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Aging-Related Changes in Male Reproductive Function

A number of cross-sectional and longitudinal studies (e.g., The Baltimore Longitudinal Study of Aging and the Massachusetts Male Aging Study) have established that testosterone concentrations decrease with advancing age. This age-related decline starts in the third decade of life and progresses slowly; the rate of decline in testosterone concentrations is greater for men with chronic illness and for those taking medications than in healthy older men. Because SHBG concentrations are higher in older men than in younger men, free or bioavailable testosterone concentrations decline with aging to a greater extent than total testosterone concentrations. The age-related decline in testosterone is due to defects at all levels of the hypothalamic-pituitary-testicular axis: pulsatile GnRH secretion is attenuated, LH response to GnRH is reduced, and testicular response to LH is impaired. However, the gradual rise of LH with aging suggests that testis dysfunction is the main cause of declining androgen levels. The term *andropause* has been used to denote age-related decline in testosterone concentrations; this term is a misnomer because there is no discrete time when testosterone concentrations decline abruptly.

It is speculated that age-related decline in testosterone concentrations contributes to sexual dysfunction, loss of muscle mass and function, frailty, gain in fat mass, cognitive impairment, and loss of body hair. Initial studies of testosterone supplementation in older men with low or low normal testosterone levels have demonstrated a modest increase of fat-free mass and grip strength; a decrease in fat mass; an improved sense of well being, energy, visuo-spatial orientation, and verbal memory; and a modest increment in bone mineral density. However, the long-term risks of testosterone supplementation in older men remain largely unknown. In particular, physiologic testosterone replacement might increase the risk of prostate cancer or exacerbate cardiovascular disease. Population screening of all older men for low testosterone levels is not recommended, and testing should be restricted to men who have symptoms or physical features attributable to androgen deficiency. In men with documented androgen deficiency, testosterone replacement may be considered on an individualized basis and should be instituted after careful discussion of the risks and benefits (see Testosterone Replacement, below).

Testicular morphology, semen production, and fertility are maintained up to a very old age in men. Although concern has been expressed about age-related increases in germ cell mutations and impairment of DNA repair mechanisms, the frequency of chromosomal aneuploidy or structural abnormalities does not increase in the sperm of older men. However, the incidence of autosomal dominant diseases, such as achondroplasia, polyposis coli, Marfan syndrome, and Apert syndrome, increases in the offspring of men who are advanced in age, consistent with transmission of sporadic missense mutations.

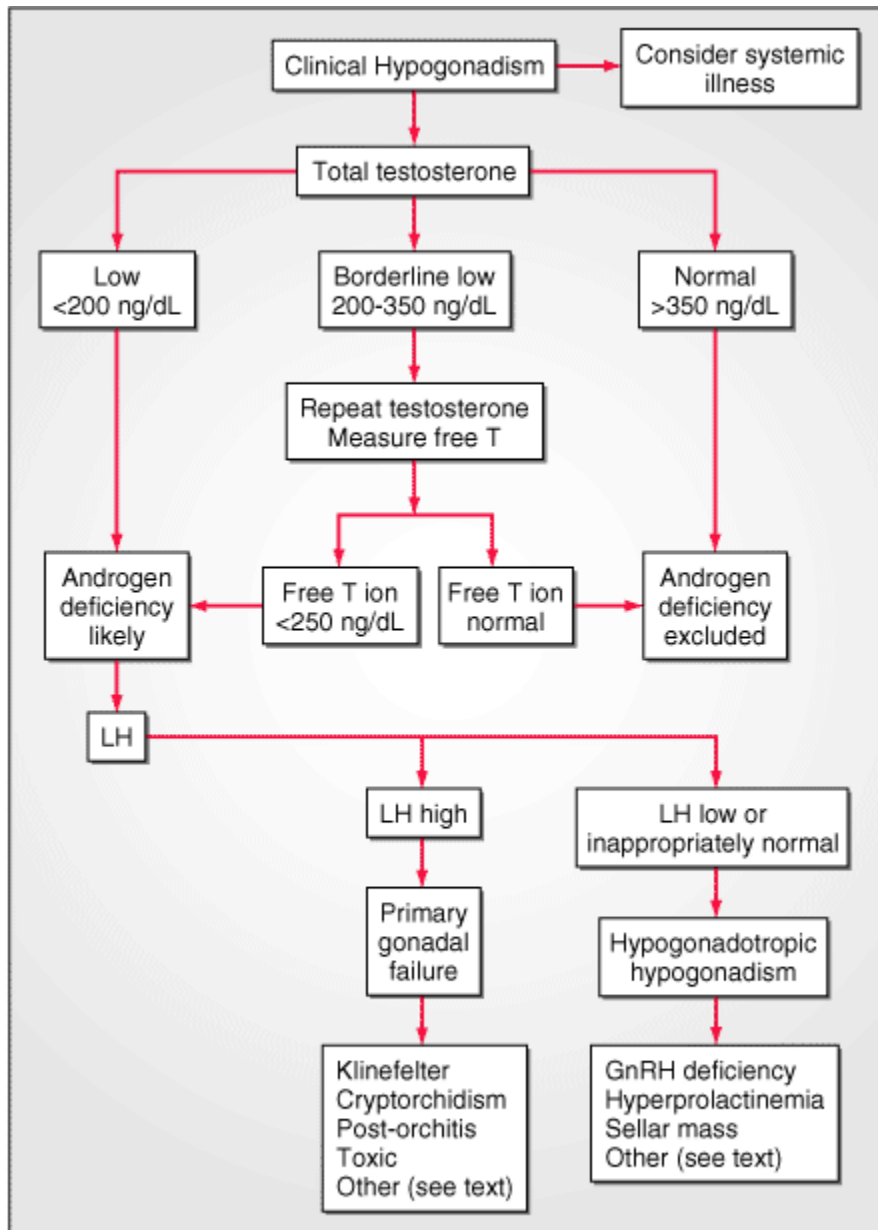
APPROACH TO THE PATIENT

Hypogonadism is often heralded by decreased sex drive, reduced frequency of sexual intercourse or inability to maintain erections, reduced beard growth, loss of muscle mass, decreased testicular size, and gynecomastia. Less than 10% of patients with erectile dysfunction alone have testosterone deficiency. Thus, it is useful to look for a constellation of symptoms and signs suggestive of androgen deficiency. Except when extreme, these clinical features may be difficult to distinguish from changes that occur with normal aging. Moreover, androgen deficiency may develop gradually. Population studies, such as the Massachusetts Male Aging Study, suggest

that about 4% of men between the ages of 40 and 70 have testosterone levels <150 ng/dL. Thus, androgen deficiency is not uncommon. The changes for the clinician are (1) to decide when to evaluate a man for possible androgen deficiency, (2) to assess when there is laboratory evidence for androgen deficiency and determine its cause, and (3) to decide when and how to treat patients with androgen deficiency.

When symptoms or clinical features suggest possible androgen deficiency, the laboratory evaluation is initiated by the measurement of total testosterone, preferably in the morning (Fig. 325-6). A total testosterone level <200 ng/dL, in association with symptoms, is evidence of testosterone deficiency. An early-morning testosterone level >350 ng/dL makes the diagnosis of androgen deficiency unlikely. In men with testosterone levels between 200 and 350 ng/dL, the total testosterone level should be repeated and a free testosterone level should be measured. In older men and in patients with other clinical states that are associated with alterations in SHBG levels, a direct measurement of free testosterone level by equilibrium dialysis can be useful in unmasking testosterone deficiency.

Figure 325-6



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Evaluation of hypogonadism. T, testosterone; LH, luteinizing hormone; GnRH, gonadotropin-releasing hormone.

When androgen deficiency has been confirmed by low testosterone concentrations, LH should be measured to classify the patient as having hypergonadotropic (high LH) or hypogonadotropic (low or inappropriately normal LH) hypogonadism. An elevated LH level indicates that the defect is at the testicular level. Common causes of primary testicular failure include Klinefelter syndrome, HIV infection, uncorrected cryptorchidism, cancer chemotherapeutic agents, radiation, surgical orchiectomy, or prior infectious orchitis. Unless causes of primary testicular failure are known, a karyotype should be performed in men with low testosterone and elevated LH to exclude Klinefelter syndrome. Men who have a low testosterone but "inappropriately normal" or low LH levels have hypogonadotropic hypogonadism; their defect resides at the hypothalamic-pituitary level. Common causes of acquired hypogonadotropic hypogonadism include space-occupying lesions of the sella, hyperprolactinemia, chronic illness, hemochromatosis, excessive exercise, and substance abuse. Measurement of PRL and MRI scan

of the hypothalamic-pituitary region can help exclude the presence of a space-occupying lesion. Patients in whom known causes of hypogonadotropic hypogonadism have been excluded are classified as having IHH. It is not unusual for congenital causes of hypogonadotropic hypogonadism, such as Kallmann syndrome, to be diagnosed in young adults.

TREATMENT

Gonadotropins

Gonadotropin therapy is used to establish or restore fertility in patients with gonadotropin deficiency of any cause. Several gonadotropin preparations are available. Human menopausal gonadotropin (hMG) (purified from the urine of postmenopausal women) contains 75 IU FSH and 75 IU LH per vial. hCG (purified from the urine of pregnant women) has little FSH activity and resembles LH in its ability to stimulate testosterone production by Leydig cells. Recombinant hCG is now available. Because of the expense of hMG, treatment is usually begun with hCG alone, and hMG is added later to promote the FSH-dependent stages of spermatid development. Recombinant human FSH (hFSH) is now available and is indistinguishable from purified urinary hFSH in its biologic activity and pharmacokinetics in vitro and in vivo, although the mature β subunit of recombinant hFSH has seven fewer amino acids. Recombinant hFSH is available in ampoules containing 75 IU ($\approx 7.5 \mu\text{g}$ FSH), which accounts for >99% of protein content. Once spermatogenesis is restored using combined FSH and LH therapy, hCG alone is often sufficient to maintain spermatogenesis.

Although a variety of treatment regimens are used, 1500 to 2000 IU of hCG administered intramuscularly three times weekly is a reasonable starting dose. Testosterone levels should be measured 6 to 8 weeks later, and 48 to 72 h after the hCG injection; the hCG dose should be adjusted to achieve testosterone levels in the mid-normal range. Sperm counts should be monitored on a monthly basis. It may take several months for spermatogenesis to be restored; therefore, it is important to forewarn patients about the potential length and expense of the treatment and to provide conservative estimates of success rates. If testosterone levels are in the mid-normal range but the sperm concentrations are low after 6 months of therapy with hCG alone, FSH should be added. This can be done by using hMG, highly purified urinary hFSH, or recombinant hFSH. The selection of FSH dose is empirical. A common practice is to start with the addition of 75 IU FSH three times each week in conjunction with the hCG injections. If sperm densities are still low after 3 months of combined treatment, the FSH dose should be increased to 150 IU. Occasionally, it may take ≈ 18 to 24 months for spermatogenesis to be restored.

The two best predictors of success using gonadotropin therapy in hypogonadotropic men are testicular volume at presentation and time of onset. In general, men with testicular volumes >8 mL have better response rates than those who have testicular volumes <4 mL. Patients who became hypogonadotropic after puberty experience higher success rates than those who have never undergone pubertal changes. Spermatogenesis can usually be reinitiated by hCG alone, with high rates of success for men with postpubertal onset of hypogonadotropism. The presence of a primary testicular abnormality, such as cryptorchidism, will attenuate testicular response to gonadotropin therapy. Prior androgen therapy does not affect subsequent response to gonadotropin therapy.

GnRH

In patients with documented GnRH deficiency, both pubertal development and spermatogenesis can be successfully induced by pulsatile administration of low doses of GnRH. This response requires normal pituitary and testicular function. Therapy usually begins with an initial dose of 25 ng/kg per pulse administered subcutaneously every 2 h by a portable infusion pump. Testosterone, LH, and FSH levels should be monitored. The dose of GnRH is increased until testosterone levels reach the mid-normal range. Doses ranging from 25 to 200 ng/kg may be required to induce virilization. Once pubertal changes have been initiated, the dose of GnRH can often be reduced. Increased sperm counts and testicular volume have been reported in >70% of treated

men, and improvements in sexual function and virilization can be induced in >90% of patients. Cutaneous infections occur but are infrequent and minor. Carrying a portable infusion device can be cumbersome, and follow-up of these patients requires physician supervision and laboratory monitoring. Some patients with IHH have cryptorchidism; men with this additional testicular defect may not respond to GnRH or gonadotropin therapy.

Comparative studies of gonadotropin therapy and pulsatile GnRH administration demonstrate that these two therapies are similar in terms of the time to first appearance of sperm or pregnancy rates; both approaches are equally effective in inducing spermatogenesis in men with hypogonadotropic hypogonadism caused by GnRH deficiency. However, most patients find intermittent gonadotropin injections preferable to wearing a continuous infusion pump.

Testosterone Replacement

Androgen therapy is indicated to restore testosterone levels to normal to correct features of androgen deficiency. Testosterone replacement improves libido and overall sexual activity, increases energy, lean muscle mass, and bone density and provides the patient a better sense of well-being. The benefits of testosterone replacement therapy have only been proven in men who have documented androgen deficiency, as demonstrated by testosterone levels that are well below the lower limit of normal (<250 ng/dL).

Testosterone is available in a variety of formulations with distinct pharmacokinetics (Table 325-3). Testosterone serves as a prohormone and is converted to 17 β -estradiol by aromatase and to 5 α -dihydrotestosterone by 5 α -reductase. Therefore, when evaluating testosterone formulations, it is important to consider whether the formulation being used can achieve physiologic estradiol and DHT concentrations, in addition to normal testosterone concentrations. Although testosterone concentrations at the lower end of the normal male range can restore sexual function, it is not clear whether low-normal testosterone levels can maintain bone mineral density and muscle mass. The current recommendation is to restore testosterone levels to the mid-normal range.

Table 325–3. Clinical Pharmacology of Testosterone Formulations

Formulation	Regimen	Pharmacokinetics	DHT and Estradiol	Advantages	Disadvantages
Testosterone enanthate or cypionate	100 mg IM weekly or 200 mg IM every 2 weeks	After a single IM injection, testosterone levels rise into the supraphysiologic range and then decline gradually into the hypogonadal range by the end of the dosing interval	DHT and estradiol levels rise in proportion to the increase in testosterone levels; T:DHT and T:E ₂ ratios do not change	Corrects symptoms of androgen deficiency Relatively inexpensive, if self-administered Flexibility of dosing	Requires IM injection Peaks and valleys in testosterone levels
Scrotal testosterone patch	One scrotal patch designed to deliver 6 mg over 24 h applied daily	Normalizes testosterone levels in many but not all androgen-deficient men	Estradiol levels are in the physiologic male range, but DHT levels rise into the supraphysiologic range	Corrects symptoms of androgen deficiency	To promote optimum adherence of the patch, scrotal skin needs to be shaved High DHT levels

Nongenital transdermal system	One or two patches, designed to deliver 5–10 mg testosterone over 24 h applied daily on nonpressure areas	Restores testosterone, DHT, and estradiol levels into the physiologic male range	T:DHT and T:estradiol levels are in the physiologic male range	Ease of application, corrects symptoms of androgen deficiency, and mimics the normal diurnal rhythm of testosterone secretion. Lesser increase in hemoglobin than injectable esters	Testosterone levels in some androgen-deficient men may be in the low-normal range; these men may need application of two patches daily Skin irritation at the application site in some patients
Testosterone gel	Testosterone gel containing 50 to 100 mg testosterone should be applied daily	Restores testosterone and estradiol levels into the physiologic male range	DHT levels and T:DHT ratios are lower in hypogonadal men treated with the testosterone gel than in healthy eugonadal men	Corrects symptoms of androgen deficiency, provides flexibility of dosing, ease of application, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; moderately high DHT levels
17 α -methyl testosterone	Orally active, 17 α -alkylated compound that should not be used because of potential for liver toxicity	Orally active			Clinical responses variable; potential for liver toxicity; should not be used for treatment of androgen deficiency
Buccal adhesive testosterone	An adhesive, 10-mg tablet applied to buccal mucosa twice daily	Absorbed through buccal mucosa	Serum T and DHT in the normal male range	Ease of application	Limited experience, no evidence of liver toxicity, effects of food and brushing unclear

Note: DHT, dihydrotestosterone; T, testosterone, E₂, 17 β -estradiol.

Adapted from: American College of Physicians/American Society of Internal Medicine Disease Management Module on Male Hypogonadism.

ORAL DERIVATIVES OF TESTOSTERONE

Testosterone is well-absorbed after oral administration but quickly degrades during the first pass through the liver. Therefore, it is not possible to achieve sustained blood levels of testosterone after oral administration of crystalline testosterone. 17 α -alkylated derivatives of testosterone (e.g., 17 α -methyl testosterone, oxandrolone, fluoxymesterone) are relatively resistant to hepatic degradation and can be administered orally; however, because of the potential for hepatotoxicity, including cholestatic jaundice, peliosis, and hepatoma, these

formulations should not be used for testosterone replacement. Hereditary angioedema due to C1 esterase deficiency is the only exception to this general recommendation; in this condition, oral 17 α -alkylated androgens are useful because they stimulate hepatic synthesis of the C1 esterase inhibitor.

INJECTABLE FORMS OF TESTOSTERONE

The esterification of testosterone at the 17 β -hydroxy position makes the molecule hydrophobic and extends its duration of action. The slow release of testosterone ester from an oily depot in the muscle accounts for its extended duration of action. The longer the side chain, the greater the hydrophobicity of the ester and longer the duration of action. Thus, testosterone enanthate and cypionate with longer side chains have longer duration of action than testosterone propionate. Within 24 h after intramuscular administration of 200 mg testosterone enanthate or cypionate, testosterone levels rise into the high-normal or supraphysiologic range and then gradually decline into the hypogonadal range over the next 2 weeks. A bimonthly regimen of testosterone enanthate or cypionate therefore results in peaks and troughs in testosterone levels that are accompanied by changes in a patient's mood, sexual desire, and energy level. The kinetics of testosterone enanthate and cypionate are similar. Estradiol and DHT levels are normal if testosterone replacement is physiologic.

TRANSDERMAL TESTOSTERONE

Three transdermal testosterone patches are commercially available: a scrotal testosterone patch (Testoderm) and two nongenital patches (Androderm and Testoderm TTS). The scrotal transdermal testosterone patch, when applied daily to the scrotal skin, produces mid-normal testosterone levels in hypogonadal men 4 to 8 h after application followed by a gradual decrease in testosterone levels over the next 24 h. Estradiol levels are normal but DHT levels are increased due to the conversion of testosterone to DHT by the high amounts of 5 α -reductase in scrotal skin. There was initial concern that exposure to high DHT levels might have deleterious effects on the prostate; however, long-term follow-up of men treated with the scrotal patch has not revealed an unexpected increase in prostate problems.

With nongenital testosterone patches, testosterone, DHT, and estradiol levels are in the mid-normal range 4 to 12 h after application. Sexual function and a sense of well-being are restored in androgen-deficient men treated with the nongenital patch. One 5-mg patch may not be sufficient to increase testosterone into the mid-normal male range in all hypogonadal men; some patients may need daily administration of two 5-mg patches to achieve the targeted testosterone concentrations. The transdermal systems are more expensive than testosterone esters. The use of nongenital patches may be associated with skin irritation in some individuals.

TESTOSTERONE GEL

Two testosterone gels (Androgel) and Testim are available in 2.5- and 5-g unit doses that nominally deliver 25 and 50 mg of testosterone to the application site. Initial pharmacokinetic studies have demonstrated that 50-, 75-, and 100-mg doses applied daily to the skin can maintain total and free testosterone concentrations in the mid- to high-normal range in hypogonadal men. Total and free testosterone concentrations are uniform throughout the 24-h period. The current recommendations are to begin with a 50-mg dose and adjust the dose based on testosterone levels. The advantages of the testosterone gel are in its ease of application, its invisibility after application, and its flexibility of dosing. A major concern is the potential for inadvertent transfer of the gel to a sexual partner or to children who may come in close contact with the patient. The ratio of DHT to testosterone concentrations is higher in men treated with the testosterone gel.

A buccal adhesive testosterone tablet, which adheres to the buccal mucosa and releases testosterone as it is slowly dissolved, has been approved. After twice daily application of 10 to 20 mg tablets, serum testosterone levels are maintained within the normal male range in a majority of treated hypogonadal men. The adverse effects include buccal ulceration in a few subjects. The clinical experience with this formulation is limited, and the effects of food and brushing on absorption have not been studied in detail.

TESTOSTERONE FORMULATIONS NOT AVAILABLE IN THE UNITED STATES

Testosterone undecanoate, when administered orally in oleic acid, is absorbed preferentially through the lymphatics into the systemic circulation and is spared the first-pass degradation in the liver. Doses of 40 to 80 mg orally, two or three times daily, are typically used. However, the clinical responses are variable and suboptimal. DHT-to-testosterone ratios are higher in hypogonadal men treated with oral testosterone undecanoate, as compared to eugonadal men.

Implants of crystalline testosterone can be inserted in the subcutaneous tissue by means of a trocar through a small skin incision. Testosterone is released by surface erosion of the implant and absorbed into the systemic circulation. Four to six 200-mg implants can maintain testosterone in the mid- to high-normal range for up to 6 months. Potential drawbacks include incising the skin for insertion and removal, and spontaneous extrusions and fibrosis at the site of the implant.

NOVEL ANDROGEN FORMULATIONS

A number of androgen formulations with better pharmacokinetics or more selective activity profiles are under development. A biodegradable testosterone microsphere formulation provides physiologic testosterone levels for 10 to 11 weeks. Two long-acting esters, testosterone buciclate and testosterone undecanoate, when injected intramuscularly, can maintain circulating testosterone concentrations in the male range for 7 to 12 weeks. Initial clinical trials have demonstrated the feasibility of administering testosterone by the sublingual or buccal routes. 7α -methyl-19-nortestosterone is an androgen that cannot be 5α -reduced; therefore, compared to testosterone, it has relatively greater agonist activity in muscle and gonadotropin suppression but lesser activity on the prostate.

Analogous to the selective estrogen receptor modulators, such as raloxifene, it may be possible to develop selective androgen receptor modulators (SARMs) that exert the desired physiologic effects on muscle, bone, or sexual function but without adversely affecting the prostate and the cardiovascular system.

PHARMACOLOGIC USES OF ANDROGENS

In addition to hypogonadism, androgens have been used to treat a variety of disorders with the hope that anabolic actions of the agents (such as increase in nitrogen retention and muscle mass, increased hemoglobin) would outweigh any deleterious (e.g., virilization) actions of the drugs. The most common nonreplacement uses of androgen have been attempts to improve nitrogen balance in catabolic states (e.g., AIDS), self-administration by athletes to increase muscle mass and/or athletic performance, attempts to enhance erythropoiesis in refractory anemias (including the anemia of renal failure), treatment of hereditary angioedema and endometriosis, and management of growth retardation of various etiologies. Most of the expected benefits in these disorders have not been realized. The modest pharmacologic doses of androgens have little physiologic effect in men when superimposed on normal testicular androgen; in women, the virilizing side effects of androgens are formidable.

The most pervasive form of androgen abuse is by male athletes with the expectation that it will improve muscle development and athletic performance. In controlled studies using modest pharmacologic doses (two to four times the usual replacement doses), these agents do not consistently improve performance. However, at the doses frequently taken by athletes (which sometimes exceed 10 times the replacement dose), androgens enhance nitrogen balance and muscle mass; since the drugs have multiple side effects at high doses, these benefits do not outweigh the risks associated with androgen abuse in men, while androgen use by female athletes is associated with disfiguring virilization. The only established indications for androgen therapy aside from male hypogonadism are in selected patients with anemia due to bone marrow failure (an indication largely supplanted by erythropoietin) or for hereditary angioedema.

RECOMMENDED REGIMENS FOR ANDROGEN REPLACEMENT

Testosterone esters are administered weekly at doses of 75 to 100 mg intramuscularly, or 150 to 200 mg every

2 weeks. One 6-mg scrotal patch should be applied daily after shaving the scrotal skin. One or two 5-mg nongenital testosterone patches can be applied daily over the skin of the back, thigh, or upper arm away from pressure areas. Testosterone gel is typically applied over a covered area of skin at a dose of 50 to 100 mg daily; patients should wash their hands after gel application.

ESTABLISHING EFFICACY OF TESTOSTERONE REPLACEMENT THERAPY

Because a clinically useful marker of androgen action is not available, restoration of testosterone levels into the mid-normal range remains the goal of therapy. Measurements of LH and FSH are not useful in assessing the adequacy of testosterone replacement. Testosterone should be measured 3 months after initiating therapy to assess adequacy of therapy. In patients who are treated with testosterone enanthate or cypionate, testosterone levels should be 350 to 600 ng/dL 1 week after the injection. If testosterone levels are outside this range, adjustments should be made to either the dose or the interval between injections. In men on transdermal patch or gel therapy, testosterone levels should be in the mid-normal range (500 to 800 ng/dL) 4 to 12 h after application. If testosterone levels are outside this range, the dose should be adjusted.

Restoration of sexual function, secondary sex characteristics, and energy level and one's sense of well being are important objectives of testosterone replacement therapy. The patient should also be asked about sexual desire and activity, the presence of early morning erections, and whether he is able to achieve and maintain erections that are adequate for sexual intercourse. Some hypogonadal men continue to complain about sexual dysfunction even after testosterone replacement has been instituted; these patients may benefit from counseling. The hair growth in response to androgen replacement is variable and depends on ethnicity. Hypogonadal men with prepubertal onset of androgen deficiency who begin testosterone therapy in their late 20s or 30s may find it difficult to adjust to their newly found sexuality and may benefit from counseling. If the patient has a sexual partner, the partner should be included in counseling because of the dramatic physical and sexual changes that occur with androgen treatment.

CONTRAINDICATIONS FOR ANDROGEN ADMINISTRATION

Testosterone administration is contraindicated in men with a history of prostate cancer because androgens can promote tumor growth (Table 325-4). Testosterone should not be prescribed to men with severe symptoms of benign prostatic hypertrophy (AUA symptom score > 22), because even small increases in prostate volume may exacerbate obstructive symptoms. Testosterone replacement should not be administered to men with baseline hematocrit \geq 52%. Testosterone can induce and exacerbate sleep apnea because of its neuromuscular effects on the upper airway.

Table 325–4. Contraindications for Androgen Replacement

- The presence or history of prostate cancer
- Baseline PSA \geq 4 ng/mL or a palpable abnormality of the prostate without urologic evaluation to rule out prostate cancer
- Severe symptoms of lower urinary tract obstruction as indicated by IPSS or AUA symptom score of \geq 22
- Baseline hematocrit > 52%
- Severe sleep apnea
- Class IV congestive heart failure

Note: PSA, prostate-specific antigen, IPSS, International Prostate Symptom Score; AUA, American Urological Association.

MONITORING POTENTIAL ADVERSE EXPERIENCES

The clinical effectiveness and safety of testosterone replacement therapy should be performed 3 and 6 months after initiating testosterone therapy and annually thereafter.

Hemoglobin Levels

Administration of testosterone to androgen-deficient men is typically associated with a 3 to 5% increase in hemoglobin levels. Clinically significant erythrocytosis is uncommon in young hypogonadal men but can occur in men who have sleep apnea, a significant smoking history, chronic obstructive lung disease, or who are older in age. The magnitude of hemoglobin increase during testosterone therapy appears related to the peak testosterone levels. Transdermal testosterone replacement may produce a smaller hemoglobin increase than testosterone esters.

Digital Examination of the Prostate and Serum Psa Levels

Testosterone replacement therapy increases prostate volume to the size seen in age-matched controls but should not increase prostate volume beyond that expected for age. There is no evidence that testosterone replacement causes prostate cancer. However, androgen administration can exacerbate preexisting prostate cancer. Many older men harbor microscopic foci of cancer in their prostates. It is not known whether long-term testosterone administration will induce these microscopic foci to grow into clinically significant cancers.

Prostate-specific antigen (PSA) levels are lower in testosterone-deficient men and are restored to normal after testosterone replacement. There is considerable test-retest variability in PSA measurements; the average interassay coefficient of variation of PSA assays is 15%. The 95% confidence interval for the change in PSA values, measured 3 to 6 months apart, is 1.4 ng/mL. Increments in PSA levels after testosterone supplementation in androgen-deficient men are generally <0.5 ng/mL, and increments >1.0 ng/mL over a 3 to 6-month period are unusual. Nevertheless, administration of testosterone to men with baseline PSA levels between 2.5 and 4.0 ng/mL will cause PSA levels to exceed 4.0 ng/mL for some, and many of these men may undergo prostate biopsies. PSA velocity criterion can be used for patients who have sequential PSA measurements for >2 years; a change of >0.40 ng/mL per year merits closer urologic follow-up.

Cardiovascular Risk Assessment

The long-term effects of testosterone supplementation on cardiovascular risk are unknown. Testosterone effects on lipids depend on the dose (physiologic or supraphysiologic), the route of administration (oral or parenteral), and the formulation (whether aromatizable or not). Physiologic testosterone replacement by an aromatizable androgen has a modest effect on high-density lipoprotein (HDL) or no effect at all. In middle-aged men with low testosterone levels, physiologic testosterone replacement has been shown to improve insulin sensitivity and reduce visceral obesity. In epidemiologic studies, testosterone concentrations are inversely related to waist-to-hip ratio and directly correlated with HDL cholesterol levels. These data suggest that physiologic testosterone concentrations is correlated with factors associated with reduced cardiovascular risk. However, no prospective studies have examined the effect on testosterone replacement on cardiovascular risk.

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