as 75 mg testosterone per implant.
- Insertion of 10 to 12 pellets will maintain testosterone concentrations in the adult male range for 4 to 6 weeks with relief of symptoms
- Extrusions can occur that may depend on the number of the pellets inserted and work activity

Non-testosterone treatment for testosterone deficiency

- There are modified androgens that are not hepatotoxic and more potent than testosterone, but efficacy and safety of these compounds have yet to be verified in hypogonadal men.
- Selective androgen receptor modulators are not usually designed for testosterone deficiency but for treatment of sarcopenia and frailty.
- Human chorionic gonadotropin is used to in boys with hypogonadotropic hypogonadism and delayed puberty to initiate puberty and spermatogenesis. Because of the cost and frequency of injections, they are not generally used for testosterone replacement in hypogonadal men unless fertility is desired.
- Estrogen receptor antagonists and aromatase inhibitors increase LH and FSH and testosterone production. These agents are not useful in men with primary hypogonadism and patients with anatomically deficient FSH and LH. Aromatase

Summary

Men with testosterone deficiency should be replaced with testosterone unless there are contraindications or near-term fertility is desired. Testosterone ester injections have proven safety and efficacy for over 70 years. Since 2000, many options are available to deliver testosterone to correct testosterone deficiency. All testosterone replacement methods have been shown to be efficacious as shown by the normalization of serum testosterone levels. These methods include transdermal patches and gels, oral capsules, intranasal testosterone, long-acting intramuscular injections, subcutaneous injections, and testosterone implants. Dose adjustment strategies to achieve serum testosterone in the mid adult male range and relief of symptoms depend on the method used. Human chorionic gonadotropin, SERMs, estrogen antagonists and aromatase inhibitors stimulate the endogenous production of testosterone and improve symptoms of hypogonadism when the testis can respond. Non-aromatizable potent modified androgens and aromatase inhibitors may cause bone loss, long-term use may not be advisable in hypogonadal men.

Key points:

- Testosterone replacement is efficacious in elevating serum testosterone into the adult male range and improve symptoms in hypogonadal men.
- Many testosterone methods of delivery are available and are safe when used according to recommendations.
- The method of testosterone replacement is decided by the patient in consultation with the physician.
- Dose adjustment requires monitoring testosterone concentrations to achieve the desired testosterone concentration usually in the mid adult male range.
- Modified androgens that are potentially hepatotoxic should not be used; those androgens that do not aromatize to estrogens should be used with caution because of bone loss.

Synopsis

All approved testosterone replacement methods, when used according to recommendations, can restore normal serum testosterone concentrations, and relieve symptoms in most hypogonadal men. Selection of the method depends on patient's preference with advice from the physician. Dose adjustment is possible with most delivery methods but may not be necessary in all hypogonadal men. Use of hepatotoxic androgens must be avoided. Testosterone treatment induces reversible suppression of spermatogenesis; if fertility is desired in the near future, human chronic gonadotropin, selective estrogen receptor modulator, estrogen antagonist or an aromatase inhibitor that stimulate endogenous testosterone production may be used.

Clinical Care Points

- Men with testosterone deficiency should be treated with testosterone.
- Selection of the method of delivering testosterone depends on the needs of the patient and his preference.
- Some modified androgens such as the 17 alpha-alkylated androgens are hepatotoxic and non-aromatizable androgens may cause bone loss that needs to be monitored.
- All existing approved testosterone formulations achieve serum testosterone in the adult male range and improve symptoms in most hypogonadal men.
- Dose adjustment should be individualized depending on the method used and treatment goals.
- Stimulators of endogenous testosterone production are usually used for limited periods of time mainly during puberty and when the man desires fertility.
- Prior long-term treatment with testosterone products will suppress spermatogenesis that is reversible upon discontinuation of treatment and human chorionic gonadotropin may accelerate the recovery of spermatogenesis.

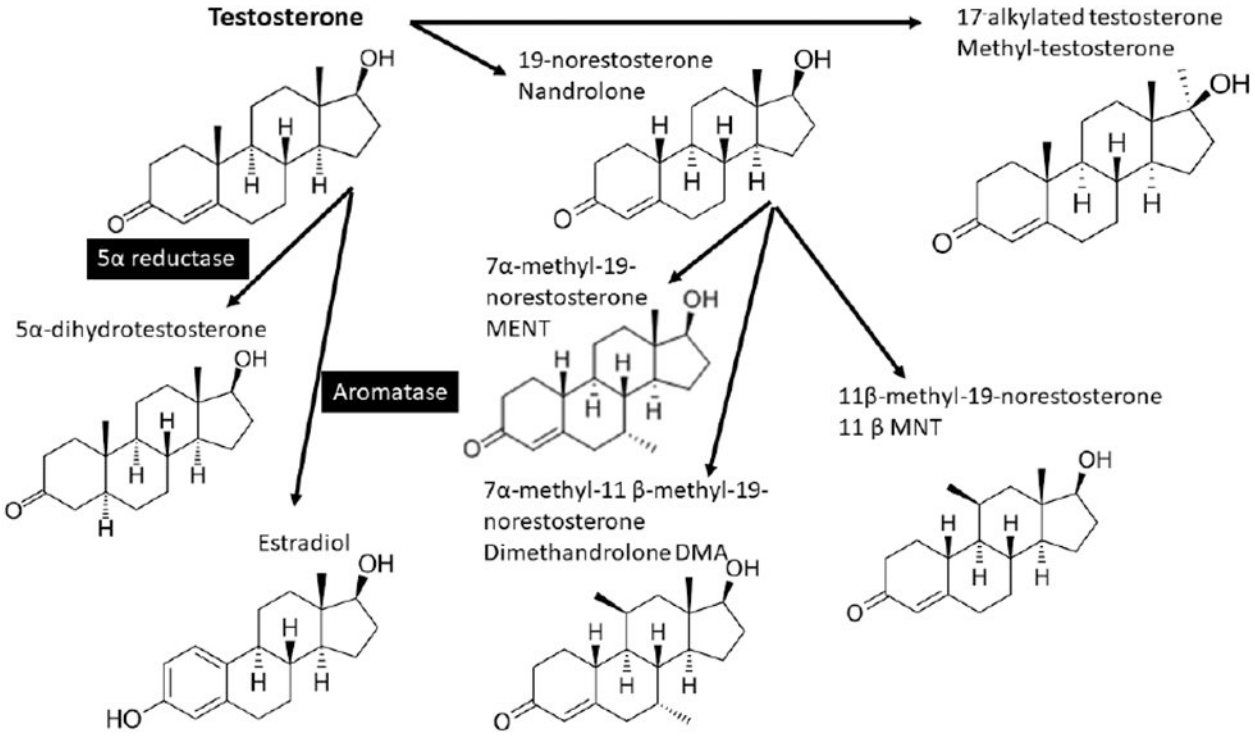

Figure 1.

Chemical structure of testosterone and is conversion to 5α-dihydrotestosterone and estradiol. Addition of a methyl group at 17α position testosterone results in methyl-testosterone that is hepatotoxic. Removal of a methyl group at the 19-position from testosterone results in 19-nortestosterone. 19-nortestosterone and its derivatives are not hepatotoxic.

Table 1.

Testosterone Products Approved by the Food and Drug Administration in Unites States (2021)

Delivery System/Drug	Brand Name	Recommended Dose Regimen	Available Format
Topical/ Transdermal			
Testosterone patch	Androderm	2 or 4 mg patch/day	4 mg starting dose, should not apply the patch to the same are within 7 days applied to back, abdomen, upper arms
Testosterone gel	AndroGel	1% gel – 50 to 100 mg of testosterone per day 1.62 % gel – 40.5 to 81 mg of testosterone per day	25 or 50 mg testosterone packets 20.25 mg testosterone one pump actuation or a 20.25 mg packet. 40.5mg testosterone two pump actuation or a 40.5 packet Applied to shoulders and upper arms
Testosterone gel	Testim	1% gel – 50mg of testosterone /tube	50 mg /day starting dose Applied to shoulder and upper arms
Testosterone gel	Fortesta	2% gel 10mg/0.5 g per pump actuation	40 mg (4 pump actuations)/day starting dose Applied to inner thighs
Testosterone gel	Vogelxo Testosterone Gel	1% gel 50 or 100mg per tube or packet, 12.5mg per actuation for pump 1.62% gel similar to AndroGel (1.62%)	Generic testosterone gel Generic, same as AndroGel 1.62%
Testosterone lotion	Axiron	2% lotion 30 mg/pump actuation	Start with 60 mg Applied to axilla Discontinued
Buccal/Nasal			
Buccal tablets	Striant	30 mg twice/day	Applied to gum, dislodging of tablets Discontinued
Nasal gel	Natesto	11 mg gel intranasal three times per day	Start with 1 actuation (5.5 mg) one into each nostril total 11mg Apply to nose three times per day.
Oral Capsule			
Testosterone undecanoate	Andriol	40 mg capsules two or three times a day	80 to 120 mg per dayNot available in US
Testosterone undecanoate	Jatanzo	158 to 396 mg twice per day	Start with 237mg twice a day with food.
Testosterone undecanoate	Tlando	225 mg twice per day	Tentative approval by FDA
Injection			
Testosterone enanthate	Xyosted Delatestryl	50, 75 and 100mg in 0.5mL sesame oil 200mg/mL sesame oil	Autoinjector Start with 75 mg once per week subcutaneously injection to abdomen Intramuscular injection once in 2 weeks Not available in US
Testosterone cypionate	Depo-Testosterone	100 mg/mL or 200 mg/mL in cottonseed oil	Administered by deep intramuscular injection to gluteal muscle once in 2 weeks. Can be administered subcutaneously every week
Testosterone undecanoate	Aveed	750 mg/3mL (250 mg/mL) in castor oil	Start with 750 mg, repeat 750 mg after 4 weeks and then every 10 weeks. Deep IM slowly into gluteal muscle. 30 minutes observation for pulmonary oil embolism, most last for few minutes to some several hours.

Delivery System/Drug	Brand Name	Recommended Dose Regimen	Available Format
Implants			
Testosterone	Testopel pellets	75 mg per pellet	Inserted subcutaneously by health professional in fat in hip area Implant 2 to 6 implants will last 3 to 4 months; 6 to 10 implants will last for 4 to 6 months