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Andropause: Clinical Implications of the Decline in Serum Testosterone Levels With Aging in Men

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IT is now well accepted that serum testosterone (T) levels decline progressively with aging in men (1–5). This decline is associated with alterations in body composition; diminished energy, muscle strength, and physical function; reduced sexual function; depressed mood; and decreased cognitive function. Similar changes occur in young men with androgen deficiency and are improved with T replacement therapy. However, the physiological and clinical significance of the aging-associated decline in serum T levels in men is unclear, particularly because T levels may remain within the normal range for young men. From a practical clinical standpoint, it is most appropriate to define "andropause" as an age-related decline in serum T levels in older men to below the normal range in young men that is associated with a clinical syndrome (i.e., symptoms and signs) consistent with androgen deficiency. The decline in T levels is a consequence both of aging per se and age-associated comorbid illnesses and medications that are used to treat them (6–13). However, regardless of the etiology, androgen deficiency may contribute, at least in part, to age-related decrements in physiological function and may be associated with a clinical syndrome.

Andropause has also been referred to by some as "androgen deficiency in the aging male (ADAM)," "partial androgen deficiency in the aging male (PADAM)," or "aging-associated androgen deficiency (AAAD)." The term "male menopause" is inappropriate because there is no interruption or cessation of menses, and "viropause" is inaccurate because there is no loss of virilization. "Male climacteric" refers to the syndrome of endocrine, somatic, and psychic changes that occur in normal men with aging. This term emphasizes the multidimensional nature of age-related changes, including decreases in other hormones such as growth hormone (GH), insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone (DHEA), and melatonin (1,14–17), but it does not relate aspects of the male aging syndrome specifically with androgen levels. The term "andropause" is not completely accurate because androgen secretion does not cease altogether. However, because it is the only term that relates the syndrome of age-related physiological changes with the gradual and progressive decline in T levels that occurs with aging, andropause will be used in this review. Andropause is a term also used commonly by experts in the field and by lay persons because it retains some analogy to menopause in women.

Physiological Basis of Andropause

Age-Related Decline in Serum T Levels

In both cross-sectional (5,6,18–38) and longitudinal studies (39–42), beginning in the third decade, aging is associated with a gradual and progressive decline in serum T levels at a rate of approximately 1% per year. As a result, ~20% of men older than 60 and ~50% of men older than 80 years of age have serum total T levels below the normal range for young men (39,43,44).

Circulating T is approximately 98% bound to serum proteins, predominantly to sex hormone-binding globulin (SHBG), the major binding protein for T in blood, and albumin (45–47). Only 1% to 2% of T in circulation is completely unbound or free. Because T is bound with high affinity (i.e., tightly) to SHBG, SHBG-bound T is not available to most tissues for action. In contrast, T is bound with low affinity (weakly) to albumin, so both albumin-bound and free T are bioavailable to most tissues for action. Because the concentration of SHBG increases with aging, serum-free T and bioavailable T (free plus albumin-bound T) concentrations decline more markedly than total T levels with aging (13, 16,20,24,26,27,29,31,33,36,39,41,48). Therefore, a much larger percentage of older men have levels of these biologically active fractions of circulating T below the normal range for young men (39,49).

Age-related and other alterations in SHBG have important practical clinical implications in the diagnosis of androgen deficiency. Because total T assays measure both free T and T bound to SHBG and albumin, alterations in SHBG and/or albumin result in changes in total T levels in the same direction. Measurements of bioavailable or free T are not affected by alterations in SHBG. Therefore, they provide a better assessment of biologically active T in blood, especially in common clinical states such as aging in which SHBG increases or moderate obesity in which SHBG decreases (47,50–52).

Because SHBG levels increase with aging, many older men with low-normal total T levels have free or bioavailable T levels that are below the normal range for young men. Therefore, measurements of bioavailable or free T using ammonium sulfate precipitation or equilibrium dialysis, respectively, or calculated from measurements of total T and SHBG are recommended to diagnose androgen deficiency in older men. Unfortunately, these measurements of

free and bioavailable T are not usually performed in local laboratories and are only available through commercial reference laboratories. Most local laboratories measure free T using a solid-phase direct analog immunoassay kit. Although free T measurements using this method correlate with those using equilibrium dialysis, values obtained differ substantially [e.g., by more than an order of magnitude in women (53)] from those obtained by equilibrium dialysis or calculated from SHBG, and vary directly with alterations in SHBG levels (52–56). Therefore, free T measurements using direct analog immunoassay kits may not provide useful clinical information beyond that of total T levels. They tend to underdiagnose older men with androgen deficiency and overdiagnose androgen deficiency in men with low SHBG levels (e.g., moderately obese men). Free T levels measured using a direct analog immunoassay should not be used in situations where SHBG levels may be altered (e.g., older men).

Decline in Both Testis Function and Hypothalamic GnRH Regulation With Aging

The decline in serum T levels with aging is due both to impaired testis production of T and hypothalamic secretion of gonadotropin-releasing hormone (GnRH) resulting in inadequate stimulation of luteinizing hormone (LH) secretion by the pituitary gland.

Older men demonstrate a decrease in the number of Leydig cells (57–59), the cells of the testis that produce T, reduction in basal T production (60,61), and marked decreased in T secretion by the testis in response to maximal stimulation by administration of human chorionic gonadotropin (hCG), an LH-like hormone (62–66). The impact of reduced T production on circulating T levels is lessened by the decrease in metabolic clearance of T that also occurs with aging (35). The normal circadian variation in serum T levels with peak concentrations in the morning is blunted in healthy older men compared to young men (65,67–72), suggesting an alteration in the hypothalamic circadian pacemaker function. Because of age-related blunting of the normal circadian variation in T levels, early morning serum T levels are lower but late afternoon values are more similar in older compared with young men (23).

Function of the seminiferous tubule compartment of the testis also declines with aging. In older compared with young men, spermatogenesis assessed histologically is reduced (58,73,74), but ejaculated sperm concentration is unchanged or increased as a result of diminished ejaculatory volume and frequency (28,75). The number of sperm with normal motility and morphology also decreases but in vitro fertilizing capacity is relatively well preserved in older men (28,76). Despite overall well-preserved fertility potential (77) and documented instances of paternity in men older than age 90 years, overall fertility rates decline with age (78,79), largely as a result of diminished sexual activity (80). With older paternal age, the risk of inherited autosomal dominant diseases increases in offspring (79,81). The number of Sertoli cells (57,82), seminiferous tubule cells that support spermatogenesis, and serum levels of inhibin B, a Sertoli cell peptide product responsible for feedback inhibition of follicle-stimulating hormone (FSH) secretion from the pituitary gland, decrease with aging (83,84). Most of the decline of inhibin B levels appears to occur by middle age with stable concentrations from middle to old age.

In both cross-sectional and longitudinal studies, the decline in serum T levels with aging is associated with a gradual increase in serum gonadotropins, FSH, and to a lesser extent, LH concentrations (19,25,41,85–87). Although gonadotropin levels increase with aging, they often remain within the wide normal range for younger men. The resulting hormonal pattern of a low serum T and normal gonadotropin levels suggests concomitant hypothalamic-pituitary dysfunction in conjunction with primary testicular failure in aging men. Low serum T and normal gonadotropin levels, consistent with secondary hypogonadism, are found commonly during the work-up of older men with symptoms of androgen deficiency (see below) (88).

Detailed studies of pulsatile gonadotropin secretion provide indirect evidence for age-related alterations in pulsatile GnRH secretion from the hypothalamus. Compared with normal men, young hypogonadal men with low serum T levels demonstrate an increase in LH pulse frequency and amplitude associated with diminished T negative feedback (89,90). Compared with young men, healthy older men with low serum T levels demonstrate an abnormal LH pulse frequency, reduced LH pulse amplitude, and more disorderly LH secretion, suggesting an age-associated impairment of the hypothalamic GnRH pulse generator (71,91–98). Basal FSH secretion and pulse amplitude increase, but orderly secretion of FSH is maintained in older compared with young men (99–101). Older men also demonstrate an attenuated stimulation of gonadotropin secretion induced by naltrexone or naloxone, opioid receptor antagonists, suggesting altered central nervous system (CNS) endogenous opiate regulation of GnRH secretion with aging (97,102). The sensitivity of gonadotropin suppression to T negative feedback is increased (103–105), and gonadotropin responsiveness to androgen deprivation induced by an androgen receptor antagonist (flutamide) or androgen synthesis inhibitor (ketoconazole) is attenuated in older compared with young men (106,107).

Compared with young men, older men demonstrate slightly diminished gonadotropin responsiveness to acute GnRH (85,87,108–110) but a normal LH response to chronic pulsatile GnRH administration (111), suggesting that pituitary gonadotropin secretion remains intact with aging. Together, these findings suggest that aging is associated with impairments in both testis function and hypothalamic GnRH regulation of gonadotropin secretion.

Age-Related Alterations in Androgen Action and Active Metabolism of T

Besides the limited studies of T negative feedback mentioned previously, a systematic evaluation of age-related changes in androgen action in androgen-responsive target organs has not been performed. Androgen receptor gene expression in the CA1 region of the hippocampus and the number of androgen receptor binding sites in genital skin are decreased in older compared with young men (112–114). Androgen receptor expression and nuclear androgen receptor levels in the prostate are unchanged in older men with-

out benign prostatic hyperplasia (BPH) and are similar to those in young men (115–117). However, prostate androgen receptor expression is reduced, and nuclear androgen receptor levels are increased in older men with BPH compared with young men.

The length of trinucleotide CAG repeats in the androgen receptor gene is variable and is associated with differences in transcriptional activity, with a shorter CAG repeat length associated with greater androgen receptor activity and possibly overall greater androgen action (118). In the Massachusetts Male Aging Study (MMAS), serum total and free T levels were found to be associated with the CAG repeat length in the androgen receptor gene (40). Older men with lower serum T levels had an androgen receptor genotype characterized by a shorter CAG repeat length, suggesting overall greater androgen activity. It is hypothesized that, in older men with shorter CAG repeat length, increased androgen action at the level of the hypothalamic-pituitary axis may result in greater feedback suppression of gonadotropin and, in turn, endogenous T secretion. This may be an intrinsic mechanism that underlies the physiological decline in serum T levels with aging. A shorter CAG repeat length in the androgen receptor gene also has been associated with an increased risk and severity of BPH and prostate cancer (119–125) and an earlier age at diagnosis and aggressiveness of prostate carcinoma (126–129).

Androgen action is not simply a function of androgen receptor expression in target tissues and CAG repeat length, but involves a complex interaction among androgen ligands such as T, the androgen receptor, and tissue-specific coactivators and corepressors with androgen-response elements in specific genes (130,131). Age-related alterations of the latter and other transcription factors in androgen target tissues and their effects on androgen action have not been investigated. However, the preliminary findings reviewed suggest that, in addition to circulating T levels, age-associated changes in androgen action may play important roles in the alterations of physiological function that occur with normal aging and in the pathophysiology of age-related pathologies.

T is actively metabolized to the potent estrogen, estradiol (E2), by the enzyme aromatase, which is located primarily in adipose tissue, and to 5 alpha-dihydrotestosterone (DHT), a more potent androgen than T, by the enzymes 5 alpha-reductase type 1 and 2, which are located predominantly in skin and the prostate (132–134). Many of the actions of T are mediated, at least in part, by its active metabolites, E2 (e.g., bone, brain, and lipids) and DHT (e.g., prostate). Despite declining T levels, serum total E2 and DHT levels do not change or decrease only slightly with aging (24,26,34,37, 38,135–139). This suggests that, with aging, there is a relative increase in aromatization of T to E2 (perhaps due to increased adipose tissue mass) and 5 alpha-reduction of T to DHT and/or reductions in the metabolic clearance of E2 and DHT. Because serum SHBG levels increase with aging, serum bioavailable or free E2 and DHT levels would be expected to decrease with aging. The physiological significance of bioavailable E2 and DHT is not clear. However, recent studies suggest that bioavailable E2 levels decline with aging and correlate better than T with bone mineral density in men (26,137,139,140).

Serum markers of peripheral androgen action such as 3 alpha-, 17 beta-androstanediol glucuronide (3 alpha-diol G) decrease markedly with aging, suggesting an overall decline in the total circulating androgen pool (24,138,141). Tissue concentrations of DHT decrease within the epithelial compartment and E2 increase within the stromal compartment of the normal and BPH prostate gland with aging, emphasizing the importance of active metabolism of T in androgen target organs and within specific regions of these organs (142–144).

Age-Related Comorbid Illnesses and Medications Suppress Serum T Levels Further

In addition to the decline in serum T levels associated with healthy aging, age-related comorbid illnesses (e.g., chronic renal, liver, or pulmonary disease, malignancy) increase, and the use of certain medications that are often used to treat these illnesses (e.g., glucocorticoids and CNS-active medications) and malnutrition that is often associated with illness suppress serum T levels even further (11,12,51,145–148). Compared with community-dwelling healthy older men, old men with significant illnesses, such as cancer or stroke, and those in an inpatient rehabilitation unit or nursing home have substantially lower serum T levels (6–10,21). These sicker old men also have a higher prevalence of T levels below the normal range for either healthy young (~60-90%) or older men (~20-30%).

Age-Related Decline in Adrenal Androgens

Serum concentrations of DHEA, a weak adrenal androgen that is a precursor of T, decline more rapidly and more profoundly than those of T with aging (149–152). This has been referred to as "adrenopause." However, the physiological significance of circulating DHEA is unclear at this time. Preliminary controlled studies of DHEA treatment failed to demonstrate significant clinical effects in older men and conflicting effects on general well being (149,153–157). Therefore, the term andropause is reserved for the age-related decline in T, the major circulating androgen in blood.

Age-Associated Physiological Changes Consistent With Androgen Deficiency

Aging is associated with a number of changes in physiological functions, many of which are regulated by androgens. Physiological alterations that are associated with the age-related decline in serum T levels include decreased lean body mass and muscle mass (predominantly in fast twitch type II muscle fibers) (158–174); reduced muscle strength and power (164,175–180); decreased physical function, aerobic capacity, and balance (175,181–187); increased risk of falls and loss of independent living; increased fat mass during middle to old age, in particular increased amounts of visceral adiposity, which is associated with insulin resistance and increased risk of type 2 diabetes mellitus, hypertension, and atherosclerotic vascular disease, followed by stable or decreased fat mass in very old age (159,188–193); decreased bone mineral density (BMD) and increased risk of osteoporosis and fractures (194–201); decreased skin thickness and body hair, and poor wound healing (202,203);

diminished vigor, energy, and general well being; irritability and depressed mood (204); decreased sexual function (reduced libido, sexual activity, and erectile function) (80,205–208); impaired concentration and cognitive function (209,210); sleep disturbances and impaired sleep quality (211,212); and decreased hematopoiesis (213,214).

Similar alterations in physiological function occur in younger hypogonadal men with androgen deficiency and T replacement therapy: increases lean body mass, muscle mass, and strength; decreases body fat mass; improves energy, well being, mood, and libido; increases spontaneous erections during sleep (nocturnal penile tumescence) and induced by sexual thoughts; improves sexual function; and increases erythropoiesis and hematocrit (215–268). Therefore, it is hypothesized that the decline in serum T levels with aging contributes, at least in part, to these age-related alterations in physiological function, especially in older men with serum T levels below the normal range for young men. Although not uniform, most descriptive studies find a correlation between serum T levels and most of these physiological functions, independent of age.

Some descriptive studies find a positive correlation between T levels and lean body mass, and muscle mass and strength in older men (7,139,269), while others do not (269–272), and most studies (273–277) find an inverse correlation between T and total or abdominal fat mass, suggesting a relationship between serum T and age-related alterations in body composition and muscle strength. Furthermore, serum T levels are lower in men with type 2 diabetes mellitus, and low T levels are associated with a higher risk of developing type 2 diabetes (278–282). However, many studies investigating the association of T levels with total or visceral adiposity and diabetes may have been confounded by the use of total or free T assays that were affected by SHBG concentrations, which are significantly lower in moderately obese men (283,284).

Most epidemiological studies find a positive correlation between free T levels within the physiological range and high-density lipoprotein (HDL) cholesterol levels, and an inverse correlation between T concentrations and hypertension, insulin and glucose levels, prothrombotic factors, atherosclerotic vascular disease, and the presence or severity of coronary artery disease (CAD) (31,285–303). In prospective studies, no correlation is found between T levels and CAD disease incidence (285). No studies have reported an association between T and cardiovascular mortality. Therefore, epidemiological studies suggest a protective or neutral rather than an adverse effect of T on heart disease risk.

A relatively weak positive correlation is found between free, bioavailable, or total T levels and BMD and fracture risk in some studies (137,139,273,304–310), but no correlation is found in others (140,311–319). In recent studies, a stronger correlation is found between bioavailable E2 levels and BMD and fracture risk than between T and these outcomes, suggesting that the age-related reduction in bioavailable E2 levels may be a more important determinant of bone loss with aging in men than T levels (139,140,306,308,311,318,320,321). The findings of severe osteoporosis in men with estrogen resistance or deficiency caused by estrogen receptor or aromatase gene mutations, respectively, and an increase in BMD with E2 treatment in a man with aromatase deficiency provide strong support for a vital importance of E2 in developing and maintaining normal bone mass (322–328). In older men, administration of an aromatase inhibitor increases markers of bone resorption, and E2 replacement in these men decreases markers of bone resorption, suggesting an important role for T to E2 conversion in the prevention of bone resorption (329,330). However, men with androgen resistance caused by androgen receptor gene mutations have reduced BMD, suggesting that androgens also play an important role in the development and maintenance of bone mineral content in men (331–333). The specific roles of T and E2 in regulating bone turnover were investigated recently in older men with T and E2 deficiency (induced by a GnRH agonist plus an aromatase inhibitor) treated with either physiological T or E2 replacement (334). E2 but not T was found to be dominant in preventing bone resorption, whereas both T and E2 were found to be important in maintaining bone formation. Because E2 is derived from aromatization of T, it is likely that the age-related decline in serum E2 levels is related, at least in part, to the reduction in its substrate, T, with aging. Finally, low T levels are a risk factor for hip fractures in older men (335–337).

Most descriptive studies also find significant associations between T levels and aspects of brain function. In a recent study, an inverse correlation was found between bioavailable T and depression score, suggesting a role for T in the regulation of mood (338). The correlation between T levels and libido and sexual activity is weak (339–345), and such an association is not found in some studies (346). This is consistent with the findings that relatively low serum T levels are required to sustain sexual interest and desire (219,347,348). Although androgen deficiency may contribute to sexual dysfunction, it is rarely the only or major cause of erectile dysfunction in older men. Erectile dysfunction is most commonly due to vascular disease, neuropathy, and medications (88,349,350). T levels are associated with sleep efficiency and architecture (351) and inversely with measures of psychosocial stress (352). Finally, a correlation between bioavailable T and general or spatial cognitive function has been reported, suggesting a potentially very important role for T in the maintenance of cognition and memory (353–357).

Given the multifactorial nature of age-related physiological alterations (see below), it is not surprising that there is a relatively weak correlation between serum T levels and these physiological changes that occur with aging. In fact, recent large epidemiological studies suggest that much of the age-associated decline in serum T levels is attributable to age-related comorbid illnesses, medications, and lifestyle (8,13,358–360).

Multifactorial Etiology of Age-Related Physiological Changes

It would be naïve to assume that age-associated androgen deficiency is the only cause of the physiological changes that occur with aging. As is the case for many geriatric syndromes, the etiology of most age-related alterations in physiological function is multifactorial, and many of the factors

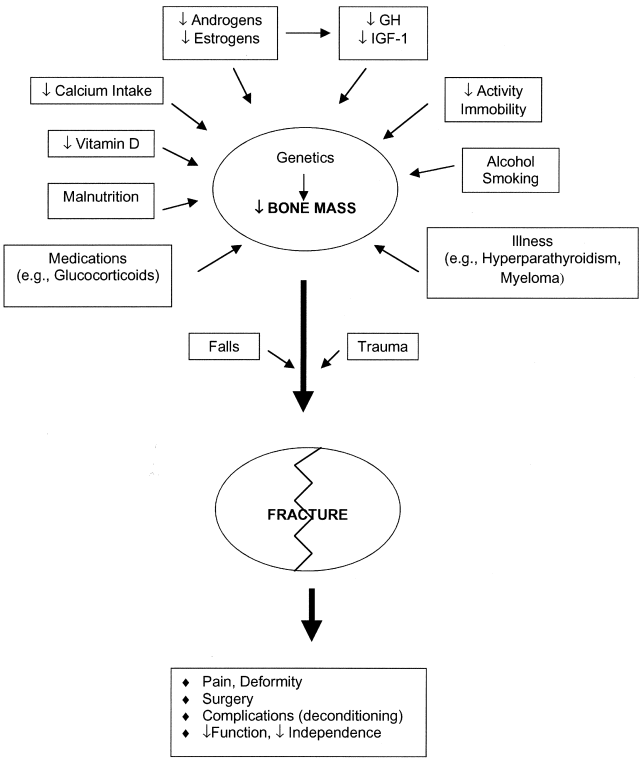

Figure 1. Schematic diagram of the multiple factors that may contribute to decreased bone mass and abnormal bone architecture in older men. These include low free or bioavailable T and E2 levels, low growth hormone (GH) and insulin-like growth factor-1 (IGF-1) concentrations, reduced calcium intake, vitamin D deficiency, malnutrition, use of medications that reduce bone mass (e.g., glucocorticoids, or anticonvulsants), decreased exercise or activity, immobility (e.g., from severe arthritis), lifestyle (excessive alcohol use or tobacco smoking), illnesses that reduce bone mass (e.g., primary or secondary hyperparathyroidism or multiple myeloma), and genetic factors that influence bone metabolism. Reduced bone mass and abnormal bone architecture predispose to fracture following falls or trauma, and fractures may cause significant clinical morbidity and mortality [e.g., pain, deformity, need for surgery, complications (e.g., deconditioning or pneumonia), and loss of function and independence].

that contribute to physiological decline are modifiable or treatable. Therefore, optimal clinical management of these changes requires careful attention to all potential etiological factors. For example (Figure 1), in addition to low T levels, the age-related decrease in BMD and abnormalities in bone architecture may be due to low E2 concentrations; low GH and IGF-1 levels; inadequate calcium intake; vitamin D deficiency; poor nutrition; use of medications (e.g., glucocorticoids or anticonvulsants); lack of exercise or inactivity due to weakness or immobilization (e.g., as a result of severe osteoarthritis); lifestyle (excessive alcohol intake, smoking); age-related illness (e.g., primary and secondary hyperparathyroidism, multiple myeloma); predisposing genetic background; and/or low peak bone mass during puberty and young adulthood as a result of prolonged illness, medications, or delayed puberty (361). The latter two potential etiologies emphasize the need for geriatricians and gerontologists to consider aging as starting from conception and extending throughout the life span of an individual, not just from young adulthood to old age. Finally, it is important to recognize the essential contribution of falls and trauma to the major clinical consequence of decreased bone mass and abnormal bone architecture, fracture, which may lead to pain, deformity, need for surgery, and associated complications (e.g., deconditioning or pneumonia), and loss of function and independent living.

Interactions among the potential etiological factors that contribute to age-related physiological decline increase the clinical complexity and highlight the importance of using a multifactorial approach in managing older patients. For example, low serum T levels may contribute to reductions in E2, GH, and IGF-1 levels (362), decreased exercise or inactivity as a result of weakness and/or poor motivation, and increased risk of falls related to muscle weakness and poor balance. T treatment may increase BMD indirectly by increasing E2, GH, and IGF-1 levels and physical activity, and reducing the likelihood of falls by improving muscle strength, balance, and spatial cognition. Conversely, many of the factors that decrease BMD (e.g., poor nutrition, medications, comorbid illnesses, and excessive alcohol intake) also may contribute to the reduction in serum T levels. Correction of poor nutrition, discontinuation of certain medications such as glucocorticoids, treatment of comorbid illnesses, and discontinuation of alcohol abuse may increase serum T levels and obviate the need for T treatment. In the clinical approach to older men with low serum T levels, a similar multifactorial evaluation of possible etiological factors contributing to other age-related physiological alterations should be adopted.

Potential Consequences and Importance of Age-Associated Physiological Changes

Age-associated changes in physiological function have important potential consequences, including reduced physical function, endurance, and activity; increased risk of disease (e.g. coronary heart disease, diabetes mellitus, osteoporosis); diminished quality of life; impaired balance and increased risk of falls; impaired ability to regain function after an acute illness; and, most importantly, increased susceptibility to frailty (2,363). In turn, frailty may lead to a loss of independence, chronic disability, and a need for assisted living or long-term care; severe psychological and socioeconomic sequelae; and an increase in mortality.

A major clinical focus of geriatric medicine is the prevention of frailty. A multifaceted approach is employed to prevent frailty in elderly persons. This includes interventions to prevent acute and chronic diseases (e.g., influenza vaccination, smoking cessation); prevent falls and injury (e.g., discontinuation of medications that predispose to falls and hip protectors); adequately treat acute and chronic diseases; identify and treat conditions that impede recovery of function (e.g., delirium and depression); improve physical conditioning (e.g., aerobic and resistance exercise); improve nutritional intake; and replace hormonal loss (e.g., estrogen replacement therapy in postmenopausal women). With regard to the more gradual and less profound age-related decline in serum T levels, major unanswered clinical questions are whether T replacement therapy of older men will im-

prove functional status, prevent disease, increase the quality of life, and, most importantly, reduce the risk of frailty (2,364).

Potential Benefits and Risks of T Replacement Therapy in Older Men

When considering T replacement therapy in older men, the potential benefits of T treatment must be weighed against the possible risks (365). The potential benefits and risks of T replacement therapy in older men (Table 1) are based mostly on the clinical studies of the effects of T replacement in severely androgen-deficient, young, hypogonadal men (discussed in the previous section) and a small number of controlled trials of T treatment in older men (discussed in the following section).

Potential benefits of T replacement therapy in older men include increased lean body mass; decreased fat mass and visceral adiposity, and reduced risk of diabetes mellitus; increased muscle mass and strength; increased BMD and reduced risk of osteoporosis and fractures; increased body hair and skin thickness, and improved wound healing; improved physical function, aerobic capacity, and balance; improved libido and sexual function; improved feeling of well being and improved energy; reduced irritability and depressed mood; improved concentration and cognitive function; improved sleep quality; increased hematopoiesis and hematocrit; and decreased risk of CAD.

Short-term risks of T administration in older men include stimulation of erythropoiesis, resulting in excessive erythrocytosis and, if severe, increased blood viscosity and risk of thrombotic complications (e.g., stroke and myocardial infarction); induction or worsening of obstructive sleep apnea; worsening of peripheral edema; and development of gynecomastia.

The most concerning long-term potential risk of T administration in older men is the stimulation of previously unrecognized local or metastatic prostate cancer (366). Prostate cancer is the most common malignancy in men, and many older men harbor microscopic foci of prostate cancer that do not become clinically apparent during their lifetime (367). In most (368–370) but not all (371) epidemiological studies, serum T levels were not associated with a risk of prostate cancer. However, because prostate cancer growth is initially androgen-dependent, there is concern that T treatment of older men will stimulate growth of preexisting subclinical (microscopic) prostate cancer to become clinically detectable. This concern is heightened by reports that find a high prevalence of prostate cancer (~25%) on surveillance biopsies of older men with low serum T, and normal prostate-specific antigen (PSA) levels and digital rectal examinations (372,373). However, biopsies were not performed in an age-matched control group of men with normal T levels in these studies, and in other studies, the prevalence of prostate cancer in older men with normal PSA levels and digital rectal examinations is comparable to those found in these reports (374). As a consequence of more intensive monitoring of digital rectal examinations and PSA levels, another underappreciated potential risk of T treatment in older men is the increased likelihood of detecting subclinical localized prostate cancer for which treatment is unclear. Even if subclinical disease discovered on biopsy does not affect overall prognosis, the potential medical, surgical, psychological, socioeconomic, legal, and ethical consequences of a diagnosis of subclinical prostate disease may be quite great.

Benign prostate growth is also androgen-dependent (375,376). At the time of puberty, prostate size increases in response to the increases in endogenous T production. Patients with severe prepubertal androgen deficiency have small, underdeveloped prostate glands, and if left untreated, these men do not develop BPH. Long-term T treatment of young hypogonadal men increases prostate size to volumes that are comparable to age-matched eugonadal men (377,378). In men with BPH, treatment with a 5 alpha-reductase inhibitor (e.g., finasteride, which inhibits the conversion of T to the potent androgen DHT) decreases prostate size, improves urine flow, reduces symptoms of BPH, and decreases the need for BPH-related surgery (379). Therefore, another potential long-term risk and concern of T treatment in older men is the stimulation of BPH growth and worsening of symptoms, urine flow, and urinary retention that may require invasive intervention, such as a transurethral resection of the prostate (TURP).

Although rarely an issue, T replacement may suppress already compromised sperm production in older men and potentially reduce fertility. Men have a higher risk of CAD than women. Also, treatment of severely androgen-deficient, young, hypogonadal men with physiological T dosages and eugonadal men with supraphysiological T dosages decreases HDL cholesterol levels, producing a more atherogenic profile (286,380–385). Therefore, there is concern by some that T replacement in older men may increase the risk of cardiovascular disease. As discussed previously, most epidemiological studies suggest that low T levels are associated with an increase in the prevalence and severity of CAD in men. However, in the absence of long-term studies to evaluate the effects of T on major cardiovascular outcomes such as coronary death, myocardial infarction, and stroke,

Table 1. Testosterone Treatment in Older Men: Potential Benefits and Risks

Potential Benefits	Potential Risks
Improve body composition	Erythrocytosis, hyperviscosity
↑ Lean body mass	Induce or worsen sleep apnea
↓ Fat mass, ↓ visceral fat	Worsen edema
↑ Muscle mass and strength	Gynecomastia
↑ BMD, ↓ fractures	Clinical prostate disease
↑ Hair, skin thickness	Worsen BPH requiring intervention
↑ Physical function	Hasten clinical prostate cancer
Improve brain function	Suppress sperm production
↑ Libido, sexual function	Increase cardiovascular risk
↑ Well being, energy	
↓ Irritability, depression	
↑ Cognitive function	
↑ Sleep quality	
Increase hematocrit	
Decrease cardiovascular risk	

Notes: ↑ Signifies a potential increase or improvement in the endpoint with testosterone treatment. ↓ Signifies a potential decrease or reduction in the endpoint with testosterone treatment. BMD = bone mineral density; BPH = benign prostatic hyperplasia.

the possibility remains that T therapy in older men may increase cardiovascular disease risk.

Clinical Trials of T Therapy in Older Men

Relatively few randomized controlled studies have been reported that investigate the effects of T treatment in older men (386–423). In these studies, a variety of T formulations and dosages were used to treat a relatively small number of mostly healthy older men, and differing methods were used to assess outcomes. However, these preliminary controlled studies suggest that T treatment in older men has beneficial effects on body composition (increase in lean body mass and decrease in fat mass), bone mineral density, LDL cholesterol, angina and exercise-induced cardiac ischemia, and possibly on muscle strength, sexual function, general well being, and aspects of cognitive function (Table 2).

No formal evaluation of the dose-response effects of T treatment on relevant outcomes has been performed in older compared to young, androgen-deficient men. Therefore, the impression that the effects of T treatment are attenuated in older men relative to young men is not supported by evidence. Also, most studies have been performed on relatively healthy older men with T levels in the lower part of the normal range or slightly below normal. Therefore, it is difficult to compare the effects of T therapy in these studies of mildly androgen-deficient older men to those found in studies of more severely T-deficient young men.

Table 2. Testosterone Treatment of Older Men: Summary of Controlled Studies

Benefits		Risks	
↑	Lean body mass	↑	Hematocrit, risk of erythrocytosis
↓	Fat mass	η	Sleep apnea
↑/η	Grip and leg strength	η	Clinical prostate disease
↑	BMD (if low T initially)	η	BPH symptoms, size, urine flow
	? ↓ Fractures	↑/η	PSA (<4 ng/ml)
↑/η	Sexual function, well being	?	↑ BPH intervention
	↑ Libido	?	↑ Clinical prostate cancer
	η Erectile dysfunction	η	HDL cholesterol
	↑ Well being, ? ↓ depression	?	↑ Cardiovascular events
↑/η	Cognitive function		
	↑ Spatial, working memory		
	↑ Verbal memory		
	η Visual memory		
	? Slow dementia onset		
↓	Total and LDL cholesterol		
↓	Angina and exercise ischemia		
	?↓ Cardiovascular events		
?	↑ Physical function		
?	↓ Frailty		
?	↑ Quality of life		

Notes: Composite of benefits and risks of testosterone treament in older men derived from references (385–422). ↑ Signifies that most controlled studies found an increase in the endpoint with testosterone treatment. ↓ Signifies that most controlled studies found a decrease in the endpoint with testosterone treatment. η Signifies that most controlled studies found no change in the endpoint with testosterone treatment. ↑/η Signifies that some controlled studies found an increase and others found no change in the endpoint with testosterone treatment. ? Signifies that controlled studies have not been performed to address the endpoint sufficiently. BMD = bone mineral density; LDL = low-density lipoprotein; BPH = benign prostatic hyperplasia; PSA = prostate-specific antigen; HDL = high-density lipoprotein.

Beneficial Effects of T Therapy in Studies of Older Men

In most controlled trials of older men, T treatment resulted in improvements in body composition. In both controlled (388,390,401,405,406,415,417,418,424) and uncontrolled (425) studies, the most consistent effects of T therapy in older men were an increase in lean body mass and/or a decrease in total fat mass. One study found a decrease in visceral fat mass and improvement in insulin sensitivity with T treatment (406). The effects of T supplementation in older men on muscle strength were more variable. Some studies found an increase in upper extremity grip strength (408,415,424), and one uncontrolled study found an increase on lower extremity strength with T therapy (425). However, other carefully performed controlled studies found no increase in either upper or lower extremity strength with T treatment of older men (388,391,394,405, 417,418). The lack of consistent effects of T therapy on muscle strength may be due to differences in the methods used to assess strength and the dosages and duration of T that were administered. In a preliminary report, timed walking and stair climbing improved in older men with short-term T administration (391). Self-assessment of physical function was maintained in older men treated with transdermal T compared to placebo for 3 years (417). Supraphysiological but not physiological T administration also has been reported to increase the secretion of another anabolic hormone, GH, in older but not young men (398). No controlled studies have investigated systematically the effect of T therapy in older men on muscle power, balance, or endurance, which together with strength play important roles in the maintenance of physical function in older men.

Controlled studies in which T was administered for at least 1 year demonstrated an increase in lumbar spine and hip BMD and prevention of bone loss in the femoral neck with T compared to placebo treatment in older men with low T levels (388,405,424). In one study, T prevented loss of BMD in the femoral neck despite calcium and vitamin D supplementation in all subjects (405). In another study that included older men with normal serum T levels and in which some but not all subjects received calcium and vitamin D (if dietary intake was inadequate), both T- and placebo-treated men exhibited an increase in BMD without a significant difference in response between the two groups (416). However, further analysis revealed that T treatment increased BMD in older men who had low serum T levels (<300 ng/dl) at baseline, suggesting that a beneficial effect of T treatment on BMD may occur only in older men with androgen deficiency. These studies emphasize the importance of considering other etiologies besides low T levels that may contribute to clinical manifestations consistent with androgen deficiency in older men (e.g., low calcium intake and vitamin D deficiency in older men with low BMD) (426). No controlled studies have evaluated the effect of T on bone architecture or the risk of falls that together with BMD contribute to the age-related increase in the risk of fractures in men. Furthermore, no studies have investigated sufficient numbers of older men for long

enough (i.e., had sufficient statistical power) to determine whether T treatment decreases the incidence of fractures in older men.

T treatment in older men increased libido and sexual activity and improved energy and well being in some controlled studies (400,406,410,413,418,419) but not in others (388,389,403,404,408,415,417). An uncontrolled trial also reported improvements in energy, mood, well being, libido, and sexual activity (427). One controlled study found no effect of T therapy on clinical depression in older men (415). Other studies have not investigated the effect of T on depression in older men. In a recent small, double-blind, randomized, placebo-controlled study of depressed hypogonadal middle-aged men, short-term T administration (6 weeks) improved sexual function but did not improve depression scores compared to placebo (266). In preliminary placebo-controlled studies, certain domains of cognitive function, specifically spatial, verbal, and working memory, improved with T treatment in older men (392,403,404) but had no effect on general memory, recall, or verbal fluency (415). In one preliminary study, very short-term T administration (5 days) prevented the improvement in verbal fluency observed in placebo-treated older men (423). Studies have not investigated whether T treatment will slow the onset of clinical dementia in older men.

Most controlled studies of T therapy in older men found a decrease in total and low-density lipoprotein (LDL) cholesterol with no significant effect on high-density lipoprotein (HDL) cholesterol (393,406,408,415,418,420,424). T treatment inhibited triglyceride uptake and lipoprotein lipase activity in abdominal but not femoral subcutaneous adipose tissue depots (407). In several small, randomized, placebo-controlled studies of middle-aged to older men with coronary heart disease, chronic T treatment decreased angina and exercise-induced cardiac ischemia (i.e., increased the time to ST segment depression during exercise testing) (397,402,414,428). Also, acute intravenous administration of T during cardiac catheterization was shown to improve exercise-induced ischemia in older men with CAD, probably by inducing coronary artery vasodilation (411,412, 421,422). Subjects with angina also reported significant improvements in quality of life, especially in pain perception and limitation resulting from physical problems (397). Therefore, in contrast to the general perception that androgens are bad for the heart, T administration may have beneficial effects in older men with cardiovascular disease. No clinical trials have studied sufficient numbers of men for long enough periods of time to evaluate the effects of T replacement in older men on major cardiovascular events, such as cardiac death, myocardial infarction, or stroke.

In a recent small controlled study, T treatment improved physical functional status, grip strength, and mood compared to placebo in a small number of relatively frail older men undergoing rehabilitation on a Geriatric Evaluation and Management unit (387). In older men undergoing elective knee or hip arthroplasty, serum T levels were suppressed significantly postoperatively in men treated with placebo, and perioperative supraphysiological T administration tended to improve postoperative strength, physical function, and hematocrit (386). More significant improvements in muscle strength and physical function, and reduction in hospitalization and rehabilitation duration were probably not observed in this study because the subjects studied were healthy, independently living, older men who were functioning at a relatively high level prior to surgery.

Except for the limited studies mentioned, the effects of T replacement on physical function, health-related quality of life, and the prevention of frailty have not been investigated fully in older men. The prevention of frailty is an important potential goal of T treatment in older men. The frail older population is at high risk for disability, loss of independence, and long-term care, and they utilize a major proportion of health care resources and dollars. Compared with healthy older men, frail older men have lower serum T levels and may derive more functional benefit from T treatment.

Adverse Effects of T Replacement in Studies of Older Men

In controlled studies of up to 3 years in duration, T therapy in older men has been tolerated very well. The only adverse effect that has been found consistently in controlled trials of T treatment in older men is stimulation of excessive erythrocytosis. However, a major caveat is that studies have been powered insufficiently to evaluate the long-term risks of T therapy on prostate and cardiovascular disease, and therefore these potential risks remain unknown.

Stimulation of erythropoiesis and an increase in hematocrit of 3% to 5% over baseline has been found in most controlled trials of T treatment in older men. The development of erythrocytosis (hematocrit over 51%) during T therapy has been reported in 6% to 25% of older men (394,395, 399,402,415,416,418). Erythrocytosis has occurred in older men with both parenteral and transdermal T administration, but it has been less common with the latter (397,405). This may be related to the supraphysiological T levels that are produced during the first few days following T ester injections and overall higher mean serum T concentrations compared with the more physiological T levels that are produced with the use of T patches or gel. An excessive increase in hematocrit of more than 55% to 60% results in a substantial increase in blood viscosity and, if untreated, may result in significant hyperviscosity and an increased risk of thrombotic complications. The latter, more serious complications of excessive erythrocytosis have not been observed in T treatment trials in older men.

Although T administration has been reported to induce or worsen obstructive sleep apnea syndrome in younger hypogonadal men (429,430), this complication has not been reported in clinical trials of T therapy in older men (416). Obstructive sleep apnea may be associated with low serum T concentrations (431,432). Therefore, older men with risk factors (e.g., obesity) or symptoms of obstructive sleep apnea (e.g., daytime somnolence and snoring) should be evaluated for symptoms of sleep apnea prior to institution of T treatment and should be monitored for this potentially serious risk during therapy. Validated instruments, such as the Berlin Questionnaire or Epworth Sleepiness Scale, may be used for screening and monitoring (433–436).

The most worrisome potential risk of T replacement ther-

apy in older men is the induction of clinical prostate disease. Most (368,369,437) but not all (371,438,439) descriptive studies have failed to find a significant relationship between endogenous T levels and the development of BPH or prostate cancer. In controlled trials, there has been no significant increase in prostate size, worsening of BPH symptoms, or reduction in urine flow rate in T-treated compared with placebo-treated older men (386,388,399,400,405,406,415,416, 418). In some trials of T therapy in older men, serum PSA levels increased slightly, mostly within the normal range (below 4 ng/ml) (392,405,408,416,418), but in most studies, PSA did not change significantly during T treatment. No increase in the need for invasive or surgical therapy for BPH or incidence of clinically apparent prostate cancer has been reported. However, the total number of men treated with T and length of exposure have been limited, and studies have not had the statistical power to evaluate the long-term risks of clinical BPH and prostate cancer in older men treated with T.

In contrast to the suppression of HDL cholesterol that occurs with T replacement in younger men with severe hypogonadism and supraphysiological T administration in young eugonadal men (286,380–385), most controlled trials of T treatment in older men have not found a significant decrease in HDL cholesterol (393,406,415,418,420). As mentioned previously, total and LDL cholesterol decreased in most studies (393,406,418,420) and were unchanged in the remaining trials (394,415) during T therapy of older men. As with prostate disease, clinical trials have not investigated the long-term cardiovascular risk of T replacement treatment in older men. They have not had sufficient statistical power to determine whether T treatment affects the rates of major cardiovascular events such as coronary death, myocardial infarction, and stroke.

Other known adverse effects of T therapy in younger hypogonadal men, such as development or worsening of edema, especially in men with underlying edematous states (e.g., congestive heart failure, hepatic cirrhosis, nephrotic syndrome, and renal failure), gynecomastia, especially in moderate obese men, and suppression of spermatogenesis have not been reported in clinical trials of older men.

Approach to the Diagnosis of Androgen Deficiency in Older Men

Although an increasing proportion of men exhibit low serum T levels with increasing age, a substantial number of older men maintain T levels within the normal range. These individuals may exhibit clinical manifestations consistent with androgen deficiency. It may be argued that they have relative androgen deficiency (i.e., a significant age-related decline in T levels within the wide normal range) contributing to their clinical manifestations. However, the clinical manifestations of androgen deficiency are not specific and are usually multifactorial in nature, and there is no evidence that these men would benefit from T therapy. Furthermore, the clinical significance of slightly low serum T levels in the absence of clinical manifestations consistent with androgen deficiency is not clear. Therefore, the diagnosis of andropause requires both the presence of clinical manifestations or a clinical syndrome, and confirmed serum-free or bioavailable T levels below the normal range for younger men. A rational approach to the diagnosis of androgen deficiency in older men is outlined in Figure 2 and is discussed in the following sections.

The Clinical Syndrome of Androgen Deficiency in Older Men

In order to define a clinical syndrome associated with low T and to identify older men at high risk for low serum T levels, two screening instruments were developed recently. The ADAM questionnaire is a symptom-based instrument that identifies older men with symptoms of low T, with 88% sensitivity and 60% specificity (49). Symptoms associated with low serum T levels in this questionnaire are reduced libido; lack of energy; decreased strength and/or endurance; loss of height; decreased enjoyment of life; feeling sad and/or grumpy; reduced strength of erections; decreased ability to play sports; falling asleep after dinner; and reduced work performance. This symptom complex is similar to that reported by others for the androgen deficiency in older men (440–443). The MMAS questionnaire is an epidemiology-derived instrument that identifies risk factors for low T levels in older men, with 75% sensitivity and 50% specificity (444). Risk factors that are associated with low total T levels include age of 60 years or older; treated diabetes mellitus; treated asthma (a surrogate for glucocorticoid use); sleeplessness ($\leq$5 hours); nonsmoking; headaches in the past 2 weeks (a surrogate for stress); low dominance (dislike of a directing role); and body mass index (BMI) 27–30 or $>$30.

A combination of symptoms and risk factors may better identify individuals with low T levels. Therefore, a composite of the most prominent clinical manifestations of androgen deficiency in older men is presented in Table 3. Symptoms of androgen deficiency in older men include decreased muscle strength and/or endurance; diminished work and/or athletic performance; loss of height; history of nontraumatic fracture; decreased pubic and axillary hair; reduced physical function; diminished sexual interest and desire; decreased strength and adequacy of erections; fatigue, tiredness, and lack of energy; irritability; depressed mood; decreased general well-being and enjoyment of life; sleep disturbance; sweats; and hot flushes. Signs include decreased muscle mass and strength; increased visceral adiposity; low BMD [osteoporosis or BMD $<$ $-$2.5 SD below that of young men (T-score $<$ $-$2.5) or osteopenia (T-score $-$1 to $-$2.5)]; vertebral and/or hip fracture; decreased pubic and axillary hair; depressed mood; decreased testis size; gynecomastia; and a normocytic, normochromic anemia.

Repeated Low Serum T Levels in the Absence of Reversible or Remediable Causes

If clinical manifestations suggest androgen deficiency, an early morning (e.g., 8 AM) T level should be measured to confirm low serum T levels. In order to avoid the confounding effects of alterations in SHBG levels on total T, a free or bioavailable T level by equilibrium dialysis or ammonium sulfate, respectively, is recommended for confirmation of androgen deficiency in older men (52,445,446). Alternatively, free or bioavailable T levels may be calculated from

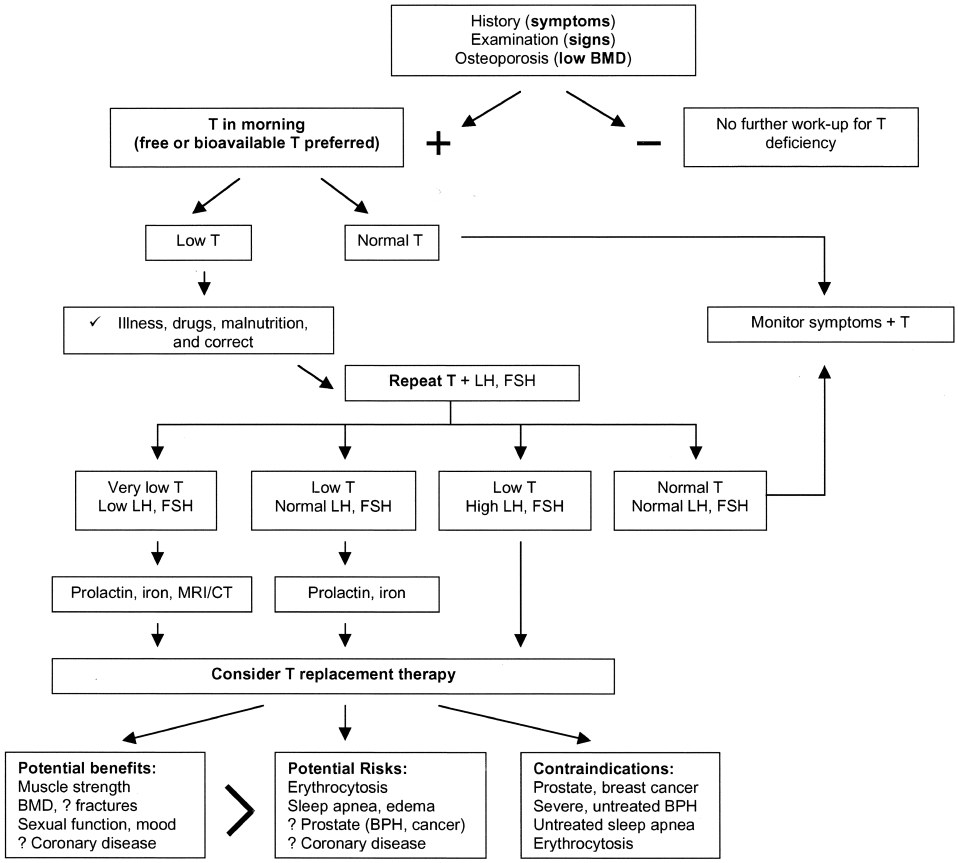

Figure 2. Approach to the diagnosis and treatment of androgen deficiency in older men. Diagnostic evaluation for androgen deficiency in older men should be instituted only in individuals with symptoms and signs consistent with androgen deficiency. Initially, androgen deficiency should be confirmed with the measurement of a morning serum-free or bioavailable T level. Individuals with an initially low free or bioavailable T level should be evaluated for remediable causes of androgen deficiency (e.g., illness, medications, or malnutrition) and have serum T levels repeated in conjunction with gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) levels. Men who demonstrate secondary hypogonadism (low T and normal to low gonadotropin levels) should have measurements of serum prolactin and iron to rule out hyperprolactinemia and hemochromatosis. Imaging of the hypothalamus and pituitary to rule out a tumor or destructive lesion should be reserved for men with very low T and low gonadotropin levels, and/or those with markedly elevated prolactin levels (e.g., >100 ng/ml). T replacement therapy should be considered in men with clinical manifestations of androgen deficiency and repeatedly low serum T levels after appropriate correction or treatment of remediable causes, and if the clinician and patient feel that the potential benefits of treatment outweigh the potential risks, and there are no contraindications. BMD = bone mineral density; MRI/CT = magnetic resonance imaging/computed tomography; BPH = benign prostatic hyperplasia.

total T and SHBG measurements; calculated values are comparable to those measured by equilibrium dialysis and ammonium sulfate precipitation methods (52).

Because total T assays and free T by direct analog immunoassay vary with alterations in SHBG levels, they are not recommended (52,53,55,56,446). However, these assays are usually the only ones that are currently available in local clinical laboratories. If total T or free T using direct analog immunoassay method is used initially to evaluate older men with clinical manifestations of androgen deficiency, values that are in the low-normal to moderately low range (e.g., total T of 350–200 ng/dl) should be confirmed with a free or bioavailable T level measured using a more accurate method. Unless SHBG levels are very low (e.g., nephrotic syndrome), total T levels <200 ng/dl in the presence of consistent clinical manifestations are usually diagnostic of androgen deficiency.

In younger hypogonadal men, T levels below the normal range are usually associated with symptoms of androgen deficiency. Therefore, the normal range in younger men is used as the reference range for older men as well. This approach is analogous to that used for the interpretation of BMD where values are compared to those in younger men (T-score or SD from young controls) and are used to define a clinically significant BMD that is associated with an increased risk of fracture (e.g., osteoporosis defined as a T-score <-2.5).

If the initial serum T level is low, evaluation of underlying acute and chronic illnesses, medications, and nutritional state should be undertaken to determine whether there are reversible or remediable causes of low T levels. In these instances, T level should be repeated after the stress of a current or recent illness is resolved, medications that may lower T (e.g., glucocorticoids or CNS-active drugs) are dis-

Table 3. Androgen Deficiency in Older Men: Clinical Manifestations

Symptoms	Signs
↓ Muscle strength and/or endurance	↓ Muscle mass and strength
↓ Work and/or athletic performance	↑ Visceral adiposity
Loss of height, history of fractures	Low BMD (osteoporosis)
↓ Pubic and axillary hair	Vertebral and/or hip fracture
↓ Physical function	↓ Pubic and axillary hair
↓ Sexual interest and desire	Depressed mood
↓ Strength of erections	↓ Testis size
Fatigue, tiredness, lack of energy	Gynecomastia
Irritability, depressed mood	Normocytic, normochromic anemia
↓ Well-being, enjoyment of life	
Sleep disturbances	
Sweats, hot flushes	

Notes: Composite of symptoms and signs from references (49,438–442). BMD = bone mineral density.

continued, and nutritional compromise (e.g., associated with illness) is corrected.

If no correctable cause of androgen deficiency is found, a T level should be repeated together with serum gonadotropin (LH and FSH) levels. There are significant biological and methodological variations in serum T measurements such that as many as 15% of healthy young men may have a T level below the normal range in a 24-hour period (447). Older men with initially low T values may have normal levels on a subsequent blood sample. Therefore, before committing someone to T replacement therapy, a repeat serum T level should always be obtained to confirm androgen deficiency.

If the initial serum-free or bioavailable T level is within the normal range in a man with symptoms and/or signs of androgen deficiency, the patient's clinical status and serum T levels should be monitored on follow-up visits. Finally, because clinical manifestations of androgen deficiency usually have multiple etiologies in older men, evaluation and appropriate treatment of other causes of clinical findings should be undertaken concomitantly with the work-up for androgen deficiency.

Further Evaluation of Older Men With Low T Levels

If the repeated serum-free or bioavailable T level is low and is associated with inappropriately normal or low gonadotropin levels (i.e., a hormonal pattern of secondary hypogonadism) serum prolactin and iron should be obtained to rule out hyperprolactinemia and hemochromatosis (iron overload), both of which can suppress gonadotropin and T secretion. In individuals with very low T (e.g., total T $<$ 150 ng/dl) and low gonadotropin levels, and/or those with markedly elevated prolactin levels (e.g., $>$100 ng/ml), an MRI or CT scan of the hypothalamus and pituitary should be performed to rule out a tumor or destructive lesion in this area (448). Men with hyperprolactinemia, hemochromatosis, or hypothalamic-pituitary tumor or destructive lesion should be treated appropriately with consultation from an endocrinologist. In the absence of these conditions, and in older men in whom repeated serum T level is low and is associated with elevated gonadotropin levels, T replacement treatment should be considered. If the repeat serum-free or bioavailable T and gonadotropin levels are within the normal range, the patient's clinical status should be monitored together with serum T levels.

Consideration of T Treatment in Older Men With Repeatedly Low T Levels

The state of knowledge regarding the benefits and risks of T treatment in older men is based on a limited number of short-term controlled studies (3,449–453). No controlled studies have evaluated the long-term benefits and risks of T therapy in older men. Therefore, there are insufficient data to formulate firm evidence-based clinical guidelines and general recommendations for T therapy in older men. Routine treatment of older men cannot be recommended at this time. After a thorough assessment and discussion of potential benefits and risks of T therapy, individual practitioners must rely on sound clinical judgment and informed patient preferences before deciding to recommend and prescribe T treatment for older men with clinical manifestations consistent with androgen deficiency and repeatedly low serum T levels.

As outlined in Figure 2, T therapy should be considered only in older men with clinical manifestations of androgen deficiency and repeatedly low serum T levels, in whom remediable causes of low T have been corrected or treated appropriately. This approach is consistent with that recommended by consensus panels of experts in the field (446,454). T treatment should be instituted in these men if both the clinician and the patient feel that the potential benefits (e.g., severe muscle weakness, osteoporosis, or alterations in sexual function or mood) of treatment outweigh the potential risks (e.g., erythrocytosis and prostate disease) and if no contraindications exist. Absolute contraindications to T therapy are prostate and breast cancer, and relative contraindications are untreated BPH with severe bladder outlet obstruction, untreated obstructive sleep apnea syndrome, and erythrocytosis.

T Therapy and Monitoring in Older Men

Baseline Evaluation and Goals of T Replacement

Prior to institution of T therapy, a careful baseline clinical evaluation should be performed in order to determine whether there is a history of: prostate or breast cancer, or family history or risks for these androgen-dependent malignancies; severe symptoms of BPH [e.g., using the International Prostate Symptom Score (IPSS) or American Urological Association (AUA) Symptom Score] or sleep apnea (e.g., using the Berlin Questionnaire or Epworth Sleepiness Scale); an abnormal digital rectal examination (e.g., induration or nodule) requiring prostate ultrasound and biopsy; erythrocytosis (hematocrit $>$52); or an elevated PSA level $>$4 ng/ml (after empiric treatment for prostatitis and repeat PSA determination).

In the absence of knowledge regarding the dose-response effects of T treatment and lack of evidence for altered androgen requirements in older men, a reasonable goal of T replacement is to restore serum T levels into the mid-normal

range for younger men and to alleviate the clinical manifestations of androgen deficiency.

Preparations Available and Under Development for T Replacement Therapy

There are several formulations available for T replacement therapy in older men (455,456). The most commonly used preparations for T replacement are parenteral 17 beta-hydroxy-esters of T, T enanthate, or cypionate, usually administered by intramuscular injections at a dosage of 150–200 mg every 2 weeks (457). These T esters are safe, effective, and the least expensive formulation available for androgen replacement therapy. However, serum T levels rise to supraphysiological levels during the first few days following injection of T esters and fall into the low-normal range or below normal just before the next injection. The extreme variations in T levels between injections are often accompanied by fluctuations in energy, libido, and mood that may be bothersome to patients. Transient supraphysiological T levels and overall higher average T levels during treatment with T esters may be associated with a higher incidence of side effects, such as erythrocytosis. It is possible that low-dosage androgen supplementation with T enanthate or cypionate (e.g., 50–100 mg every 2 weeks) may have beneficial effects (e.g., on libido, energy, and well-being) without these side effects (458), but this has not been evaluated in controlled clinical trials.

Three transdermal T patches are available for T replacement therapy (459,460). They require daily application but provide more physiological serum T levels (usually in the low- to mid-normal range) than T ester injections. T patches have the advantage that treatment may be discontinued rapidly if adverse effects were to develop in older men, but they are more expensive than replacement with T ester injections. The Testoderm® patch (Alza, Palo Alto, CA) is effective but requires application to a clean, dry, often shaven scrotum, and many men find this site of application unacceptable (218). This patch also produces high serum DHT levels, probably as a result of high 5 alpha-reductase activity in scrotal skin. The clinical consequences of high DHT levels, however, are not known. The Androderm® patch (Watson, Corona, CA) may be applied to nonscrotal skin, but the adhesive and/or enhancing agents used in this patch may cause significant skin irritation (461–463). Skin irritation may be reduced by coapplication of a glucocorticoid cream such as triamcinolone (464). The Testoderm TTS® patch (Alza, Palo Alto, CA) is also applied to nonscrotal skin and causes much less skin irritation because it has less adhesive and does not use enhancing agents (465). However, it is larger than the Androderm patch and may adhere poorly to skin, especially with vigorous exercise or excessive sweating, resulting in lower serum T levels.

Recently, a transdermal T gel, AndroGel® (Unimed/Solvay, Buffalo Grove, IL), became available for T replacement therapy (260,261,466,467). Daily application of this hydroalcoholic gel formulation of T produces physiological serum T levels. The dosage of T gel may be adjusted to achieve T levels in the low-, mid-, or upper-normal range without significant skin irritation. AndroGel may also produce serum DHT levels above the normal range, probably as a result of the large surface area of skin covered. Transfer of T to partners or children is possible if the skin surface on which T gel is applied is not covered or washed (which is acceptable 1 hour after application).

Oral 17 alpha-alkylated androgens (e.g., methyltestosterone) should not be used for androgen replacement therapy (456). They are less effective than parenteral and transdermal T formulations and are associated with potentially serious hepatotoxicity and greater suppression of HDL cholesterol levels. Outside the United States, an oral T ester formulation, T undecanoate, has been used successfully and safely for many years for T replacement therapy in both young and older androgen-deficient men (449,456,468). Unlike 17 alpha-alkylated androgens, T undecanoate is absorbed directly from the gastrointestinal tract into lymphatics, bypassing initial hepatic inactivation, and it is not associated with hepatotoxicity (468). However, absorption of oral T undecanoate is quite variable and is dependent on coingestion of a meal. T undecanoate may become available in the United States in the future. A buccal T formulation is also being developed for androgen replacement therapy. Both the T undecanoate and buccal T have the advantage of rapid withdrawal if adverse effects develop, but the disadvantage of requiring twice daily administration, making compliance more difficult in older patients.

A number of longer-acting T formulations that require injections only every few months are being developed for T replacement therapy (e.g., T undecanoate, T buciclate, and T microspheres), and T implants have been used for androgen replacement outside the United States (456). Although more convenient than currently available T esters, these preparations are probably less suitable for T therapy in older men because rapid withdrawal of androgen would not be possible if adverse effects were to develop during treatment.

Analogous to recently developed selective estrogen receptor modulators used for hormone replacement therapy in post-menopausal women, selective androgen receptor modulators (SARMs) or "designer" androgens are being developed for T replacement therapy. An ideal SARM would be an agent that had all the beneficial effects of T on muscle, bone, sexual function, mood, cognition, and the cardiovascular system without any of the adverse effects on the prostate and cardiovascular system. 7 alpha-methyl-19-nortestosterone (MENT) is synthetic androgen that does not undergo 5 alpha-reduction but is aromatizable to an estrogen. In animal studies, it is approximately 10 times more potent than T in suppressing gonadotropin levels and increasing muscle size, but only two-times more active than T in stimulating prostate growth (469,470). Therefore, it is possible that a low dose of MENT given to hypogonadal men may be able to maintain muscle strength and brain function without stimulating the prostate gland. MENT is being developed as an implant, and preliminary studies suggest that it is able to maintain libido and sexual function in hypogonadal men (471).

Monitoring During T Therapy in Older Men

In older men, clinical examination including a digital rectal examination, hematocrit, and PSA should be repeated 3 and/or 6 months after institution of T treatment, then moni-

tored every 12 months or possibly more frequently thereafter, depending on the clinical status of the patient. Efficacy is determined primarily by subjective and objective clinical responses to T therapy. If symptomatic clinical improvement does not occur in 6–12 months and/or BMD does not improve in 24 months, patients should be re-evaluated and discontinuation of T therapy should be considered. Serum T levels measured at the midpoint of the interval between T ester injections or T patch applications may be useful to confirm that levels are within the midnormal range. Nadir serum T levels (i.e., just before the next T ester injection or patch application) may be helpful in identifying the need for a dosage adjustment.

During T treatment, the following clinical situations require further urological evaluation: development of findings suspicious for prostate cancer on digital rectal examination (e.g., a nodule or induration); PSA level >4 ng/ml that is not complicated by a urinary tract infection (e.g., prostatitis) (472,473); a confirmed increase in PSA of >1.5 ng/ml between two consecutive values over 3–6 months (474); a rate of rise in PSA levels of >0.75 ng/ml/y on sequential values performed over at least 2 years (475); or severe symptoms of BPH (e.g., as assessed using the AUA Symptom Score or IPSS instruments) that are not complicated by medications (e.g., decongestants or antihistamines) or a urinary tract infection (e.g., prostatitis). A urological evaluation including a transrectal ultrasound and prostate biopsy is indicated for an abnormal digital rectal examination or PSA elevation (i.e., a persistent elevation of PSA after empiric antibiotic treatment for prostatitis). Development of an increase in hematocrit >52% requires reduction in T dosage or discontinuation of therapy. For severe erythrocytosis (e.g., hematocrit >55%), T therapy should be discontinued, and a therapeutic phlebotomy should be performed to acutely reduce the red cell mass and prevent hyperviscosity. After the hematocrit is normalized, T treatment may be reinstituted using a lower dosage or a transdermal formulation. Other causes of erythrocytosis (e.g., obstructive sleep apnea that may be induced or worsened by T treatment, or chronic hypoxic lung disease) should be evaluated and treated appropriately. The development of daytime somnolence, loud snoring, hypertension, edema, and erythrocytosis in an obese older man on T therapy suggests obstructive sleep apnea syndrome. Instruments such as the Berlin Questionnaire or Epworth Sleepiness Scale may be used to assess symptoms of sleep apnea.

Summary and Conclusions

In men, there is a gradual and progressive decline in serum T levels with aging that is accentuated by age-associated comorbid illnesses, medications, and malnutrition. Age-related alterations in body composition, sexual function, mood, cognitive function, sleep, and erythropoiesis occur in conjunction with the declining serum T levels. Similar alterations occur in young androgen-deficient hypogonadal men and are improved with T replacement therapy. Therefore, it is reasonable to posit that age-related androgen deficiency may contribute, at least in part, to the changes in physiological function that occur with aging.

Initial short-term controlled studies of T therapy in small numbers of healthy older men suggest beneficial effects on body composition, BMD, LDL cholesterol, angina, and exercise-induced cardiac ischemia, and possibly muscle strength, libido, general well-being, and certain aspects of cognitive function. In these studies, there have been no significant adverse effects except for erythrocytosis requiring a reduction in dose in some men. Given these findings, it is reasonable to consider T replacement therapy in older men with a clinical syndrome consistent with androgen deficiency and repeatedly low serum-free and bioavailable T levels, in whom the potential benefits of therapy outweigh the potential risks. Because age-related alterations in physiological function are usually a result of multiple etiologies, it is important to evaluate and treat other factors (e.g., inadequate nutritional intake, confounding illness and medication, inactivity or poor conditioning, excessive alcohol, and smoking) in addition to low T levels that may contribute to the clinical syndrome.

A major caveat in treating older men with T is that long-term benefits on fracture incidence, onset of dementia, major cardiovascular outcomes, physical function, frailty and quality of life, and risks of clinical prostate disease (BPH and prostate cancer) and cardiovascular disease are not known. Therefore, routine T treatment of older men cannot be recommended. The balance of benefits and risks of T therapy in older men with low T levels needs to be determined in carefully designed, large, long-term, randomized, placebo-controlled studies. Until the results of these studies are available, practitioners must rely on sound clinical judgment in managing older men with symptoms and signs of andropause. At present, the most prudent course of action is to treat only older men with repeatedly low serum T levels and symptoms and signs consistent with androgen deficiency in whom the potential benefits of therapy clearly outweigh the potential risks, and to carefully monitor treated men for adverse effects. Attention to appropriate exercise and nutrition, and evaluation and treatment of other etiological factors that may contribute to clinical manifestations are essential for optimal management of age-related functional decline in older men.

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