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An integrative review on current evidence of testosterone replacement therapy for the andropause

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Abstract

Objectives: This paper examines the evidence supporting testosterone replacement in aging males. Confounding factors contributing to low testosterone levels and challenges to diagnosis of the andropause will also be considered. *Methods:* A thorough review using an integrative approach citing published literature and the ongoing work of the authors. A search was performed using National Library of Medicine PubMed. Electronic and print journals available at the Texas Medical Center library were also considered. *Results:* Information based on collective trials in older men has added to evidence for benefits and side effects of testosterone replacement inferred from studies in younger hypogonadal patients and animal models. In general, most investigators agree with short-term safety but long-term safety is unknown. Testosterone therapy in aging males improves body composition, certain domains of brain function and may also decrease cardiovascular risk in biological models. Measurable clinical effects are less apparent. Potential risks include erythrocytosis, edema, gynecomastia, and prostate stimulation. The possibility of increased risk of clinically significant prostate cancer and cardiovascular disease has been considered. *Conclusion:* The search continues for an ideal replacement androgen and larger long-term studies are needed. At this time, androgen replacement is on a case-by-case basis and prostate cancer screening should be completed prior to instituting therapy. Routine androgen replacement therapy for aging males will have significant economic implications, and is not currently recommended.

Keywords: Testosterone; Andropause; Aging

1. Introduction

The availability of new products in men's health has sparked interest in the issue of androgen replacement in aging males. Testosterone was first synthesized more than 60 years ago and its application has been mainly in younger hypogonadal patients [1]. Interest in the clinical use of testosterone in aging males has waxed and waned. Increasing life span has resulted in a steady rise in the proportion of older men who now make up the bulk of the hypogonadal population. The aging process leads to the physiological lowering of androgens including testosterone. This biochem-

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ical and physiological state has been referred to as andropause, as it in many ways parallel the changes in the aging female during menopause and the postmenopause period. The real distinction lies in the fact that andropause does not imply infertility and that this process in males is much more gradual. A definition of the andropause may best be summarized as follows:

- The decline in androgens is gradual, and as such alternative terminologies have been suggested: Partial Androgen Decline in Aging Males (PADAM) and Androgen Decline in Aging Males (ADAM) [2].
- Besides the decline in androgens, there may be also insensitivity to androgens in target organs. Reliance on absolute levels of testosterone to define an andropausal state is, therefore, difficult [3].
- This biochemical and physiological state can be symptomatic or asymptomatic [4]. Symptoms can include decrease in well-being, energy levels, and sexual functioning.
- The long-term effects of androgen deprivation may be seen in muscle, bone, brain and lipids.

2. Diagnostic challenges of the andropause

The andropause is a biochemical and physiological state of lowered androgens. It does not refer to symptoms. The symptomatic stage should be referred to as the "andropausal syndrome". This is akin to HIV infection and the "AIDS syndrome". In diagnosing the andropause syndrome, the following caveats may be useful:

- It is of utmost importance to rely on the history and physical examination for evidence of hypogonadism.
- Laboratory testing can sometimes be misleading due to numerous potential confounding factors including obesity, age and levels of albumin and sex-hormone binding globulin (SHBG).
- There is currently no gold standard laboratory test. However, for older patients bioavailable testosterone (BT) levels may be most accurate [5].
- Age matched controls are rarely available for comparison.
- Concomitant illnesses like clinical depression, personality disorders, mild cognitive impairment, hypothyroidism, fibromylagia can confound the diagnosis.
- Other confounders can include chronic illnesses, stress, circadian rthym and medications.

It is well established that testosterone levels decline with age. What has not been established is whether the decline in testosterone is associated with a symptom complex. Morley et al. evaluated a questionnaire for androgen deficiency in aging males (ADAM) to examine whether certain symptoms are more commonly present in males with low BT levels. The validity of the ADAM questionnaire to screen for low BT was tested in 316 Canadian physicians aged 40–62 years. Low BT levels were present in 25% of this population. None had elevated luteinizing hormone (LH) levels. In this population, the ADAM questionnaire was found to have 88% sensitivity and 60% specificity [6].

By and large, laboratory measurements should be a guide to the diagnosis of the andropause syndrome. One of the major problems with laboratory assessments is the pulsatile release of androgens. Most laboratories measure the three domains of testosterone: total testosterone, free testosterone (FT) and BT [7]. Total testosterone refers to all the testosterone that is measurable including those bound and unbound portions. Testosterone is bound to proteins like albumin and SHBG. Changes in protein concentrations can alter levels true levels and give false impressions. Testosterone is loosely bound to SHBG, and as such comes off easily, making it "free". The actual free amount and that bound to SHBG is referred to as BT. Laboratories can measure FT using analog ligand radiommunoassay and dialysis equilibrium methods or they can sometimes calculate it based on a formula. In older men, the binding of testosterone to SHBG is increased, making it less likely for it to be released and become FT. As such, total testosterone in older men is much less

reliable, and BT is recommended instead. BT represents the "active form" of testosterone, and has a satisfactory correlation with androgenicity. It is also reduced more rapidly than total testosterone and as such approaches a real time view of the androgen status of the patient. Unfortunately, most laboratories charge more for this test as it is more difficult to perform.

It has also been generally agreed that FT rather than total testosterone gives a better measure of androgenicity [7]. It is prudent that the clinician be aware of the different methods of obtaining a FT level, and interpret it in the context of the patient, as different laboratories may report FT using various methodologies. Testosterone circulates in plasma and binds to SHBG and albumin. Testosterone binding to transcortin and orosomucoid is negligible. Albumin bound testosterone is released into the plasma easily as compared with those bound to SHBG. There are several measures of free and BT:

i) apparent free testosterone as measured by equilibrium dialysis (AFTC);
ii) calculated free testosterone from total testosterone and immunoassayed SHBG (FT);
iii) free androgen index (FAI) = 100T/immunoassayed SHBG (FAI);
iv) direct immunoassay of free testosterone with a labeled testosterone analog (aFT);
v) BT as the fraction of serum testosterone not precipitated by 50% ammonium sulfate concentration (BT).

AFTC or testosterone as determined by equilibrium dialysis at 37 °C is arguably the method of choice for measuring FT in vivo. Care must be taken to ensure that the labeled tracer testosterone used for measuring the FT fraction is highly purified. Vermeulen et al. correlated AFTC with other accepted clinical measures of testosterone. In that study, the authors reported the correlation coefficient of AFTC to be 0.987 with calculated FT, 0.937 with immunoassayed free testosterone (aFT), and 0.848 with FAI. A perfect correlation has a coefficient of 1.0. Calculated FT can, therefore, approaches the accuracy of measuring testosterone by dialysis equilibrium. It must be noted that conditions that alter SHBG may alter the results of not only total testosterone but also FT. In men, conditions like obesity, hypothyroidsim and acromegaly can lead to lowered levels of SHBG, and as such confound the results of FT. Incidentally, pregnancy also leads to altered levels of SHBG, and as a result leads to false levels of FT as well. Otherwise, calculated FT may be a practical means for the clinician to measure FT, as it is less time consuming and expensive than testosterone by equilibrium dialysis (AFTC). BT is a more expensive test, but will be more useful and accurate in older patients as SHBG binding increases with age, and BT measures only the free amounts and those loosely bound to albumin. In older patients, one often finds normal levels of total testosterone, but BT is often significantly depressed.

3. Overview of potential benefit of testosterone therapy in aging males

Most information related to the benefits of testosterone therapy has been postulated from studies in younger hypogonadal patients and animal models, however, there is increasing information from small trials in older men. Although long-term safety is yet to be determined, in general, there is confidence of safety for at least 3–4 years of therapy. There is agreement among investigators that testosterone therapy in aging males improves body composition and certain domains of brain function and decreases cardiovascular risk. Potential risks include erythrocytosis, edema, gynecomastia, prostate stimulation, and suppression of sperm production. The possibility of increased risk of clinically significant prostate cancer and cardiovascular disease has been considered [8].

4. Economic realities and implications of androgen replacement in aging males

Given the fact that estrogens are the most prescribed drugs in the United States for the past several years, the economic implications of testos-

terone replacement are great. Since 1993, testosterone prescriptions have increased at an annual rate of 25–30%. In 2000, following the release of a topical testosterone in the United States, there was a 67% increase. Overall, there has been a 500% increase since 1993 [9]. In spite of this trend, most men in andropause have not been treated. Another consideration is that if indicated, treatment can be for life. It is not that testosterone should not be recommended, but that managed care companies, health departments and ministries should be aware of the potential long-term costs. These costs, however, may translate into long-term gains from lower or delayed incidence of osteoporosis and falls that lead to fractures. Other ''downstream'' benefits may be lower incidence of cardiac, cognitive and chronic health problems that can have a tremendous impact on long-term healthcare expenditures.

Testosterone affects multiple systems in the body, and the results of some trials will be summarized. As it will be impossible to include all the literature, the most important will be included.

5. Effect of testosterone on cognition in aging males

It is now thought that testosterone effects the brain both directly and indirectly through its aromatization to estradiol. The following findings support a direct role of androgens in cognition:

- Researchers have found many different types of androgen receptors in the brain [10].
- Testosterone has been shown to increase intercellular communication between neurons [11].
- Testosterone can have non genomic effects on serotonin, dopamine, acetylcholine and calcium signaling [12].
- It has been demonstrated in rat models that testosterone decreases tau protein by preventing the hyperphosphorylation of tau protein [13,14]. Tau protein is the precursor of amyloid tissue, the pathological lesion often seen in brains of patients with Alzheimer's disease.

The effect of testosterone on brain function appears to be domain specific, with improved performance seen in visual spatial tests as demonstrated in Janowsky et al. [15]. In that study, the authors examine whether testosterone may play a maintenance role in behavior as well. Verbal and visual memory, spatial cognition, motor speed, cognitive flexibility, and mood were assessed using a double-blind design in a group of healthy older men who were supplemented for 3 months with testosterone were assessed. The increase in testosterone levels to 150% of baseline levels resulted in a significant enhancement of spatial cognition, but no change in any other cognitive domain was found. Testosterone supplementation influenced the endogenous production of estradiol, and estradiol was found to have an inverse relationship to spatial cognitive performance. These results suggest that testosterone supplementation can modify spatial cognition in older men; however, it is likely that this occurs through testosterone's influence on estrogen. There have been several clinical trials demonstrating this effect including our own clinical trial on patients with Alzheimer's disease [16–18]. However, one clinical trial failed to demonstrate a significant cognitive change after treatment with testosterone [19]. This could be due to different sample sizes and the use of insensitive neuropsychological tests. The results of our study on the cognitive effects of testosterone replacement in Alzheimer's disease patients are illustrated in Fig. 1. In this placebo controlled pilot trial, we studied the effects of 200 mg intramuscular testosterone enanthate on cognitive function in ten hypogonadal patients with Alzheimer's disease. Altogether, 36 male patients with Alzheimer's disease were screened, ten were deemed hypogonadal as defined by a laboratory value of 250 ng/dl, using the radiommunonassay method. Five subjects received testosterone enanthate (IM; 200 mg) every 2 weeks, and five subjects received a placebo. The study subjects had monthly assessments of their testosterone, blood counts, prostate specific antigen (PSA) as well as cognitive measurements including the ADASCog, MMSE and Folstein Mini Mental State Examination. Follow-up was up to 9 months.

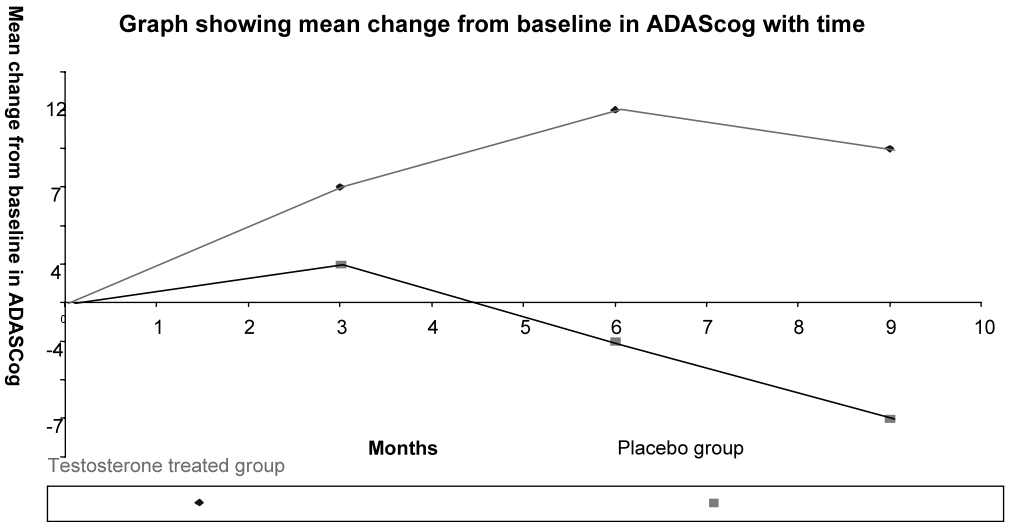

Fig. 1. Graph showing mean change from baseline in ADAScog with time.

6. Effect of testosterone on sexuality in aging males

Sexual function is a complex and multi-faceted area of physiology. It is overly simplistic to presume that sexuality and libido in men is dependent on testosterone alone. The loss of libido and erectile dysfunction are two very separate but co dependent processes [20]. Generally speaking, libido tends to be a central event and is dependent on brain function. In contrast, erectile dysfunction tends to be a local event, commonly caused by vascular insufficiency. Erectile dysfunction can sometimes result from psychological issues including stress, and thus may have a central component. Interestingly, it has been reported that testosterone may help with erectile dysfunction through its vasodilator effects. In animal models, testosterone has been shown to regulate nitrous oxide in penile cavernosal smooth muscle [21]. The clinical significance of this work is unclear.

The effect of testosterone on libido can be from as a result of its action on receptors in the brain as well as receptors in the penis. Studies have revealed that many, but not all men, experience improvement in libido with testosterone replacement. In Hajjar et al.'s study, self-assessment of libido was dramatically improved in the testosterone-treated group ($P < 0.0001$), but approximately one third of the subjects discontinued therapy [22]. In another study by Carani et al., nocturnal penile tumescence (NPT) and erectile response to visual erotic stimuli (VES) were measured, by means of a Rigiscan device, in nine hypogonadal men, and repeated after 3 months of androgen replacement. The same assessments were carried out once in 12 eugonadal controls. The number of satisfactory NPT responses, in terms of both circumference increase and rigidity, were less in the hypogonadal men than the controls and were significantly increased by androgen replacement, confirming the results of earlier studies. In terms of circumference increase, erectile response to VES did not differ between the hypogonadal men and the controls, and did not increase with androgen replacement. In terms of rigidity, the erectile response to VES did not differ between hypogonadal men and controls. However, in terms of both duration and maximum level of rigidity, there was a significant increase following androgen replacement in the hypogonadal men [23].

To summarize, the general consensus according to a large meta-analysis is that libido is improved with testosterone as compared with a placebo [24]. The effects on libido are generally accepted, but the effect on erectile function is minimal.

7. Effect of testosterone on heart disease in aging males

Supraphysiological doses of testosterone have been found to decrease high-density lipoprotein (HDL) levels in young body builders [25]. Studies in older males have found no such correlation and show only modest or no change in HDL [19,26–28]. Epidemiological studies reveal a proportional relationship between serum testosterone and HDL, with high levels of testosterone correlated to high levels of HDL [29]. Potential confounding factors include the relationship between exercise, diet and HDL.

In a study by Kenny et al. on older men, it was demonstrated that transdermal testosterone decreased HDL, but not vascular reactivity [30]. Sixty-seven men (mean age 76 ± 4 years, range 65–87) with BT levels below 4.44 nmol/l (lower limit for adult normal range) were randomized to receive transdermal testosterone (2–2.5 mg patches/day) or placebo patches for 1 year. Twenty-three men (34%) withdrew from the study; 44 men completed the trial. In this study, while total cholesterol, triglyceride, and low-density lipoprotein cholesterol levels did not significantly change during the year of therapy, HDL levels ($P = 0.004$) and, specifically, HDL(2) subfraction ($P = 0.02$) decreased in men receiving testosterone supplementation. Vascular tone was measured by brachial artery reactivity in 36 men. Endothelium-dependent brachial artery reactivity did not change from baseline measurements in men receiving transdermal testosterone (0.3 ± 6.7–1.6 ± 4.6%; $P = 0.58$) or in the placebo group (3.2 ± 5.5–0.7 ± 5.5%; $P = 0.23$).

Contrary to previous beliefs, several workers have also demonstrated improvement in coronary blood flow after testosterone administration [31–34]. Webb et al. studied 13 men (aged 61 ± 11 years) with coronary artery disease. They underwent measurement of coronary artery diameter and blood flow after a 3-min intracoronary infusion of vehicle control (ethanol) followed by 2-min intracoronary infusions of acetylcholine ($10(-7)$ to $10(-5)$ mol/l) until peak velocity response. A dose–response curve to 3-min infusions of testosterone ($10(-10)$ to $10(-7)$ mol/l) was then determined, and the acetylcholine infusions were repeated. Finally, an intracoronary bolus of isosorbide dinitrate (1000 μg) was given. Coronary blood flow was calculated from measurements of blood flow velocity using intracoronary Doppler and coronary artery diameter using quantitative coronary angiography. Testosterone significantly increased coronary artery diameter compared with baseline (2.78 ± 0.74 vs. 2.86 ± 0.72 mm [$P = 0.05$], 2.87 ± 0.71 mm [$P = 0.038$], and 2.90 ± 0.75 mm [$P = 0.005$] for baseline vs. testosterone $10(-9)$ to $10(-7)$ mol/l, respectively). As such, short-term intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and increases coronary blood flow in men with established coronary artery disease [33].

The current thinking is that testosterone may not be harmful to the cardiovascular system in aging males. Although, there is data suggesting vasodilatory properties of testosterone, there are no trials so far to demonstrate that testosterone can indeed reduce myocardial infarction rates.

8. Effect of testosterone on obesity in aging males

Obesity has been increasing for all age groups and in most parts of the world. In the United States, the prevalence of obesity in older males has increased from 11.4 to 14.6% during the years 1991–1998 [35]. Obesity is associated with hypogonadism, diabetes, insulin resistance and also increased leptin levels. An increased waist/hip ratio has been linked to increased morbidity and cardiovascular mortality. Adipose tissue can compound the hypogonadal state as it contains an abundance of the aromatase enzyme. It is believed that aromatase converts testosterone to estradiol [36]. Severe obesity also influences the hypothalamic–pituitary–testicular axis adversely.

Association does not prove causality, and as such, intervention studies may help us to understand the role of testosterone in treating obesity in aging males. Unfortunately, we are guided only by small studies with few numbers. Several investigators have reported improvement in lean body mass

and decrease in fat [19,27,28,37]. For example in the study by Snyder et al, they randomized 108 men over 65 year of age to wear either a testosterone patch or a placebo patch in a double blind study for 36 months. They measured body composition by dual energy X-ray absorptiometry and muscle strength by dynamometer before and during treatment. Ninety-six men completed the entire 36-month protocol. Fat mass decreased (-3.0 ± 0.5 kg) in the testosterone-treated men during the 36 months of treatment, which was significantly different ($P = 0.001$) from the decrease (-0.7 ± 0.5 kg) in the placebo-treated men. Lean mass increased (1.9 ± 0.3 kg) in the testosterone-treated men, which was significantly different ($P < 0.001$) from that (0.2 ± 0.2 kg) in the placebo-treated men. The decrease in fat mass in the testosterone-treated men was principally in the arms (-0.7 ± 0.1 kg; $P < 0.001$ compared with the placebo group) and legs (-1.1 ± 0.2 kg; $P < 0.001$), and the increase in lean mass was principally in the trunk (1.9 ± 0.3 kg; $P < 0.001$). The change in strength of knee extension and flexion at 60 and 180° angular velocity during treatment, however, was not significantly different between the two groups. They concluded that increasing the serum testosterone concentrations of normal men over 65 year of age to the midnormal range for young men decreased fat mass, principally in the arms and legs, and increased lean mass, principally in the trunk, but did not increase the strength of knee extension and flexion, as measured by dynamometer.

Overall, a number of factors appear to affect the success of reversing obesity. These are highlighted below:

- Duration of treatment. The optimal time needed to reverse obesity is variable but occurs over months rather than weeks.
- Pre-treatment composition. Success has been most often reported in people with moderate obesity. Success in severe obesity is not proven.

Age is associated with responsiveness as well. In general, ''younger'' older males respond better than ''older'' old males.

In summary, BT does not change substantially with body mass index (BMI), but in severe obesity BT is decreased.

9. Effect of testosterone on muscle in aging males

Intuitively, a decrease in muscle mass leads to loss of muscle strength [38–40]. Muscle fiber loss and selective atrophy of Type II fibers results in a substantial decrease in muscle strength in men above 70 years. It can also be inferred that muscle loss would lead to functionality loss especially with elderly men.

Most blinded and well-controlled studies of testosterone replacement in older men have demonstrated an increase in body mass using CT and Dexa scans [19,26,27,41,42]. Changes in measurable muscle strength have been more variable. There may be several explanations for the lack of consistency in clinical trials reporting measurable gains in muscle strength. Some studies have used relatively insensitive methods (e.g. stair walking) and significant variation in methods used to quantify strength. Different dosages and duration of treatments also created additional variability.

Bakshi et al. demonstrated that lean mass improved with a combination of testosterone and rehabilitation versus placebo and rehabilitation, and that the instrument of functional measure improved from 70.7 to 93.6 as compared with the placebo group which went from 73.7 to 78.0. This study also demonstrated that grip strengths improved with testosterone from 55.3 to 68.7 lb ($P = 0.03$) [43].

Interestingly, testosterone replacement has also been shown to benefit the wasting syndrome in AIDS patients [44]. This work has great implications perhaps in treating the frailty syndrome associated with the very elderly. In AIDS, endocrine hypofunction is secondary to the well-known effects of severe illness. HIV-infected patients are in a catabolic state and adaptive mechanisms, which normally decrease energy expenditure and preserve lean body mass are either overridden or not operative. Strategies to reverse the catabolic state have been successfully demonstrated with anabolic hormones like testosterone.

In summary, testosterone has been shown to improve biological end points such as muscle strength in studies. Falls in geriatric patients are usually the result of muscle weakness. As such, it would also be interesting to see if testosterone replacement may indeed decrease falls in older males as falls are considered major morbidity events in the elderly.

10. Effect of testosterone on bone in aging males

There is clear evidence for bone loss in both females and males with aging. Fracture rates in men lag behind women, but become comparable when men reach their eighties. Epidemiological studies have found that BMI is positively correlated to BT and estradiol [45,46]. Although bioavailable estradiol appears to be a better overall predictor of bone density, it cannot be disputed that there are androgen receptors found in osteoblasts and mesenchymal cells [47]. The effect of testosterone on the bone is both a direct effect as well as through aromatization to estradiol. Most short-term studies have found that androgens reduce bone resorption rather than affecting the formation of new bone. In the study by Kenny et al., 76 men (mean age 76 ± 4 years, range 65–87) with BT levels below 4.44 nmol/l (lower limit for adult normal range) were randomized to receive transdermal testosterone (two 2.5-mg patches/day) or placebo patches for 1 year. All men received 500 mg supplemental calcium and 400 IU vitamin D. Outcome measures included sex hormones (testosterone, BT, SHBG, estradiol, and estrone), bone mineral density (BMD; femoral neck, Ward's triangle, trochanter, lumbar spine, and total body), bone turnover markers, lower extremity muscle strength, percent body fat, lean body mass, hemoglobin, hematocrit, prostate symptoms, and PSA levels, 44 men completed the trial. In these men, BT levels increased from 3.2 ± 1.2 (S.D.) to 5.6 ± 3.5 nmol/l ($P < 0.002$) at 12 months in the testosterone group, whereas no change occurred in the control group. Although there was no change in estradiol levels in either group, estrone levels increased in the testosterone group (103 ± 26 to 117 ± 33 pmol/l; $P < 0.017$). The testosterone group had a 0.3% gain in femoral neck BMD, whereas the control group lost 1.6% over 12 months ($P = 0.015$). No significant changes were seen in markers of bone turnover in either group. Improvements in muscle strength were seen in both groups at 12 months compared with baseline scores. Strength increased 38% ($P = 0.017$) in the testosterone group and 27% in the control group ($P = 0.06$), with no statistical difference between the groups. In the testosterone group, body fat decreased from 26.3 ± 5.8 to $24.6 \pm 6.5\%$ ($P = 0.001$), and lean body mass increased from 56.2 ± 5.3 to 57.2 ± 5.1 kg ($P = 0.001$), whereas body mass did not change. Men receiving testosterone had an increase in PSA from 2.0 ± 1.4 to 2.6 ± 1.8 μg/l ($P = 0.04$), whereas men receiving placebo had an increase in PSA from 1.9 ± 1.0 to 2.2 ± 1.5 μg/l ($P = 0.09$). No significant differences between groups were seen in hemoglobin, hematocrit, symptoms or signs of benign prostate hyperplasia, or PSA levels. The group concluded that transdermal testosterone (5 mg/day) prevented bone loss at the femoral neck, decreased body fat, and increased lean body mass in a group of healthy men over age 65 with low BT levels. In addition, both testosterone and placebo groups demonstrated gains in lower extremity muscle strength, possibly due to the beneficial effects of vitamin D. It is, therefore, likely that testosterone can prevent fractures by increasing both bone and muscle strength, which in turn can prevent falls. The most common cause of preventable falls in the elderly is muscle wasting [48].

While the effects of testosterone on bone remains somewhat controversial as not all investigators have found an improvement with testosterone, an interesting concept was developed by Christmas et al. In a study by that group, testosterone combined with growth hormone was given to the study population. In andropausal men, T administration to achieve physiologic levels did not result in significant effects on bone metabolism or BMD, whereas GH+T increased one marker of bone formation and decreased one marker of bone resorption. Given the known biphasic actions of GH on bone and the apparent favorable biochemical effects of GH+T in men,

the longer-term effects of GH + T on BMD in aged men remain to be clarified [49].

In summary, there is evidence that testosterone may have biological benefits on the bone in studies, but there are no long-term studies yet on whether testosterone replacement may actually decrease fracture rates in men.

11. Effect of testosterone on the prostate in aging males

There is general agreement that testosterone administration does not cause prostate cancer [50]. This statement is based on clinical trials demonstrating insignificant rises in PSA over 3–5 year periods [26,27]. It also appears that prostate cancer tends to develop in older men when endogenous testosterone is lowest.

There are several studies on adverse effects on the prostate, but in a preliminary study by Kenny et al., it was observed that after 9 weeks of treatment, there were no ill effects on prostate size, symptoms or PSA [30]. The objective of that study was to determine whether short-term testosterone administration to older men with low BT would have any immediate adverse effects, especially on the symptoms of benign prostate hyperplasia, preliminary to embarking on a long-term study of testosterone treatment. A non-randomized trial of 9 weeks intervention with either intramuscular testosterone, transdermal testosterone or neither followed by a 9-week observation period. Twenty-seven men over age 70 years with no medical conditions known to affect bone turnover and total testosterone levels below 350 ng/dl (normal range 350–1230 ng/dl) or BT levels below 128 ng/dl (normal range 128–430 ng/dl) received either testosterone via transdermal patch (TP; two 2.5 mg patches/day), intramuscular testosterone enanthate (IM; 200 mg every 3 weeks) or no testosterone for 9 weeks of treatment followed by a 9 week observation period. Nine men were enrolled in each group. The mean age of the men was 74 ± 3 years (range 70–83 years). While all men receiving testosterone treatment increased levels above their own baseline, only six of nine men receiving transdermal testosterone achieved BT levels in the normal range for young men. Neither treatment group demonstrated changes in estradiol levels. No side effects were reported using the intramuscular testosterone while 5/9 men using transdermal testosterone developed a rash. There were no ill effects on prostate size, symptoms or PSA level. PSA levels of 1.5 ± 0.7 and 1.6 ± 0.7 ng/dl in the TP and IM groups, respectively, were 2.0 ± 1.0 and 1.8 ± 0.9 ng/dl following treatment. The results of this study were similar to others in the sense that most are over a short term and found no correlation to prostate cancer [26,27,50]. Long-term data beyond 5 years is not yet available.

Rather unfortunately, PSA may not be sensitive enough to pick up microscopic prostate cancer. Prostate cancer increases as a function of age. At age 70, at least 50% of males may have microscopic cancer, but only 5–10% will actually develop clinical cancer, and the role of prostate biopsy remains controversial in some parts of the world. It is also important to realize that some men with normal PSA and rectal examinations may have biopsy detectable prostate cancer [51]. It is important to discuss these points with patients before contemplating testosterone replacement therapy. There are doubtless benefits to testosterone replacement therapy to older males but informed consent is mandatory. The following is recommended prostate screening for men on testosterone replacement therapy [47]:

- PSA, digital examination on initial visit and every 3 months.
- If PSA is above 4.0 ng/dl, to biopsy the prostate before testosterone replacement.
- Contraindicated if there is a history of prostate cancer.
- If PSA rise more than 1.5 ng/dl over 3–6 months, to repeat, followed by biopsy of the prostate.

12. Summarizing effects of testosterone on erythrocytosis, sleep apnea, breast, fertility and health related quality of life

Although prostate cancer is the most feared complication of testosterone replacement therapy, the most common side effect is a clinically insig-

nificant increase in hematocrit [26,37]. For this reason, testosterone replacement therapy is contraindicated in individuals with hematocrit of 52% and above. A rise of 3–5% may be expected with testosterone replacement. The effect is less with a transdermal system [52].

It has been reported that testosterone administration can cause sleep apnea in younger males [8,53]. This is likely due to a direct effect on the laryngeal muscles. It is very infrequent in older males. Sleep apnea is a relative contraindication for testosterone replacement therapy.

Testosterone can rarely cause breast enlargement. Gynecomastia is due to estradiol, which is converted from testosterone. This can be minimized with aromatase inhibitors such as flavones and zinc. There have been rare reports of breast cancer with testosterone. This is more frequent in patients with the Klinefelter's syndrome.

Testosterone administration can suppress the hypothalamic–pituitary axis, and as such inhibit LH and FSH. The possibility of sterility must be discussed with older patients prior to instituting treatment, as they may wish to retain the option of fatherhood. This concept was investigated by Anderson and colleagues and they reported that the administration of testosterone to eugonadal men causes suppression of gonadotrophin secretion and thus of spermatogenesis. However, complete suppression of spermatogenesis to azoospermia is induced in only 50–70%. The basis of the polymorphism is unclear but it was felt that 5 alpha reductase is important in the mechanism [54]. As such, testosterone supplementation of spermatogenesis in physiological doses is questionable. Even so, supraphyioslogical doses of testosterone in the absence of progestatives have only moderate and inconsistent effects on spermatogenesis.

Reddy et al. assessed the effect of short-term testosterone supplementation on health-related quality of life (HRQOL) in elderly males in a small study. As part of a double-blind, placebo-controlled study, healthy males $>$ or $=$ 65-year-old were randomized to receive a total of four doses of 200 mg testosterone enanthanate ($n = 14$) or placebo ($n = 8$) intramuscularly every 2 weeks. HRQOL was assessed using the Short Form 36-item (SF-36) and Psychological General Well-Being (PGWB) scales, at baseline, week 8 and during therapy withdrawal, 6 weeks after the last dose. The pilot study suggests that intramuscular testosterone, administered at a dose of 200 mg every 2 weeks, does not affect the HRQOL of elderly males [55].

13. Current recommendations on androgen replacement

There is increasing evidence of benefits in testosterone replacement for aging males [56]. Unfortunately, in contrast to studies on estrogen replacement in women, the trials in aging males are much smaller. It is estimated that approximately 5000–10 000 men need be randomized and treated for 5–7 years to assess for long-term safety and a general recommendation for all men [57]. Currently, the following guidelines seem prudent:

- it should be individualized and with informed consent;
- treatment should be reserved for the symptomatic individuals with hypogonadism;
- there should be a detailed discussion of the benefits and risks;
- patients should be followed up with PSA, hematocrit measurements;
- blood pressure, general health issues should be addressed;
- lifestyle modifications including exercise and weight loss should be stressed.

14. Conclusion: adjuncts and future possibilities

Prevention may be at the very core of solving health issues in the modern world. Obesity leads to many problems including heart problems and arthritis. Hypogonadism and quality of life may be affected by obesity. As such, weight loss may be a preventive strategy. It has been demonstrated that weight loss can decrease visceral as well as abdominal fat. Less body fat may mean better cardiovascular health and also perhaps less aromatization of testosterone to estradiol [58].

Paradoxically, investigators have found that an extremely high protein diet without fat may actually reduce blood levels of testosterone [59]. It is postulated that fat is needed along with protein to synthesize natural testosterone in the body through conversion of the cholesterol ring structure. Good fats such as those from monosaturated fats and polyunsaturated fats may be useful. Such fats are found in nuts and fish.

The response of the body to intense anaerobic exercise such as weight lifting has been studied [60]. Researchers have found that weight lifting, rather than aerobic exercise, may increase blood testosterone. Testosterone levels peak at 20 min after exercise and returns to baseline after 10 min. Several mechanisms of elevated testosterone have been postulated including hemoconcentration, decreased metabolic clearance and increased synthesis. Researchers have found that the rise in testosterone is LH independent, which suggests that the elevation in testosterone could be local at the Leydig cell level. Testosterone response to exercise has also been observed in older men [61].

We are still searching for the ideal androgen. The ideal androgen for replacement should be organ and target specific. It should target bones, muscle and the brain specifically. It should not have untoward effects on the prostate or heart. Selective estrogen receptor modulators have been used to treat female osteoporosis. Several biotechnology companies have been working on selective androgen receptor modulators (SARMs). Trials on animal models have proven promising. One androgen, 7 alpha methyl 19 nortestosterone (MENT) is currently being investigated for male contraception [62]. This synthetic androgen is not affected by alpha reductase and may have some benefits for aging males. Dihydrotestosterone (DHT) itself has been studied as an alternative to testosterone as it does not undergo aromatization. That study found no adverse prostate effects [63].

In conclusion, it is anticipated that the need for androgen replacement will continue to grow as new and safer products are available for patients and as more clinical trials document efficacy. At the present time, the response of testosterone seems more marked in cases of severe hypogonadism [64]. Although many studies support the biological effects of testosterone in many organ systems, evidence based long-term clinical effects are not yet available.

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