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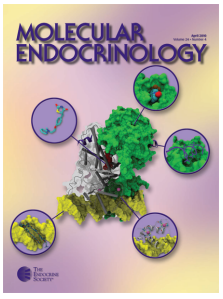

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Why Is Androgen Replacement in Males Controversial?

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Context: Symptoms and signs consistent with androgen deficiency and low testosterone levels are recognized frequently in clinical practice. Recent population-based epidemiological studies indicate that low testosterone levels in men are associated with increased morbidity and mortality. The clinician must be able to counsel patients to help them determine whether testosterone replacement therapy is appropriate for them.

Evidence Acquisition: The authors have conducted a literature search in PubMed, and we have reviewed references in the multiple systematic reviews and meta-analyses that have been published on this topic.

Evidence Synthesis: We have attempted to provide the reader with an appreciation of the evidence that can be used to support the diagnosis of androgen deficiency, the efficacy of treatment, the potential risks of treatment, the therapeutic options, and the recommendations for monitoring treatment.

Conclusions: We think that published clinical experience justifies testosterone replacement therapy in males who have not initiated puberty by age 14 and in males with low testosterone levels due to classical diseases of the hypothalamic-pituitary-gonadal axis. The benefit:risk ratio is less certain in older men and in those with chronic diseases associated with low testosterone levels. The decision to treat in this setting is much more controversial because there are few large clinical trials that have demonstrated efficacy and no large clinical trials that have determined potential risks of increasing the incidence of clinical prostate cancers or cardiovascular events. We provide a critical review of the evidence that supports treatment and potential risks and ways to reduce the risks if the physician and patient elect testosterone replacement. (***J Clin Endocrinol Metab*** **96: 38–52, 2011)**

Evaluation and treatment of males suspected of having testosterone deficiency entails multiple controversial issues. Recognition of the high prevalence of low testosterone levels in many men with common chronic diseases, an aging population, and greater recognition that testosterone levels fall with aging have greatly expanded the number of men who are diagnosed to have low testosterone levels. The development of new delivery systems and increased marketing of these delivery systems have combined with the larger number of potential patients to make testosterone replacement more common. It is a hot topic for the lay press and primary care clinicians, as well as for urologists and endocrinologists.

Modern medicine is striving to provide evidence-based care. To do this we need large, randomized, placebo-controlled trials (RPCTs), preferably multicentered, and preferably government funded. Treatment of testosterone deficiency due to classical diseases affecting the hypothalamus, pituitary, and/or testes has been accepted for decades, although there were no multicenter trials. Some of the testosterone delivery systems predate the requirement for multicenter studies, and most of the more recently developed testosterone delivery systems were approved by the Food and Drug Administration on the basis of their pharmacokinetic profile and their ability to achieve physiological blood levels. Approval was not

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Abbreviations: BMD, Bone mineral density; CI, confidence interval; HDL, high-density lipoprotein; HPG, hypothalamic-pituitary-gonadal; PSA, prostate-specific antigen; RPCT, randomized, placebo-controlled trial.

based on long-term studies of efficacy and risk. Some outcome studies have provided sufficient data to permit meta-analyses. However, most of these analyses have relied on a limited number of small clinical trials of short duration, and they have used a variety of testosterone delivery systems. Thus, their conclusions often are compromised. This review will identify many of the issues that continue to challenge clinicians, investigators, and patients. This is even truer for most busy primary care clinicians who write a large percentage of the prescriptions for testosterone treatment.

Epidemiology

Cross-sectional and longitudinal population-based studies have evaluated the prevalence of low testosterone levels, and some of them have used questionnaires to evaluate associated symptoms. The Baltimore Longitudinal Study of Aging found low total testosterone levels in approximately 20% and low free testosterone index levels in approximately 35% of men 60–69 yr of age (1). Low testosterone levels were much more prevalent in older age groups. In the Massachusetts Male Aging Study, total testosterone levels declined cross-sectionally at 0.8%/yr of age, whereas both free and bioavailable testosterone levels declined at about 2%/yr of age (2). The longitudinal decline for subjects between baseline and follow-up was 1.6%/yr for total testosterone and 2–3%/yr for bioavailable testosterone. A cross-sectional survey of 3200 community-dwelling men aged 40–79 yr from a prospective cohort study in eight European countries found an age-related decrease in calculated free testosterone levels of 9 pg/dl · yr (3). The prevalence of symptomatic hypogonadism increases with age, especially after age 70 (4). The Boston Area Community Health survey of men 40–70 yr of age at baseline did not find significant differences in the prevalence of testosterone deficiency among non-Hispanic whites, Hispanics, and African-Americans (5).

Until recently, it was thought that testosterone deficiency in middle-aged and older men mainly affected the quality of life, but it was unlikely to affect morbidity or mortality. However, population-based studies indicate that testosterone deficiency predicts future development of type 2 diabetes mellitus (6), metabolic syndrome (7), cardiovascular events (8–11), mobility limitation (12), frailty (13), and mortality (8–11). Whether testosterone treatment can improve health and prolong active lifestyles is unknown. No large, multicenter, long-term RPCTs have addressed these issues.

Diagnosis

Definition of hypogonadism

The Endocrine Society's Clinical Practice Guideline for Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes has defined hypogonadism in men as "a clinical syndrome that results from failure of the testis to produce physiological levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal (HPG) axis" (14).

Symptoms and signs associated with classical causes of hypogonadism

The Endocrine Society Guidelines Committee identified signs and symptoms that are more suggestive of androgen deficiency (14). They include incomplete sexual development, reduced libido, decreased spontaneous erections, breast discomfort or gynecomastia, loss of body hair or reduced shaving, very small or shrinking testis, inability to father children or low sperm counts, decreased bone mineral density (BMD) and osteoporosis, decreased muscle mass and strength, and hot flushes. Other manifestations that are associated with androgen deficiency but are less specific include decreased energy and motivation, dysthymia, decreased intellectual capacity, poor concentration, depression, fatigue, sleep disturbance, mild anemia (normochromic, normocytic, in the female range), increased body fat, increased body mass index, and diminished physical performance (14). The less specific symptoms and signs can be caused by other conditions, and comorbidities make the diagnosis more difficult in older men.

Zitzmann *et al.* (15) surveyed 434 consecutive male patients aged 50–86 yr in an andrological outpatient department to determine whether psychosomatic complaints and metabolic factors were related to sex hormone levels in a symptom-specific manner. No clear-cut threshold for late-onset hypogonadism was found. Rather, prevalence of psychosomatic symptoms and metabolic risk factors increased with decreasing androgen levels. The prevalence of loss of libido or vigor increased with testosterone concentrations less than 432 ng/dl, and depression and type 2 diabetes mellitus were more common in men with testosterone concentrations less than 288 ng/dl. Testosterone concentrations below 230 ng/dl contributed to erectile dysfunction.

Using the large European Male Ageing Study database of 3369 men between the ages of 40 and 79, Wu *et al.* (16) have found that poor morning erections, low sexual desire, erectile dysfunction, inability to perform vigorous activity, depression, and fatigue were significantly related to the testosterone level. They found that late-onset hy-

pogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone of less than 320 ng/dl and a free testosterone less than 6.5 ng/ml. The three sexual symptoms had a syndromic relationship with decreased testosterone levels.

Questionnaires

Questionnaires can help patients and clinicians recognize medical conditions. Lack of specificity has been the greatest problem with existing questionnaires used to detect hypogonadism, and lack of sensitivity of these questionnaires is an issue in assessing treatment (14). A new screening questionnaire has been developed that promises greater specificity (17). However, it has not been used in large populations, and it is not known whether it will be useful in assessing testosterone treatment.

Laboratory diagnosis

The diagnosis of testosterone deficiency requires the presence of symptoms and low serum testosterone levels, but the normal ranges for different assays vary greatly. It is well recognized that serum testosterone levels exhibit a diurnal pattern in younger men, with higher levels in the early morning (18). The diurnal pattern is blunted in most older men (18, 19). Thus, sampling time is important because normal ranges are based on early morning sampling in younger healthy men. The Endocrine Society appointed a task force to address issues related to sensitivity, variability, and standardization of testosterone assays (20). They have stated that "laboratory proficiency testing should be based on the ability to measure accurately and precisely samples containing known concentrations of testosterone, not only in agreement with others using the same method."

One should recognize factors that affect SHBG levels and thus total testosterone levels and know techniques used to estimate bioavailable or free testosterone levels. SHBG concentrations are decreased in patients with moderate to severe obesity, nephrotic syndrome, hypothyroidism, acromegaly, and in those who are taking glucocorticoids, progestins and androgenic steroids. SHBG levels are increased with aging and in patients with cirrhosis, hepatitis, hyperthyroidism, or HIV disease, and in those men who are taking anticonvulsants or estrogens (14).

Total testosterone levels are now being measured by liquid chromatography-tandem mass spectrophotometer in large reference laboratories and in some research laboratories (21). Liquid chromatography-tandem mass spectrophotometer provides greater accuracy than either platform assays or RIAs because it does not encounter issues of cross-reactivity. However, the equipment is expensive, so this methodology is not available in smaller regional and hospital laboratories. Until recently, there was no effort to use a common standard for testosterone assays. Under the leadership of the Centers for Disease Control (CDC), there is a national effort to correct this problem (20, 21). Although there is some uncertainty as to how best to estimate testosterone concentrations that are available to peripheral tissues, determination of free testosterone by equilibrium dialysis has been the gold standard (22). Because equilibrium dialysis requires greater technical expertise, time, and cost, it is not a practical test for most laboratories. Many think that both albumin-bound testosterone and unbound testosterone are available to peripheral tissues. Bioavailable (free and albumin-bound) testosterone can be assayed after ammonium sulfate precipitation of SHBG-bound testosterone (23). Vermeulen *et al.* (22) have popularized the use of calculated free testosterone and calculated bioavailable testosterone measurements based on measuring total testosterone, SHBG, and albumin and then using a mass action equation. These values correlate well with those obtained by equilibrium dialysis or by actual measurement of bioavailable testosterone, but it requires accurate measurement of total testosterone and SHBG. Furthermore, there are different equations, which give somewhat different results (24). Finally, normal ranges using this approach are not readily available. Unlike the preceding techniques to measure or estimate free testosterone, the direct measurement of free testosterone by RIA does not provide valid results when there are alterations in SHBG (22). This technique should not be used! Thus, whereas there have been improvements in assaying total, bioavailable, and free testosterone levels, uncertainties remain. Hopefully, the effort undertaken by the CDC will lead to much more accurate assays, better standardization of assays, and the establishment of similar normal ranges.

It is important to determine whether the patient has primary or secondary hypogonadism. To do this, one must measure serum LH, and prolactin should be assayed in patients with secondary hypogonadism to identify the rare patient who has a prolactinoma. The majority of men who do not have a classical cause of hypogonadism will have low testosterone levels and low or inappropriately normal LH and FSH levels. The Endocrine Society Guidelines recommend imaging the hypothalamus and pituitary only if there are other findings suggesting hypothalamic or pituitary disease or if the total testosterone level is below 150 ng/dl. This recommendation is based on one report of 164 men 27 to 79 yr of age whose chief complaint was erectile dysfunction and who had serum testosterone levels less than 230 ng/dl and low or inappropriately normal LH levels (25). Macroadenomas and hypothalamic lesions

TABLE 1. Testosterone replacement RPCTs in men 20–80 yr of age

First author, year (Ref.)	n (T/P)	Age (yr)	T criteria (ng/dl)	TRT	Duration (months)	Outcomes
Sih, 1997 (70)	22 (10/12)	≥50	Bioavailable T < 60	TC im	12	↑ Strength, ↑ hemoglobin, no change in memory
Steidle, 2003 (122)	406 (307/99)	20–80	T < 300	T gel, 50 and 100 mg/d; T patch, two 2.5 mg/d	6	↑ Body composition, ↑ libido, ↑ hematocrit
Merza, 2006 (123)	38 (20/18)	>40	T < 288 or FAI < 30%[a]	T patch, 5 mg/d	6	↓ FM, ↑ hemoglobin; no change LBM, BMD, or markers of bone turnover
Brockenbrough, 2006 (124)	40 (19/21)	≥18	T ≤ 300	T gel, 10 g/d	6	No change lipids, body composition, sexual function, or BMD
Marks, 2006 (125)	44 (22/22)	44–78	T < 300	TE im, 150 mg every 2 wk	6	No change prostate tissue androgens, cellular function, or gene expression; ↑ hematocrit
Chiang, 2009 (126)	30 (15/15)	20–75	T < 300 or free T < 8.7	T gel, 5g/d	3	↑ Erectile function, no change in libido
Shores, 2009 (65)	33	≥50	T ≤ 280	T gel, 7.5 g/d	3	↓ Subthreshold depression
Legros, 2009 (115)	322	≥50	Free T < 7.5	Oral TU, 80, 160, or 240 mg/d	12	↑ Sexual domain of AMS[b] but only with 160 mg/d

We only included parallel studies of 3 months or longer and men with baseline testosterone levels less than 300 ng/dl (<10.4 nmol/liter), bioavailable testosterone levels less than 150 ng/dl (<5.2 nmol/liter), or free testosterone levels less than 9.0 ng/dl (<0.31 nmol/liter). n (T/P), Total number of men included in trial (number of men treated with testosterone therapy/number of men treated with placebo); TRT, type of testosterone replacement therapy used in the trial; T, testosterone; TC, testosterone cypionate; TE, testosterone enanthate; TU, testosterone undecanoate; FFM, fat-free mass; FM, fat mass; LBM, lean body mass. To convert nanograms per deciliter to nanomoles per liter, multiply by 0.0347.

[a] Free androgen index (FAI), which is total T/SHBG × 100.

[b] Aging Males' Symptoms (AMS) rating scale.

were confined to six subjects with testosterone levels of 104 ng/dl or less. Assessment of the karyotype to diagnose Klinefelter's syndrome is recommended for those men with a testicular volume less than 4 ml, low testosterone levels, and elevated LH levels (26, 27).

Most middle-aged and older men with symptoms consistent with hypogonadism and low testosterone levels will have one or more chronic diseases, and many of these men are obese. The majority of these men will have functional abnormalities of the HPG axis rather than anatomical or congenital abnormalities. Whether their symptoms are due to the comorbid condition or to the low testosterone levels is the question. The majority of these men will increase their serum LH and testosterone levels when treated with clomiphene citrate (28). We interpret this response to indicate that the abnormality is functional. One also frequently observes low total and sometimes free testosterone levels in men with moderate or severe obesity. When obese patients lose significant weight, their serum testosterone levels usually increase (29, 30). This provides further support for functional abnormalities of the HPG axis in many of these men.

Clinical Trials

Age considerations

We think that age must be considered when deciding to prescribe and monitor testosterone treatment. Studies that have included men 20 yr of age and older are listed in Table 1. We only included parallel studies of 3 months or longer and men with baseline testosterone levels below 300 ng/dl, bioavailable testosterone levels below 150 ng/dl, or free testosterone levels below 9.0 ng/dl. The total and free testosterone cutoffs are those recommended by The Endocrine Society Clinical Practice Guideline (14), and the bioavailable testosterone cutoff is that proposed by Vermeulen (31) and endorsed by The Endocrine Society Position Statement (20). Comorbid diseases may make older patients less responsive to testosterone replacement, so a separate table lists studies that were limited to men 60 and older (Table 2). Because SHBG levels increase with age, we have included studies with total testosterone levels below 350 ng/dl. We recognize that there are many informative trials that have included men with higher cutoffs and several relatively large studies that do not meet our inclusion criteria but may provide efficacy information (32–36); however, these trials are at greater risk of failure to dem-

TABLE 2. Testosterone replacement RPCTs in men age 60 yr or older

First author, year (Ref.)	n (T/P)	Age (yr)	T criteria (ng/dl)	TRT	Duration (months)	Outcomes
Kenny, 2001 (78)	44 (24/20)	>65	Bioavailable T < 128	T patch, two × 2.5 mg/d	12	↓ Bone loss at femoral neck, ↑ FFM, ↓ FM, no change in lower extremity strength
Kenny, 2002 (71)	44 (24/20)	>65	Bioavailable T < 128	T patch, 2–2.5 mg/d	12	No change cognition
Tan, 2003 (66)	10 (5/5)	68–80	T < 240	TE im, 200 mg every 2 wk	12	↑ Cognition
Cavallini, 2004 (61)	130 (40/45/45)[a]	>60	Free T < 6 pg/ml	Oral TU, 160 mg/d	6	↑ Erectile function, libido, mood, and vitality
Kenny, 2004 (63)	11 (6/5)	73–87	Bioavailable T < 128	TE im, 200 mg every 3 wk	12	No change in mood or cognition
Amory, 2004 (79)	50 (17/18/15)[b]	65–83	T < 350	TE im, 200 mg every 2 wk; or TE + finasteride 5 mg/d[c]	36	↑ BMD lumbar vertebrae and hip, ↑ hematocrit
Page, 2005 (127)	50 (17/18/15)[b]	65–83	T < 350	TE im, 200 mg every 2 wk; or TE + finasteride, 5 mg/d[c]	36	↑ Hand grip strength, ↑ FFM, ↓ FM, ↑ physical function
Nair, 2006 (128)	87 (27/29/31)[d]	≥60	Bioavailable T < 103	T patch, 5 mg/d	24	↑ FFM, no change strength, no change QOL, ↑ BMD femoral neck
Vaughan, 2007 (129)	69 (24/23/22)[b]	≥65	T < 350	TE im, 200 mg every 2 wk; or TE + finasteride, 5 mg/d[c]	36	No change cognition
Agledahl, 2008 (130)	26 (13/13)	60–80	T < 317	TU im, 1000 mg every 6–12 wk	12	No change lipids or lipase activity, ↑ FFM, ↓ FM
Basurto, 2008(131)	48 (25/23)	≥60	T ≤ 320	TE im, 250 mg every 3 wk	12	↑ Lumbar BMD
Svartberg, 2008 (132)	35 (17/18)	60–80	<317	TU im, 1000 mg every 6–12 wk	12	↑ FFM, ↓ FM, ↑ hip BMD, ↑ handgrip strength, ↑ hemoglobin and hematocrit; no change weight, glucose, lipids, knee extension, QOL, or cognition
Agledahl, 2009 (133)	26 (13/13)	60–80	<317	TU im, 1000 mg every 6–12 wk	12	No change in tissue factor coagulation or in tissue factor pathway inhibitor
Srinivas-Shankar, 2010 (64)	274 (138/136)	≥65	T < 345 or free T < 7.2	T gel, 5 g/d[c]	6	↑ FFM, ↓ FM, ↑ strength, ↑ physical function and sexual domain of AMS,[e] ↑ QOL
Basaria, 2010 (82)	106/103	≥65	T < 350 or free T < 5.0	T gel, 10 g/d[c]	6	Study stopped early; ↑ cardiac, dermatological and respiratory events; ↑ leg-press and chest-press strength; ↑ stair-climbing power with load

Because SHBG levels increase with age, we have included men with total testosterone levels less than 350 ng/dl (<12.3 nmol/liter), bioavailable testosterone levels less than 150 ng/dl (<5.2 nmol/liter), or free testosterone levels less than 9.0 ng/dl (<0.31 nmol/liter). n (T/P), Total number of men included in trial (number of men treated with testosterone therapy/number of men treated with placebo); TRT, type of testosterone replacement therapy used in the trial; T, testosterone; TC, testosterone cypionate; TE, testosterone enanthate; TU, testosterone undecanoate; FFM, fat-free mass; FM, fat mass; QOL, quality of life. To convert nanograms per deciliter to nanomoles per liter, multiply by 0.0347.

[a] Testosterone/placebo/carnitine treatment arms.

[b] Testosterone/placebo/testosterone + finasteride.

[c] Then dose adjusted.

[d] Testosterone/dehydroepiandrosterone/placebo.

[e] Aging Males' Symptoms (AMS) rating scale.

onstrate efficacy of testosterone treatment because they included eugonadal men. Values above 350 ng/dl do not require substitution, according to the recommendations of International Society of Andrology, International Society for the Study of Aging Male, European Association of Urology, European Academy of Andrology, and American Society of Andrology (37). There also are several relatively large phase III trials that have not been placebo controlled but have used another testosterone delivery system for comparison (38–41). Some open-label trials have compared long-acting injectable testosterone undecanoate with testosterone enanthate or a testosterone gel (42). These trials also provide considerable useful information. Finally, most testosterone trials can provide useful information regarding potential side effects; however, no trial has been powered to assess the potential risk that testosterone replacement will increase clinical prostate cancers or cardiovascular events.

Ages 14–19 yr

Most endocrinologists consider testosterone treatment if puberty has not been initiated spontaneously by age 14 (43). When sexual development is delayed, it can cause psychological problems, and it may reduce adult bone mass (44). Whether chronic testosterone treatment will be required is dependent on factors that include the underlying cause for the testosterone deficiency, age, and desire for fertility in the near future. We are unaware of any RPCTs evaluating testosterone treatment in boys with constitutional delayed puberty, isolated gonadotropin deficiency, Klinefelter's syndrome, or prepubertal or pubertal acquired causes of hypogonadism. Testosterone can cause pubertal changes, and these changes usually are desirable in this setting. Most clinicians use injectable testosterone cypionate or enanthate, and effective dosing regimens have been developed (45). Transdermal testosterone gel can be used; however, it is more difficult to titrate to the desired dose and to ensure compliance. Human chorionic gonadotropin or recombinant human LH can be used in boys with hypogonadotropic hypogonadism, but these regimens are more expensive and they require greater patient compliance (46, 47). Pulsatile GnRH treatment also can be effective, but it is more cumbersome and more expensive (48). Unlike testosterone treatment, these treatments increase testicular size as well as testosterone levels. This may be of psychological benefit, and there could be benefit to future fertility. Although testosterone treatment can cause suppression of spermatogenesis, development of gynecomastia, and less commonly premature closure of the epiphyses, strategies for managing or preventing these conditions usually are effective.

Ages 20–49 yr

Testosterone treatment for hypogonadal men between the ages of 20 and 49 also is effective and is associated with a low frequency of serious adverse events. Many of the men in this age range will have a congenital or acquired disease or condition that is known to impair one or more components of the HPG axis. An example of the benefits of treating men with such abnormalities is the study of Snyder *et al.* (49). They treated 18 previously untreated men who were 18 yr of age or older and who developed acquired hypogonadism after having gone through puberty. Their mean ± SD serum testosterone was 78 ± 77 ng/dl, and they were treated for up to 3 yr. There were striking improvements in energy, sexual function, body composition, bone density, and hematocrit. No serious side effects were reported, but prostate volume did increase. Some of the RPCTs have included some men in this age group (Table 1).

Testosterone treatment is not appropriate for the men with hypogonadotropic hypogonadism who seek fertility. Most of these men will require gonadotropin or pulsatile GnRH treatment (48, 50, 51). A few may respond to an antiestrogen (clomiphene citrate or tamoxifen) (52). Whereas testosterone treatment will suppress the HPG axis, these agents stimulate both testosterone secretion and spermatogenesis.

Ages 50–60 yr

Several common chronic diseases including obesity, type 2 diabetes, and several inflammatory conditions are associated with low testosterone levels and are common in middle-aged and older men. They can be associated with symptoms suggesting androgen deficiency. Aging *per se*, without apparent comorbidity, also is associated with symptoms and low testosterone levels in some men in this age group. Most investigator-initiated as well as phase II and phase III clinical trials have included men more than 50 yr of age (Table 1).

Age 60 and older

Several investigators have attempted to determine whether aging impairs tissue response to testosterone. The studies of Bhasin and colleagues (53–57) and those of Sattler *et al.* (57) provide some of the most convincing data showing that several organ systems of older men are responsive to testosterone treatment.

Several single-center RPCTs have been conducted in men 60 and older (Table 2). Most of the men in these studies did not have known anatomical disease involving the HPG axis, and many of them had comorbid conditions that could have been responsible for their symptoms and low testosterone levels. An Institute of Medicine panel recommended additional studies to know whether testosterone replacement therapy is beneficial for older men

with low testosterone levels. Based on these recommendations, The National Institute of Aging has funded The Testosterone Trial (http://www.clinicaltrials.gov/ct2/show/NCT00799617). This is a 1-yr, multicenter RPCT of men 65 yr of age and older. To qualify for the trial, men must complain of mobility issues, decreased libido, and/or decreased vitality, and they must have testosterone levels of less than 275 ng/dl. This study also will assess the effects of testosterone replacement on cognition, anemia, and several cardiovascular measures.

Potential benefits of testosterone replacement

Increasing serum testosterone levels to the mid-normal range for a young male with testosterone replacement therapy has been proposed to improve libido, erectile function, mood, cognition, vitality, body composition, strength, mobility, type 2 diabetes, metabolic syndrome, some cardiovascular risk factors, anemia, and BMD. Usually, we do not treat men with low testosterone levels who are acutely ill or acutely stressed.

Sexual function, libido, and erectile function

Several RPCTs have shown benefits of testosterone therapy on some aspects of sexual function. Two meta-analyses analyzed the effects of testosterone on different domains of sexual function (58, 59). Testosterone treatment moderately improved the number of nocturnal erections, sexual thoughts and motivation, number of successful intercourses, scores of erectile function, and overall sexual satisfaction in men with baseline testosterone levels below 346 ng/dl. Several of the trials shown in Tables 1 and 2 have reported benefits of testosterone treatment on sexual function. Most consistently, there have been more positive effects on libido than on erectile function.

Mood and energy

Some RPCT studies have found that testosterone treatment improved mood, but others have not (60–64). In a meta-analysis reviewing the effects on depression, testosterone therapy was found to have beneficial effects on mood (60, 65), especially in patients with hypogonadism and HIV/AIDS. Some studies have found that testosterone treatment improved symptom scores in older men (Table 2) (61, 64).

Cognition

Small RPCTs have reported mixed results on cognition. Some studies found benefit even in men with mild cognitive deficits or memory disorders such as Alzheimer's disease (66). Testosterone administration has been shown to improve spatial ability (67), verbal fluency (68), and working memory (69) in elderly men, but other studies did not observe beneficial changes (34, 63, 70, 71). Most of these studies have included relatively small numbers of men, and treatment has been short-term.

Body composition, muscle mass, and strength

The studies shown in Tables 1 and 2 that have assessed body composition have found significant changes. A meta-analysis concluded that testosterone therapy decreased fat mass and increased lean body mass with no overall change in body weight (72). These changes were noted both in men with baseline testosterone levels that averaged less than 300 ng/dl and in a larger number of studies in which the average baseline was considerably greater than 300 ng/dl. The effects of testosterone on muscle strength were heterogeneous, showing a tendency toward improvement only with leg/knee extension and handgrip of the dominant arm. Effects on physical function also have been inconsistent, and few trials have included men with functional limitations.

Metabolic syndrome and type 2 diabetes mellitus

Several clinical trials have been conducted to determine whether testosterone treatment will improve glucose control. Some small studies have found improvement in hemoglobin A1c and/or homeostasis model of assessment for insulin resistance (73–75). However, an unpublished, multicenter RPCT funded by Solvay Pharmaceuticals failed to demonstrate significant changes in homeostasis model of assessment for insulin resistance or hemoglobin A1c, although there was a significant increase in lean body mass in men treated with testosterone gel (http://www.solvaypharmaceuticals.com/static/wma/pdf/1/3/4/4/2/S176.2.101.pdf).

Bone mineral density

Fink *et al.* (76) reported that the prevalence of osteoporosis in hypogonadal males was twice that of men with normal testosterone levels (6 *vs.* 2.8%). Two meta-analyses of RPCTs showed a moderate increase in lumbar BMD in men and inconclusive results on femoral neck BMD (72, 77). Studies in Table 2 of 12 months or longer found that testosterone treatment improved BMD (78, 79). No fracture studies have been reported.

Potential risks of testosterone replacement

The potential risks of testosterone replacement include acne; worsening of male pattern baldness; gynecomastia; precipitating or worsening of sleep apnea; increasing benign prostatic hyperplasia; and increasing lower urinary tract symptoms, causing an occult prostate cancer to become a clinical prostate cancer, accelerating the growth of

metastatic prostate cancer, accelerating the growth of a breast cancer, suppressing spermatogenesis, erythrocytosis, liver toxicity, dyslipidemia, and increasing cardiovascular events. Calof *et al.* (80) published a meta-analysis of adverse events in middle-aged and older men who have been treated with testosterone. They found that older men treated with testosterone had more prostate events and more erythrocytosis. In a recent meta-analysis of adverse events, Fernández-Balsells *et al.* (81) found that testosterone treatment was associated with a significant increase in hematocrit [3.18%; 95% confidence interval (CI), 1.35–5.01], hemoglobin (0.80 g/dl; 95% CI, 0.45–1.14), and a decrease in high-density lipoprotein (HDL) cholesterol (−0.49 mg/dl; 95% CI, −0.85 to −0.13). There was no significant effect on mortality, prostate, or cardiovascular outcomes. The Testosterone in Older Men with Mobility Limitations (TOM) trial was not included in either of these meta-analyses (82). This RPCT was discontinued early because 23 men in the testosterone group *vs.* five men in the placebo group, out of the 209 men who were enrolled in the trial, had cardiovascular-related adverse events. These men had a high prevalence of chronic disease, and the mean ± SD testosterone levels were 574 ± 403 and 292 ± 160 ng/dl in the testosterone and placebo groups, respectively.

The greatest concerns about testosterone treatment are in older men. It is thought that the potential benefits are less certain and the potential risks are greater. There is concern that testosterone treatment may increase clinical prostate cancers and cardiovascular events. The latter concern has been lessened by epidemiological studies indicating that men with lower testosterone levels have increased cardiovascular events; however, the study by Basaria *et al.* (82) renews this issue.

Acne and male pattern baldness

Testosterone therapy can increase secretion of sebum, cause acne, and accelerate male pattern baldness (83). Because these effects require metabolism of testosterone to dihydrotestosterone, it may be possible to minimize the effects by treatment with a 5-α-reductase inhibitor. Acne tends to be more common in younger males. Usually, it can be managed by good personal hygiene, an antiseptic soap, and topical retinoids, benzoyl peroxide, sulfacetamide, or azelaic acid (84).

Gynecomastia

Gynecomastia at puberty is common in boys. Usually it regresses without treatment. It is thought to be due to an alteration in the free estrogen:free androgen ratio, although it is not possible to demonstrate this in many patients (85). Testosterone treatment can cause or worsen gynecomastia in some men, but usually it does not require stopping treatment. If the gynecomastia is tender or painful, treatment with an antiestrogen such as tamoxifen can be beneficial (85).

Sleep apnea

Sleep apnea is reported to cause low testosterone levels, and treatment of sleep apnea may increase testosterone levels (86, 87). Testosterone treatment with supraphysiological doses has been reported to cause or worsen sleep apnea, but evidence that replacement doses of testosterone cause sleep apnea is poor (88). Nonetheless, it is prudent to evaluate patients with symptoms suggesting sleep apnea before testosterone replacement. If they have sleep apnea, reassessment of testosterone levels after treatment of sleep apnea is suggested.

Prostate

There are theoretical concerns that testosterone treatment of older men could increase clinical prostate cancer; however, available evidence is not convincing. The prostate is an androgen-responsive organ. It increases in size at puberty as testosterone levels increase, but it does not increase in size at puberty in males with 5-α-reductase deficiency or in individuals with androgen resistance (89–91). Testosterone replacement of younger, androgen-deficient males is associated with an increase in prostate volume, but only to that of normal, eugonadal men (92). Testosterone treatment can accelerate metastatic prostate cancer (93). Although androgen ablation causes temporary regression of metastatic prostate cancers and a 20–30% reduction in prostate volume of men with benign prostatic hyperplasia (94, 95), prostate cancer incidence and benign prostatic hyperplasia prevalence increase in older men when serum testosterone levels are falling (96–98). Furthermore, a rigorous analysis of all prospective epidemiological studies did not find a relationship between testosterone levels and future incidence of prostate cancer (99). Nonetheless, the prevalence of occult prostate cancer increases with age (100), and it is not known whether increasing the serum testosterone levels into the range observed in young normal men will increase the incidence of clinical prostate cancer.

The limited number of testosterone trials in older men have not reported an increase in clinical prostate cancer from what would be expected in this age group, but the man-years of exposure is too limited to assess risk (80, 81). We have estimated that it will take a 5-yr study in which 6000 hypogonadal men are randomized to testosterone or placebo to detect a 30% increase in clinical prostate cancer. Although short-term studies like The Testosterone Trial can strengthen or refute the potential benefits of tes-

tosterone treatment in older men, short-term studies are not powered to assess long-term potential risks of prostate cancer or cardiovascular disease. In the interim, a testosterone registry has been established in Europe. A registry will not obviate the need for a long-term safety study, but it can provide useful interim data that will help to assess the potential benefit:risk ratio for treating older men with testosterone.

Breast cancer

A recent report found increased risk of breast cancer in men with Klinefelter's syndrome (relative risk = 16.83; 95% CI, 6.81–41.62) (101). Most breast cancers in men are estrogen receptor positive (102), and testosterone is partially metabolized to estradiol. Reports of breast cancers in men treated with testosterone are rare (103), but it is wise to examine the breasts before and during treatment.

Erythrocytosis

In the meta-analysis of adverse events, testosterone-treated men were nearly four times more likely than placebo-treated men to have a hematocrit greater than 50% (odds ratio = 3.69; 95% CI, 1.82–7.51) (80, 81). Of the 35 testosterone-treated men in the first meta-analysis with a hematocrit greater than 50%, one patient had a cerebral hemorrhage. Higher hematocrits are associated with increased blood viscosity and decreased blood flow (104, 105). Higher hematocrits have been associated with increased myocardial infarctions, coronary insufficiency, and coronary heart disease deaths (106). More recent studies have associated carotid atherosclerosis, ischemic heart disease, and stroke with hematocrit and blood viscosity (107, 108). Therefore, careful monitoring of the hematocrit and hemoglobin during testosterone treatment is indicated.

Suppression of spermatogenesis

Testosterone treatment will suppress gonadotropins and spermatogenesis (109, 110). Testosterone treatment is not appropriate for treatment of testosterone-deficient men who desire to father a child in the near future.

Cardiovascular

Men have more cardiovascular events than women through age 74 (111). Initially, it was thought that either testosterone increased or estrogen decreased cardiovascular events. However, most epidemiological studies have found that men with lower testosterone levels are at increased risk for having cardiovascular events when compared with men with higher levels (112). Furthermore, treatment of postmenopausal women with estrogen increased rather than decreased cardiovascular events (113). Although two meta-analyses have failed to find that testosterone treatment increases the risk of cardiovascular events (80, 81), one of the two studies in men 65 and older that was published in 2010 reported a significant increase in cardiovascular events (64, 82).

Liver toxicity

Oral 17-alkylated testosterone derivatives have been associated with liver toxicity, and because of this they are not recommended for testosterone replacement treatment in men (14).

Lipids

In the meta-analysis conducted on RPCT trials by Isidori *et al.* (72), there was a significant decrease in total cholesterol that was more pronounced in the group with lower testosterone levels. A reduction in HDL cholesterol was detectable only in studies with higher pretreatment testosterone concentrations. The effects on low-density lipoprotein cholesterol were not significant. Fernández-Balsells *et al.* (81) also noted a small but significant decrease in HDL cholesterol.

Treatment options

We now have multiple testosterone delivery systems, and they vary in their pharmacokinetics and in their side effect profiles (Table 3). Oral testosterone undecanoate fails to maintain physiological levels of testosterone during the night, and outcome studies suggest that it is less effective (114, 115). Injectable testosterone cypionate and enanthate deliver supraphysiological levels of testosterone for the initial treatment period, and they seem to be more likely to cause erythrocytosis and perhaps sleep apnea (41, 82, 88, 116). Testosterone patches are likely to cause dermatological reactions (41). Topical application of transdermal gels can achieve physiological levels of testosterone in most men, but they leave a film of testosterone on the skin that can be transferred to a child or female (117). Subcutaneous testosterone pellets and im testosterone undecanoate can provide physiological levels of testosterone for many weeks (118, 119), but this could be a disadvantage in men who develop erythrocytosis or a prostate issue. Cost of testosterone replacement therapy ranges from relatively inexpensive injections of generic testosterone cypionate or enanthate to expensive testosterone gels and long-acting delivery systems. Thus, pharmacokinetics, pharmacodynamics, side effects, and cost must be considered when choosing a specific delivery system for a given patient.

Monitoring Treatment

Patients who choose testosterone replacement therapy must be monitored for effectiveness of treatment. One

TABLE 3. Advantages and disadvantages of testosterone formulations

Formulation	Regimen	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg/2 wk im or 75–100 mg/wk im	Corrects symptoms of androgen deficiency; relatively inexpensive, if self-administered; flexibility of dosing.	Requires im injection; peaks and valleys in serum T levels.
1% T gel	Available in sachets, tubes and pumps; 5–10 g T gel containing 50–100 mg T should be applied daily.	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; skin irritation in a small proportion of treated men; moderately high DHT levels.
Transdermal T patch	1 or 2 patches, designed to nominally deliver 5–10 mg T over 24 h; applied daily on nonpressure areas.	Ease of application, corrects symptoms of androgen deficiency.	Serum T levels in some androgen-deficient men may be in the low-normal range; these men may need application of 2 patches daily. Skin irritation at the application site occurs in many patients.
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets used twice daily.	Corrects symptoms of androgen deficiency in healthy, hypogonadal men.	Gum-related adverse events in 16% of treated men.
T pellets	Three to six pellets implanted sc; dose and regimen vary with formulation used.	Corrects symptoms of androgen deficiency.	Requires surgical incision for insertions; pellets may extrude spontaneously.
17-α -methyl T	This 17-α-alkylated compound should not be used because of potential for liver toxicity.		Clinical responses are variable; potential for liver toxicity. Should not be used for treatment of androgen deficiency in men.
Oral T undecanoate[a]	40 to 80 mg orally, 2 or 3 times daily with meals.	Convenience of oral administration.	Not approved in the United States. Variable clinical responses; variable serum T levels; high DHT:T ratio.
Injectable long-acting T undecanoate in oil[b]	The regimen used in Europe typically involves 1000 mg injected im, followed by 1000 mg at 6 wk, and 1000 mg every 10–14 wk	Corrects symptoms of androgen deficiency; requires infrequent administration.	Requires im injection of a large volume (4 ml). Cough has been reported immediately after injection in a very small number of treated men.
T-in-adhesive matrix patch[c]	2 $\times$ 60 cm^2 patches delivering approximately 4.8 mg of T/d	Lasts 2 d.	Some skin irritation.

Modified from The Endocrine Society Guidelines (14). T, Testosterone; DHT, dihydrotestosterone. Certain formulations are available in other countries but not in the United States. These include: [a] oral testosterone undecanoate (typically used at a dose of 40 to 80 mg orally two or three times daily with meals); [b] injectable testosterone undecanoate 1000 mg followed by a second 1000 mg injection 6 wk later, and then 1000 mg every 10 to 14 wk; and [c] two testosterone matrix patches 30, 45, or 60 cm^2 applied every 2 d.

would like to ensure that the patient is achieving physiological levels of testosterone. Usually, this is done within the first 1–2 months. Sampling time varies depending on the delivery system (Table 4). We try to achieve testosterone levels in the mid-normal (400–700 ng/dl) range for young men (14). One may choose to lower this range some in older men. Assessment of clinical responses should be made within 2–4 months of initiating treatment. Some symptoms such as libido, energy, and mood are improved within 1–3 months, whereas it usually takes longer to see changes in body composition and BMD. If erectile dysfunction persists, treatment with a phosphodiesterase type 5 inhibitor may be helpful (120). One also should recognize that organ systems respond differently to testosterone levels within the physiological range. Libido, erectile function, and mood seem to be improved with levels in the low normal range (121), whereas skeletal muscle responds in a dose-responsive manner in younger and older men (55). Demonstrable changes in BMD are dependent on dose and duration of treatment (72). Most clinicians evaluate treatment effectiveness by reassessing the patient's presenting symptoms and by physical examination.

TABLE 4. Monitoring of men receiving testosterone therapy

1. Evaluate the patient 3 to 6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.
2. Monitor testosterone level 3 to 6 months after initiation of testosterone therapy:
   - Therapy should aim to raise serum testosterone level into the mid-normal range.
   - Injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/liter) or <350 ng/dl (12.3 nmol/liter), adjust dose or frequency.
   - Transdermal patches: assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range.
   - Buccal testosterone bioadhesive tablet: assess level immediately before or after application of fresh system.
   - Transdermal gels: assess testosterone level any time after patient has been on treatment for at least 1 wk; adjust dose to achieve serum testosterone level in the mid-normal range.
   - Testosterone pellets: measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels in the normal range.
   - Oral testosterone undecanoate: monitor serum testosterone level 3 to 5 h after ingestion.
   - Injectable testosterone undecanoate: Measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone in mid-normal range.
3. Check hematocrit at baseline, at 3 to 6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose.
4. Measure BMD of lumbar spine and/or femoral neck after 1–2 yr of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care.
5. In men 40 yr of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3 to 6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient.
6. Obtain urological consultation if there is:
   - An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment.
   - A PSA velocity of >0.4 ng/ml · yr using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 yr).
   - Detection of a prostatic abnormality on digital rectal examination.
   - An AUA/IPSS prostate symptom score of >19.

Modified from The Endocrine Society Guidelines (14).

Patients also must be evaluated for potential side effects associated with testosterone treatment and for those that are delivery system specific (Table 4). The frequency of monitoring and the parameters that should be monitored are dependent on age. Patients should be questioned about skin reactivity, and application sites should be monitored when patients are treated with transdermal delivery systems. Middle-aged and older men are at potential risk for developing or worsening of sleep apnea, so they and their mates should be questioned for symptoms of sleep apnea.

The American Urological Association Best Practice Statement (2009) recommends evaluation of a prostate-specific antigen (PSA) level and a digital rectal examination of the prostate at age 40 (http://www.auanet.org/content/guidelines-and-quality-care/clinical-guidelines/main-reports/psa09.pdf). Individuals with PSA levels above the median (0.6 ng/dl) for this age should be monitored annually, whereas monitoring can be less frequent for those below the median. When lower urinary tract symptoms are significant or when treatment is increasing male pattern baldness, one can consider using a 5-α-reductase inhibitor; however, trial data showing that this is effective in patients being treated with testosterone are limited.

Conclusion

The diagnosis and treatment of androgen deficiency are less controversial in younger men with classical causes of androgen deficiency who have unequivocally low testosterone levels. The diagnosis is less certain in middle-aged and older men with comorbid diseases and borderline low testosterone levels. Clinical trials in these men have produced more equivocal outcomes. Several RPCTs in older testosterone-deficient men have shown improvement in outcomes. A large, multicenter, National Institute on Aging-sponsored study is under way. It should provide definitive answers to potential benefits of testosterone replacement in older men. However, it is not powered to assess potential risks of prostate cancer and cardiovascular events. For now, clinicians should discuss the available efficacy and risk data for testosterone replacement and should help each patient make the decision that is best for him.

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