REVIEW ARTICLE

MEDICAL PROGRESS

Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring

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Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms, including diminished libido and sense of vitality, erectile dysfunction, reduced muscle mass and bone density, depression, and anemia (Table 1). When hypogonadism occurs in an older man, the condition is often called andropause, or androgen deficiency of the aging male.

Hypogonadism affects an estimated 2 million to 4 million men in the United States; its prevalence increases with age (Fig. 1).[1,2] However, it has been estimated that only 5 percent of affected men currently receive treatment.[3] Recent interest in testosterone therapy has been fueled not only by increased medical awareness of the effects of hypogonadism, but also by media attention regarding hormone-replacement therapy in both men and women, the marketing of new topical testosterone formulations, and the desire of "baby boomers" to maintain vigor and health into their more mature years.

Although reports indicate that testosterone-replacement therapy may produce a wide range of benefits for men with hypogonadism that include improvement in libido,[4-6] bone density,[7,8] muscle mass,[6,7,9] body composition,[6,9,10] mood,[11] erythropoiesis,[6,11] and cognition,[11-13] considerable controversy remains regarding indications for testosterone supplementation in aging men.

Perhaps the most controversial topic in the ongoing discussion of testosterone-replacement therapy is the issue of risk (Table 2). Recent reports suggesting increased risks associated with hormone replacement in women[14,15] have aroused concern that men receiving hormone replacement may also be vulnerable to increased health risks. However, no large-scale, long-term studies have yet been initiated to assess the benefits and risks of testosterone-replacement therapy in men, in part because of theoretical concern regarding the risks of therapy, especially possible stimulation of prostate cancer by testosterone.

Despite this controversy, testosterone supplementation in the United States has increased substantially over the past several years, with an increase of more than 500 percent in prescription sales of testosterone products since 1993.[16] The purpose of this review is to discuss what is known and not known regarding the risks of testosterone-replacement therapy and to provide recommendations for the monitoring of men receiving testosterone treatment.

Forms of Testosterone Available for Administration

Injectable, transdermal, buccal, and oral testosterone formulations are available for clinical use in the United States, and other preparations are under development. These forms of treatment differ in several key areas, including their risk profiles.[4,17,18]

Testosterone enanthate and testosterone cypionate are supplied as esterified oil-soluble preparations for injection. A typical dose is 100 mg per week, or 200 to 300 mg every

two to three weeks. Peak serum levels occur 2 to 5 days after injection, and a return to base line is usually observed 10 to 14 days after injection. The advantages of this form of therapy include low cost and high peak serum levels of testosterone. The disadvantages include the pain of injection and the need for frequent medical visits for administration of the injections. A "roller coaster" effect can also occur, characterized by alternating periods of symptomatic benefit and a return to base-line symptoms, corresponding to the fluctuations in serum testosterone levels.[4,17-19]

Transdermal testosterone is available in either a scrotal or a nonscrotal skin patch and more recently has become available as a gel preparation. Daily application is required for each of these. They are designed to deliver 5 to 10 mg of testosterone per day. The advantages include ease of use and maintenance of relatively uniform serum testosterone levels over time.[19,20] Skin irritation is a frequent adverse effect of testosterone patches but is uncommon with gel preparations.[20,21] Inadequate absorption through the skin may limit the value of transdermal preparations in some persons.

Oral preparations available in the United States, such as methyltestosterone and fluoxymesterone, are infrequently prescribed, because of their association with substantial hepatotoxicity, including the development of benign and malignant neoplasms.[22] Use of these agents is discouraged because of their potential toxicity.

RISKS OF TESTOSTERONE-REPLACEMENT THERAPY

Testosterone is a steroid hormone with actions in a wide variety of organs and tissues. The major sites of potential risks and side effects are discussed in detail below and are represented in Figure 2.

TESTOSTERONE SUPPLEMENTATION AND CARDIOVASCULAR RISK

CORONARY ARTERY DISEASE

The belief that testosterone is a risk factor for cardiac disease is based on the observation that men have both a higher incidence of cardiovascular events and higher testosterone levels than women. However, few, if any, data support a causal relation between higher testosterone levels and heart disease.[23-26] Indeed, several studies suggest that higher testosterone levels may actually have a favorable effect on the risk of cardiovascular disease.[27-30]

Table 1. Hypogonadism.

Definition*

Hypogonadism is a clinical condition characterized by low serum testosterone levels occurring in association with any of the signs and symptoms listed below
- Sexual symptoms
  - Diminished libido
  - Erectile dysfunction
  - Difficulty achieving orgasm
  - Diminished intensity of the experience of orgasm
  - Diminished sexual penile sensation
- Diminished energy, sense of vitality, or sense of well-being
- Increased fatigue
- Depressed mood
- Impaired cognition
- Diminished muscle mass and strength
- Diminished bone density
- Anemia

Treatment of hypogonadism with testosterone supplementation may result in clinical benefits in some, all, or none of these areas

Terminology

In older men, hypogonadism is often referred to as andropause, or androgen deficiency of the aging male

The causes of hypogonadism may be classified as primary (due to inadequate testicular Leydig-cell function), secondary (due to inadequate pituitary stimulation of the testes by luteinizing hormone), or combined (common in older men)

* The definition is adapted from the 2002 position statement on diagnosis, treatment, and monitoring of hypogonadism by the Sexual Medicine Society of North America, a specialty society of the American Urological Association.

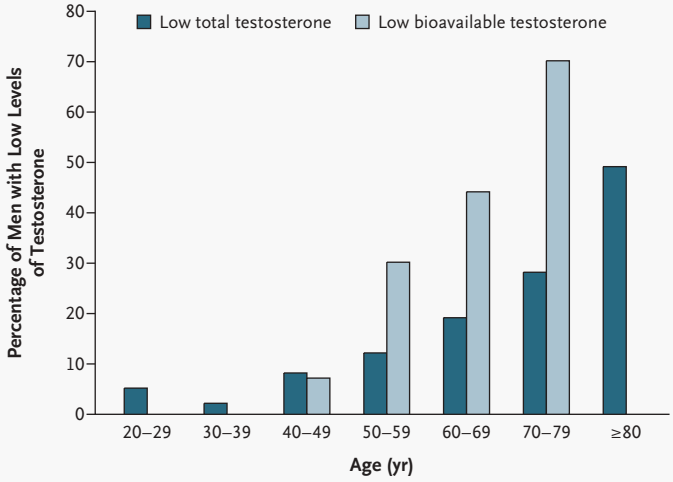

Figure 1. Prevalence of Low Levels of Total and Bioavailable Testosterone as an Index of Male Hypogonadism According to Decade of Life.

Dark bars represent the percentage of the population with total testosterone levels under 325 ng per deciliter,[1] and light bars represent the percentage of the population with bioavailable testosterone levels under 70 ng per deciliter.[2] Bioavailable testosterone was not measured in some age groups.

Table 2. Potential Risks Associated with Testosterone-Replacement Therapy.

Potential Risk	Comments
Cardiovascular disease	Existing evidence suggests a neutral or possible beneficial effect
Lipid alterations	Most studies show no change with physiologic replacement doses
Erythrocytosis	Wide range of risk, depending on mode of administration: 3–18% with transdermal administration, up to 44% with injection; requires monitoring
Fluid retention	Rarely of clinical significance
Benign prostatic hyperplasia	Rarely of clinical significance
Prostate cancer	Controversial; unknown level of risk; requires long-term monitoring
Hepatotoxicity	Limited to oral agents, which are infrequently used in the United States
Sleep apnea	Infrequent
Gynecomastia	Rare, usually reversible
Skin reactions	High incidence with patch (up to 66%), low incidence with gel (5%), rare with injections
Acne or oily skin	Infrequent
Testicular atrophy or infertility	Common, especially in young men; usually reversible with cessation of treatment

Kabakci et al.[24] failed to find any consistent relation between serum levels of free or total testosterone and coronary atherosclerosis in men undergoing coronary angiography. Similar results were reported by English et al.,[29] who found that men with established cardiovascular disease documented by angiograms had lower levels of free and bioavailable testosterone than men with normal angiograms. In the population-based Rotterdam Study, serum levels of total and bioavailable testosterone were evaluated in 504 men; those in the highest two thirds of the study group in terms of these levels had age-adjusted relative risks of severe aortic atherosclerosis of 0.4 and 0.2, respectively, as compared with men in the lowest third.[30] These results argue against a deleterious role of testosterone in the causation of cardiovascular disease in men.

Evidence that testosterone-replacement therapy may be beneficial for men with cardiac disease was provided by English et al., who found that 22 men with chronic stable angina who were treated with transdermal testosterone-replacement therapy had greater angina-free exercise tolerance than 24 placebo-treated controls.[27] Furthermore, direct injection of physiologic levels of testosterone into the coronary arteries led to an increase in mean coronary-artery diameter and blood flow as compared with base line.[28] However, it is unknown how this observation may relate to cardiovascular risk during long-term testosterone supplementation.

In a study of 32 men treated for 52 weeks, Anderson et al.[31] investigated the effects of supraphysiologic doses of testosterone (200 mg of intramuscular testosterone enanthate weekly) on factors involved in hemostasis and thrombosis, which are potential surrogates for cardiovascular disease. Decreases in prothrombotic factors, prothrombinase activity, and proteins C and S appeared to be counterbalanced by increases in antithrombin III activity and fibrinolytic activity. There was no effect on platelet activity.

Studies of testosterone-replacement therapy have not demonstrated an increased incidence of cardiovascular disease or events such as myocardial infarction, stroke, or angina.[32] Although the data appear reassuring, definitive assessment of the long-term effects of testosterone-replacement therapy on cardiovascular health will require prospective, large-scale, placebo-controlled studies.

LIPID PROFILES

Available data regarding the relation of testosterone-replacement therapy to lipid profiles are inconsistent. Supraphysiologic doses of androgens, particularly oral nonaromatizable androgenic steroids, appear to lower high-density lipoprotein (HDL) levels.[33] However, numerous controlled studies using physiologic replacement doses of testosterone have shown no change, or only a minimal reduction, in HDL, often accompanied by a reduction in total cholesterol.[6,9,11,20,33-37] Whitsel et al.[38] performed a meta-analysis of the effects of intramuscular testosterone esters on serum lipids in men with hypogonadism and reported that HDL levels were reduced in 3 studies and unchanged in 15. Total cholesterol levels were reduced in 5 studies, increased in 2, and unchanged in 12. Low-density lipoprotein (LDL) levels were unchanged or reduced in 14 of the 15 studies in which they were measured. Thus, the limited information available would suggest a neutral effect of testosterone-replacement therapy on lipid profiles.

Some of the variability in the effects of testosterone-replacement therapy on lipids may be explained by dosage. In one study,[33] 61 eugonadal men 18 to 35 years old were randomly assigned to five groups receiving monthly injections of long-acting gonadotropin-releasing hormone agonist to sup-

press endogenous testosterone secretion and weekly injections of testosterone enanthate (25, 50, 125, 300, or 600 mg) for 20 weeks. There were no changes in total cholesterol, LDL, very-low-density lipoprotein, triglycerides, or C-reactive protein levels, glucose metabolism, or insulin sensitivity at any dose of testosterone. Only the highest dose of testosterone (600 mg per week), well into the supraphysiologic range, was associated with a significant reduction in HDL, and a small, nonsignificant increase in HDL was seen with the lowest dose.

Transdermal administration of testosterone also appears to have minimal effects on lipid profiles. A double-blind, placebo-controlled study involving 108 healthy men receiving transdermal testosterone failed to show any significant difference between groups in serum levels of lipids and apolipoprotein during 36 months of treatment.[10] In a 24-week, multicenter, randomized, parallel-group study, Dobs et al.[11] compared transdermal and intramuscular administration of androgens in 58 men and did not detect any significant difference in HDL levels or in the ratio of total cholesterol to HDL in either group, regardless of the mode of therapy.

Thus, the present data, taken together, suggest that testosterone-replacement therapy within the physiologic range is not associated with worsening of the lipid profile.

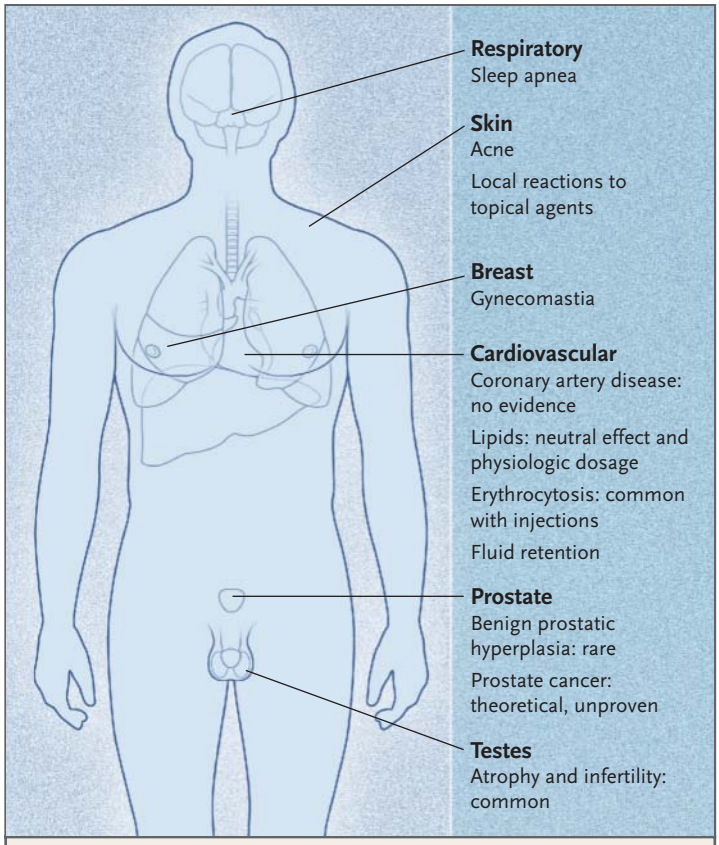

Figure 2. Sites of Potential Risks Associated with Testosterone-Replacement Therapy.

POLYCYTHEMIA

Higher testosterone levels appear to act as a stimulus for erythropoiesis. Hemoglobin levels increase by 15 to 20 percent in boys at puberty, in parallel with increasing serum testosterone levels. Adult men have higher hemoglobin levels than adult women. Men with hypogonadism have lower hemoglobin levels than age-matched controls, and testosterone-replacement therapy can restore their hemoglobin levels to the normal range. The mild anemia prevalent in elderly men has been postulated to be due to declining testosterone levels.[39]

Although a rise in the hematocrit is generally beneficial for patients with anemia, elevation above the normal range may have grave consequences, particularly in the elderly, since an attendant increase in blood viscosity could aggravate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation.[39,40] The risk of hemoconcentration is greater if the patient also has a condition that may itself be associated with an increase in the hematocrit, such as chronic obstructive pulmonary disease.[5,41]

Injections appear to be associated with a greater risk of erythrocytosis than topical preparations.[9,11,20,33,41] Dobs et al.[11] compared a transdermal nonscrotal testosterone patch with intramuscular injections of testosterone enanthate and observed that 15.4 percent and 43.8 percent of patients, respectively, had at least one documented elevated hematocrit value (defined as over 52 percent) during the course of the study. Erythrocytosis was associated with supraphysiologic levels of bioavailable testosterone and estradiol, and it occurred more frequently in the group that received intramuscular injections of testosterone.

Although Snyder et al.[6] observed erythrocytosis in only 5.5 percent of patients using a scrotal transdermal testosterone patch, the mean hemoglobin and hematocrit values in the testosterone-treated group rose from slightly subnormal to mid-normal during treatment, with most changes occurring over the first three months. Wang et al.[20] demonstrat-

ed a direct relation between testosterone dosage and the incidence of erythrocytosis. Erythrocytosis occurred in 2.8 percent of men receiving 5 mg per day by nonscrotal patches and in 11.3 percent and 17.9 percent of men treated with gel preparations of 50 mg per day (delivering 5 mg per day) and 100 mg per day (delivering 10 mg per day), respectively.

Although untoward events are unlikely with mild erythrocytosis of relatively short duration, the hematocrit or hemoglobin level should be monitored in men receiving testosterone-replacement therapy so that appropriate measures, such as dosage reduction, the withholding of testosterone, therapeutic phlebotomy, or blood donation, may be instituted if erythrocytosis develops. It is reassuring that as far as we can determine, no testosterone-associated thromboembolic events have been reported to date.

TESTOSTERONE-REPLACEMENT THERAPY AND THE PROSTATE

BENIGN PROSTATIC HYPERPLASIA

It is well recognized that the development of benign prostatic hyperplasia requires the presence of androgens and that the marked reduction in serum testosterone caused by chemical or surgical castration causes reduced prostate volume.[42] However, multiple studies[7,9,11,19,43-46] have failed to demonstrate exacerbation of voiding symptoms attributable to benign prostatic hyperplasia during testosterone supplementation, and complications such as urinary retention have not occurred at higher rates than in controls receiving placebo.

Prostate volume, as determined by ultrasonography, does increase significantly during testosterone-replacement therapy, mainly during the first six months, to a level equivalent to that of men without hypogonadism. However, urine flow rates, postvoiding residual urine volumes, and prostate voiding symptoms did not change significantly in these studies. This apparent paradox is explained by the poor correlation between prostate volume and urinary symptoms. Clinicians should nevertheless be aware that individual men with hypogonadism may occasionally have increased voiding symptoms with testosterone-replacement therapy.

PROSTATE CANCER

More than 60 years ago, Huggins et al.[42] demonstrated that suppression of testosterone levels caused regression of prostate cancer, and it is now commonplace for men with metastatic prostate cancer to undergo treatment designed to lower testosterone levels. If lowering testosterone causes prostate cancer to regress, does elevating testosterone cause prostate cancer to appear? How does one evaluate this risk, given that a high proportion of men harbor microscopic foci of prostate cancer?[47]

Case reports have suggested that testosterone-replacement therapy may convert an occult cancer into a clinically apparent lesion.[48,49] An example is the report of an 85-year-old man in whom prostate cancer was diagnosed because of a rise in the prostate-specific antigen (PSA) level six months after testosterone-replacement therapy was initiated.[49] However, one must be cautious in attributing causality to testosterone in these cases, since over 200,000 men are given a diagnosis of prostate cancer each year in the United States, and most of these cases are first detected by a rise in the PSA level unrelated to testosterone therapy.

To date, prospective studies have demonstrated a low frequency of prostate cancer in association with testosterone-replacement therapy. A compilation of published prospective studies of testosterone-replacement therapy (Table 3)[6-9,11,20,33] revealed only 5 cases of prostate cancer among 461 men (1.1 percent) followed for 6 to 36 months, a prevalence rate similar to that in the general population. These studies were performed in men with hypogonadism of varying causes and degrees, who may or may not have received testosterone treatment before the prospective studies. No follow-up data beyond 36 months are available.

It is of some concern that the underlying prevalence of occult prostate cancer in men with low testosterone levels appears to be substantial, according to our own study[50] in which 77 men with hypogonadism who had normal PSA levels and normal results on digital rectal examinations underwent sextant prostate biopsy before receiving testosterone-replacement therapy. Eleven men (14 percent of the subjects, with a median age of 64 years) had cancer. In a separate, retrospective study of men with known prostate cancer, high-grade prostate cancers were associated with low free testosterone levels.[51] These findings may be explained in part by the observation that the levels of testosterone, luteinizing hormone, and follicle-stimulating hormone all increase after radical prostatectomy, suggesting that prostate cancer itself, or possibly even normal prostate tissue, may have an inhibitory effect on serum androgen levels.[52,53] However, these reports do not address the clinical issue of

Table 3. Prostate Cancer in Trials of Testosterone-Replacement Therapy.*

Study	Duration	Increase in PSA		Prostate Cancer		Method of Administration
		Placebo	Testosterone	Placebo	Testosterone	
	mo	*number/total number*				
Hajjar et al. (1997)[32]	24	–	–	0/27	0/45	Intramuscular
Sih et al. (1997)[9]	12	0/15	0/17	0/15	0/17	Intramuscular
Dobs et al. (1999)[11]	24	–	1/33	–	2/33	Intramuscular
		–	0/33	–	1/33	Nonscrotal patch
Snyder et al. (1999)[8]	36	7/54	13/54	0/54	1/54	Nonscrotal patch
Snyder et al. (2000)[6]	36	–	–	–	0/18	Scrotal patch
Wang et al. (2000)[20]	6	–	0/76	–	0/76	Nonscrotal patch
		–	1/73	–	0/73	Transdermal (50 mg)
		–	4/78	–	1/78	Transdermal (100 mg)
Kenny et al. (2001)[7]	12	3/33	8/34	0/33	0/34	Nonscrotal patch

* An increase in prostate-specific antigen (PSA) was defined as any increase to a level above 4 ng per milliliter, except in the study by Snyder et al.,[8] in which it was defined as an increase of more than 1.5 ng per milliliter per year or an increase of 2.0 ng per milliliter between any two measurements.

whether testosterone supplementation promotes clinical prostate cancer in men with hypogonadism.

Despite decades of research, there is no compelling evidence that testosterone has a causative role in prostate cancer.[43,46,54-56] For example, studies using stored frozen plasma samples failed to show a difference in testosterone levels between men in whom prostate cancer developed 7 to 25 years later and those in whom it did not.[54-56]

In 2001, Hsing reviewed the 12 available prospective studies that examined the relation between serum androgen levels and prostate cancer.[55] Only one study (the Physicians' Health Study), a nested case–control study, suggested any significant relation between higher testosterone levels and prostate cancer.[57] However, this study found no significant difference in mean testosterone levels between patients with prostate cancer and control subjects and no significant difference in the risk of cancer between men in the highest and lowest quartiles for serum testosterone. An increased risk of prostate cancer with higher testosterone levels was observed only after simultaneous adjustment for four other hormones.[57] The clinical implications of this type of data analysis are uncertain.

Thus, there appears to be no compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk.[58,59] In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time of a man's life when testosterone levels decline.

In our opinion, proper monitoring with measurement of PSA and digital rectal examination should promote the early diagnosis, and thus potential cure, of most "unmasked" prostate cancers identified during testosterone treatment. Certainly, all men presenting for possible testosterone-replacement therapy who are found to have an abnormal PSA level or abnormal result on digital rectal examination should first undergo prostate biopsy, and there should also be a low threshold for biopsy if the PSA level rises substantially (see below) or if there is a change on digital rectal examination, such as the development of a nodule, asymmetry, or areas of increased firmness (Tables 4 and 5). Although a history of prostate cancer has been considered an absolute contraindication to testosterone-replacement therapy, this point is now under active debate for men who are deemed cured.

PSA

PSA is a serum glycoprotein made by the normal prostate that is widely used as a tumor marker, because elevated PSA levels correlate directly with the risk of prostate cancer. A PSA value greater than 4.0 ng per milliliter has been the standard indication for prostate biopsy since the introduction of this test in the 1980s, but recent work demonstrating a substantial risk of cancer in men with PSA levels of 2.6 to 4.0 ng per milliliter has prompted discussion of whether a lower threshold PSA level

Table 4. Recommendations for Monitoring Testosterone-Replacement Therapy.

Time	Recommended Steps*
Base line	Determine base-line voiding history or use standardized questionnaire.
	Determine history of sleep apnea.
	Perform digital rectal examination.
	Perform blood tests for base-line testosterone levels, PSA, and hematocrit or hemoglobin.
	Perform prostate biopsy if PSA level is above 4.0 ng/ml or digital rectal examination is abnormal.
Follow-up	Perform efficacy evaluation with dosage adjustment for suboptimal response at 1 to 2 mo.
	Perform monitoring evaluation with repeated testing every 3 to 6 mo for the first year and annually thereafter.
	Assess urinary symptoms and presence or exacerbation of sleep apnea or gynecomastia.
	Perform digital rectal examination.
	Perform blood tests for testosterone, hematocrit or hemoglobin, and PSA.
	Perform prostate biopsy if the digital rectal examination shows change or there is a substantial increase in PSA.

* PSA denotes prostate-specific antigen.

Table 5. Changes in Prostate-Specific Antigen (PSA) Levels and Prostate Biopsy.

A number of approaches exist regarding when to consider prostate biopsy or urologic referral for men with normal PSA levels at base line. These include the following:

- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml (several clinical trials).
- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml or if it increases either by more than 1.5 ng/ml/yr or by more than 0.75 ng/ml/yr over 2 yr (Endocrine Society[60]).
- Perform biopsy or refer to urologist if PSA rises above 4.0 ng/ml, or if it rises either by more than 1.0 ng/ml in the first 6 mo of treatment or by more than 0.4 ng/ml/yr thereafter (Bhasin et al.[61]).
- Perform biopsy before initiation of testosterone-replacement therapy. Repeat biopsy for PSA increase of 1.0 ng/ml in any year. If PSA rises by 0.7–0.9 ng/ml, repeat PSA measurement in 3–6 mo and perform biopsy for any further increase (Morgentaler et al.[50]).

should be adopted.[62-65] Although we recognize that this is an area under active investigation, the recommendations in this article are based on traditional PSA threshold values.

Testosterone trials in younger and older populations have inconsistently shown a rise in PSA, although the mean numerical increase of approximately 0.30 to 0.43 ng per milliliter is small (Table 3).[61] A substantial increase in PSA arouses concern that prostate cancer has developed.[66,67]

Although in the literature the PSA values used to trigger prostate biopsy include an increase of 1.5 ng per milliliter within two years or a total increase of 2.0 ng per milliliter over any period,[66] these recommendations have been based on observational population studies in untreated men. However, men in whom prostate cancer is diagnosed during clinical trials have been identified by a rise in PSA, in a period of 12 months or less.[11,20] On the basis of such reports, as well as concern about unmasking a previously occult cancer, it is our practice to perform prostate biopsy in any patient with a yearly PSA increase of 1.0 ng per milliliter or more. If the PSA level increases by 0.7 to 0.9 ng per milliliter in one year, we repeat the PSA measurement in three to six months and perform biopsy if there is any further increase. This approach is similar to other recently published recommendations.[61]

OTHER POTENTIAL ADVERSE EFFECTS

HEPATIC EFFECTS

The use of oral preparations of testosterone has been reported to lead to hepatotoxic effects and neoplasia, including benign and malignant tumors.[68] Testosterone undecanoate is an oral preparation that does not appear to have appreciable hepatotoxicity, but it is not available in the United States. Intramuscular injections and transdermal preparations do not appear to be associated with hepatic dysfunction,[69] and routine monitoring with liver-function tests is therefore unnecessary for men receiving these forms of testosterone supplementation. The use of oral forms of testosterone in the United States is strongly discouraged because of the associated hepatotoxicity.

SLEEP APNEA

Testosterone-replacement therapy has been associated with exacerbation of sleep apnea or with the development of sleep apnea,[70,71] generally in men treated with higher doses of parenteral testosterone who have other identifiable risk factors for sleep apnea. Upper-airway dimensions are unaffected by testosterone-replacement therapy, suggesting that androgen replacement contributes to sleep-disordered breathing by central mechanisms rather than by means of anatomical changes in the airway.[70,71]

MISCELLANEOUS EFFECTS OF TESTOSTERONE

A small number of men receiving testosterone-replacement therapy report breast tenderness and swelling. Testicular size and consistency often diminish, and men should be advised that fertility will be greatly compromised during testosterone-replacement therapy because of down-regulation of gonadotropins.[69]

Transdermal testosterone-replacement therapy is associated with a variety of skin reactions, mainly erythema or pruritus, which are more common with patches (in up to 66 percent of users) than with gel preparations (in 5 percent).[20] Intramuscular injections of testosterone can cause local pain, soreness, bruising, erythema, swelling, nodules, or furuncles.[11,36] Fluid retention is uncommon and generally mild, but testosterone-replacement therapy should be used cautiously in men with congestive heart failure or renal insufficiency (Table 2). Acne, oily skin, increased body hair, and flushing have also been observed but are generally considered only a minor inconvenience (Table 2). Hypertension has rarely been reported.[72] We are unaware of any data indicating acceleration of male-pattern baldness in men receiving testosterone-replacement therapy, although this possibility has not been carefully studied.

MONITORING DURING THERAPY

At base line, blood tests should be performed to measure PSA and the hematocrit or hemoglobin level, and a digital rectal examination should be performed (Table 4). Lipid evaluation is optional. Voiding symptoms should be ascertained by history taking or by the use of measures such as the International Prostatic Symptoms Score. Any history of sleep apnea should be ascertained.

Once testosterone-replacement therapy has been initiated, we recommend a first follow-up visit at one to two months to assess the efficacy of treatment, with consideration of dose escalation in cases of inadequate clinical response associated with suboptimal testosterone levels. Subsequent monitoring visits are performed at three-to-six-month intervals for the first year and yearly thereafter. At each visit there should be an assessment of the symptomatic response to treatment, voiding symptoms, and sleep apnea. Physical examination should include a digital rectal examination, and blood tests should measure serum testosterone and PSA levels and the hematocrit or hemoglobin level.

There is no universal agreement regarding target levels of replacement therapy, although many experienced clinicians aim for the mid- to upper-normal range in order to optimize the response to treatment. Treatment to raise levels above the physiologic range is discouraged, although it should be recognized that peak serum testosterone levels generally do rise transiently above the upper limit of normal with standard injection-therapy dosages.

If the patient reports an adequate clinical response to testosterone supplementation, there is no need for dosage adjustment, even if levels are in the low-normal range. If the clinical response is suboptimal and testosterone levels are no higher than the low-normal range, the testosterone dosage should be increased. If the maximal recommended dose of transdermal therapy has been prescribed without the achievement of adequate serum testosterone levels, consideration should be given to changing to intramuscular-injection therapy. For men receiving injection therapy, clinicians must interpret the results of blood tests on the basis of the interval since the most recent injection, recognizing that peak serum levels are obtained 2 to 5 days after injection and that the levels often return to base line by 10 to 14 days after injection. If the hematocrit rises above the reference range, consideration should be given to temporarily withholding testosterone-replacement therapy, reducing the dosage, or performing phlebotomy.

Monitoring for signs of prostate cancer is mandatory, given the widespread, albeit poorly substantiated, concern that testosterone treatment may stimulate the growth of an occult cancer. There is general agreement that men who present with an abnormal result on digital rectal examination or elevated PSA level should have a documented negative result from a prostate biopsy before testosterone-replacement therapy is initiated, since such men are at increased risk for prostate cancer.

Unfortunately, no clinical trials have addressed the issue of how to monitor for prostate cancer in men with normal digital rectal examinations and PSA levels. There are a number of approaches based on indirect clinical evidence and medical opinion (Table 5). The traditional approach has been to reserve prostate biopsy for those who have an abnormal digital rectal examination or a PSA level above 4.0 ng per milliliter during the course of treatment. Since a rapid rise in PSA, even at levels below 4.0 ng per milliliter, is also associated with prostate cancer, the Endocrine Society in 2001[60] recommended

urologic evaluation for possible biopsy in men with a yearly PSA increase of 1.5 ng per milliliter or more, or 0.75 ng per milliliter per year or more over two years, in addition to men whose PSA level rises above 4.0 ng per milliliter.

These indications for biopsy are no different from those for men with normal testosterone levels. Yet men with hypogonadism may theoretically be predisposed to more rapid growth of an occult cancer on normalization of serum testosterone levels, and it may thus be prudent to have a lower threshold for biopsy in this population, especially during the first year of treatment. The proposal by Bhasin et al.[61] for a standardized monitoring algorithm seems reasonable in this regard. In this algorithm, urologic referral for possible biopsy is recommended for patients with an increase in PSA of more than 1.0 ng per milliliter during the first six months of treatment or more than 0.4 ng per milliliter per year thereafter.

For the past 10 years, it has been our own practice to perform prostate biopsy before initiating testosterone treatment, since biopsy is the most definitive way to exclude the presence of cancer. However, we recognize that performance of a preliminary biopsy may be impractical for most clinicians and that others may regard this approach as overly aggressive, especially since the natural history of cancers identified solely because of the presence of low testosterone levels has not been determined. Once a negative biopsy result has been obtained, a repeated biopsy is reserved for men with a yearly increase in the PSA level of 1.0 ng per milliliter or more. For increases of 0.7 to 0.9 ng per milliliter, the PSA test is repeated in three to six months, and biopsy is performed if there is any further increase (Table 5).

In men who undergo an initial biopsy because of an elevated base-line PSA level, further biopsies should be reserved for those with increases in PSA of 1.0 ng per milliliter or more if the PSA level is under 10 ng per milliliter and those with yearly increases of 20 percent above the initial value if the PSA is 10 ng per milliliter or more.

There is no need to withhold testosterone treatment once a negative biopsy result has been obtained, since abnormalities in PSA levels or the results of digital rectal examination may be due entirely to benign causes. All of these recommendations may be modified for men less than 40 years old, since prostate cancer is uncommon in this age group.

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REFERENCES

1. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Longitudinal effects of aging on serum total and free testosterone levels in healthy men: Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31.
2. Morley JE, Kaiser FE, Perry HM III, et al. Longitudinal changes in testosterone, luteinizing hormone and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410-3.
3. Updates. Rockville, Md.: Food and Drug Administration, 1996. (Accessed January 6, 2004, at http://www.fda.gov/fdac/departs/196_upd.html.)
4. Tenover JL. Male hormone replacement therapy including "andropause." Endocrinol Metab Clin North Am 1998;27:969-87.
5. Kim YC. Testosterone supplementation in the aging male. Int J Impot Res 1999;11:343-52.
6. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670-7.
7. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2001;56:M266-M272.
8. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966-72.
9. Sih R, Morley JE, Kaiser FE, Perry HM III, Patrick P, Ross C. Testosterone replacement in older hypogonadal men: a 12-month randomized controlled trial. J Clin Endocrinol Metab 1997;82:1661-7.
10. Snyder PJ, Peachey H, Berlin JA, et al. Effects of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. Am J Med 2001;111:255-60.
11. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 1999;84:3469-78.
12. Cherrier MM, Asthana MD, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57:80-8.
13. Moffat SD, Zonderman AB, Metter EJ, Blackman MR, Harman SM, Resnick SM. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. J Clin Endocrinol Metab 2002;87:5001-7.
14. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
15. Manson JE, Hsia J, Johnson KC, et al. Estrogen plus progestin and the rise of coronary heart disease. N Engl J Med 2003;349:523-34.
16. Bhasin S, Buckwalter JG. Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl 2001;22:718-31.
17. Bhasin S, Bremner WJ. Emerging issues in androgen replacement therapy. J Clin Endocrinol Metab 1997;82:3-8.
18. Nieschlag E. If testosterone, which testosterone? Which androgen regimen should be used for supplementation in older men? Formulation, dosing, and monitoring issues. J Clin Endocrinol Metab 1998;83:3443-5.
19. Comhaire FH. Andropause: hormone replacement therapy in the aging male. Eur Urol 2000;38:655-62.
20. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonad-

al men. J Clin Endocrinol Metab 2000;85:2839-53.
21. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. BJU Int 2003;91:69-74.
22. Carrasco D, Prieto M, Pallardo L, et al. Multiple hepatic adenomas after long-term therapy with testosterone enanthate: review of the literature. J Hepatol 1985;1:573-8.
23. Zmuda JM, Cauley JÁ, Kriska A, Glynn NW, Guptai JP, Kuller LH. Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men: a 13-year follow-up of former Multiple Factor Intervention Trial participants. Am J Epidemiol 1997;146:609-17.
24. Kabakci G, Yildirir A, Can I, Unsal I, Erbas B. Relationship between endogenous sex hormone levels, lipoproteins and coronary atherosclerosis in men undergoing coronary angiography. Cardiology 1999;92:221-5.
25. Gooren LI. The age-related decline of androgen levels in men: clinically significant? Br J Urol 1996;78:763-8.
26. Gyllenborg J, Rasmussen SL, Borch-Johnsen K, Heitmann BL, Skakkebaek NE, Juul A. Cardiovascular risk factors in men: the role of gonadal steroids and sex hormone-binding globulin. Metabolism 2001;50:882-8.
27. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. Circulation 2000;102:1906-11.
28. Webb CM, McNeill JG, Hayward CS, de Zeigler D, Collins P. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690-6.
29. English KM, Mandour O, Steeds RP, Diver MJ, Jones TH, Channer KS. Men with coronary artery disease have lower levels of androgens than men with normal coronary angiograms. Eur Heart J 2000;21:890-4.
30. Hak AE, Witteman JCM, de Jong FH, Geerlings MI, Hofman A, Pols HAP. Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam Study. J Clin Endocrinol Metab 2002;87:3632-9.
31. Anderson RA, Ludlam CA, Wu FC. Haemostatic effects of supraphysiological levels of testosterone in normal men. Thromb Haemost 1995;74:693-7.
32. Hajjar RR, Kaiser FE, Morley JE. Outcomes of long-term testosterone replacement in older hypogonadal males: a retrospective analysis. J Clin Endocrinol Metab 1997;82:3793-6.
33. Singh AB, Hsia S, Alaupovic P, et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab 2002;87:136-43.
34. Kouri EM, Pope HG, Oliva PS. Changes in lipoprotein-lipid levels in normal men following administration of increasing doses of testosterone cypionate. Clin J Sport Med 1996;6:152-7.
35. Kunelius P, Lukkarinen O, Hannuksela ML, Itkonen O, Tapanainen JS. The effects of transdermal dihydrotestosterone in the aging male: a prospective, randomized, double blind study. J Clin Endocrinol Metab 2002;87:1467-72.
36. von Eckardstein S, Nieschlag E. Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study. J Androl 2002;23:419-25.
37. Barrett-Connor EL. Testosterone and risk factors for cardiovascular disease in men. Diabete Metab 1995;21:156-61.
38. Whitsel EA, Boyko EJ, Matsumoto AM, Anawalt BD, Siscovick DS. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 2001;111:261-9.
39. Basaria S, Dobs AS. Risks versus benefits of testosterone therapy in elderly men. Drugs Aging 1999;15:131-42.
40. The Endocrine Society. Clinical bulletins in andropause: benefits and risks of treating hypogonadism in the aging male. Endocr Rep 2002;2:1-6.
41. Viallard JF, Marit G, Mercie P, Leng B, Reiffers J, Pellegrin JL. Polycythaemia as a complication of transdermal testosterone therapy. Br J Haematol 2000;110:237-8.
42. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer. II. The effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941;43:209-23.
43. Krieg M, Nass R, Tunn S. Effect of aging on endogenous level of 5α-dihydrotestosterone, testosterone, estradiol, and estrone in epithelium and stroma of normal and hyperplastic human prostate. J Clin Endocrinol Metab 1993;77:375-81.
44. Pechersky AV, Mazurov VI, Semiglazov VF, Karpischenko AI, Mikhailichenko VV, Udintsev AV. Androgen administration in middle-aged and ageing men: effects of oral testosterone undecanoate on dihydrotestosterone, oestradiol and prostate volume. Int J Androl 2002;25:119-25.
45. Marcelli M, Cunningham GR. Hormonal signaling in prostatic hyperplasia and neoplasia. J Clin Endocrinol Metab 1999;84:3463-8.
46. Slater S, Oliver RTD. Testosterone: its role in development of prostate cancer and potential risk from use as hormone replacement therapy. Drugs Aging 2000;17:431-9.
47. Sakr WA, Haas GP, Cassin BF, Pontes JE, Crissman JD. The frequency of carcinoma and intraepithelial neoplasia of the prostate in young male patients. J Urol 1993;150:379-85.
48. Curran MJ, Bihrle W III. Dramatic rise in prostate-specific antigen after androgen replacement in a hypogonadal man with occult adenocarcinoma of the prostate. Urology 1999;53:423-4.
49. Loughlin KR, Richie JP. Prostate cancer after exogenous testosterone treatment for impotence. J Urol 1997;157:1845.
50. Morgentaler A, Bruning CO III, DeWolf WC. Occult prostate cancer in men with low serum testosterone levels. JAMA 1996;276:1904-6.
51. Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol 2000;163:824-7.
52. Miller LR, Partin AW, Chan DW, et al. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449-53.
53. Madersbacher S, Schatzl G, Bieglmayer C, et al. Impact of radical prostatectomy and TURP on the hypothalamic-pituitary-gonadal hormone axis. Urology 2002;60:869-74.
54. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of serum androgen levels in men with and without prostate cancer. Prostate 1995;27:25-31.
55. Heikkila R, Aho K, Heliovaara M, et al. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer 1999;86:312-5.
56. Hsing AW. Hormones and prostate cancer: what's next? Epidemiol Rev 2001;23:42-58.
57. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst 1996;88:1118-26.
58. Gustafsson O, Norming U, Gustafsson S, Eneroth P, Astrom G, Nyman CR. Dihydrotestosterone and testosterone levels in men screened for prostate cancer: a study of a randomized population. Br J Urol 1996;77:433-40.
59. Vermeulen A. Androgen replacement therapy in the aging male — a critical evaluation. J Clin Endocrinol Metab 2001;86:2380-90.
60. Summary from the second annual andropause consensus meeting. Chevy Chase, Md.: Endocrine Society, 2001.
61. Bhasin S, Singh AB, Mac RP, Carter B, Lee MI, Cunningham GR. Managing the risks of prostate disease during testosterone replacement therapy in older men: recommendations for a standardized monitoring plan. J Androl 2003;24:299-311.
62. Krumholtz JS, Carvalhal GF, Ramos CG, et al. Prostate-specific antigen cutoff of 2.6 ng/mL for prostate cancer screening is associated with favorable pathologic tumor features. Urology 2002;60:469-73.
63. Carvalhal GF, Smith DS, Mager DE, Ramos C, Catalona WJ. Digital rectal examination for detecting prostate cancer at prostate specific antigen levels of 4 ng./ml. or less. J Urol 1999;161:835-9.
64. Punglia RS, D'Amico AV, Catalona WJ, Roehl KA, Kuntz KM. Effect of verification bias on screening for prostate cancer by measurement of prostate-specific antigen. N Engl J Med 2003;349:335-42.
65. Schröder FH, Kranse R. Verification bias and the prostate-specific antigen test — is

there a case for a lower threshold for biopsy? N Engl J Med 2003;349:393-5.
66. Carter HB, Pearson JD, Metter EJ, et al. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 1992;267:2215-20.
67. Carter HB, Pearson JD, Waclawiw Z, et al. Prostate-specific antigen variability in men without prostate cancer: effect of sampling interval on prostate-specific antigen velocity. Urology 1995;45:591-6.
68. Westaby D, Ogle SJ, Paradinas FJ, Randell JB, Murray-Lyon IM. Liver damage from long-term methyltestosterone. Lancet 1977; 2:262-3.
69. Bagatell CJ, Bremner WJ. Androgens in men — uses and abuses. N Engl J Med 1996; 334:707-14.
70. Schneider BK, Pickett CK, Zwillich CW, et al. Influence of testosterone on breathing during sleep. J Appl Physiol 1986;61: 618-23.
71. Matsumoto AM, Sandblom RE, Schoene RB, et al. Testosterone replacement in hypogonadal men: effects on obstructive sleep apnea, respiratory drives, and sleep. Clin Endocrinol (Oxf) 1985;22:713-21.
72. Tangredi JF, Buxton LL. Hypertension as a complication of topical testosterone therapy. Ann Pharmacother 2001;35:1205-7.