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Testosterone Replacement Therapy for Older Men

Review

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The interest in possible medical interventions to promote healthy aging has been recently increasing, as the absolute number and the proportion of men over 60 years of age is expected to increase during the next few decades in various countries (Liu et al, 2004). Numerous studies have demonstrated lower concentrations of testosterone in older men (Vermeulen et al, 1972; Rubens et al, 1974; Pirke and Doerr, 1975; Baker et al, 1976; Purifoy et al, 1981; Bremner and Prinz, 1983; Tenover et al, 1987; Gray et al, 1991; Ferrini and Barrett-Connor, 1998). Serum testosterone concentrations have been shown to decrease longitudinally with age (Morley et al, 1997; Zmuda et al, 1997; Harman et al, 2001), but estimates of the rate of this fall in testosterone levels may differ substantially based on the type of data analysis (Liu et al, 2004). Aging has been reported to be associated with decreased muscle mass, muscle strength, physical performance, physical activity, bone mineral density, and libido (Davidson et al, 1983; Santavirta et al, 1992; Nguyen et al, 1996; Rantanen et al, 1998; Anonymous, 2002; Hughes et al, 2002; Liu et al, 2004). The presence of a combination of these nonspecific clinical features may indicate organic androgen deficiency. Thus, testosterone replacement therapy may be of special importance in this age group, as the anabolic effects of this hormone on muscle, fat, and bone may contribute to improvement in physical function and quality of life. However, various factors may be involved in determining the clinical significance of this age-related decline in serum testosterone, as well as the safety and benefit of testosterone replacement therapy in older men, including the rate of decrement in systemic testosterone exposure, possible reduced androgen responsiveness of older tissues, and the rising age-related background rates of certain androgen-dependent cardiovascular and prostatic disorders.

This review concentrates on the key issues associated with testosterone replacement therapy in older men, including the background for this intervention, the available testosterone formulations, and their possible adverse effects, and it also provides suggested protocols for screening and monitoring patients before and during this treatment, respectively.

Definition of Hypogonadism in Older Men

A health factor–independent, age-related longitudinal decrease in serum testosterone levels has been reported (Harman et al, 2001). As there is no agreement on the definition of hypogonadism in older men, a combination of clinical signs and testosterone measurements is usually used as a tool to determine whether testosterone replacement therapy is indicated. The most easily recognized clinical signs of relative androgen deficiency in older men are a decrease in muscle mass and strength, a decrease in bone mass and osteoporosis, and an increase in central body fat. However, symptoms such as a decrease in libido and sexual desire, forgetfulness, loss of memory, difficulty in concentration, insomnia, and a decreased sense of well-being are more difficult to measure and differentiate from hormone-independent aging.

Because there is no generally accepted threshold value of plasma testosterone for defining androgen deficiency, and in the absence of convincing evidence for an altered androgen requirement in older men, the normal range of testosterone levels in young males is suggested to be valid for older men as well.

As the clinical symptoms of hormone deficiency in older males may be nonspecific, and since a substantial number of relatively asymptomatic elderly men have testosterone levels outside the normal range for young adults, investigators have suggested that testosterone replacement therapy is only warranted in the presence of both clinical symptoms suggestive of hormone deficiency and decreased hormone levels (Vermeulen, 2001). However, testosterone replacement may also be warranted in older men with markedly decreased testosterone levels, regardless of symptoms (Gruenewald and Matsumoto, 2003).

Diagnosis of Hypogonadism

Based on the data currently available, the measurement of total blood testosterone is the most appropriate test to

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determine whether an older patient is hypogonadal or not (Bhasin et al, 1998; Basaria and Dobs, 2001; Blum and Harris, 2003).

Some investigators have suggested that a total testosterone level of 200 ng/dL can appropriately be used as a cut-off value, below which an individual should be considered hypogonadal, regardless of age (Bhasin et al, 1998; Swerdloff et al, 2000; Blum and Harris, 2003; Gruenewald and Matsumoto, 2003). However, the presence of hypogonadism is uncertain in patients whose total testosterone levels are in the borderline range, between 200 and 300 ng/dL (Bhasin et al, 1998). Others consider individuals whose total testosterone levels are less than 300 ng/dL to be hypogonadal (Basaria and Dobs, 2001). Some consider measurements of free testosterone (FT, non-protein bound) levels to be a more reliable clinical measure of hypogonadism, but the dependability and reproducibility of these method-dependent assays have not been established. Moreover, it has not been established that FT levels are a better marker of hypogonadism in the elderly than are total testosterone levels. The determination of bioavailable testosterone (BT, free plus albumin bound) could potentially become the most reliable measure, as it assesses the testosterone available to tissues, and some investigators suggest defining hypogonadism as a fasting morning BT less than 67 ng/dL (Korenman, 1998). Currently, however, this test is more expensive and is not widely available (Plymate, 1998; Blum and Harris, 2003; Matsumoto and Bremner, 2004). The measurement of FT (preferably by an equilibrium dialysis method, which is a reference technique, one that is not usually used by hospital or clinical labs or that is calculated from separate measurements of SHBG and testosterone) or of BT (by ammonium sulfate precipitation) may be helpful in selected cases in which there is a questionable relationship between total testosterone levels that are in the low end of the normal range and clinical symptoms suggestive of hypogonadism. It has been reported that the diurnal variation in testosterone levels in older men, if detected, tends to be attenuated and inconsistent between individuals (Basaria and Dobs, 2001; Vermuelen, 2001).

Treatment Options

Intramuscular injection of long-acting esters, such as testosterone enanthate, is a traditional form of testosterone therapy. The hydrophobicity of these agents, dictated by the length of their side chain, positively correlates with the duration of their release from the muscle depot. Therefore, testosterone enanthate or testosterone cypionate have a longer action than testosterone proprionate. Testosterone enanthate and testosterone cypionate have the same pharmacokinetic profile: serum testosterone levels reach a peak 24 hours after administration and gradually decline within a period of 2 weeks (Sokol et al, 1982). However, these large fluctuations in serum testosterone levels cause unsatisfactory shifts of mood and sexual function in some men. Combined with the frequent injections, this delivery mode is thus far from being ideal.

Two types of transdermal testosterone patches are available, scrotal and nongenital, and these are characterized by favorable pharmacokinetic behavior and have proved to be an effective mode of delivery (Findlay et al, 1989; Nieschlag and Bals-Pratsch, 1989; Bhasin et al, 1996; Brocks et al, 1996; Meikle et al, 1996; Bhasin and Bremner, 1997; Wang and Swerdloff, 1997, 1999; McClellan and Goa, 1998; Wilson et al, 1998). Daily use of the scrotal patch can produce midnormal serum testosterone levels in hypogonadal men 4 to 8 hours after application, and these levels gradually decrease over the next 24 hours (Cunningham et al, 1989). Nevertheless, the scrotal testosterone patch system is hampered by the application site, which is not easily accepted by many patients, and by the need to shave that region. Serum dihydrotestosterone (DHT) levels have been reported to be high relative to testosterone levels in hypogonadal men treated with the scrotal patches (Bhasin and Bremner, 1997), but safety data over 10 years indicate no negative effect on the prostate with the use of either patch system (Jockenhovel, 2003). The nongenital patch was not found to be associated with elevated serum DHT levels but has a high rate of skin irritation. Androderm, a nongenital patch, was reported to produce physiological levels and circadian patterns of testosterone, and its metabolites, in hypogonadal men (Arver et al, 1997; Dobs et al, 1999). The most recently approved nongenital patch (Testoderm TTS; Alza, Mountain View, Calif) has been reported to cause less skin irritation (itching in about 12% and erythema in 3%), but adherence of the patch to the skin appeared to be a problem in some patients (Yu et al, 1997a,b) Midnormal serum testosterone levels are reached 8 to 12 hours after the application of 2 nongenital patches (Meikle et al, 1992).

Transdermal testosterone gel (1% testosterone in a hydroalcoholic gel) has been available in the United States since mid-2000. Currently, 2 gel formulations are available. Testim (Auxilium Pharmaceuticals, Norristown, Pa) is a clear to translucent hydroalcoholic topical gel containing 1% testosterone. One 5-g or two 5-g tubes of Testim contain 50 mg or 100 mg of testosterone, respectively, to be applied daily to intact, clean, dry skin of the shoulders and upper arms. The skin serves as a reservoir for the sustained release of testosterone into the systemic circulation, allowing a single application of this formulation to provide continuous transdermal delivery of testosterone for 24 hours, producing circulating testosterone levels that approximate the normal levels (eg, 300–1000 ng/dL) seen in healthy men. Approximately 10% of the applied testosterone dose is absorbed across skin of average per-

meability during a 24-hour period. Recently, the pharmacokinetic and clinical profile of Testim for the treatment of male hypogonadism was reviewed, based on the findings of 5 published clinical studies. Twelve-month studies of Testim for the treatment of male hypogonadism demonstrated an increase in total serum testosterone levels, which were maintained within the normal adult range, as well as statistically significant increases in lean body mass, bone mineral density, and mean scores for sexual desire, performance, motivation, and spontaneous erections (all $P < .001$), when compared to baseline. Treatment with Testim was reported to be well tolerated, resulting in 10-fold fewer application-site reactions than patch preparations (Bouloux, 2005).

AndroGel (Montrouge, France) is a clear, colorless hydroalcoholic gel containing 1% testosterone, available in packets of 2.5 and 5.0 G or in a multidose pump, with similar pharmacokinetic properties. A daily application of AndroGel 5 g, 7.5 g, or 10 g contains 50 mg, 75 mg, or 100 mg of testosterone, respectively, to be applied daily to intact, clean, dry skin of the shoulders, upper arms, and/or abdomen. Applied once daily on the nongenital skin, the gel delivers sufficient amounts of testosterone to restore normal hormonal values (Swerdloff et al, 2000; Wang et al, 2000) and to correct the signs and symptoms of hypogonadism (Jockenhovel, 2003). The gel is well tolerated and is usually associated with minimal skin irritation compared to testosterone patches. One potential problem is transfer of the gel from person to person via direct contact. In a recent large long-term, open-label continuation study, AndroGel was found to raise serum testosterone levels in hypogonadal men and to keep them within the normal range (300–1100 ng/dL) over 3 years. Sexual function improved significantly by 6 months, and increased lean body mass occurred as early as 3 months. Both of these effects, as well as mood improvement, were sustained throughout the study. The beneficial effects of AndroGel also included a progressive increase in bone mineral density and were similar to those associated with injectables or other transdermal preparations. A low incidence of mild local skin irritation was reported, as well as an anticipated increase in hematocrit and hemoglobin. Monitoring for prostatic disease and erythrocytosis was strongly advised to reduce the risk of adverse events with testosterone replacement therapy (Wang et al, 2004a).

The intramuscular injection of 1000 mg of testosterone undecanoate every 12 to 15 weeks, investigated in phase II and III clinical studies, has led to extremely stable serum testosterone levels for a prolonged period of time and has resulted in excellent efficacy (Partsch et al, 1995; Jockenhovel, 2003). However, high first-pass inactivation and hepatotoxicity are still of concern and warrant further investigation.

Some oral testosterone formulations have proven to be problematic, as absorption can be variable, bioavailability is frequently poor (because of the first-pass effect on the liver), and frequent administration is often required. A relatively new oral testosterone, undecanoate formulation avoids, at least partially, the first-pass effect of the liver (Jockenhovel, 2004). Oral testosterone undecanoate dissolved in castor oil bypasses the liver via its lymphatic absorption. At a dosage of 80 mg twice daily, plasma testosterone levels are largely in the normal range, but plasma DHT tends to be elevated (Gooren and Bunck, 2004). This formulation also improves storage conditions markedly, as it is stable at room temperature for approximately 3 years. While oral testosterone undecanoate supplementation has been shown to increase muscle and decrease fat mass in healthy older males with low-normal gonadal status (Wittert et al, 2003), further studies will aid in the evaluation of the efficacy and safety of this formulation in the treatment of older men with late-onset hypogonadism (Kohn and Schill, 2003).

Subcutaneous implantation of three 200-mg or six 100-mg testosterone pellets has been demonstrated to provide normal testosterone levels for as long as 6 months. However, this formulation is rarely used in the United States, as it requires a skin incision for implantation of the pellet and is occasionally associated with spontaneous extrusion of the pellet (Handelsman et al, 1990).

Cyclodextrin-complexed testosterone sublingual formulation is absorbed rapidly into circulation, where testosterone is released from the cyclodextrin shell (Salehian et al, 1995). This formulation has been suggested to have a good therapeutic potential, after adjustment of its kinetics, to produce physiologic levels of testosterone.

A single intramuscular dose of biodegradable testosterone microsphere formulation can provide normal testosterone levels in hypogonadal men for up to 11 weeks (Bhasin et al, 1992).

Striant (Columbia Laboratories, Livingston, NJ) is a novel sustained-release mucoadhesive buccal testosterone tablet. One buccal system (delivering 30 mg) should be applied to the gum region twice daily, in the morning and evening, approximately 12 hours apart. This formulation has been shown to restore serum testosterone concentrations to the physiological range within 4 hours of application, with steady-state concentrations achieved within 24 hours of twice-daily dosing (Korbonits et al, 2004). In phase III clinical trials, 87%–97% of patients using Striant achieved 24-hour averaged serum testosterone concentrations within the normal range. Striant was reported to be well tolerated, with a low incidence of adverse events and a low discontinuation rate (3.5%) due to adverse events in phase III studies. In another study, gum-related adverse events occurred in 16.3% of subjects. Most of these adverse effects occurred early during treatment, did not cause interruption of treatment, and re-

solved rapidly and completely (Wang et al, 2004b). These studies indicate that Striant is an effective, well-tolerated, convenient and discreet treatment for male hypogonadism.

Risks of Testosterone Replacement Therapy

The dermatological adverse effects of testosterone replacement may include oily skin, acne, and skin reactions, the most common of which are erythema and induration. In fact, the nongenital patches have been reported to be associated with skin irritation in about one third of patients, and 10%–15% of patients have reported discontinuance of treatment as a result of chronic skin irritation (Jordan, 1997; Jordan et al, 1998). These reactions are seen less commonly with the scrotal patches.

Breast enlargement and/or tenderness are often transient and abate with continued treatment. The development of breast enlargement is uncommon at standard dosing levels.

None of the reports on testosterone supplementation in older males have mentioned the development of sleep apnea as a consequence of this treatment. Nevertheless, it is safe to consider obstructive pulmonary disease in overweight persons or heavy smokers as a relative contraindication.

The development of clinically significant polycythemia is uncommon as a consequence of testosterone replacement therapy, but it can occur in men with sleep apnea, heavy smoking history, or chronic obstructive pulmonary disease. The main risk factor for polycythemia with testosterone administration appears to be age, and the incidence of this risk factor was reported to be higher with intramuscular rather than transdermal preparations.

Possible hepatic adverse effects, including liver function abnormalities or development of liver tumors, are extremely rare with the replacement doses given by the injectable esters and the two transdermal formulations. Use of oral androgen preparations, however, has been associated with hepatic dysfunction and hepatic malignancy (Nieschlag and Behre, 1998). Another possible problem with the older oral androgen formulations is their potential for uneven absorption, as a result of the first-pass effect of the liver. However, oral testosterone undecanoate dissolved in castor oil, a newer formulation, has been reported to bypass the liver via its lymphatic absorption (Gooren and Bunck, 2004) and is clinically available and used in Europe and Canada.

Modest, usually transient, leg edema and fluid retention (up to several kilograms in weight gain) is possible, especially within the first few months of testosterone replacement therapy. Studies of testosterone replacement in men have not reported problems with peripheral edema or exacerbation of hypertension or congestive heart failure, but because current data were largely collected from relatively healthy older men, the possible impact of fluid retention on chronically ill or more frail individuals should be considered (Tenover, 1999).

Testosterone effects on plasma lipids remain controversial. Plasma high-density lipoprotein levels were reported by some investigators to either slightly decrease or remain unchanged during short-term testosterone replacement therapy, and were accompanied by a decrease in low-density lipoprotein cholesterol levels. Nevertheless, other studies have shown that short-term testosterone replacement treatment of older men with low testosterone levels was not associated with significant changes in plasma lipids. While the ultimate long-term impact on cardiovascular disease is still unknown (Tenover, 1999), current data, obtained from short-term studies, indicate that from the cardiovascular perspective, careful use of aromatizable forms of testosterone is likely to be safe for the majority of older hypogonadal men (Baker et al, 1976; Gruenewald and Matsumoto, 2003).

The possible development of symptomatic benign prostatic hyperplasia (BPH) and prostate cancer has been a concern with testosterone replacement therapy. Prostate volumes have been reported to increase with testosterone replacement therapy, but in a modest and inconsistent fashion, without any increase in the clinical symptoms of BPH (Meikle et al, 1997; Bhasin et al, 1998). It appears that nonobstructive BPH is not a contraindication for androgen substitution. However, obstructive BPH has been indicated as a contraindication (Vermeulen, 2001).

Although testosterone replacement therapy in men with erectile dysfunction and hypogonadism has been reported to be associated with a minor prostatic specific antigen (PSA) elevation (Gerstenbluth et al, 2002), available data support the safety of testosterone replacement treatment in the short term. These findings should be interpreted carefully, however, as the data were obtained from relatively small studies. Until large, long-term, well-designed studies have been conducted and analyzed, questions about the long-term safety of testosterone replacement therapy in older men will remain (Tenover, 1997; Gerstenbluth et al, 2002; Kaufman, 2003).

Finally, while testosterone increases platelet aggregation and thrombogenicity, clinical manifestations of this effect were not seen in hypogonadal men receiving replacement doses of testosterone (AACE Hypogonadism Task Force, 2002).

Pretreatment Screening

Given the possible potential for adverse effects of testosterone therapy in the older man, pretreatment screening for parameters related to potential risks of testosterone therapy is advised, including: 1) medical history for potential sleep apnea, congestive heart failure, symptoms consistent with lower urinary tract obstruction, and per-

sonal or family history of prostate or breast carcinoma (Patients should be informed that testosterone therapy will affect spermatogenesis and their fertility potential during treatment and for some time following cessation of therapy); 2) physical examination, including a digital rectal examination (DRE) of the prostate; and 3) laboratory tests, including hematocrit and PSA level.

In cases of abnormal DREs and/or elevated PSA levels, *trans*-rectal ultrasound guided biopsy of the prostate should be performed prior to the initiation of testosterone therapy.

Monitoring

We recommend periodic follow-up of patients receiving replacement testosterone therapy in intervals of 3 to 4 months during the first year of treatment. Specifically, the patient should be asked about daytime fatigue and sleep disorders, and serum testosterone level should be measured at a midpoint between injections for patients treated with this formulation. The time of measurement usually is not critical with the gel formulation; 4 to 8 hours after application of patch preparations is usually recommended.

We recommend that the hematocrit should be determined every 6 months for the first 18 months and then yearly thereafter if it is stable and normal. Testosterone therapy should be decreased or stopped if the hematocrit exceeds 52%–55%. Alternatively, periodic phlebotomy can be used to manage increased hematocrit.

With regard to the possible effects of testosterone replacement therapy on the prostate, we recommend that DRE and a prostate-related symptom assessment should be performed every 6 to 12 months. We recommend that PSA levels should be determined after 3 and 6 months, and then annually thereafter. A recent study indicated an algorithm for the management of increased PSA levels, based on the magnitude of elevation. Although a yearly PSA increase of 1.0 ng/dL or more has been suggested as an indication for prostate biopsy, increases of 0.7 to 0.9 ng/dL in one year could be managed by repeating the PSA measurement in 3 to 6 months and performing a biopsy if there is any further increase (Rhoden and Morgentaler, 2004).

Summary

A review of the currently published data indicates that testosterone replacement therapy in older men may be advantageous in terms of improving bone mineral density, increasing muscle mass and strength, and, in some men, improving libido and mood. However, the long-term clinical significance of these effects is still uncertain, as larger and longer-term studies are needed. In the short term (up to 3 years), the adverse effects of testosterone replacement therapy in older men seem predictable and manageable, but the longer-term effects on target organs, such as the cardiovascular system and the prostate, are yet to be determined.

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