The benefits and risks of testosterone replacement therapy: a review

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Abstract: Increased longevity and population aging will increase the number of men with late onset hypogonadism. It is a common condition, but often underdiagnosed and undertreated. The indication of testosterone-replacement therapy (TRT) treatment requires the presence of low testosterone level, and symptoms and signs of hypogonadism. Although controversy remains regarding indications for testosterone supplementation in aging men due to lack of large-scale, long-term studies assessing the benefits and risks of testosterone-replacement therapy in men, reports indicate that TRT may produce a wide range of benefits for men with hypogonadism that include improvement in libido and sexual function, bone density, muscle mass, body composition, mood, erythropoiesis, cognition, quality of life and cardiovascular disease. Perhaps the most controversial area is the issue of risk, especially possible stimulation of prostate cancer by testosterone, even though no evidence to support this risk exists. Other possible risks include worsening symptoms of benign prostatic hypertrophy, liver toxicity, hyperviscosity, erythrocytosis, worsening untreated sleep apnea or severe heart failure. Despite this controversy, testosterone supplementation in the United States has increased substantially over the past several years. The physician should discuss with the patient the potential benefits and risks of TRT. The purpose of this review is to discuss what is known and not known regarding the benefits and risks of TRT.

Keywords: hypogonadism, testosterone replacement therapy, erectile dysfunction, osteoporosis, cardiovascular disease

Introduction

Hypogonadism is a clinical condition in which low levels of serum testosterone are found in association with specific signs and symptoms. When hypogonadism occurs in an older man, the condition is often called andropause or androgen deficiency of the aging male or late onset hypogonadism (LOH).[1] 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, anemia, difficulty in concentration, insomnia, and a decreased sense of well-being are more difficult to measure and differentiate from hormone-independent aging. This condition may result in significant detriment to quality of life and adversely affect the function of multiple organ systems.[1–3] A health factor-independent, age-related longitudinal decrease in serum testosterone levels has been reported.[4] This LOH is important since it features many potentially serious consequences that can be readily avoided or treated, and the affected sector of the

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population is currently expanding in number. Prospective population-based studies reported in the past decade indicate that low testosterone levels are associated with an increase in the risk for developing type 2 diabetes mellitus and metabolic syndrome and possibly a reduction in survival. Results were similar for bioavailable testosterone.[5–7] In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.[8] Also, low testosterone levels were associated with increased mortality in male veterans[9] but this association could not be confirmed in the Massachusetts Male Aging Study[10] or the New Mexico Aging Study.[11]

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.[12] Restoring serum testosterone levels to the normal range using testosterone replacement therapy results in clinical benefits in some of these areas. Successful management of testosterone replacement therapy requires appropriate evaluation and an understanding of the benefits and risks of treatment.

Aging and hypogonadism

Due to the baby boom that occurred after World War II, the percentage of population in the older age group in developed countries is increasing. Testosterone deficiency is a common disorder in middle-aged and older men but it is underdiagnosed and often untreated. Clinicians tend to overlook it, and the complaints of androgen-deficient men are merely considered part of aging. Hypogonadism affects an estimated 2 million to 4 million men in the United States. Many patients can derive significant benefits from treatment. Testosterone supplementation in the United States has increased substantially over the past several years.[13] However, it has been estimated that only 5% of affected men currently receive treatment.

The decline of serum testosterone levels appears to be a gradual, age-related process resulting in an approximate 1% annual decline after age 30. In cross-sectional and longitudinal studies of men aged 30 or 40 years and above, total, bioavailable and free testosterone concentrations fall with increasing age with a steeper decline in bioavailable and free compared with total testosterone concentrations.[4,14,15] In older men above the age of 65 or 70 years, the changes in total testosterone are overshadowed by a more significant decline in free testosterone levels.[16,17] This is a consequence of the age-associated increase of the levels of sex hormone binding globulin (SHBG) demonstrated by cross-sectional studies, and has now been confirmed by longitudinal studies.[18,19] Although the fall is gradual, by the eighth decade, according to the Baltimore Longitudinal Study, 30% of men had total testosterone values in the hypogonadal range, and 50% had low free testosterone values. The rate of age-related decline in serum testosterone levels varies in different individuals and is affected by chronic disease and medications.[20] There is evidence that many of these men are not symptomatic.[21]

Multiple mechanisms are likely to influence the decline in testosterone levels in aging men.[22] Lower testosterone levels may result from reduced testicular responses to gonadotrophin stimuli with aging, coupled with incomplete hypothalamo–pituitary compensation for the fall in total and free testosterone levels.[23,24] Whether the age-dependent decline in androgen levels leads to health problems in older men is being debated vigorously.[21,25]

Diagnosis

At present, the diagnosis of hypogonadism requires the presence of symptoms and signs suggestive of testosterone deficiency.[1,26] The symptom most associated with hypogonadism is low libido.[27–29] Other manifestations of hypogonadism include erectile dysfunction, decreased muscle mass and strength, increased body fat, decreased bone mineral density and osteoporosis, mild anemia, breast discomfort and gynecomastia, hot flushes, sleep disturbance, body hair and skin alterations, decreased vitality, and decreased intellectual capacity (poor concentration, depression, fatigue).[30] The problem is many of the symptoms of late life hypogonadism are similar in other conditions[31,32] or are physiologically associated with the aging process.[33] One or more of these symptoms must be corroborated with a low serum testosterone level.[21,25,34] Depression, hypothyroidism and chronic alcoholism should be excluded, as should the use of medications such as corticosteroids, cimetidine, spironolactone, digoxin, opioid analgesics, antidepressants and antifungal drugs. Of course, diagnosis of LOH should never be undertaken during an acute illness, which is likely to result in temporarily low testosterone levels (Figure 1).

The problem with symptoms associated with low serum testosterone is that they may be found in other conditions, which become increasingly common as men age. While the questionnaires, the Androgen Deficiency in Aging Male (ADAM)[35,36] and the Aging Male Symptoms Scale
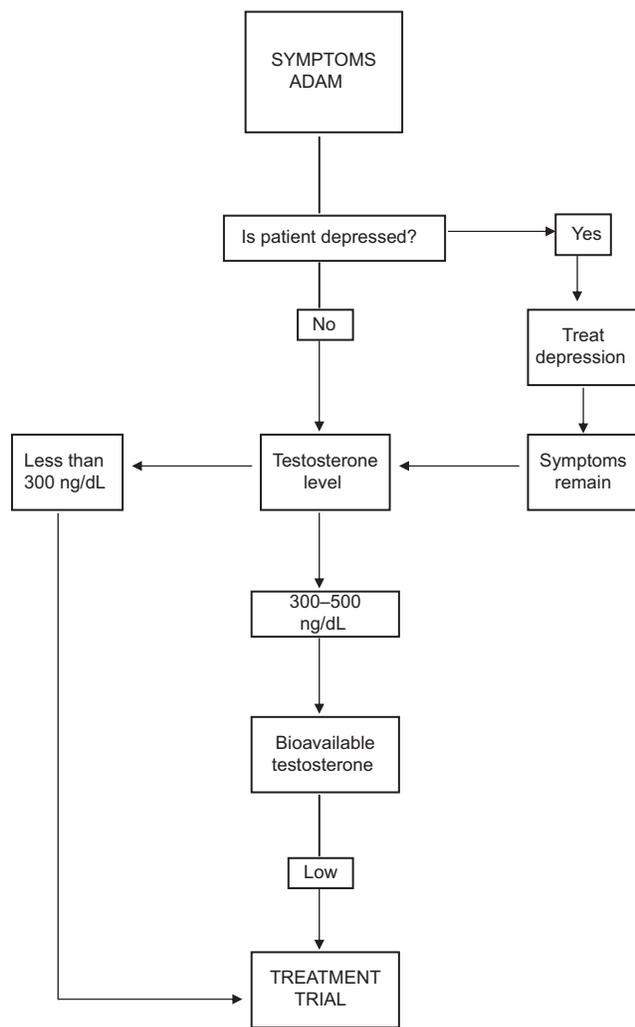
Figure 1 Approach to the diagnosis and treatment of late onset hypogonadism (ADAM = St. Louis University Androgen Deficiency in Aging Males Questionnaire).

(AMS)[37,38] (Table 1), may be sensitive markers of the low testosterone state (97% and 83%, respectively), they are not tightly correlated with low testosterone (specificity 30% and 39%), particularly in the borderline low serum testosterone range. Therefore, questionnaires are not recommended for screening of androgen deficiency in men receiving health care for unrelated reasons.[26] Moreover, healthy ambulatory elderly males over 70, assessed by the AMS, had a high perception of sexual symptoms with mild psychological and mild to moderate somatovegetative symptoms.[39] Note also that there is marked inter-individual variation of the testosterone level at which symptoms occur.[28,34,40] A low libido by itself is insufficient to allow the diagnosis of hypogonadism.[41]

Laboratory diagnosis

A thorough physical and biochemical work-up is necessary. Transient decreases of serum testosterone levels such as

those due to acute illnesses should be excluded by careful clinical evaluations and repeated hormone measurement. Hypogonadism (primary or secondary) can occur at all ages, including in elderly men. Risk factors for hypogonadism in older men may include chronic illnesses (including diabetes mellitus, chronic obstructive lung disease, and inflammatory arthritic, renal, and HIV-related diseases), obesity, metabolic syndrome, and hemachromatosis.[26] Such chronic diseases should be investigated and treated.[42] Primary hypogonadism is characterized by raised levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in response to diminished testosterone (and estradiol and inhibin B) feedback. Secondary hypogonadism is characterized by low levels of testosterone associated with low or normal levels of FSH and/or LH.[43] However, in older men, the figure is less clear-cut, testosterone deficiency being both primary and secondary.

Serum testosterone has a diurnal variation and levels peak between 08.00 and 10.00 h, a serum sample should be obtained between 07.00 and 11.00 h.[44] The most widely accepted parameters to establish the presence of hypogonadism is the measurement of serum total testosterone. Total testosterone levels above 500 ng/dL do not require substitution; patients with serum total testosterone levels below 300 ng/dL will usually benefit from testosterone treatment. If the serum total testosterone level is between 230 and 350 ng/dL in males under 50 years or between 300 and 500 ng/dL in older males, repeating the measurement of total testosterone with sex hormone binding globulin (SHBG) to calculate free testosterone or measuring free testosterone by equilibrium dialysis or bioavailable testosterone is recommended.[45] Note that SHBG is elevated in elderly patients and effected by many diseases.[30] Measurements of serum LH will assist in differentiating between primary and secondary hypogonadism and serum prolactin is indicated when the serum testosterone is lower than 150 ng/dl[46–49] or when secondary hypogonadism is suspected.[50,51] Measurement of free or bioavailable testosterone (BT, free plus albumin bound) should be considered when the serum total testosterone concentration is not diagnostic of hypogonadism, particularly in obese men. Bioavailable testosterone appears to correlate better with potential hypogonadal symptoms than does total testosterone.[52] A free testosterone level below 65 pg/mL can provide supportive evidence for testosterone treatment.[53,54] The gold standard for bioavailable testosterone measurement is by sulphate precipitation and equilibrium dialysis for free testosterone. However, both techniques are not usually available in local laboratories so that calculated values seem preferable. Salivary testosterone,

Table I Androgen Deficiency In Ageing Male (ADAM) questionnaire

1. Do you have a decrease in libido or sex drive?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost weight?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noticed a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

A positive ADAM questionnaire was defined as "yes" for question 1 and 7, and 2–4 for all other items.

a proxy for unbound testosterone, has also been shown to be a reliable substitute for free testosterone measurements.[55–57] Diagnosis of late life hypogonadism requires both symptoms and low testosterone (Figure 1).

Treatment and delivery systems

Testosterone replacement therapy aims at restoring hormone levels in the normal range of young adults and should, in theory, approximate the natural, endogenous production of the hormone produces and maintains physiologic serum concentrations of the hormone and its active metabolites without significant side effects or safety concerns and, more importantly, alleviates the symptoms suggestive of the hormone deficiency. However, the ultimate goals are to maintain or regain the highest quality of life, to reduce disability, to compress major illnesses into a narrow age range, and to add life to years.

Several different types of testosterone replacement exist including tablets, injections, transdermal systems, oral, pellets, and buccal preparations of testosterone. Selective androgen receptor modulators (SARMs) are under development but not yet clinically available.

The selection of the preparation should be a joint decision of an informed patient and physician.[58] Short-acting preparations may be preferred over long-acting depot preparations in the initial treatment of patients with LOH.[59] It has been recommended that the optimal serum testosterone level for efficacy and safety should be in the mid range to lower young-adult-male serum testosterone levels as the therapeutic goal.[60] However, older males need higher levels to obtain a therapeutic benefit.

Oral agents

The oral form of 17-alpha-alkylated androgen should not be used because of their potential liver toxicity including the development of benign and malignant neoplasm[61] in addition deleterious effects on levels of both LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C).[62] Testosterone undecanoate, which is absorbed predominantly through the lymphatic system, is widely used outside the United States and has the best safety data. However, it can rarely raise testosterone levels above the mid-range.

Intramuscular injection

Until recently, testosterone cypionate and enanthate were frequently used by intramuscular injection of short-acting testosterone esters that usually produces supraphysiological peaks and hypogonadal troughs in testosterone levels. These fluctuations in testosterone levels may yield variations in libido, sexual function, energy, and mood.[63] 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.[64,65] However, in our experience many males eventually prefer this form of therapy to the others. Compared with conventional testosterone enanthate or cypionate treatment requiring injection intervals of 2 to 3 weeks, and resulting in supraphysiological serum testosterone levels, injections of testosterone undecanoate (TU) at intervals of up to 3 months offer an excellent alternative for substitution therapy of male hypogonadism.[66] The long duration of action creates a problem if there are complications of testosterone therapy.

Transdermal systems

Currently, transdermal testosterone is available in either a scrotal or a nonscrotal skin patch and more recently as a gel preparation, 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 to 1000 ng/dL) seen in healthy men. Daily application is required for each of these. They are designed to deliver 5 to 10 mg of testosterone per day. Scrotal patches produce high levels of circulating dihydrotestosterone (DHT) due to the high 5-alpha-reductase enzyme activity of scrotal skin. The advantages include ease of use and maintenance of relatively uniform serum testosterone levels over time,[67] in addition to their efficacy in providing adequate testosterone replacement therapy.[68] A reservoir-type transdermal delivery system of testosterone (TS) was developed using an ethanol/water (70:30) cosolvent system as the vehicle. This device is available in Europe as a body patch without reservoir and applied every 2 days.[69]

Skin irritation may be associated with the use of transdermal systems especially with testosterone patches but is uncommon with gel preparations.[70] At present the two testosterone gel preparations (Androgel® and Testim®) are the most commonly used in the United States.

Sublingual and buccal

Cyclodextrin-complexed testosterone sublingual formulation is absorbed rapidly into circulation, where testosterone is released from the cyclodextrin shell.[71] This formulation has been suggested to have a good therapeutic potential, after adjustment of its kinetics, to produce physiologic levels of testosterone.

A novel sustained-release mucoadhesive buccal testosterone tablet (Striant®; Columbia Laboratories, Inc.), delivering 30 mg, applied to the upper gum region above the lateral incisors 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[72] and achieves testosterone levels within the normal range.[73] Studies indicate that Striant® is an effective, well-tolerated, convenient and discreet treatment for male hypogonadism.[74] However, it has had minimal clinical uptake, due to the difficulty of maintaining the buccal treatment in the mouth.

Subdermal implants

Subdermal testosterone implants still offer the longest duration of action with prolonged zero-order, steady-state delivery characteristics lasting 4 to 7 months.[75,76] The standard dosage is four 200 mg pellets (800 mg) implanted subdermally at intervals of 5 to 7 months.[77] Yet the in vivo testosterone release rate of these testosterone pellets and its determinants have not been studied systematically. However the risk of infection at the implant site and extrusion of the pellets which occurs in 5% to 10% of cases even with the most experienced limit their use.

Benefits of testosterone replacement therapy

Restoring testosterone levels to within the normal range by using testosterone replacement therapy can improve many of the effects of hypogonadism. Most importantly, these include beneficial effects on mood, energy levels and patients' sense of well-being, sexual function, lean body mass and muscle strength, erythropoiesis and bone mineral density (BMD),

cognition and some benefits on cardiovascular risk factors. These are summarized in Table 2. Testosterone is well known to help in libido, bone density, muscle mass, body composition, mood, erythropoiesis, and cognition. All these benefits made testosterone replacement therapy in the United States increase substantially over the past several years, with an increase of more than 500% in prescription sales of testosterone products since 1993.

Improved sexual desire, function and performance

The prevalence of erectile dysfunction increases markedly with age.[78,79] Serum-free testosterone was significantly correlated with erectile and orgasmic function domains of the International Index of Erectile Function (IIEF) questionnaire. Men with greater sexual activity had higher bio-T levels than men with a lower frequency and androgen deficiency may contribute to the age-related decline in male sexuality; correspondingly low levels of bio T were associated with low sexual activity.[80,81] Compared with younger men, elderly men require higher levels of circulating testosterone for libido and erectile function.[82,83] However, erectile dysfunction and/or diminished libido with or without a testosterone deficiency, might be related to other comorbidities or medications.[84]

Men with erectile dysfunction (ED) and/or diminished libido and documented testosterone deficiency are candidates for testosterone therapy. Adequate testosterone treatment can restore venous leakage in the corpus cavernosum which is a frequent etiological factor in ED in elderly men.[85] Overviews of randomized controlled clinical trials indicate some benefit of testosterone therapy on sexual health-related outcomes; however further investigation in this area is warranted particularly in older men who are not clearly hypogonadal.[86,87] Long-term follow-up of testosterone replacement in hypogonadal males and a control group indicates that self-assessment of libido was significantly higher in the testosterone-treated group.[88] Testosterone replacement has also been shown to enhance libido and the frequency of sexual acts and sleep-related erections.[89,90] Wang et al[67] also reported improvement of sexual function;

Table 2 Potential benefits of testosterone replacement therapy

Improve sexual desire and function

Increase bone mineral density

Improve mood, energy and quality of life

Change body composition and improve muscle mass and strength

Improve cognitive function

however, their data suggest that there is a threshold level of T above which there is no further enhancement of response. On the other hand, Two placebo-controlled trials reported on the effect of testosterone on overall sexual satisfaction, yielding imprecise results.[91,92] Transdermal testosterone replacement therapy, in particular, has been linked to positive effects on fatigue, mood, and sexual function, as well as significant increases in sexual activity.[93] 1% hydroalcoholic testosterone gel is an effective and safe treatment option in subjects with ED.[94]

In the presence of a clinical picture of testosterone deficiency and borderline serum testosterone levels, a short therapeutic trial may be tried.[95] An inadequate response to testosterone treatment requires reassessment of the causes of the erectile dysfunction.[45] There is evidence that the combined use of testosterone and phosphodiesterase type 5 inhibitors in hypogonadal or borderline eugonadal men have a synergetic effect.[96–101] The combination treatment should be considered in hypogonadal patients with erectile dysfunction (ED) failing to respond to either treatment alone. Testosterone produces this effect by enhancing the production of nitric oxide synthase. It is unclear whether PDE5-I, testosterone, or the combination of the two should be started first in men with hypogonadism and ED.[45] All men with ED should be screened for hypogonadism before treating for erectile dysfunction.[102]

In addition to improvement in sexual function, testosterone therapy may also improve lower urinary tract symptomatology (LUTS)/bladder functions by increasing bladder capacity and compliance and decreasing detrusor pressure at maximal flow in men with SLOH.[103] However, the role of testosterone supplementation in men with erectile dysfunction who are not androgen deficient or in the low to normal range needs further investigation to determine whether testosterone therapy will improve erectile function in older men and to weigh the risk–benefit ratio for testosterone therapy in this setting.[86]

Bone mineral density

Chronically ill men may have both apparent androgen deficiency and low bone mass.[104] Osteopenia, osteoporosis, and fracture prevalence rates are greater in hypogonadal younger and older men.[105] The prevalence of osteoporosis in testosterone deficient males is double that of those with normal testosterone level.[106,107] Testosterone plays a major role in BMD.[108] Bone density in hypogonadal men of all ages increases under testosterone substitution provided the dose is high enough;[109–111] although normal adult bone mass is not reached.[112] Testosterone produces this effect by increasing

osteoblastic activity and through aromatization to estrogen reducing osteoclastic activity. The role of the partial androgen deficiency in aging males in bone fracture rate remains to be established.[113] Patients with prostate cancer treated with androgen deprivation therapy have an increased risk of osteoporotic fracture.[114] The long-term benefit of testosterone requires further investigation. However, the correlation with bioestradiol, the levels of which decline in elderly males, was even stronger, suggesting that part of the androgen effects on bone are at least partially indirect, mediated via their aromatization.[115,116] An increase in osteocalcin levels, an index of osteoblast activity was observed,[90] and a decrease of hydroxyproline excretion, an index of bone resorption also was noted.[117]

Assessment of bone density at 2-year intervals is advisable in hypogonadal men, and serum testosterone measurements should be obtained in all men with osteopenia.[118,119] Trials of the effects of testosterone replacement therapy on bone mineral density yielded mixed results.[120] Increases in spinal bone density have been realized in hypogonadal men,[121] with most treated men maintaining bone density above the fracture threshold.[122] An improvement in both trabecular and cortical bone mineral density of the spine was seen, independent of age and type of hypogonadism; in addition, a significant increase in paraspinal muscle area has been observed, emphasizing the clinical benefit of adequate replacement therapy for the physical fitness of hypogonadal men.[123] The pooled results of a meta-analysis suggest a beneficial effect on lumbar spine bone density and equivocal findings on femoral neck BMD. Trials of intra muscular testosterone reported significantly larger effects on lumbar bone density than trials of transdermal testosterone, particularly among patients receiving chronic glucocorticoids.[124] Also in eugonadal men with osteoporosis, Testosterone esters (250 mg/2 weeks) increased BMD;[125] again, the effects in elderly men are less convincing, though the 3 year study of Amory et al[126] showed a significant increase in hip BMD. None of studies have been large enough to show a fracture risk reduction with testosterone replacement therapy.

Improved body composition and muscle mass and strength

The aging process is accompanied by significant changes in body composition characterized by decreased fat free mass and increased and redistributed fat mass. These changes can impose functional limitations and increase morbidity.[127,128] Maximal muscle strength correlates with muscle mass independently of age.[129] In men, declining testosterone levels

that occur with aging can be a contributing factor to these changes by direct effect on muscle cells by testosterone or by stimulating IGF-1 expression directly and indirectly leading to increased muscle protein synthesis and growth.[130] Epidemiologic studies have demonstrated a correlation between bioavailable testosterone concentrations and fat-free mass;[131] however the correlation with grip strength is not clear.[131,132]

Testosterone replacement may be effective in reversing age-dependent body composition changes and associated morbidity.[133] Testosterone administration improves body composition decrease of fat mass, increase of lean body mass.[134–136] In most of these studies, the body weight change did not differ significantly. After androgen supplementation to elderly men, generally at a biweekly dose of 200 mg T enanthate, there is a relatively modest increase in muscle mass (± 2 kg)[117] and/or arm circumference and grip strength, whereas fat mass was decreased modestly.[137–139]

Testosterone therapy was associated with a greater improvement in grip strength than placebo.[135,139,140] Changes in lower-extremity muscle strength and measures of physical function were reported in only a few studies and were inconsistent. Recent cross-sectional studies showed that in aging men there are also positive correlations between testosterone and muscle strength parameters of upper and lower extremities, as measured by leg extensor strength and isometric hand grip strength.[141] Moreover, testosterone was positively associated with functional parameters, including the doors test as well as "get up and go" test, and 5-chair sit/stand test.[142] On the other hand, some reported an increase in lean body mass (LBM) but no change in physical function,[92] or an increase in strength of knee extension or flexion.

Although there is a potential role of testosterone in the management of frailty, we do not know whether testosterone replacement improves physical function and other health-related outcomes, or reduces the risk of disability, falls, or fractures in older men with low testosterone levels in addition to the long-term risks and benefits of testosterone supplementation in older men.[143]

Mood and energy and quality of life

Men older than 50 years with low free testosterone levels had poorer quality of life. Hypogonadal men commonly complain of loss of libido, dysphoria, fatigue, and irritability.[67,70,144,145] These symptoms overlap with signs and symptoms of major depression. There is significant inverse correlation between bioavailable testosterone and a depression score in elderly men, independent of age and weight but not with total testosterone levels.[146] There was a reduced libido and reduced feelings of well being and minimal effect on mood in patients with induced testosterone deficiency; the depressive symptoms during the hypogonadal state were reversed by testosterone replacement.[147] One study showed that the relationship between testosterone level and depression was nonlinear and may be idiosyncratic.[148] The risk of depression was increased for hypogonadal and hypergonadal men, but this effect was only detectable in underweight and obese men, not in 'normal' weight men in whom a linear decrease in the risk of depression with increasing testosterone level was noted.[149]

Testosterone replacement therapy has variable effects on mood, energy and sense of well being. The results of placebo-controlled randomized trials on testosterone's effect on quality of life and depressive mood were inconsistent across trials and imprecise.[150–152] Testosterone administered to nondepressed eugonadal men at physiological doses, did not result in significant effects on mood.[153,154] Administration of supraphysiological doses of testosterone to eugonadal men has been associated with mania in a small proportion of men.[155,156]

In hypogonadal men, testosterone replacement was associated with improved mood and well-being, and reduced fatigue and irritability.[157–159] Randomized controlled trials of testosterone therapy in men without or with underlying chronic illness using a variety of testosterone formulations report equivocal improvements in quality of life measures, including general well-being and fatigue.[41,86,160] Testosterone replacement of hypogonadal men with MDD might be an effective antidepressant[161,162] or augmentation to partially effective antidepressant,[163] Testosterone gel had significantly greater improvement as augmentation therapy in depressive symptoms than subjects receiving placebo in hypogonadal men with selective serotonin reuptake inhibitor (SSRI) partial response.[164] In one study, the improvements in mood persisted.[67] These significant correlations with T levels were only observed when T levels were below the normal range, which suggests that once a minimally adequate T/dihydrotestosterone (DHT) level was achieved, further increase did not further contribute to improvement of mood.[67,157] However, the studies reported tend to be of limited size and duration, with a lack of large-scale trials with extended long-term follow-up. In HIV-infected men, testosterone therapy was well tolerated and effective in ameliorating symptoms of hypogonadism. For patients with major depression and/or dysthymia, improvement was equal to that achieved with standard antidepressants with significant improvement in depression inventory score. This effect may

be a direct effect of testosterone or related to positive effects of testosterone on weight and/or other anthropometric indices. Additional studies are needed to assess the effects of testosterone on clinical depression indices in human immunodeficiency virus-infected patients.[165,166]

On the other hand, several placebo-controlled testosterone replacement studies did not show a testosterone-placebo difference distinguishable with respect to mood.[150,164,167,168] No relationship between testosterone level and depressive symptoms was found in the Massachusetts Male Aging Study (MMAS).[14] This discrepancy in the results of the effects of testosterone replacement therapy on mood may be explained by the genetic polymorphism in the androgen receptor which defines a vulnerable group in whom depression is expressed when testosterone levels fall below a particular threshold.[169,170]

Finally, the available controlled studies using exogenous testosterone for depression in elderly men are limited, and testosterone treatment must be considered experimental. The best candidates for treatment may be hypogonadal men who are currently taking an existing antidepressant with inadequate response.[171–173] Additional studies have been recommended incorporating vitality, well-being and/or quality of life as end points.

Cognitive function

Subclinical androgen deficiency was hypothesized to enhance the expression of AD related peptides in vivo.[174] Age-related decreases in bioavailable T predicted age-related decline in visual and verbal memory.[175] Men with a higher ratio of total testosterone to SHBG predict a reduced incidence of Alzheimer's disease[176] and patients with Alzheimer's disease had a lower ratio of total testosterone to SHBG compared with age-matched controls.[177] In the Baltimore Longitudinal Study of Aging (BLSA), a prospective longitudinal study[176] risk for AD was reduced by 26% for each 10 unit (nmoL/nmoL) increase in free T at 2, 5 and 10 years prior to AD diagnosis. Altered T levels in AD may precede rather than follow diagnosis.

There is good evidence for a strong correlation between T levels and cognitive performance such as spatial abilities or mathematical reasoning.[178] Higher bioavailable and free testosterone concentrations have each been associated with better performance in specific aspects of memory and cognitive function, with optimal processing capacity found in men ranging from 35 to 90 years of age even after adjustment for potential confounders including age, educational attainment and cardiovascular morbidity;[179–181]

whereas total testosterone was not.[182] However, contradictory findings have also been reported, two cross-sectional studies did not show a relationship between total or free testosterone and measures of working memory, speed/attention or spatial relations in men aged from 48 to 80 years.[184] In another cross-sectional analyses of similarly aged men, no association was found between lower free testosterone levels and higher performance on spatial visualization tasks, and between higher free and total testosterone levels and poorer verbal memory and executive performance; however there is correlation with faster processing speed.[184,185] A possible source of conflicting results in these studies may stem from interactions between testosterone levels and other risk factors for cognitive impairment such as apolipoprotein E 4 genotype[186] and systemic illness which cause low testosterone.[24,177,187]

In men undergoing hormonal therapy for prostate cancer, suppression of endogenous testosterone synthesis and blockade of the androgen receptor resulted in a beneficial effect on verbal memory but an adverse effect on spatial ability[188] and visuomotor slowing and slowed reaction times in several attentional domains;[189] plasma amyloid levels increased as T levels decreased.[190] Discontinuation of treatment resulted in improved memory but not visuospatial abilities.[190] One of the possible protective mechanisms of action of T would be through its conversion into estradiol (E2), the most potent estrogen. Both serum E2 and T levels were lower in men with AD compared to age-matched controls.[191,192] E2 could exert protective effects on the brain structures in aging patients.[193]

Trials of testosterone therapy in men to evaluate its effects on measures of cognitive function and memory to date were all relatively small and of a relatively short duration and have shown mixed results.[177,194] Small-scale T intervention trials in elderly men suggest that some cognitive deficits may be reversed, at least in part, by short term T supplementation.[178] Androgen supplementation in elderly hypogonadal men improves spatial cognition[117,195] and verbal fluency[196,197] and in elderly men without dementia, it may reduce working memory errors.[198] In addition, transdermal testosterone or DHT treatment in men aged 34 to 70 years improved verbal memory and spatial memory respectively,[199] and intramuscular testosterone improved verbal and spatial memory and constructional abilities in non-hypogonadal men with mild cognitive impairment and Alzheimer's disease.[200] In one study of healthy men aged 50 to 90 years, intramuscular testosterone alone or in combination with anastrozole improved spatial memory, whereas verbal

memory only improved in testosterone-treated men in the absence of anastrozole, raising the possibility that part of the effect of exogenous testosterone is mediated by its aromatization to estradiol.[200]

However, in men with Alzheimer's disease testosterone treatment appeared to improve quality of life without impacting on measures of cognition.[201] In a randomized, placebo-controlled crossover trial intramuscular testosterone therapy resulted in decreased verbal memory.[202] In other placebo-controlled randomized trials, one of which studied patients with Alzheimer's dementia and low testosterone levels,[203] reported imprecise effects on several dimensions of cognition, none of which was significant after pooling.[203,204]

Therefore, although the evidence from observational studies is not uniform, lower free testosterone appears to be associated with poorer outcomes on measures of cognitive function, particularly in older men and testosterone therapy in hypogonadal men may have some benefit for cognitive performance.

Improving metabolic syndrome and diabetes type 2, cardiovascular disease

Many of the components of the metabolic syndrome (obesity, hypertension, dyslipidemia impaired glucose regulation, and insulin resistance) are also present in hypogonadal men. Lower testosterone levels are associated with surrogate markers for cardiovascular disease, including less favorable carotid intima medial thickness[205–207] ankle/brachial index as a measure of peripheral arterial disease[208] and calcific aortic atheroma.[209] Endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes. Low testosterone may be a predictive marker for those at high risk of cardiovascular disease.[8] Thus, lower testosterone levels, erectile dysfunction and conditions associated with higher cardiovascular risk appear to be interrelated.[210,211] Obesity induces a decrease of T levels via a decrease in SHBG levels, and morbid obesity also induces a decrease of FT.[212] There is evidence to suggest that an inverse relationship exists between serum testosterone levels and the degree of obesity in men.[213,214] There is a close relationship between obesity and low serum testosterone levels in healthy men.[215] Twenty percent to 64% of obese men have a low serum total or free testosterone level.[216] Visceral obesity is more strongly inversely related to total and free testosterone levels than other forms of obesity.[217,218] The Relationship between reduced testosterone and obesity in men can be explained by the hypogonadal-cytokine-obesity cycle[219,220] and it exhibits antiatherogenic

effects at the tissue level, whether mediated by classical or nonclassical pathways.[221,222]

Initially cross-sectional studies but later also longitudinal studies were able to confirm that low testosterone levels and sex hormone-binding globulin (SHBG) were predictive of the metabolic syndrome, not only in obese men but also in men with a body mass index (BMI) < 25 kg/m^2.[223,224] The metabolic syndrome and type 2 diabetes mellitus are associated with low plasma testosterone[34,225,226] and insulin sensitivity.[34,227,228] There is positive correlation between serum testosterone levels and insulin sensitivity in men across the full spectrum of glucose tolerance[229] and an improvement of insulin sensitivity was noted after replacement.[230] Although Abate et al[231] found no association between low plasma levels of bioavailable testosterone and insulin resistance in eugonadal men; a recent larger study (NHANES [National Health and Nutrition Examination Survey]) showed that low free and bioavailable testosterone levels, even in the normal range, are associated with diabetes, independent of adiposity.[216] Serum testosterone should be measured in men with type 2 diabetes mellitus with symptoms suggestive of testosterone deficiency. The effects of testosterone administration on glycemic control of men with diabetes mellitus are much less certain.[232–234] By increasing lean body mass and reducing fat mass, testosterone therapy modulates insulin resistance and risk of metabolic syndrome.[232]

Studies on androgen replacement in elderly men on LDL-C and HDL-C are controversial.[235,236] The correlation between testosterone levels and HDL-C and insulin sensitivity is only observed within the physiologic male concentration range of testosterone.[237] A physiologic dose of androgens did not cause significant change in lipids.[238] A recent randomized controlled trial showed decrease in high-density lipoprotein cholesterol.[239] A 24-week, multi-center, randomized, parallel-group study by Dobs et al[240] of transdermal and intramuscular administration of androgens in 58 men did not detect any significant change in HDL levels or in the ratio of total cholesterol to HDL in either group, apart from the mode of therapy. In addition, testosterone replacement decreases lipoprotein (a).[19] The mechanism of the fall in lipids might be related to the decrease in the visceral abdominal fat mass[241] under the influence of androgens, which inhibit lipoprotein lipase activity and increase lipolysis[242,243] with improvement of insulin sensitivity and mobilization of triglycerides from abdominal fat tissue.[244] Supraphysiological T levels induce an increase in LDL-C and a decrease of HDL-C[245–247] and may increase the risk of cardiovascular disease.

Low androgen levels increase the risk of cardiovascular disease in men.[236] Data are lacking as to whether higher testosterone levels predict reduced incidence of combined nonfatal and fatal major cardiovascular events.[101] The inverse correlation between T levels and the severity of coronary artery disease[248] may be related to the fact that low androgen levels are accompanied by an accumulation of abdominal visceral fat,[249–251] which is known to be associated with increased cardiovascular risk factors[252] impaired glucose tolerance, and non-insulin-dependent diabetes mellitus (syndrome X).[253]

No consistent relationship between the levels of free or total testosterone and coronary atherosclerosis in men undergoing coronary angiography has been observed.[151,254] Testosterone-replacement therapy does not increase the incidence of cardiovascular disease or events such as myocardial infarction, stroke, or angina.[88] A meta-analysis[255] in 2007 concluded that the current available evidence shows no association between testosterone replacement therapy and cardiac events. Transdermal testosterone replacement therapy was found to be beneficial for men with chronic stable angina as they had greater angina-free exercise tolerance than placebo-treated controls.[151]

However, trials of testosterone therapy generally have not been designed or adequately powered to detect effects on clinically significant cardiovascular events.[86,256] The outcome of most studies in men report either a favorable or neutral effect of normal T levels on cardiovascular disease in men. The administration of T in physiological concentration increases coronary blood flow in patients with coronary heart disease.[257] Beneficial effects on endothelial function[258] and myocardial ischemia have also been demonstrated,[248,259,260] but not with cardiovascular mortality.[257,258] In addition, testosterone has a negative correlation with fibrinogen, plasminogen activator inhibitor-1[261] and a direct effect on several vasoactive factors such as endothelin,[262] prostacyclin, thromboxane A_2 and platelet aggregation,[263] blood coagulation, and fibrinolysis, respectively.[248,261]

Thus, although lower testosterone levels are associated with higher cardiovascular risk and to an extent with mortality in aging men, randomized controlled clinical trials of adequate size and duration are needed to determine whether testosterone therapy will reduce morbidity and mortality from cardiovascular disease in hypogonadal or eugonadal men.

Improving anemia

Endogenous androgens are known to stimulate erythropoiesis; increase reticulocyte count, blood hemoglobin levels and bone marrow erythropoietic activity in mammals, whereas castration has opposite effects. Testosterone deficiency results in a 10% to 20% decrease in the blood hemoglobin concentration, which can result in anemia.[264,265] Young hypogonadal men usually have fewer red blood cells and lower hemoglobin levels than age-matched controls, whilst healthy older men also may have lower hemoglobin than normal young men. The main androgen involvement in the mechanism of normal hematopoiesis is thought to involve direct stimulation of renal production of erythropoietin by testosterone. Moreover, the latter may also act directly on erythropoietic stem cells.[265]

Risks of testosterone replacement therapy

The risks of testosterone replacement therapy depend upon age, life circumstances, and other medical conditions.[26] There is a risk for prostate cancer and worsening symptoms of benign prostatic hypertrophy, liver toxicity and tumor, worsening symptoms of sleep apnea and congestive heart failure, gynecomastia, infertility and skin diseases. Testosterone replacement therapy is not appropriate for men who are interested in fathering a child because exogenous testosterone will suppress the HPT axis. The risks of testosterone replacement therapy are summarized in Table 3.

The prostate and testosterone replacement therapy

In aging men with late-onset hypogonadism, TRT may normalize serum androgen levels but appears to have little effect on prostate tissue androgen levels and cellular functions[266] and causes no significant adverse affects on the prostate.[267] At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or benign prostatic hyperplasia (BPH).[45,268,269]

Benign prostatic hyperplasia

It is well known that the presence of androgen is required for the development of benign prostatic hyperplasia. Testosterone

Table 3 Potential risks for testosterone replacement therapy

Stimulate growth of prostate cancer and breast cancer
Worsen symptoms of benign prostatic hypertrophy
Cause liver toxicity and liver tumor
Cause gynecomastia
Cause erythrocytosis
Cause testicular atrophy and infertility
Cause skin diseases
Cause or exacerbate sleep apnea

supplements increase prostate volume with, eventually mild increase in prostate specific antigen (PSA) levels in old men.[90,117,270] Although a meta-analysis[58] showed that the total number of prostate events combined was significantly greater in testosterone-treated men than in placebo-treated men, the majority of events are due to prostate biopsy; and the marked reduction in serum testosterone caused by chemical or surgical castration causes reduced prostate volume. At the same time, many studies[271–273] have failed to show significant 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 nor has there been any difference in the urine flow rates, postvoiding residual urine volumes, and prostate voiding symptoms with patients receiving treatment in these studies. The poor correlation between prostate volume and urinary symptoms explain this illogicality.

Finally, although there are no compelling data to suggest that testosterone treatment exacerbates lower urinary tract symptoms (LUTS) or promotes acute urinary retention, severe LUTS, due to BPH, represent a relative contraindication which is no longer applicable after successful treatment of lower urinary tract obstruction.[45]

Prostate cancer

Prostate cancer is well known to be, in the majority of cases, an androgen sensitive disease, and prostate cancer has been treated in patterns designed to lower testosterone levels.[270] Androgen replacement therapy is an absolute contraindication. There is also no good evidence that testosterone treatment will convert subclinical prostate cancer to clinically detectable prostate cancer,[45] although some case reports reported this correlation.[274,275] In a retrospective analysis of hypogonadal men who underwent prostate biopsy prior to testosterone replacement therapy, no increase in the risk of prostate cancer in men was revealed compared to those without prostatic intraepithelial neoplasia at baseline.[276]

The prevalence of prostate cancer in many studies receiving testosterone replacement therapy was similar to that in the general population.[67,277] So far, there is no compelling evidence that testosterone has a causative role in prostate cancer.[271,272,278,279] 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. At a median of 19 months of TRT hypogonadal patients with a history of prostate cancer had no PSA recurrence and had statistically significant improvements in total testosterone

and hypogonadal symptoms. In highly select patients after radical retropubic prostatectomy TRT can be administered carefully and with benefit to hypogonadal patients with prostate cancer.[280] Hormonal replacement in patients that underwent castration seems to be feasible in improving intense symptoms associated with androgen deprivation. After 18 months, no evidence of recurrence was noted. It is an experimental alternative for highly symptomatic patients, but the short follow-up and the small number of patients cannot allow for definitive conclusions and should be studied further.[281] A recent prospective study[282] did not show definitive data to confirm the relationship between serum sex hormones and prostate cancer. There is, however, unequivocal evidence that testosterone can stimulate growth and aggravate symptoms in men with locally advanced and metastatic prostate cancer.[283,284] Men successfully treated for prostate cancer and diagnosed with hypogonadism are candidates for testosterone replacement after a prudent interval if there is no clinical or laboratory evidence of residual cancer.[285,286] In addition, no effect was found of testosterone replacement therapy on PSA levels[287–289] and the change in PSA were not influenced by the mode of testosterone replacement therapy, patient age, or baseline levels of PSA or testosterone.[290]

The online prostate cancer risk calculator is one of the most commonly used tools to assist the clinician in assessing the risk of prostate cancer.[291–293] All men who present for TRT should undergo prostate biopsy if they have abnormal PSA level or abnormal result on digital rectal examination with low threshold to do or repeat prostate biopsy if the PSA level or digital rectal exam changes. Prostatic biopsy or referral to a urologist is recommended if PSA rises above 4.0 ng/mL or if it increases either by more than 1.5 ng/mL/year or by more than 0.75 ng/mL/year over 2 years,[294] or if PSA rises by more than 1.0 ng/mL in the first 6 months of treatment or by more than 0.4 ng/mL/year thereafter.[295]

In summary, there is no convincing evidence that the normalization of testosterone serum levels in men with low levels is deleterious. TRT can be cautiously considered in selected hypogonadal men treated with curative intent for prostate and without evidence of active disease.[296]

Liver problems

Benign and malignant hepatic tumors, intrahepatic cholestasis, hepatotoxicity, and liver failure have been reported with testosterone replacement therapy.[297,298] These unfavorable hepatic effects do not appear to be associated with transdermal or intramuscular injections. For this

reason the oral forms of testosterone, with the exception of testosterone undecanoate, are discouraged. Other liver abnormalities associated with TRT include Peliosis hepatis, hepatocellular adenoma, and carcinoma.[299]

The risk of polycythemia

There is a correlation between high testosterone levels and high hemoglobin, most likely because testosterone stimulates erythropoiesis. Erythrocytosis can develop during testosterone treatment, especially in older men treated by injectable testosterone preparations.[45] Hemoglobin at puberty increases 15% to 20% in boys, men have higher levels of hemoglobin than women, and hypogonadism causes a decline in hemoglobin levels that can be restored with testosterone replacement therapy.[139,300] But the elevation in hemoglobin above certain levels may have bad outcomes, particularly in elderly, because the increase in blood viscosity could exacerbate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation, especially in people with other diseases that cause secondary polycythemia, ie, chronic obstructive pulmonary disease.[301–303] Injection is associated with higher potentials for erythrocytosis than topical preparations.[240] Snyder et al noticed that erythrocytosis occurred in 5.5% of scrotal transdermal users, and the majority of changes took place over the first three months of treatment.[92] It has been demonstrated that testosterone dosage correlates with the incidence of erythrocytosis,[67] The frequency of polycythemia (hematocrit over 51%) is related most of the time to supra-physiological levels.[240] The resolution of erythrocytosis (hematocrit $> 52\%$), untreated obstructive sleep apnea, or untreated severe congestive heart failure, is required before starting on testosterone treatment.[19,58,304]

Periodic hematological assessment is indicated (ie, before treatment, then at 3 to 4 months and at 12 mo in the first year of treatment and annually thereafter). While it is not yet clear what critical threshold is a desirable, dose adjustment and/or periodic phlebotomy may be necessary to keep hematocrit below 52% to 55%.[45,58,305]

Other effects of testosterone replacement therapy

Psychotic symptoms, excessive libido and aggression, in addition to physical and psychological dependence and withdrawal syndromes have been rarely described with testosterone treatment,[306,307] though the validity of testosterone or the cause is uncertain. Kenny et al[204] did not find that significant changes in behavior, function, depression, or cognitive performance occurred following 12 weeks of testosterone replacement in men with low testosterone levels and early-to-moderate cognitive impairment.

Gynecomastia is a benign complication of testosterone treatment. It is related to aromatization of testosterone into estradiol in peripheral fat and muscle tissue. Even the ratio of estradiol to testosterone usually remains normal. It occurs especially with testosterone enanthate or cypionate. Dose adjustment may be necessary.

Diminished testicular size and compromised fertility during testosterone replacement therapy occur because of the down-regulation of gonadotropins.[308] The administration of exogenous testosterone as a means of male contraception is under study.[309] In these men, azoospermia usually results within approximately 10 weeks of beginning therapy. Rebound of the sperm count to baseline levels occurs within six to 18 months of cessation, and subsequent fertility has been demonstrated.[310] Supraphysiologic doses of androgens may cause decreased testicular size, and azoospermia.[311]

Testosterone-replacement therapy has been associated with exacerbation of sleep apnea.[312,313] The effect of testosterone is not on the dimensions of the upper airway, but it most likely contributes to sleep disorder breathing by central mechanisms.[314] The development of signs and symptoms of obstructive sleep apnea during testosterone therapy warrants a formal sleep study and treatment with continuous positive airway pressure (CPAP) if necessary. If the patient is unresponsive or cannot tolerate CPAP, the testosterone must be reduced or discontinued.

Transdermal testosterone-replacement therapy is associated with a variety of skin reactions, mainly erythema or pruritus, which are more common with patches than with gel preparations.[67] Intramuscular injections of testosterone can cause local pain, soreness, bruising, erythema, swelling, nodules, or furuncles.[315] Supraphysiologic doses of androgens may cause acne.[311]

Testosterone is anabolic, and it will cause some nitrogen, sodium and water retention. Edema may be worsened in patients with preexisting cardiac, renal, or hepatic disease. Hypertension has rarely been reported.[316]

Hyperandrogenism was reported in a female whose partner was using testosterone gel.[317]

Monitoring patients on testosterone replacement

Laboratory parameters that should be monitored before and during treatment include PSA, hemoglobin, hematocrit, lipid profiles, and liver function tests. Patients should also

be monitored for signs of edema, gynecomastia, sleep apnea, lower urinary tract symptoms, and low BMD. There are clinical practice guidelines from the Endocrine Society for monitoring patients receiving TRT.[45] Testosterone level, digital rectal exam, PSA, hematocrit, BMD, lipids, and liver function tests should be checked at baseline then evaluate the patient 3 and 6 months after treatment starts and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects.

Testosterone levels should be monitored 3 months after initiation of testosterone therapy. A mid-morning total serum testosterone level should be obtained. A target range of 400 to 500 ng/dL (14.0 to 17.5 nmol/L) for older men is suggested. However, if there is no symptomatic response, higher levels may be necessary. For injectable testosterone, the serum level can be measured between injections. For men treated with a transdermal testosterone patch, the serum level should be measured 3 to 12 hours after patch application. In patients receiving buccal testosterone tablets, the serum level should be measured immediately before application of a fresh system. Patients on testosterone gel may have levels checked anytime after at least 1 week of therapy.[45] In all cases, bioavailable testosterone levels should also be monitored as testosterone therapy lowers SHBG.

The hematocrit should be checked at baseline, at 3 and 6 months, and then annually. If hematocrit is more than 54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose. BMD of lumbar spine and/or femoral neck should be measured at baseline every 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture. A digital rectal examination and PSA level should be obtained before initiating treatment, at 3 months, and then in accordance with guidelines for prostate cancer screening, depending on the age and race of the patient. A urologic consultation is mandatory if any of the following is present (Table 4).

The use of testosterone preparations should be discussed with patients and then closely monitored for efficacy and toxicities.[3,318–320] Failure to benefit from clinical manifestations should result in discontinuation of treatment after 3 months for libido and sexual function, muscle function, and improved body fat; and a longer interval for bone mineral density. Further investigation for other causes of symptoms is then mandatory.[45]

Contraindications to testosterone replacement therapy

Before starting patients on TRT, health care providers must rule out contraindications to treatment (Table 5). The presence of a clinical prostatic carcinoma is an absolute contraindication for HRT and should be carefully excluded by PSA, rectal examination and, eventually, biopsy before starting any therapy.[45] There is also no clear recommendation for men successfully treated for prostate cancer who would be potential candidates for testosterone substitution after a 'prudent' interval if there is no clinical or laboratory evidence of residual cancer.[45]

The presence of breast cancer is also a contraindication for TRT as well as a prolactinoma, as their growth may be stimulated by HRT.[26] Very high risk of serious adverse outcomes, undiagnosed prostate nodules or indurations, unexplained PSA elevation, erythrocytosis (hematocrit > 50%), severe lower urinary tract symptoms with benign prostatic hyperplasia with an International Prostate Symptom Score (IPSS) > 19, and unstable congestive heart failure (class III or IV), untreated obstructive sleep apnea are considered as moderate- to high-risk factors for potential adverse outcomes.[26,45,319]

Conclusion

Male hypogonadism and its treatment is a rapidly evolving area. While male hypogonadism has previously been underdiagnosed, the apparently increasing incidence and expanding range of treatment options may facilitate greater

Table 4 When a urological consultation is needed

1. Verified serum PSA concentration more than 4.0 ng/mL

2. An increase in serum PSA concentration more than 1.4 ng/mL within any 12-month period of testosterone treatment

3. A PSA velocity of more than 0.4 ng/mL/year using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data available >2 years)

4. Detection of a prostatic abnormality on digital rectal examination

5. An American Urological Association (AUA) or International Prostate Symptom Score (IPSS) prostate symptom score of more than 19

Abbreviation: PSA, prostate specific antigen.

Table 5 Contraindications to testosterone replacement therapy

Very high risk of serious adverse outcomes

Prostatic carcinoma

Breast cancer

Prostate nodules or indurations

Unexplained prostate-specific antigen (PSA) elevation

Erythrocytosis (hematocrit > 50%)

Severe lower urinary tract symptoms with benign prostatic hyperplasia with an International Prostate Symptom Score (IPSS) >19

Unstable congestive heart failure (class III or IV)

Severe untreated sleep apnea

awareness of the condition. The symptoms in the elderly have a complex origin. It may be reasonably assumed that the age-associated decrease in T levels is in part responsible for the symptoms of aging. The benefits and risks of testosterone therapy must be clearly discussed with the patient and assessment of prostate and other risk factors considered before commencing testosterone treatment. There is some benefit from testosterone replacement therapy on muscle mass and strength, fat mass, BMD, sexual function, mood and general sense of well-being. Therefore, it seems logical to consider that in elderly men with subnormal T levels and clinical symptoms suggestive of androgen deficiency, hormone replacement therapy in combination with physical activity (resistance training) and adequate nutrition will result in an optimal increase in muscle strength, BMD, and general sense of well-being. However, data on clinical effects of androgen substitution, such as cardiovascular morbidity and mortality, falls and bone fracture rates are not yet available. Response to testosterone treatment should be assessed. If there is no improvement of symptoms and signs, treatment should be discontinued and the patient investigated for other possible causes of the clinical presentations. The major contraindication for androgen supplementation is the presence of a prostatic carcinoma.

Future of TRT

Hypogonadism may present to a range of specialties. Previously, late-onset hypogonadism has not been well understood. Studies conducted to date have been too small to address potential long-term adverse effects, and there are risks in extrapolating benefit from epidemiological studies. Many questions in the treatment of hypogonadism remain unanswered, and there is a need for large clinical trials; or at least a meta-analysis of the extensive short-term data combined with analysis of long-term clinical experience

which many physicians working in the field now have; to assess the long-term benefits and risks of TRT in older men with late-onset hypogonadism.

Disclosures

The authors disclose no conflicts of interest.

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