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AGE-RELATED CHANGES IN THE MALE REPRODUCTIVE AXIS

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OUTLINE

Aging of male mammals is a very recent evolutionary event observed mostly in humans and animals in captivity. Most animal species in the wild do not live beyond their reproductive years; during periods of food deprivation, many small animals may not even live beyond puberty. Even among humans, only the men and women of the past two generations have enjoyed a life expectancy of greater than fifty years. With increasing life expectancies on all continents except Africa, the reproductive problems of aging men and women have begun to receive the attention that they deserve. Aging of humans is associated with functional alterations at all levels of the reproductive axis that affect both the steroidogenic and gametogenic compartments. Even after forty years of investigation, the controversy surrounding the use of hormone replacement in postmenopausal women has grown only louder (1-4); in contrast, the issue of testosterone replacement in older men has been shrouded in acerbic debate from its very inception, even though not a single, adequately powered, long term, randomized trial of testosterone replacement has yet been conducted. There is agreement that in young men with classical hypogonadism due to known diseases of the testis, pituitary and the hypothalamus, testosterone replacement is relatively safe and has many beneficial effects in improving lean body mass, sexual function, energy, mood, and sense of well being and reducing fat mass (5-8). However, the data from otherwise healthy, young, men with classical hypogonadism should not be directly extrapolated to older men with age-related decline in serum testosterone concentrations (9-10). As discussed in this chapter, there is agreement that serum testosterone levels decline as a function of age; however, the effects of testosterone supplementation on health-related outcomes in older men have not been studied. Long term data on the effects of testosterone supplementation on the risk of prostate disease and cardiovascular events are lacking. Thus, the risks and benefits of long term testosterone replacement in older men remain unknown.

I. CHANGES IN THE STEROIDOGENIC COMPARTMENT OF THE TESTIS

A. Age Related Changes in Circulating Concentrations of Reproductive Hormones

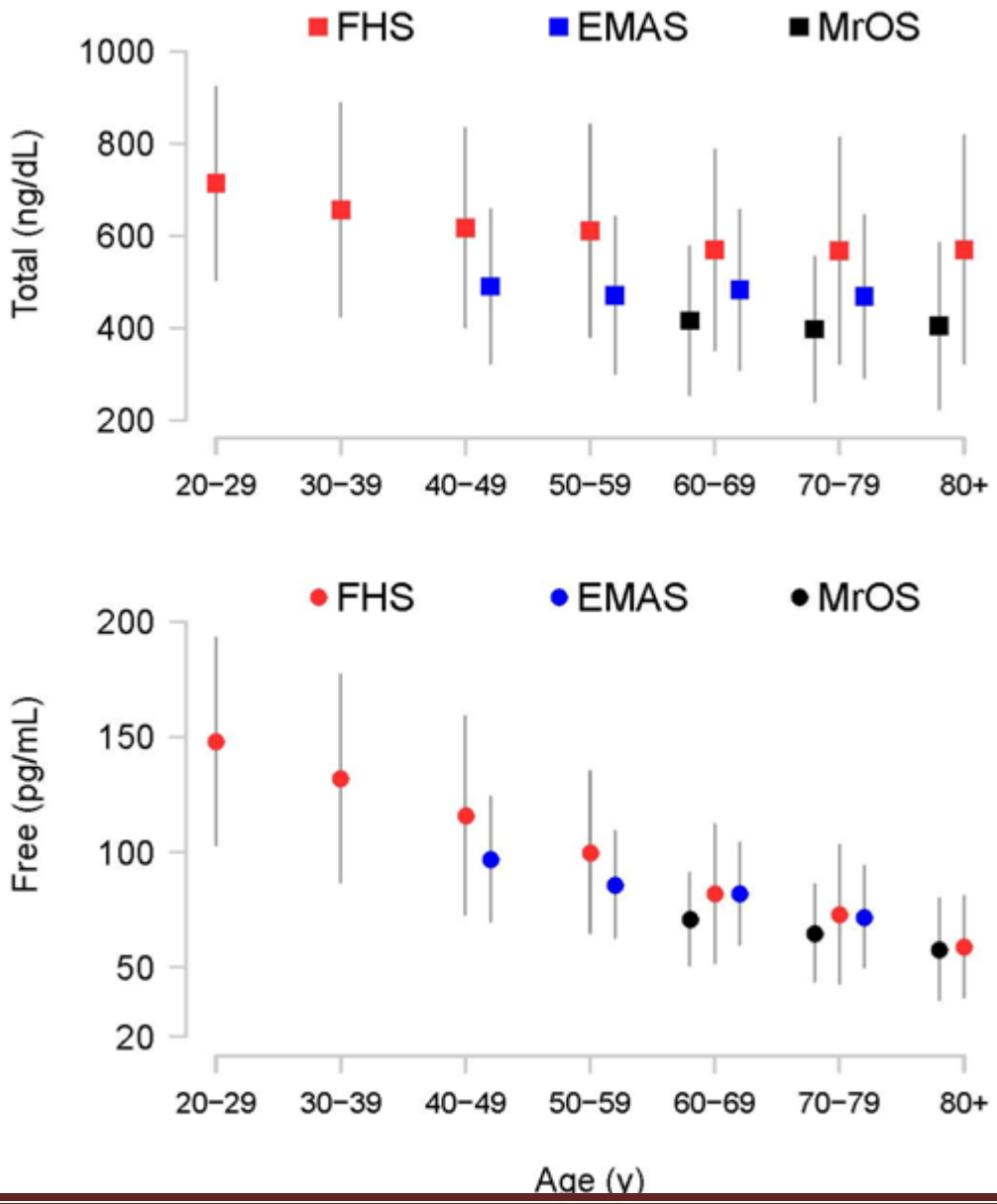
For many years, there was considerable controversy over whether serum total testosterone levels were lower in healthy older men; it was argued that older men had lower testosterone levels because of the confounding influence of chronic illness and medications. However, a number of cross-sectional studies are in agreement that even after accounting for the potential confounding factors such as time of sampling, concomitant illness and medications, and technical issues related to hormone assays, serum total testosterone levels are lower in older men in comparison to younger men (11-33). Several longitudinal studies (11, 13, 14, 16, 17) have confirmed a gradual but progressive decrease in serum testosterone concentrations from age 20 to 80. In contrast to the sharp reduction in ovarian estrogen production at menopause, the age-related decline in men does not start at a discrete coordinate in old age; rather, total testosterone concentrations, after reaching a peak in the second and third decade, decline inexorably throughout a man's life (**Figure 1**). Because of the absence of an identifiable inflection point at which testosterone levels begin to decline abruptly or more rapidly, many investigators have questioned the validity of the concept of "andropause", which misleadingly implies an abrupt cessation of androgen production in men (20, 34).The term 'late-onset hypogonadism' has been proposed to reflect the view that in some middle-aged and older men (> 65 years), the age-related decline in testosterone concentration is associated with a cluster of symptoms and signs in a syndromic constellation which resembles that observed in men with classical hypogonadism (28, 35).

Figure 1. The distribution of total and free testosterone levels by decades of age in male participants of the

Framingham Heart Study, the European Male Aging Study (EMAS) and the Study of Osteoporotic Fractures in Men

(MrOS).Means and standard deviations are shown. To convert total testosterone from ng/dL to nmol/L, multiply

concentrations in ng/dL with 0.0347. To convert free testosterone from pg/mL to pmol/L, multiply concentrations in


FHS
EMAS
MrOS
Total (ng/dL)
1000
800
600
400
200
20–29
30–39
40–49
50–59
60–69
70–79
80+
FHS
EMAS
MrOS
Free (pg/mL)
200
150
100
50
20
20–29
30–39
40–49
50–59
60–69
70–79
80+
Age (y)

Most studies of age-related change in testosterone levels included healthy, older men. Adiposity, chronic illness, weight gain, medications and genetic factorsaffect testosterone levels and the trajectory of the age-related decline in testosterone levels in men (12-13, 36-38). The rate of age-related decline is greater in older men with chronic illness and adiposity than in healthy, non-obese older men (12, 36-37).

Sex-hormone binding globulin concentrations are higher in older men than younger men (13, 24, 29). Thus, the age-related decline in free testosterone levels is of a greater magnitude than that in total testosterone levels. Similarly, there is a greater percent decline in bioavailable testosterone concentrations (the fraction of circulating testosterone which is not bound to SHBG) than in total testosterone concentrations.

B. Age-Related Decline in Testosterone Levels in Middle-Aged and Older Men

An Expert Panel of the Endocrine Society defined androgen deficiency as a syndrome resulting from reduced production of testosterone and characterized by a set of signs and symptoms in association with unequivocally low testosterone levels (5). Many epidemiologic studies have defined androgen deficiency solely in terms of serum testosterone concentrations below the lower limit of the normal range for healthy, young men leading to exaggerated estimates of the prevalence of androgen deficiency in older men.Additionally, serum testosterone levels in most studies were measured using direct immunoassays, whose accuracy in the low range has been questioned. Not surprisingly, the estimates of the prevalence of androgen deficiency in older men have varied greatly among different studies. In the Baltimore Longitudinal Study of Aging (BLSA) (11), 30% of men over the age of 60 and 50% of men over the age of 70 had total testosterone concentration below the lower limit of normal range for healthy young men (325 ng/dL, 11.3 nmol/L). The prevalence was even higher when these investigators used a free testosterone index to define androgen deficiency (11). Several other studies have also reported a similarly high prevalence of low total and free testosterone levels in older men. In contrast, more recent studies, using liquid chromatography tandem mass found the prevalence of androgen deficiency to be significantly lower than that observed in the MMAS and BLSA (20-21, 28-31). Although 10–15% of men aged ≥65 years have low total testosterone levels (28-31), the prevalence of late-onset hypogonadism defined by symptoms and a total testosterone level <8 nmol/l in the EMAS was 3.2% for men aged 60–69 years and 5.1% for those aged 70–79 years (28). A cross-sectional survey performed in Finland (20), which did not use a random probability sample, found that only 27% of those who had high andropausal symptom score had androgen deficiency, defined as serum testosterone less than 287 ng/dL (10 nmol/L). In this study, most of the older men with low testosterone levels had a systemic disease; less than 3% of healthy, older men had low testosterone levels. The Healthy Man Study in Australia also found no significant age-related decline in testosterone

or dihydrotestosterone in men who reported being in good health (39). These authors have argued that ill health, rather than aging itself, is the major contributor to androgen deficiency in older men.

C. Mechanisms of Age-Related Decline in Testosterone Levels

Circulating testosterone concentrations are a function of testosterone production and clearance rates; the age-related decline in serum testosterone concentrations is primarily a consequence of decreased production rates in older men (9, 10, 24-26, 29). Plasma clearance rates of testosterone are,in fact, lower in older men than in younger men (37-38). The decline in testosterone production in older men is the result of abnormalities at all levels of the hypothalamic-pituitary-testicular axis (23-25, 39-50)

C.1. Gonadotropin Secretion and Regulation in Older Men. There is considerable heterogeneity in circulating LH and FSH concentrations in individual older men; both hypogonadotropic and hypergonadotropic hypogonadism have been reported (35, 37). As a group, serum LH and FSH concentrations are higher in older men than in young men (13-14). Serum LH and FSH levels show an age-related increase in longitudinal studies. However, serum LH concentrations do not increase in proportion to the age-related decline in circulating testosterone levels, probably due to the impairment of GnRH secretion and alterations in gonadal steroid feedback and feedforward relationships (39-50); both of these mechanisms are operative in older men.

The data on LH response to GnRH are somewhat contradictory. Urban et al (44) used an interstitial cell bioassay to measure serum concentrations of bioactive LH and found that although basal bioactive LH concentrations were similar in this sample of young and older men, older men demonstrated diminished LH response to GnRH administration. However, in a subsequent study, Zwart et al (45) found greater gonadotropin responsiveness to GnRH in older men than younger men; the maximal and incremental LH and FSH secretory masses in response to graded doses of GnRH were significantly higher in healthy, older men than in younger men. The estimated half-lives of LH, FSH, or alpha-subunit were not significantly different between young and older men.

The Brown Norway rat has been widely used as a model of reproductive aging. In this experimental model, theprepro-GnRH mRNA content and the number of neurons expressing prepro-GnRH mRNA are lower in older male rats in comparison to young rats (46-47). The GnRH content of several hypothalamic areas is also lower in intact older rats than younger rats (46). Older Brown Norway rats exhibit significant reductions in glutamate and Ɣ-aminobutyric acid (GABA) levels in the hypothalamus compared to young rats (47). These observations suggest that the decreased hypothalamic excitatory amino acid expression

and the reduced responsiveness of GnRH neurons to NMDA may contribute to the altered LH pulsatile secretion observed in old rats (47).

Infusions of testosterone and DHT are associated with greater reductions in mean serum LH and FSH levels and the frequency of LH pulses in older men in comparison to young men (48). Winters et al (43) reported that the degree of LH inhibition during testosterone replacement of older, hypogonadal men was significantly greater than in young, hypogonadal men suggesting that older men are more sensitive to the feedback inhibitory effects of testosterone on LH. Deslypere et al (48) also found decreased LH pulse frequency and a greater degree of LH inhibitory response to estradiol administration in older men than young controls. Age-related increase in FSH levels is not associated with a progressive or proportionate decrease in inhibin B levels (49). Thus the mechanistic basis of FSH increase in not fully understood, although the lack of change in inhibin B levels suggests that Sertoli cell function is relatively preserved in older men.

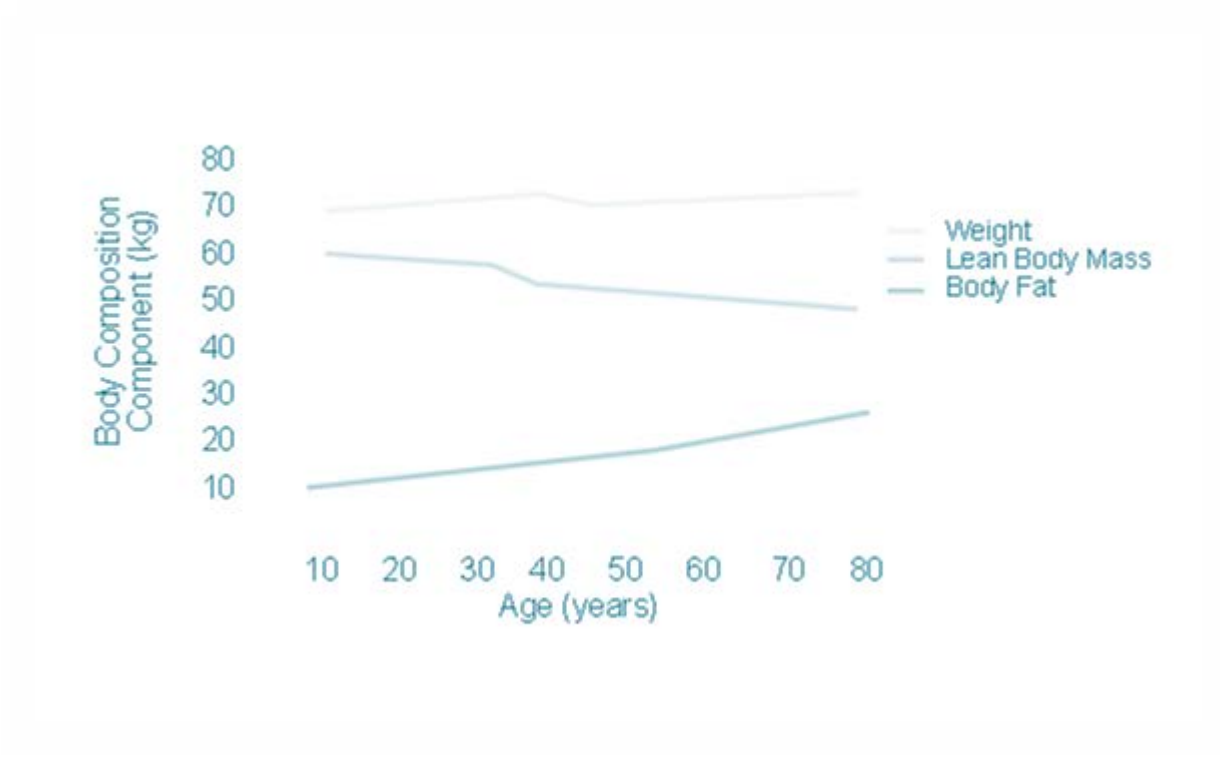
Pulsatile GnRH secretion is attenuated in older men. In addition, there are disturbances of the feedback and feed-forward relationships between testosterone and LH secretion (42, 50-51). Thus, the sensitivity of pituitary LH secretion to androgen-mediated ***feedback*** inhibition is increased; in addition, the ability of LH to stimulate synchronously testicular testosterone secretion (***feedforward***) is attenuated (42, 50-51). This insight has emerged largely from the research of Veldhuis who used novel algorithms to quantitate the orderliness of pulsatile hormone secretion, and the synchrony between secretion of related hormones (e.g., LH and testosterone, and LH and FSH) (42, 50-51). This research has revealed that the orderliness of LH pulses and the synchrony between LH and testosterone pulses are decreased in older men (50-51); in addition, there is greater variability in LH pulse frequency, amplitude, and secretory mass in older men, in comparison to younger men (50-51).

C.2. Testicular Testosterone Production in Older Men. Testosterone secretion in healthy, young men is characterized by a diurnal rhythm with higher concentrations in the morning and lower levels in later afternoon. Many studies have revealed that the diurnal rhythm of testosterone secretion is dampened in older men (22, 32). Testosterone response to LH and human chorionic gonadotropin is decreased in older men in comparison to younger men (23-25).

D. Physiological and Clinical Correlates of Age-Related Decline in Circulating Testosterone in Epidemiological Studies

Many of the physiological changes that occur with advancing age, such as loss of bone and muscle mass, increased fat mass, impairment of physical, sexual and cognitive functions, loss of body hair, and decreased hemoglobin levels, are similar to those associated with androgen deficiency in young men. Aging is associated with loss of skeletal muscle mass (**Figure 2**),

muscle strength and power, and progressive impairment of physical function (52-76). Epidemiological studies of older men have reported associations between low testosterone levels and health outcomes, although these associations are weak. For instance, in a number of epidemiologic studies, such as the St. Louis Inner City Study of Aging Men(55), the Olmsted County Epidemiological Study (54), and the New Mexico Elderly Health Study (57-58), low bioavailable testosterone levels were associated with low appendicular skeletal muscle mass. Low bioavailable testosterone levels also have been associated with decreased strength of upper as well as lower extremity muscles (55-56) and decreased performance in self-reported as well as performance-based measures of physical function (77-81). Low free testosterone levels have also been associated with the development of mobility limitation and the frailty syndrome (82-85).



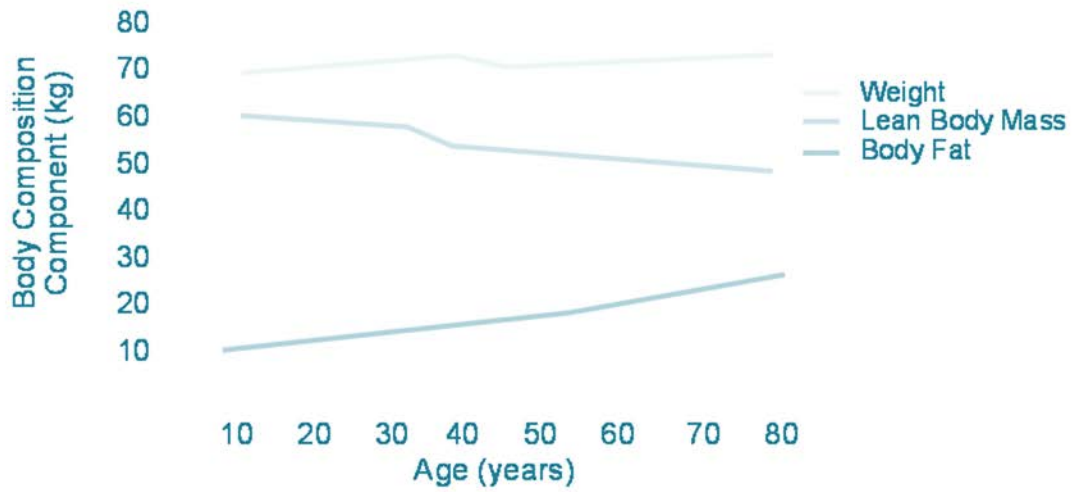


Figure 2. A schematic diagram of the age-related changes in lean body mass, body weight, and body fat. Adapted with permission from: Forbes et al, Metabolism 1970;19:653

The association of testosterone levels with sexual dysfunction has been inconsistent across studies because of the heterogeneity of instruments used to define sexual dysfunction, varying quality of instruments used to assess sexual function, problems of testosterone assay quality, and failure to distinguish among various categories of sexual dysfunction (86-91). Androgen deficiency and erectile dysfunction are two independently distributed clinical disorders; in general, serum total and bioavailable testosterone levels are not significantly different between men who report erectile dysfunction and those who do not (90-91). In the MMAS, decreased libido, as assessed by a single question, was associated only with very low testosterone levels (86). In the EMAS, total and free testosterone levels were associated with overall sexualfunction in middle-aged and older men (28). This relationship was

observed more robustly at testosterone concentrations <8 nmol/L, but not at higher testosterone concentrations (92). Men deemed to have low total and free testosterone levels in EMAS, using reference ranges generated in healthy young men, were more likely to report decreased morning erections, erectile dysfunction, and decreased frequency of sexual thoughts than those with normal testosterone levels (29).In another study of men over the age of 50 who had benign prostatic hyperplasia, sexual dysfunction, assessed by the Sexual Function Inventory, was reported only in men with serum total testosterone levels less than 225 ng/dL (88).

Aging of humans is attended by a decline in several aspects of cognitive function; of these multiple domains of cognition that decline with aging, declines in verbal memory, visual memory, spatial ability, and executive function are associated with the age-related decline in testosterone(87-101).

The relationship of testosterone levels with depression has been inconsistent across epidemiologic studies(102-106). Low testosterone levels in older men appear to be associated more with subsyndromal depression and dysthymia than with major depression (105-106). In one study, testosterone levels were lower in older men with dysthymic disorder than in those without any depressive symptoms (106). In another study (107), men with low testosterone levels had higher Carrol Rating Index scores, indicating more depressive symptoms than those who had normal testosterone levels.

Several epidemiologic studies of older men (108-112), including MrOS(108), Rancho Bernardo Study (109), Framingham Heart Study (110), and the Olmsted County Study (111) – have found bioavailable testosterone levels to be associated with bone mineral density, bone geometry, and bone quality (112); the associations are stronger with bioavailable testosterone and estradiol levels than with total testosterone levels. In the MrOS Study, the odds of osteoporosis in men with a total testosterone less than 200 ng/dL were 3.7 fold higher than in men with normal testosterone level (108); free testosterone was an independent predictor of prevalent osteoporotic bone fractures (115).

Several studies have evaluated the association of testosterone levels and mortality(116-119)(118). Some, but not all, studiesfound higher all-cause mortality and cardiovascular mortality in men with low testosterone levels than in those with normal testosterone levels. In a meta-analyses of epidemiologic studies of community-dwelling men, low testosterone levels were associated with an increased risk of all-cause and CVD death (**Figure 3)** (120-121).However, the strength of the inferences of these meta-analyses was limited by considerable heterogeneity in study populations; it is possible that effects may have been driven by differences in the age distribution and the health status of the study populations (120-124).

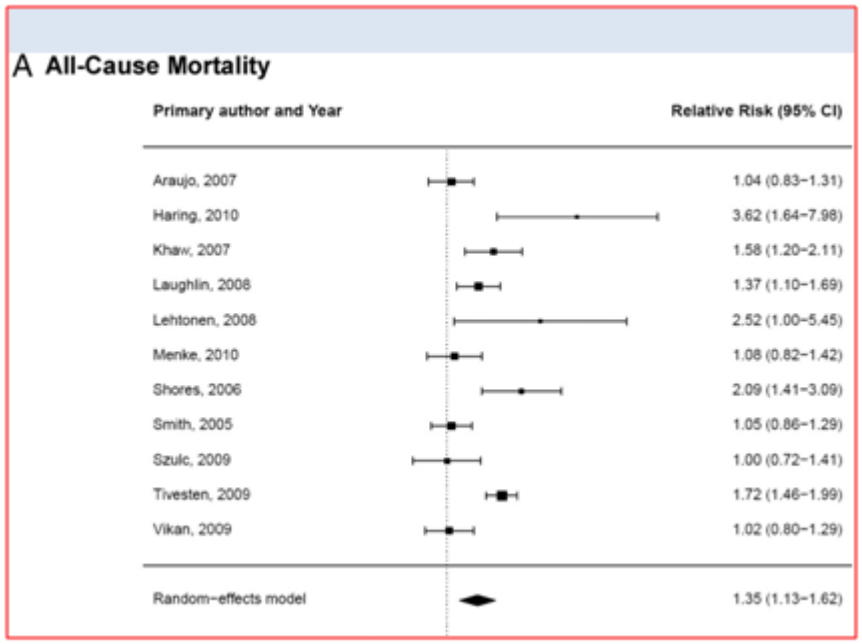


Figure 3. The relationship of low testosterone level with all-cause mortality in a meta-analysis of epidemiologic studies of community-based men.

Eleven studies which enrolled 16,184 subjects were included in this meta-analysis. There was considerable heterogeneity of the age distribution, health status, and other subject characteristics. Reproduced with permission from Araujo et al, JCEM (Araujo AB, Dixon JM, Suarez EA, Murad MH, Guey LT, Wittert GA. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis.J Clin Endocrinol Metab 2011;96:3007-19.)

Testosterone levels are not correlated with aging-related symptoms assessed by the Aging Male Symptom (AMS) score or with lower urinary tract symptoms assessed by the IPSS/AUA prostate symptom questionnaire (122). Some cross-sectional studies found no difference in serum testosterone levels between men who had coronary artery disease and those who did not have coronary artery disease; other studies have reportedtestosterone levels to be lower in men with coronary artery disease than in men without coronary artery disease(123-128).

E.

Epidemiologic studies can only demonstrate associations; a cause and effect relationship cannot be inferred from these studies, especially cross-sectional studies. Furthermore, even the associations between testosterone levels and health-related outcomes that have been found to be statistically significant are weak. The inferences are further confounded by the colinearity of aging-related co-morbid conditions, low testosterone levels, and age-related changes in body composition and inflammatory markers. Consequently, we do not know whether the age-related changes in the skeletal muscle mass and physical function, sexual and cognitive functions, and mood are the consequence or simply a coincidental association of low testosterone levels in older men; reverse causality also cannot be excluded

F. Potential Beneficial Effects of Testosterone Therapy in Older Men with Low Testosterone Levels

It has been hypothesized that increasing serum testosterone concentrations in older men with low testosterone levels into a range that is mid-normal for healthy, young men would improve physical function and mobility, some domains of sexual and cognitive functions, energy and sense of wellbeing, and reduce the risk of falls and fractures, and improve overall quality of life. A number of randomized trials have demonstrated improvements in surrogate markers, such as lean and fat mass; however, there has been a paucity of long-term, placebo-controlled, randomized trials that are adequately powered to detect clinically

meaningful changes in health outcomes such as fracture rates, physical function, disability, progression to dementia, and overall quality of life. Furthermore, none of the previously published studies had sufficient power to address the long term risks of prostate and cardiovascular disease.

The following section describes the effects of testosterone supplementation on multiple organs systems focusing on muscle mass and performance, physical function, bone mineral density and fracture risk, sexual function, mood, and cognitive function.

E.1. Effects of Testosterone Supplementation on Muscle Mass and Performance and Physical Function in Older Men with Low Testosterone Levels.

E.1.a. Age-Related Changes in Muscle Mass and Performance. Sarcopenia, the loss of muscle mass and function, is an important consequence of aging (53-57). The prevalence of sarcopenia, depending on the definition used, varies from 10-30% in men over the age of 70 (53-57). The principal component of the decrease in fat-free mass is the loss of muscle mass; there is little change in non-muscle lean mass (59-65). Between 20 and 80 years of age, the skeletal muscle massdecreases by 35-40% in men (63), in part due to decreased muscle protein synthesis (70). Although there is a loss of both type I and type II fibers, there is a disproportionate decrease in the number of type II muscle fibersthat are important for generation of power (71-72). In spite of the significant depletion of muscle mass, body weight does not decrease, and may even increase because of the corresponding accumulation of body fat (59-65) (Figure 3).

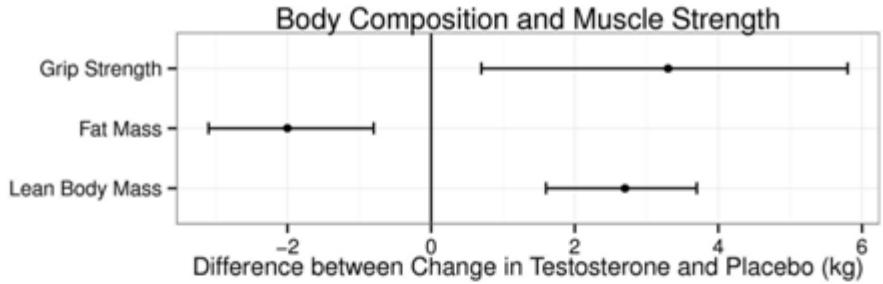
The loss of muscle mass that occurs with aging is associated with a reduction in muscle strength (73-76). There is a substantial decrease in muscle strength and power between 50 and 70 years of age, primarily due to muscle fiber loss and selective atrophy of type II fibers (71-76). The loss of muscle strength is even greater after the age of 70; 28% of men over the age of 74 could not lift objects weighing more than 4.5 kg (75). With increasing age, there is a progressive reduction in muscle power (129-130), the speed of strength generation, and fatigability, the ability to persist in a task.

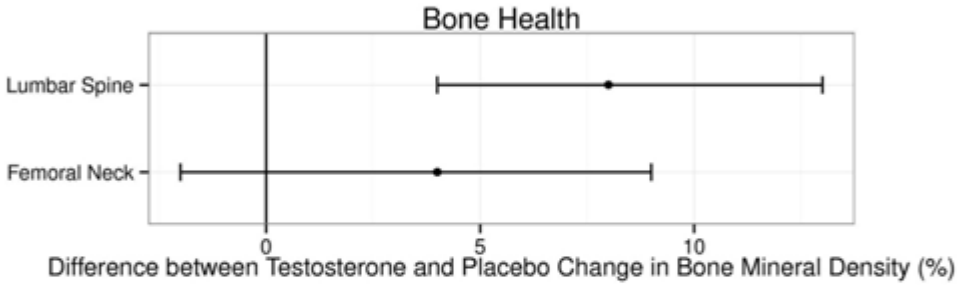
Loss of muscle mass and strength leads to impairment of physical function, as indicated by the impaired ability to arise from a chair, climb stairs, generate gait speed, and maintain balance (129-132). The impairment of physical function contributes to loss of independence, depression, and increased risk of falls and fractures in older men. Therefore, function promoting therapies that can reverse or prevent aging-associated sarcopenia are desirable.

E.1.b. Anabolic Effects of Testosterone in Humans: Testosterone Trials in Healthy, Hypogonadal Men, Men with Chronic Illness, and Older Men. The anabolic effects of testosterone on the muscle have been a source of intense controversy for over

sixty years. The athletes and recreational body builders abuse large doses of androgenic steroids with the belief that these compounds increase muscle mass and strength. Until recently, the academic community was skeptical about such claims because of the problems of study design. However, a number of studies in healthy hypogonadal men, men with chronic illness, and in healthy older men have established that testosterone administration increases skeletal muscle mass, maximal voluntary strength, and leg power (132-139).

In a systematic review of testosterone trials in healthy, hypogonadal men, testosterone therapy increased fat-free mass and body weight (**Figure 4**) (132-139). Some studies of testosterone replacement therapy have reported significant improvements in maximal voluntary strength (135, 138), and decreases in whole body fat mass (134, 137-139). The administration of supraphysiologic doses of testosterone in eugonadal men also increases fat-free mass, muscle size, and maximal voluntary strength (140-143). Resistance exercise training augments the anabolic response to androgens; thus men receiving testosterone and resistance exercise training together experience greater gains in fat-free mass and muscle strength than those receiving either intervention alone (143).


Body Composition and Muscle Strength
Grip Strength
Fat Mass
Lean Body Mass
−2
0
2
4
6
Difference between Change in Testosterone and Placebo (kg)


Bone Health
Lumbar Spine
Femoral Neck
0
5
10
Difference between Testosterone and Placebo Change in Bone Mineral Density (%)

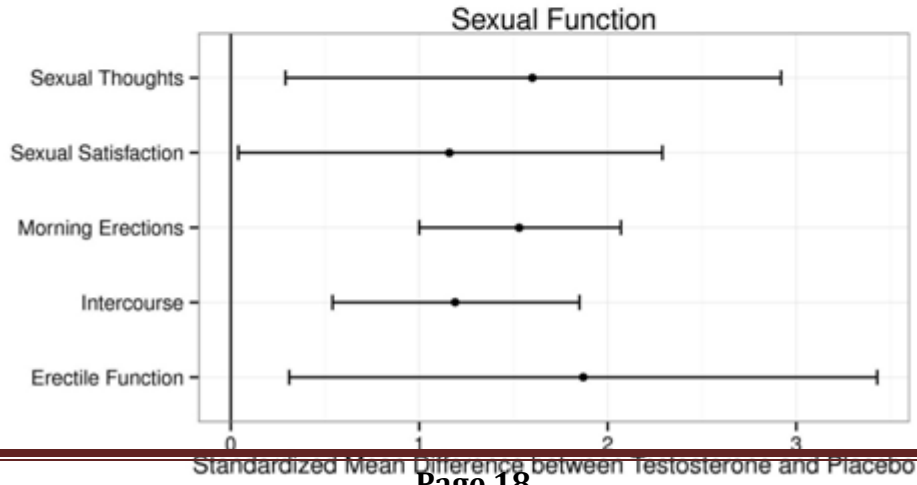

Sexual Function
Sexual Thoughts
Sexual Satisfaction
Morning Erections
Intercourse
Erectile Function
0
1
2
3
Standardized Mean Difference between Testosterone and Placebo

Figure 4. The effects of testosterone therapy on body composition, muscle strength, and bone mineral density in intervention trials. The point estimates and the associated 95% confidence intervals are shown. Upper panel shows the effects of testosterone therapy on lean body mass, grip strength, and fat mass in a meta-analysis of randomized trials (data derived from Bhasin et al. Nature CPEM 2006; figure reproduced with permission from Nature Reviews in Endocrinology). The middle panel shows the effects of testosterone therapy on lumbar and femoral bone mineral density in a meta-analysis of randomized trials.Data derived from a meta-analysis by Tracz et al, JCEM 2006; figure reproduced with permission from Nature Review in Endocrinology. The effects of testosterone therapy on measures of sexual function in men with baseline testosterone less than 10nmol/L (290ng/dL) are shown in the lower pa nel. The data were derived from a meta-analysis by Isidori et al, Clin Endocrinol 2005. Figure reproduced from Spitzer et al, Nature Review in Endocrinology 2013.

The anabolic effects of testosterone on fat-free mass, muscle size, and maximal voluntary strength are related to the administered testosterone dose and the circulating testosterone concentrations (140-142) (**Figure 5**). Testosterone effects on muscle performance are domain-specific: testosterone administration increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension (141). The gains in maximal voluntary strength during testosterone administration are proportional to the increase in muscle mass; unlike resistance exercise training, testosterone does not improve the contractile properties of the human skeletal muscle (141).

Testosterone replacement of young, hypogondal men increases muscle protein synthesis (136, 144-145); the effects of testosterone replacement on muscle protein degradation need further investigation.

Systematic reviews(133, 146-147) of randomized, placebo-controlled trials in HIV-infected men with weight loss (147-152)have revealed that testosterone therapy for 3 to 6 months was associated with greater gains in lean body mass than placebo administration (difference in lean body mass change between placebo and testosterone arms 1.22 kg, 95% CI 0.23-2.22 for the random effect model). In two (147, 151) out of three trials that measured muscle strength (147, 151-152), testosterone administration was associated with significantly greater improvements in maximal voluntary strength than placebo. Testosterone therapy had a moderate effect on depression indices (-0.6, 95% CI -1.0, -0.2) (153)and fatigue (154), but did not improve overall quality of life (153-154). Changes in CD4+ T lymphocyte counts, HIV copy number, PSA, plasma HDL cholesterol, and adverse event rates were not significantly different between the placebo and testosterone-treatment groups (147-154). Overall, short-term (3-6 months) testosterone use in HIV-infected men with low testosterone levels and weight loss can induce modest gains in body

weight and lean body mass with minimal changes in quality of life and mood. This inference is weakened by inconsistency of results across trials, heterogeneity in inclusion and exclusion criteria, disease status, testosterone formulations and doses, treatment duration, and methods of body composition analysis (133). There are no data on testosterone effects on physical function, risk of disability, or long term safety.

Testosterone administration increases fat-free mass and decreases fat mass in older men with low testosterone levels. Meta-analyses (133, 154) of randomized trials (156-160) that included middle-aged and older men with low or low normal testosterone levels, and that used testosterone or its esters in replacement doses for ≥90 days, have confirmed that testosterone administration is associated with a significantly greater increase in fat-free mass, hand grip strength, and a greater reduction in whole body fat mass than placebo (**Figure 5**). The average gains in fat-free mass generally were greater in trials that used injectable testosterone esters than in those which used transdermal testosterone gel. The change in body weight did not differ significantly between the testosterone and placebo groups. Testosterone administration improves stair climbing speed and power, and self-reported physical function, as assessed by the SF-36 questionnaire. Changes in other performance-based measures of physical function, such as gait speedhave been inconsistent across trials (157, 160-162).

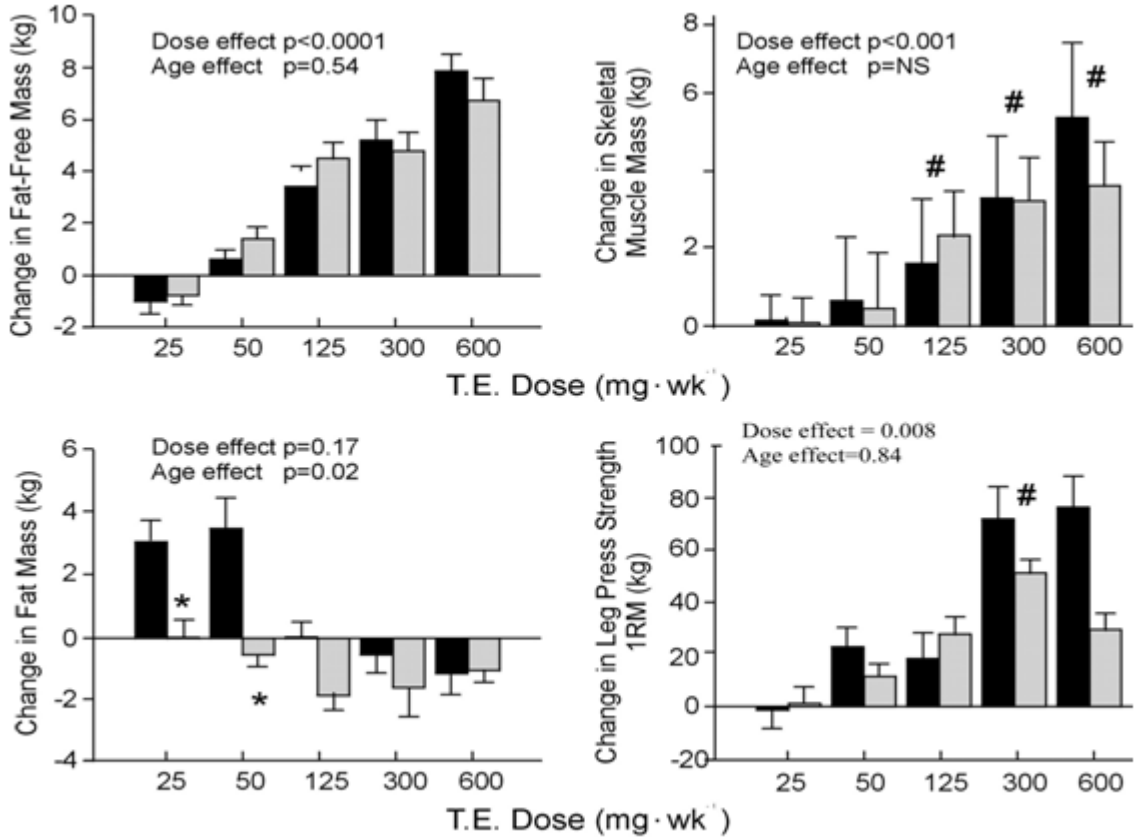


Figure 5. Testosterone Dose Response Relationship in Young and Older Men.In this study, healthy, young men (18-34 years of age) and healthy older men (60-75 years of age) were treated with a long acting GnRH agonist plus graded doses of testosterone enanthate for 20 weeks. Shown are mean (±SEM) changes from baseline in fat free mass (upper left), skeletal muscle mass (upper right), fat mass (lower left), and leg press strength (lower right) in young (black bars) and older (lightly shaded bars) men.Adapted with permission from Bhasin et al, Older men are as responsive as young

men to the anabolic effects of graded doses of testosterone on the skeletal muscle. J Clin Endocrinol Metab 2005;90:678-88.

One reason for the failure to demonstrate improvements in physical function is that the measures of physical function used in previous studies had low ceilings. The widely used measures such as 0.625 m stair climb, standing up from a chair, and 20-meter walk are tasks that require only a small fraction of an individual's maximal voluntary strength. In most healthy, older men, the baseline maximal voluntary strength is far higher than the threshold below which these measures would detect impairment. Another confounder of the effects of anabolic interventions on muscle function is the learning effect. For instance, subjects who are unfamiliar with weight lifting exercises often demonstrate improvements in measures of muscle performance because of increased familiarity with the exercise equipment and technique. Because of the considerable test-to-test variability in tests of physical function, it is possible that previous studies did not have adequate power to detect meaningful differences in measures of physical function between the placebo and testosterone-treated groups. It is also possible that neuromuscular adaptations needed to translate strength gains into functional improvements require a lot longer than the 3 to 6 month duration of most of the previous trials.

Although most randomized testosterone trials have been conducted in healthy older men, three recent trials were conducted in older men with functional limitations (163-166).In a trial of pre-frail or frail men (166), administration of 50 mg testosterone gel daily for 6 months induced greater improvements in lean mass, knee extension peak torque and sexual symptoms than did placebo gel (166). Performance-based measures of physical function did not differ significantly between groups, but they improved in the subgroup of frail elderly men (166). In Testosterone in Older Men (TOM) Trial, older men with mobility limitation were randomly assigned to either placebo or 10 g testosterone gel daily for 6 months (163-164). The testosterone dose was adjusted to achieve testosterone levels between 17.4 nmol/l and 34.7 nmol/L (500 to 1000 ng/dL).The improvements in leg-press strength, chest-press strength and power, and loaded stair-climbing speed and power were significantly greater in men assigned to testosterone arm than in those receiving placebo (**Figure 6**). A greater proportion of men in the testosterone arm improved more than the minimal clinically important difference for leg-press and chest-press strength and stair-climbing speed than that in the placebo arm. Because of a higher frequency of cardiovascular-related events in the testosterone arm compared with the placebo arm, the trial's data and safety monitoring board stopped further administration of study medication (163-164).

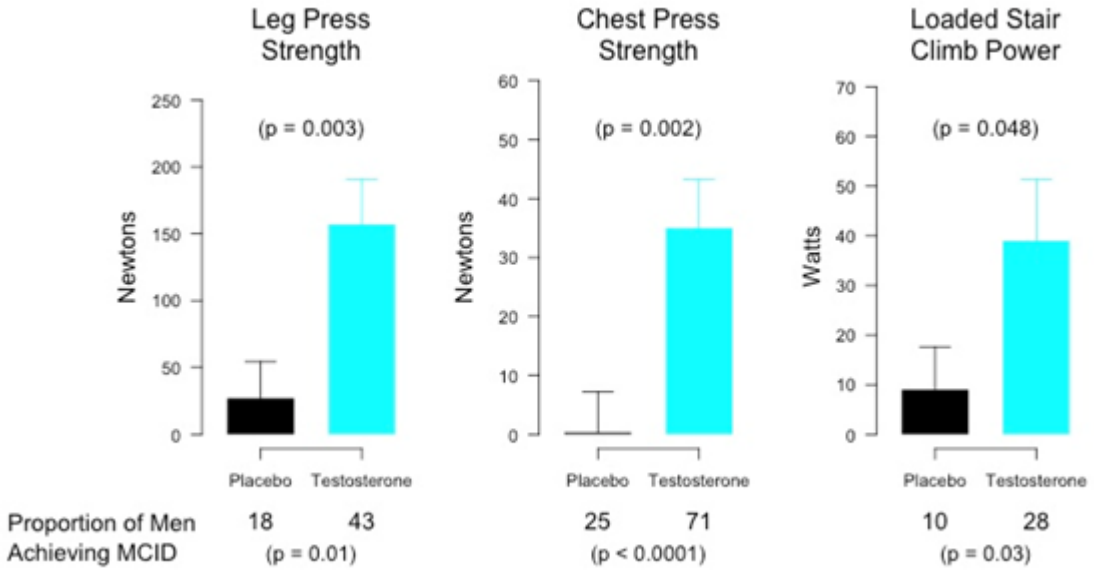


Figure 6. Effects of testosterone administration on maximal voluntary strength in the leg press and chest press exercises and on loaded stair climbing power in a randomized testosterone trial in older men with mobility limitation (The TOM Trial) The TOM Trial was a randomized, placebo-controlled trial in which men, 65 years of age or older with mobility limitation, were randomized to receive either placebo or testosterone gel daily for 6-months (Basaria et al, N Engl J Med 2010, and Travison et al, J Gerontol 2011). The dose of testosterone was adjusted to achieve target testosterone levels between 500 and 1000 ng/dL. The mean (SD) change from baseline to either the end of the intervention period or to the last measurement performed in subjects who dropped out before study completion. The minimal clinically important difference (MCID) for each outcome was determined using an anchor-based method within the trial. The proportion of men (percent) whose change from baseline either equaled or exceeded the MCID is shown below the figure along with the *P*-value for the comparison of placebo and testosterone groups. Figure reproduced with permission from Spitzer et al, Nature Reviews in Endocrinology 2013.

Therefore, while there is strong evidence that testosterone supplementation increasesskeletal muscle mass and strength, the clinically important improvements in health outcomes - physical function, falls, fractures and disability - in men with clinical conditions such as mobility limitation or fall propensity have been difficult to demonstrate. Innovative strategies to translate gains in muscle mass and strength induced by testosterone into functional improvements are needed (167). Adjunctive exercise training might be required to induce the neuromuscular and behavioural adaptations that are necessary to translate the gains in muscle mass and strength into functional improvements (167). The findings of the TOM trial and other epidemiologic studies have heightened the concern that frail elderly men with a high burden of chronic co-morbidities may be at an increased risk of adverse events (164), providing the impetus to develop, strategies to achieve increased selectivity and a more favourable risk to benefit ratio (164).

E.1.c. Mechanisms of Androgen Action on the Muscle Testosterone-induced increase in muscle mass is associated with hypertrophy of both type I and II muscle fibers(168). The absolute number and the relative proportion of type I and type II fibers do not change during testosterone administration. Testosterone-induced muscle fiber hypertrophy is associated with dose-dependent increases in myonuclear number and satellite cell number (169).

Testosterone administration has been shown to increase fractional muscle protein synthesis and improve the reutilization of amino acids (144-145). The effects of testosterone on muscle protein degradation have not been well studied. However, the muscle protein synthesis hypothesis does not explain the reciprocal decrease in fat mass or the increases in myonuclear and satellite cell number that occur during testosterone administration (169). Testosterone promotes the differentiation of mesenchymal multipotent muscle progenitor cells into the myogenic lineage and inhibits the differentiation of these precursor cells into the adipogenic lineage (170-171). Thus, testosterone promotes the formation of myosin heavy chain II positive myotubes in multipotent cells and up-regulates markers of myogenic differentiation, such as MyoD and myosin heavy chain (170-171). Testosterone and DHT inhibit adipogenic differentiation and downregulate markers of adipogenic differentiation, such as PPAR-ϒ and C/EBP∝.

Testosterone’s effects on myogenic differentiation are mediated largely through its binding to the classical androgen receptor, which induces a conformational change in the androgen receptor protein, promoting its association with its co-activator, beta-catenin, causing the complex to translocate into the nucleus (171-172). The androgen receptor – beta-catenin complex associates with TCF-4 and activates a number of Wnt target genes (171-172), including follistatin. Follistatin cross-communicates the signal from the AR-beta- catenin pathway to the TGF-beta signaling pathway, blocking signaling through the TGF-beta / Smad 2/3 (173-174). Follistatin plays an essential role in mediating the effects of testosterone on myogenic

differentiation (174-175). In a remarkable discovery, Jasuja et al (175) found that the administration of recombinant follistatin selectively increased muscle mass and decreased fat mass but had no effect on prostate growth. Recombinant follistatin and testosterone each regulated the expression of a large number of common genes in the skeletal muscle, but they differed substantially in the expression profile of genes activated in the prostate (175). Among the genes activated differentially by testosterone but not by follistatin in the prostate, Jasuja et al (175) identified polyamine pathway as an important signaling pathway. The polyamine pathway has been known to be involved in regulating prostate growth. Administration of testosterone in combination with an inhibitor of ornithine decarboxylase, a key enzyme in the polyamine pathway, to castrated male mice restored levator ani muscle mass but not prostate mass, indicating that ODC1 plays an important role in mediating the effects of testosterone on the prostate(**Figure 7**) (175). Therefore, combined administration of testosterone plus ODC1 inhibitor provides a novel approach for achieving selectivity of testosterone's anabolic effects on the muscle while sparing the prostate (175).

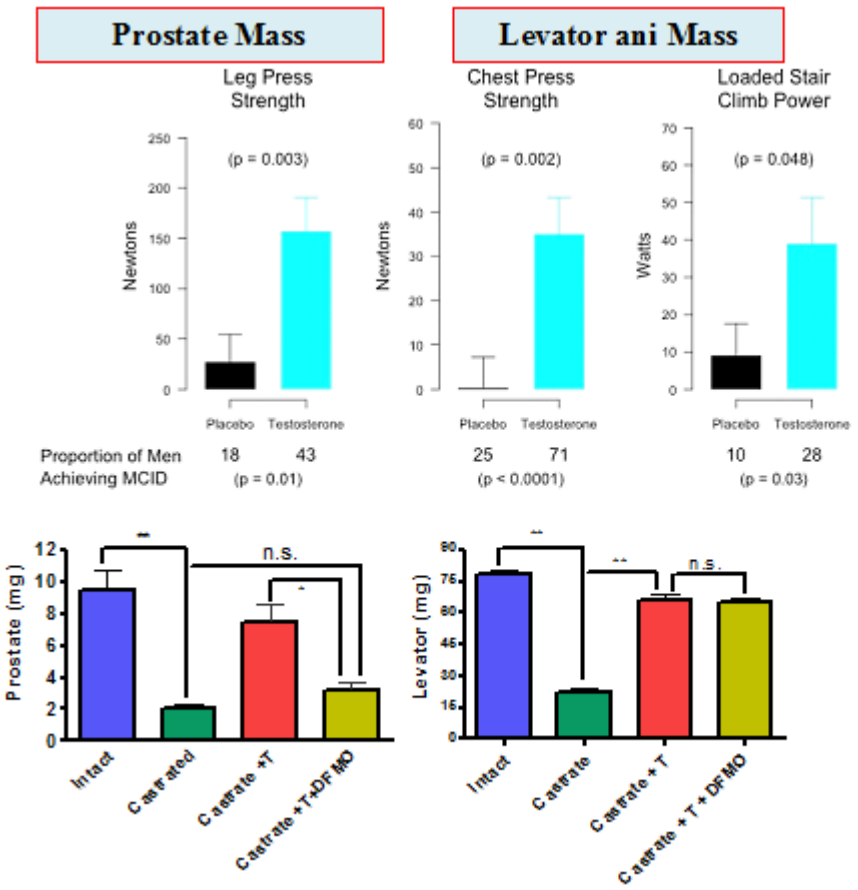


Figure 7. Testosterone Plus Ornithine Decarboxylase 1 Inhibitor as a Selective Prostate Sparing Anabolic Therapy.ntact and castrated adult male mice were treated for 2-weeks with vehicle or testosterone with and without □ difluoromethylornithine (DFMO), a specific Odc1 inhibitor, as follows: Intact, castrated (Cx), castrated + 15 □g/day T (Cx+T), castrated +15 □g/day T + DFMO (Cx+T+DFMO). Levator ani weights (right panel) in DFMO-treated with testosterone plus DFMO were similar to those in intact controls and testosterone-treated castrated mice. Prostate weights in castrated mice were lower than in intact controls and were restored by testosterone administration to levels seen in intact mice (left panel). Mice treated with testosterone plus DFMO had significantly lower prostate weights than intact controls or castrated mice treated with testosterone alone, but not significantly different from those in castrated

mice treated with vehicle alone. Thus, testosterone plus ODC1 inhibitor could serve as prostate-sparing selective anabolic therapy. Reproduced with permission from Jasuja et al, Aging Cell 2013.

E.1.d. The Role of Steroid 5-alpha Reductaseand DHT in Mediating Androgen Effects in the Muscle. Although the enzyme steroid 5-alpha-reductase is expressed at low concentrations within the muscle (176-177), we do not know whether conversion of testosterone to dihydrotestosterone is required for mediating the androgen effects on the muscle. Men with benign prostatic hypertrophy who are treated with a 5-alpha reductase inhibitor do not experience muscle loss (178). Similarly, individuals with congenital 5-alpha-reductase deficiency have normal muscle development at puberty (178). These data suggest that 5-alpha reduction of testosterone to DHT is not obligatory for mediating its effects on the muscle. However, all the kindred with 5-alphareductse deficiency that have been published to-date have had mutations of type 2 isoform of the enzyme. Similarly, finasteride is a weak inhibitor of only the type 2 isoform of the enzyme. The circulating concentrations of DHT in male patients with congenital mutation of type 2 5-alpha reductase enzyme or in men treated with finasteride are lower than eugonadal men; however, these patients still produce significant amounts of DHT and their circulating DHT concentrations are often in the lower end of the male range. It is reassuring that long term administration of dutasteride, a dual and potent inhibitor of both 5-alpha reductase isoforms, has not been associated with significant reductions in bone mineral density (178); the data on the effects of duatasteride on muscle mass are not available. This issue is important because if 5-alpha reduction of testosterone to DHT were not obligatory for mediating its anabolic effects on the muscle, then it might bebeneficial to administer testosterone with an inhibitor of 5-alpha reductase or to develop selective androgen receptor modulators that do not undergo 5-alpha reduction.

To determine whether testosterone's effects on muscle mass and strength, sexual function, hematocrit, prostate, sebum production, and lipids are attenuated when its conversion to DHT is blocked, we administered to healthy men, 18-50 years, a long-acting GnRH-agonist to suppress endogenous testosterone. We randomized them to placebo or dutasteride (dual inhibitor of steroid 5-alpha reductase type 1 and 2) 2.5-mg daily, plus 50, 125, 300, or 600-mg testosterone enanthate weekly for 20-weeks (179). Changes in lean and fat mass, leg-press and chest-press strength, were related to testosterone dose but did not differ between placebo and dutasteride groups (179). The relationship between testosterone concentrations and the change in lean mass, muscle strength, hematocrit, sebum production and PSA were similar between dutasteride and placebo arms(**Figure 8**) (179). Changes in sexual-function scores, bone markers, prostate volume, and PSA did not differ between groups (179). These data indicate that testosterone's conversion to DHT is not essential for mediating its effects on muscle mass and strength, sexual function, hematocrit, or sebum in men over the range of testosterone concentrations achieved in this trial (179). These

data are consistent with studies that have reported that administration of 5α-reductase inhibitors has little or no effect on muscle or bone mass (180-182).

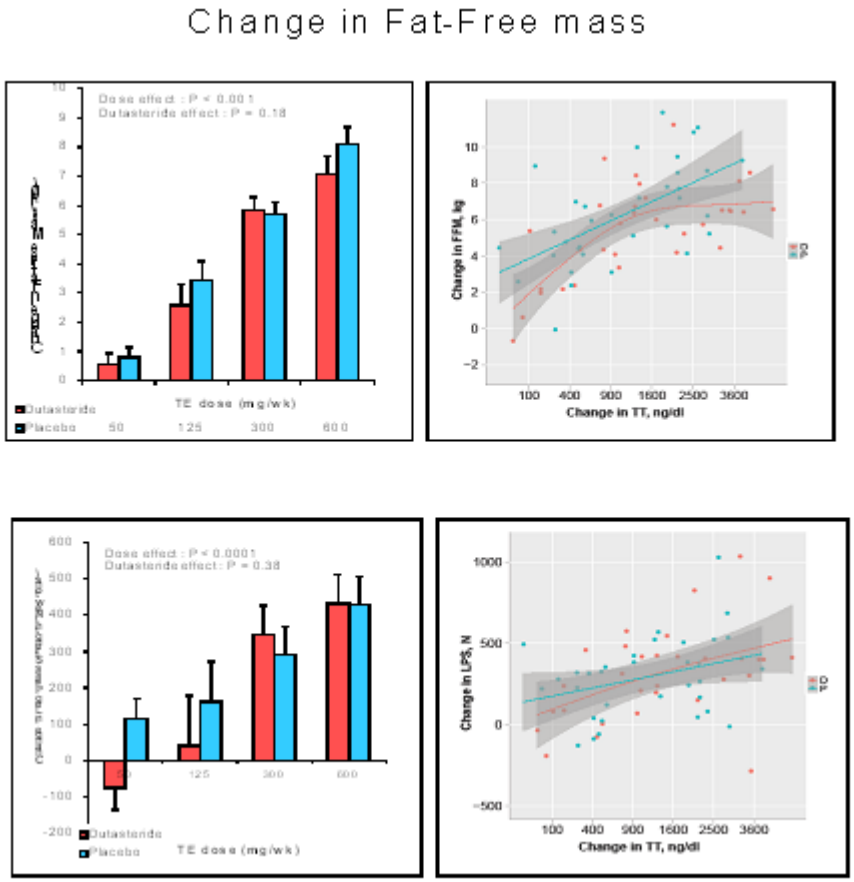


Figure 8. The Role of 5-alpha-Dihydrotestosterone in Men In this randomized trial, healthy men, 18-50 years, received a long-acting GnRH-agonist to suppress endogenous testosterone. They were then randomized to either placebo or dutasteride (dual inhibitor of steroid 5-alpha reductase types 1 and 2) 2.5-mg daily, plus 50, 125, 300, or 600-mg testosterone enanthate weekly for 20-weeks (535). Changes in fat-free mass (upper panel) and leg-press strength (lower panel), were related to testosterone dose but did not differ between placebo and dutasteride groups (535).The

relationship between change in total testosterone (TT) levels and change in fat-free mass and leg press strength (right panels) did not differ between men assigned to placebo or duatsteride arms. Reproduced with permission from Bhasin et al, JAMA 2012.

E.1.e. The Role of CYP19aromatase in Mediating Testosterone Effects on the Muscle. Studies of aromatase knockout mice have revealed higher fat mass and lower muscle mass in mice that are null for the P450-linked CYP19aromatase gene (183). Similarly, humans with CYP19 aromatase mutations have decreased muscle mass and increased fat mass, and they exhibit insulin resistance (184). Data from these gene-targeting experiments suggest that aromatization of testosterone to estradiol might also be important in mediating androgen effects on body composition. Finkelstein et al (185) have recently examined the relative roles of testosterone and estradiol in regulation of muscle and fat mass, and sexual function. These investigators found that testosterone's effects on lean mass, muscle size, and strength were not significantly attenuated when its conversion to estradiol was blocked by administration of an aromatase inhibitor (185). However, testosterone's effects on fat mass and sexual desire appeared to be mediated by estradiol (185).

E.2. Testosterone and Sexual Function in Older Men

E.2.a. Regulation of Sexual Function by Testosterone Sexual function in men is a complex process that includes central mechanisms for regulation of sexual desire and arousability, and local mechanisms for penile tumescence, orgasm, and ejaculation (186). Primary effects of testosterone are on sexual interest and motivation (186-191). Testosterone replacement of young, androgen deficient men improves a wide range of sexual behaviors including frequency of sexual activity, sexual daydreams, sexual thoughts, feelings of sexual desire, spontaneous erections, and attentiveness to erotic stimuli (186-194).Kwan et al (190) demonstrated that androgen-deficient men have decreased frequency of sexual thoughts and lower overall sexual activity scores; however, these men can achieve erections in response to visual erotic stimuli. Hypogonadal men have lower frequency and duration of the episodes of nocturnal penile tumescence; testosterone replacement increases both the frequency and duration of sleep-entrained, penile erections (192-194). Although both orgasm and ejaculation are believed to be androgen-independent, hypogonadal men have decreased ejaculate volume and their orgasm may be delayed.

Although hypogonadal men can achieve erections, it is possible that achievement of optimal penile rigidity might require physiologic testosterone concentrations. Testosterone regulates nitric oxide synthase activity in the cavernosal smooth muscle

(195). Testosterone administration in orchidectomized rats increases penile blood flow and has trophic effects on cavernosal smooth muscle (196-198).

In male rodents, all measures of mating behavior are normalized by relatively low testosterone levels that are insufficient to maintain prostate and seminal vesicle weight (199-200). Similarly, in men, sexual function is maintained at relatively low normal levels of serum testosterone(185, 191, 201). Testosterone's effects on libido may be mediated through its conversion to estradiol (185).

E.2.b. Relationship of Androgen Deficiency and Erectile Dysfunction in Middle-Aged and Older Men Erectile dysfunction and androgen deficiency are two common but independently distributed, clinical disorders that sometimes co-exist in the same patient (186, 202-204). Hypogonadism is a clinical syndrome that results from androgen deficiency (5); in contrast, erectile dysfunction is usually a manifestation of a systemic vasculopathy, often of atherosclerotic origin. Thus androgen deficiency and erectile dysfunction have distinct pathophysiology. Eight to ten percent of men presenting with erectile dysfunction have low testosterone levels (203-206). The prevalence of low testosterone levels is not significantly different between middle aged and older men with impotence and those without impotence (203-206). Testosterone administration does not improve sexual function in men with erectile dysfunction who have normal testosterone levels (207-210). In men with sexual dysfunction who have unequivocally low testosterone levels, testosterone therapy improves libido and overall sexual activity (209-210). The response to testosterone supplementation in this group of men is variable because of the co-existence of other disorders such as diabetes mellitus, hypertension, cardiovascular disease, and psychogenic factors. Several meta-analyses of the usefulness of androgen replacement therapy concluded that testosterone administration is associated with greater improvements in sexual function compared to placebo treatment in men with sexual dysfunction and unequivocally low testosterone levels (208-210).

It had been speculated that testosterone administration might improve erectile response of men with ED to selective phosphodiesterase inhibitors (211-213). To determine whether the addition of testosterone to a phosphodiesterase-5-inhibitor improves erectile response,we conducted a randomized, placebo-controlled trial (214), in men, 40-to-70 years, with erectile dysfunction andlow total testosterone< 11.5 nmol/L (330ng/dL) and/or free testosterone<173.5 pmol/L (50pg/mL). All participants were initially started on sildenafil alone and the sildenafil dose was optimized based on their response during a 3-7 week run-in period (214). The participants were then randomized to 10-g testosterone or placebo gel for 14-weeks in combination with theoptimized sildenafil dose (214). The administration of sildenafil alone was associated with substantial increases in erectile function domain (EFD) score and total and satisfactory sexual encounters (214). However, the change in EFD score in men assigned to testosterone plus sildenafil did not differ significantly from that in men assigned to placebo plus sildenafil (214).

Changes in total and successful sexual encounters, quality-of-life, and marital-intimacy did not differ between testosterone and placebo groups. Even among the subsets of men with baseline testosterone<250ng/dL or those without diabetes, there were no significant differences in EFD scores between the two arms (214). Another placebo-controlled trial of men with erectile dysfunction who were non-responders to tadalafil also did not show a greater improvement in erectile function in men assigned to the testosterone arm than in those assigned to the placebo arm (213). Thus, in randomized trials, the addition of testosterone to PDE5Is has not been shown to improve erectile function in men with erectile dysfunction (213-214).

Androgen deficiency is an important cause of low sexual desire disorder (186). Therefore, serum testosterone concentrations should be measured in the diagnostic evaluation of hypoactive sexual desire disorder, recognizing that low sexual desire is often multifactorial; systemic illness, relationship and differentiation (the ability of individuals in a relationship to maintain their distinct identities) issues, depression, and many medications can be important antecedents or contributors to low sexual desire and sexual dysfunction.

E.3. Testosterone Effects on Bone Mineral Metabolism

E.3.a. The Effects of Androgen Deficiency on Bone Mass. Testosterone deficiency is associated with a progressive loss of bone mass (215-218). In one study performed in sexual offenders (215), surgical orchiectomy was associated with a progressive decrease in bone mineral density of a magnitude similar to that seen in women after menopause. Similarly, androgen deficiency induced by the administration of a GnRH agonist, surgical orchiectomy, or an androgen antagonist for the treatment of prostate cancer leads to loss of bone mass (216-218). In male rats, surgical orchiectomy or androgen blockade by administration of an androgen receptor antagonist is associated with loss of bone mass (219).

Androgen deficiency that develops before the completion of pubertal development is associated with reduced cortical and trabecular bone mass (220-221). During the pubertal years, significant bone accretion occurs under the influence of sex steroids; therefore, individuals with sex-steroid deficiency before or during peri-pubertal years may end up with suboptimal peak bone mass. Similarly, men with acquired androgen deficiency have lower bone mineral density than age-matched controls(133).

E.3.b. Effects of Testosterone Administration in Young, Androgen-Deficient Men. Testosterone therapy of healthy, young, hypogonadal men is associated with significant increases in vertebral bone mineral density (134, 222-226). However, bone mineral density is typically not normalized after 1-2 years of testosterone replacement therapy (134). The reasons for the failure of testosterone replacement therapy to normalize bone mineral density in androgen-deficient men are not entirely clear. Some hypogonadal participants patients included in these testosterone trials had panhypopituitarism and also suffered from growth

hormone deficiency. It is possible that concomitant GH replacement might be necessary for restoration of normal bone mineral density. Excessive glucocorticoid replacement might also contribute to bone loss in these patients. In addition, some participants had experienced testosterone deficiency before the onset and completion of pubertal development. Because maximal bone mass is achieved in part through bone accretion during the peripubertal period under the influence of sex-steroid hormones, the individualswho develop androgen deficiency during the critical pubertal developmental window of bone accretion, may end up with decreased peak bone mass, and testosterone administration may not be able to restore bone mass to levels seen in eugonadal age-matched controls. Many testosterone replacement trials were less than 3 years in duration, and it is possible that a longer period of testosterone administration might be necessary to achieve maximal improvements in bone mineral density. Indeed, Behre et al (222) reported that bone mineral density in some hypogonadal men continued to increase even after many years of testosterone treatment using a scrotal transdermal patch and reached the levels expected for age-matched eugonadal controls.

E.3.c. Cross-sectional Studies of the Relationship Between Sex-Hormone Concentrations and Osteoporosis in Older Men. The age-related decline in sex hormones is associated with age-related changes in bone mineral density and increased risk of osteoporotic fractures (108-115). Older men with hip fractures have lower testosterone levels than age-matched controls (227). In general, epidemiologic studies have reported bioavailable testosterone and estradiol levels to be more strongly associated with bone mineral density of the spine, hip, and distal radius than total testosterone levels (109, 111-112, 114).

E.3.d. Testosterone Replacement Studies in Older Men. Three long-term studies of testosterone replacement of relatively healthy older men have examined the effects of testosterone on bone mineral density but have reported inconsistent results (162, 228-230). One study found greater increases in vertebral bone mineral density in the testosterone arm of the trial than in the placebo arm, while another study did not find any significant differences between the change in vertebral or femoral bone mineral density between testosterone and placebo groups (230). The third study reported greater gains in bone mineral density of the femoral neck but not of other regions in men randomized to receive testosterone compared to those who received placebo. A meta-analysis of randomized trials found a significantly greater increase in lumbar bone mineral density but not in femoral bone mineral density in the testosterone arms of trials that used intramuscular testosterone than in placebo arms (231); transdermal testosterone had no significant impact.

E.3.e. Mechanisms of Androgen Action on the Bone. Testosterone increases bone mass by several mechanisms (232). Short-term studies of androgen replacement have shown inconsistent increases in markers of bone formation, but a more consistent reduction in markers of bone resorption (232-235). These observations suggest that testosterone increases bone

mineral density in part through its aromatization to estrogen, which inhibits bone resorption. Estrogen deficiency contributes to increased bone resorption and remodeling by multiple mechanisms. Estrogens regulatethe activation frequency of bone functional basic multicellular units, the duration of the resorption phase and the formation phase, and osteoclast recruitment (236). The protective effects of estrogen on bone in both male and female mice during growth and maturation are mediated largely through estrogen receptor-alpha (237-243). In men androgens and estrogens both play independent roles in regulating bone resorption (236). In addition, there is increasing evidence that testosterone might also directly stimulate osteoblastic bone formation. Androgen receptors have been demonstrated on osteoblasts and on mesenchymal stem cells (244). Testosterone stimulates cortical bone formation (245). Testosterone also stimulates the production of several growth factors within the bone, including IGF-1; these growth factors may contribute to bone formation(246). Testosterone increases muscle mass, which may indirectly increase bone mass by increased loading. Testosterone might inhibit apoptosis of osteoblasts through non-genotropic mechanisms (247-248). In addition to its effects on bone mineral density, testosterone might reduce fall propensity because of its effects on muscle strength and reaction time.

E.3.f. Synopsis. Testosterone replacement has been shown to increase vertebral bone mineral density in young and older men with unequivocally low testosterone levels (5). Testosterone increases bone mass by multiple mechanisms. However, testosterone effects on fracture risk have not been studied.

E.4. Testosterone Effects on Cognitive Function

E.4.a. Cross-sectional Studies Correlating Sex-Hormone Levels and Cognitive Function. Androgens effects on cognitive function are domain-specific. For instance, observations that men outperform women in a variety of visuo-spatial skills suggest that androgens enhance visuo-spatial skills (249). In !Kung San Bushmen of Southern Africa, testosterone, but not estradiol, levels correlated with better spatial ability and with worse verbal fluency (250). Circulating levels of dihydrotestosterone, a metabolite of testosterone that is not converted to estrogen, positively correlated with verbal fluency (250). Barrett-Conner et al (251) found positive associations between total and bioavailable testosterone levels, and global cognitive functioning and mental control, but not with visuospatial skills. In the Baltimore Longitudinal Study of Aging(252), higher free testosterone index was associated with better scores on visual and verbal memory, visuospatial functioning, and visuomotor scanning. Men with low testosterone levels had lower scores on visual memory and visuospatial performance (252). Neither total testosterone level nor the free testosterone index was correlated with verbal knowledge, mental status, or depressive symptoms (252). Other studies have reported a complex relationship between androgen levels and spatial ability (253--256). Women with congenital adrenal hyperplasia with

high androgen levels score higher on tests of spatial cognition than their age- and gender-matched siblings (257). 46, XY rats with androgen insensitivity perform worse on tests of spatial cognition than their age-matched controls (258).

E.4.b. Intervention Trials of the Effects of Testosterone Supplementation on Cognitive Function. Several small clinical trials in elderly hypogonadal men have provided conflicting results(259-265); not surprisingly, a systematic review of clinical trials revealed no significant effects of testosterone on cognition (5). Janowsky et al (259) tested verbal and visual memory, spatial cognition, motor speed and cognitive flexibility in a group of healthy older men who received 3 months of testosterone supplementation. Testosterone replacement was associated with a significant improvement in spatial cognition only. Serum testosterone levels were not significantly correlated with spatial performance, but estradiol levels showed a significant inverse relationship with spatial performance suggesting that estradiol might inhibit spatial ability. Vaughan et al (260) found no effect of testosterone administration on cognition, while Cherrier et al (261-263) reported an effect on visuo-spatial cognition. Testosterone also enhanced verbal fluency. Hypogonadal men performed worse on tests of verbal fluency than eugonadal men, and showed improvement after testosterone replacement (264-266). In transsexual males (267), administration of anti-androgen and estrogen, prior to surgery for gender reassignment, decreased anger and aggression proneness, sexual arousability, and spatial skills, and increased verbal fluency ability. Conversely, testosterone administration to females decreased verbal fluency and increased spatial skills. Testosterone administration may also improve verbal memory in women (268).

Testosterone is aromatized to estrogen in the brain, and some effects of testosterone on cognition might be mediated through its conversion to estradiol. Androgen receptors are expressed in the brain (269), and androgen effects on brain organization during development (270-271) are mediated through androgen receptor. Androgens increase neurite arborization, facilitating intercellular communication (270-273). Testosterone also affects serotonin, dopamine, acetylcholine (272), and calcium signaling (273).

E.4.c. Synopsis of the Effects of Testosterone on Cognition. The literature on testosterone and cognition is highly equivocal; some, but not all studies, demonstrate improvements in tests of spatial cognition, verbal fluency and verbal memory. The inconsistency in findings cannot yet be interpreted as evidence that there is no effect. Rather methodological problems appear to limit the generalizability of results. Limitations of previous studies include limited sample sizes with heterogeneous, poorly defined samples; the use of a variety of neuropsychological tests, including some that lack psychometric validation; and the use of differing protocols in clinical trials. The effects of testosterone therapy on clinically important outcomes in men with cognitive impairment have not been studied.

E.5. Testosterone Effects on Mood, Energy, and Health-Related Quality of Life Circulating concentrations of testosterone have not been consistently associated with mood indices and depressive symptoms in older men and in men with chronic illnesses (102-107).In intervention trials in eugonadal men, testosterone replacement did not have a significant effect on mood(274); in hypogonadal men, some studies have shown an effect whereas others have not. In an open-label trial, androgens improved positive aspects of mood and reduced negative aspects of mood in young, hypogonadal men (275).

In general, androgen deficiency does not appear to be an important factor in the pathophysiology of major depression. Placebo-controlled trialsof testosterone in men with refractory depression have not consistently shown a beneficial effect of testosterone (275-278). A meta-analysis of randomized clinical trials did not reveal a clinically meaningful effect of testosterone on depression (5).

In HIV-infected men with low testosterone levels, testosterone supplementation was more effective than placebo in restoring libido and energy, and alleviating depressed mood (279-280). The depression scores in HIV-infected men were increased in association with hypogonadism in men with AIDS wasting, and administration of testosterone resulted in a significant improvement in depression inventory score (279).

There is anecdotal evidence that androgens improved energy and reduced sense of fatigue (280). Testosterone administration increases hemoglobin and red cell mass, stimulates 2, 3 BPG concentrations thereby shifting the oxygen – hemoglobin dissociation curve favorably to improve greater oxygen delivery, and induces muscle capillarity (281-283). Additionally, testosterone stimulates mitochondrial biogenesis and mitochondrial quality (284). All of these adaptations would be expected to improve net oxygen delivery to the muscle, improve aerobic performance and reduce fatigability. However, the effects of testosterone on fatigue have not been studied in randomized trials.

Supraphysiologic doses of androgenic steroids such as those abused by athletes and recreational body builders have been associated with aggressive responses to provocative situations (285), increased scores on Young's manic scale, and with affective and psychotic disorders in some individuals (286); these adverse effects have not been reported with physiologic testosterone replacement.

Physical, sexual, and cognitive functions are important determinants of the health-related quality of life. For instance, in HIV-infected individuals, health-related quality of life correlated significantly with lean body mass (287). Cognitive function is an important determinant of an individual's ability to live independently. By improving some aspects of physical, sexual, and cognitive functions, testosterone supplementation might be expected to improve health-related quality of life. However, only a

few small trials have evaluated the effects of testosterone on health-related quality of life. A systematic review of a small number of randomized trials has not revealed a significant improvement in composite health-related quality of life scores, but testosterone therapy has been shown to improve scores on the physical function domain of SF-36 (5, 137).

F. Considerations in Testosterone Therapy of Older Men with Low Testosterone Levels

The risks and benefits of long-term testosterone therapy on health-related outcomes in older men with symptomatic conditions associated with low testosterone levels are unknown. Recognizing the lack of evidence of the safety and effectiveness of testosterone therapy in older men with symptomatic androgen deficiency, the expert panel of the Endocrine Society recommended against testosterone therapy of all older men with low testosterone levels (5). Instead the panel suggested that "*clinicians consider offering testosterone therapy on an individualized basis to older with consistently low testosterone levels on more than one occasion and significant symptoms of androgen deficiency, after appropriate discussion of the uncertainties of the risks and benefits of testosterone therapy in older men*" (5). The panel's recommendations were guided by the recognition of the paucity and low quality of evidence, and by the sober realization that high quality evidence of the efficacy and safety will not be available for a very long time.

Although the prevalence of low testosterone levels in older men is arguably high, the usefulness of population screening cannot be evaluated for several reasons. Because of the lack of agreement on a case definition, the paucity of data on the performance characteristics of the screening instruments (e.g., the ADAM questionnaire (289), the Aging Male Symptoms questionnaire (290), and the MMAS questionnaire (291) and the lack of clarity on the public health impact of the androgen deficiency syndrome in the general population, screening of all older men for androgen deficiency is not justified.

Prior to prescribing testosterone therapy, a careful general health evaluation is necessary to identify any potential conditions that might increase the risk of testosterone therapy. The contraindications to testosterone therapy are listed in **Table 1**. Also, an explicit discussion of the uncertainties about the benefits and risks of testosterone therapy should precede prescription of testosterone therapy. Men receiving testosterone therapy should be monitored using a standardized monitoring plan to facilitate early detection of adverse events and to minimize the risk of unnecessary prostate biopsies (**Table 2**), as recommended by the Endocrine Society expert panel (**Table 3**).

Table 1. Disorders that Constitute Relative or Absolute Contraindications for Androgen Supplementation and in Which Testosterone Administration is Associated with High Risk of Adverse Outcome

Very High Risk of Serious Adverse Outcomes (Absolute Contraindications)

1. Metastatic prostate cancer
2. Breast cancer

Moderate to High Risk of Adverse Outcomes (Relative Contraindications)

1. Undiagnosed prostate nodule or induration
2. Unexplained PSA elevation
3. Erythrocytosis (hematocrit >50%)
4. Severe lower urinary tract symptoms associated with benign prostatic hypertrophy as indicated by IPSS/AUA symptom score >19
5. Class III or IV congestive heart failure
6. Untreated severe sleep apnea

Adapted with permission from the Endocrine Society Guideline for the Management of Androgen Deficiency Syndrome in Men in: Bhasin et al J Clin Endocrinol Metab 2010;95(6):2536-59**.**

Table 2. Potential Adverse Effects of Testosterone Replacement in Older Men

Adverse Events for Which There is Evidence of Association with Testosterone Administration

1. Erythrocytosis
2. Acne and oily skin
3. Detection of subclinical prostate cancer
4. Growth of metastatic prostate cancer
5. Reduced sperm production and fertility

Potential Adverse Events for Which There is Weak Evidence of Association with Testosterone Administration

1. Gynecomastia
2. Male pattern balding (familial)

3. Growth of breast cancer
4. Induction of worsening of obstructive sleep apnea

Formulation Specific Adverse Effects

1. Oral Tablets
    - ♦ Effects on liver enzymes and HDL cholesterol (methyltestosterone)
3. Pellet Implants
    a. Infection, extrusion of pellet
4. Intramuscular Injections
    a. Fluctuations in mood or libido
    b. Pain at injection site
    c. Excessive erythrocytosis especially in older individuals
    d. Transient cough
5. Transdermal Patches
    a. Skin reaction at the patch application site
6. Transdermal Gel
    a. Potential risk of transference to partner
7. Buccal Testosterone Tablets
    a. Alterations in taste
    b. Irritation of gums

Adapted with permission from the Endocrine Society Guideline for the Management of Androgen Deficiency Syndrome in Men in: Bhasin et al J Clin Endocrinol Metab 2010;95(6):2536-59.

Table 3. Recommendations for Monitoring of Men Receiving Testosterone Therapy

A. Baseline Evaluation

1. Hemoglobin and hematocrit
2. Digital prostate examination*
3. Serum PSA*
4. AUA/IPSS symptom scores for benign prostatic hyperplasia
5. Bone mineral density**

B. Follow-Up Evaluation at 3, 6 and 12 months and annually thereafter

1. Serum total and/or free testosterone levels***
2. Hemoglobin and hematocrit
3. Serum PSA*
4. Digital rectal examination*
5. AUA/IPSS symptom scores for benign prostatic hyperplasia

***In men 40 yr of age or older who have a baseline PSA greater than 0.6 ng/ml, the Endocrine Society Guidelines recommends a digital examination of the prostate and PSA measurement before initiating treatment, at 3 to 6 months, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the patient.**

**The Endocrine Society Guidelines suggests measurement of bone mineral density of lumbar spine and femoral neck after 1-2 years of testosterone therapy in androgen deficient men with osteoporosis or low trauma fracture, consistent with regional standard of care

***Endocrine Society Guidelines suggests measurement of free testosterone levels, using an accurate and reliable assay, in some men in whom total testosterone concentrations are near the lower limit of the normal range and in whom alterations of SHBG are suspected

Adapted with permission from the Endocrine Society Guideline for the Management of Androgen Deficiency Syndrome in Men in: Bhasin et al J Clin Endocrinol Metab 2010;95(6):2536-59**.**

The clinical pharmacology of the available testosterone formulations is summarized in **Table 4**. Testosterone therapy can be instituted using any of the available approved formulations based on considerations of pharmacokinetics, patient convenience and preference, cost, and formulation-specific adverse effects. Suggestions for initial treatment regimens are provided in **Table 5** with the caveat that dose and regimen should be adjusted based on measurement of serum testosterone levels after initiation of therapy. The aim should be to raise testosterone levels into the mid-normal range for healthy young men.

Table 4. Clinical Pharmacology of Some of the Available Testosterone Formulations

Formulation	Regimen	Pharmacokinetic profile	DHT and estradiol	Advantages	Disadvantages
Testosterone enanthate or cypionate (127-129)	**100 mg IM weekly or 200 mg IM every two weeks**	**After a single IM injection, serum testosterone levels rise into the supraphysiological range and then decline gradually into the hypogonadal range by the end of the dosing interval (127-129).**	**DHT and estradiol levels rise in proportion to the increase in testosterone levels. T:DHT and T:E2 ratios do not change.**	Corrects symptoms of androgen deficiency **Relatively inexpensive, if self-administered** **Flexibility of dosing**	**Requires IM injection** **Peaks and valleys in serum testosterone levels**
Non-genital Transdermal System (133-134)	**One or two patches, designed to nominally deliver 5-10 mg testosterone over 24-hour applied daily on non-pressure areas**	**Restores serum testosterone, DHT and estradiol levels into the physiological male range.**	**T:DHT and T:Estradiol levels are in the physiological male range**	**Ease of application, corrects symptoms of androgen-deficiency, and mimics the normal diurnal rhythm of testosterone secretion. Lesser increase in hemoglobin than injectable esters**	**Serum testosterone levels in some androgen-deficient men maybe in the low normal range; these men may need application of two patches daily. Skin irritation at the application site may be a problem for some patients.**
Topical Testosterone	**Testosterone gel containing 50 to 100**	**Restores serum testosterone and estradiol levels into the**	**Serum DHT levels are higher and T:DHT ratios are lower**	**Corrects symptoms of androgen deficiency, provides flexibility of**	**Potential of transfer to a female partner or child by**

Preparations	**mg testosterone should be applied daily. With the axillary liquid solution, apply 30 to 90 mg topical in the axilla.**	**physiological male range.**	**in hypogonadal men treated with the testosterone gel than in healthy eugonadal men.**	**dosing, ease of application, good skin tolerability**	**direct skin-to-skin contact; moderately high DHT levels**
17-∝-methyl testosterone (135)	**Orally active, 17-∝-alkylated compound that should not be used because of potential for liver toxicity**	**Orally active**			**Clinical responses variable; potential for liver toxicity. Should not be used for treatment of androgen deficiency**
Buccal Testosterone Tablets	**30 mg controlled release, bioadhesive tablets used twice daily**	**Absorbed from the buccal mucosa**	**Normalizes serum testosterone and DHT levels in hypogonadal men**	**Corrects symptoms of androgen deficiency in healthy, hypogonadal men**	**Gum-related adverse events in 16% of treated men**
Oral T undecanoate	**40 to 80 mg orally 2 or 3 times daily with meals**	**When administered in oleic acid, T undecanoate is absorbed through the lymphatics, bypassing the portal system. Considerable variability in T levels in the same individual on different days and among individuals**	**High DHT to T ratio**	**Convenience of oral administration**	**Not approved in the USA. Variable T levels and clinical responses; high DHT to T ratio**
T Pellets	**Four to six 200-mg pellets implanted SC**	**Serum T levels peak at 1 month and then sustained in the normal range for 4-6 months**	**T:DHT and T:E2 ratios do not change**	**Corrects symptoms of androgen deficiency; long acting**	**Requires surgical incision; pellets may extrude spontaneously**
Injectable long-acting T undecanoate in oil	**1000 mg injected IM, followed by 1000 mg at 6 week, and 1000 mg every 12 weeks thereafter**	**When administered at a dose of 1000 mg IM, Serum T levels maintained in the normal range in a majority of treated men**	**T:DHT and T:E2 ratios do not change**	**Corrects symptoms of androgen deficiency; long acting**	**Requires IM injections of a large volume**

Reproduced with permission from: Bhasin et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010 Jun;95(6):2536-59**.**

Table 5. Some Recommended Regimens for Testosterone Replacement Therapy

- 75-100 mg of testosteroneenanthate or cypionate administered intramuscularly weekly, or 150 to 200 mg administered every 2 weeks.
- One or two 5 mg non-genital, testosterone patches applied nightly over the skin of the back, thigh, or upper arm, away from pressure areas.
- 5 to 10 g of1% T gel applied daily over a covered area of skin (patients should wash hands after application).
- 60 mg of axillary topical liquid applied in the axillary region
- 30 mg of a bioadhesive, buccal T tablet applied to buccal mucosa twice daily.
- 40 to 80 mg of oral testosterone undecanoate taken twice daily.
- An initial dose of 1000 mg testosterone undecanoate in 4 ml castor oil followed by 1000 mg at 6 weeks and 1000 mg every 12 weeks thereafter

Legend: These regimens should be viewed as suggestions for initiation of testosterone replacement therapy; dose and regimen should be adjusted based on measurement of serum testosterone levels. Outside the USA, oral testosterone undecanoate, injectable formulation of testosterone undecanoate, and testosterone pellets are available for clinical use in many countries.

Adapted with permission from: Bhasin et al. Testosterone therapy in adult men with androgen deficiency syndromes: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2010 Jun;95(6):2536-59**.**

G. Risks of Testosterone Administration in Older Men

Short-term testosterone administration is associated with a low frequency of relatively mild adverse effects such as acne, oiliness of skin, and breast tenderness in healthy, young, androgen-deficient men with classical hypogonadism. However, the long term risks of testosterone supplementation in older men are largely unknown. There are several unique considerations in older men that may increase their risks of testosterone administration. Serum total and free testosterone concentrations are higher in older men than young men at any dose of testosterone therapy, presumably due to decreased testosterone clearance (40). Altered responsiveness of older men to testosterone administration might make them susceptible to a higher frequency of adverse events, such as erythrocytosis, or to unique adverse events not observed in young hypogonadal men. The baseline prevalence of disorders such as prostate cancer, benign prostatic hypertrophy, and cardiovascular disease that might be exacerbated by testosterone administration is high in older men; therefore, small changes in risk in either direction could have enormous public health impact. Furthermore, the clustering of co-morbid

conditions in the frail elderly might render these men more susceptible to the adverse effects of testosterone therapy than healthy young hypogonadal men.

The contraindications for testosterone administration include history of prostate or breast cancer (**Table 1**). Benign prostatic hypertrophy is by itself not a contraindication, unless it is associated with severe symptoms, as indicated by IPSS symptom score of greater than 19. Testosterone should not be given without prior evaluation and treatment to men with baseline hematocrit greater than 50%, severe untreated sleep apnea, or congestive heart failure with Class III or IV symptoms (5).

The risks of testosterone administration include acne, oiliness of skin, erythrocytosis, induction or exacerbation of sleep apnea, leg edema, and breast tenderness or enlargement (5) (**Table 2**). Abnormalities of liver enzymes, hepatic neoplasms, and peliosis hepatis that have been reported previously with orally administered, 17-alpha alkylated androgens, have not been observed with replacement doses of parenterally administered testosterone formulations. The two major areas of concern and uncertainty are the effects of long-term testosterone administration on prostate cancer and cardiovascular events.

F.1. Testosterone Effects on the Risk of Atherosclerotic Heart Disease The long-term consequences of testosterone supplementation on the risk of heart disease remain unknown and have been the subject of contentious debate. (123, 292-294).

F.1.a. Androgen Effects on Plasma Lipids. Cross-sectional studies of middle-aged men found a positive relationship between serum testosterone levels and plasma HDL-cholesterol concentrations(294-296). Lower testosterone levels in men are associated with higher levels of dense LDL particles (295) and prothrombotic factors (297).

The effects of androgen supplementation on plasma lipids depend on the dose, the route of administration (oral or parenteral), the type of androgen (aromatizable or not) and the subject population(whether young or old, and hypogonadal or not). Supraphysiological doses of testosterone and non-aromatizable androgens frequently employed by body-builders undoubtedly decrease plasma HDL-cholesterol levels (298-301). However, administration of replacement doses of testosterone in older men has been associated with only a modest or no decrease in plasma HDL-cholesterol (5, 156-162).

It has been suggested that the decrease in HDL cholesterol with testosterone administration might be the result of increased cholesterol efflux from endothelial macrophages stimulating reverse cholesterol transport, and therefore, a beneficial effect, rather than the result of increased HDL catabolism (302).

F.1.c. Androgens and Other Cardiovascular Risk Factors. Cross-sectional studies have found a positive association between circulating testosterone concentrations and tissue plasminogen activator activity (303), and a negative relationship between testosterone and plasminogen activator inhibitor-1 activity, fibrinogen, and some other prothrombotic factors (303), suggesting an antithrombotic effect of testosterone. However, intervention trials of testosterone or hCG administration generally have not found a significant effect of testosterone

on inflammatory markers (304). Similarly, in another study, even supraphysiological doses of testosterone did not affect C-reactive protein (305).

F.1.d. Androgens and Coronary Artery Disease. Whether variation of testosterone within the normal range is associated with risk of coronary artery disease remains controversial. Of the 30 cross-sectional studies reviewed by Alexandersen (123), 18 reported lower testosterone levels in men with coronary heart disease, 11 found similar testosterone levels in controls and men with coronary artery disease and 1 found higher levels of DHEAS. Prospective studies have failed to reveal an association of total testosterone levels and coronary artery disease (124-128, 306-308). The Rotterdam Study found that the common carotid artery intimal media thickness, a marker of generalized atherosclerosis, was the highest in older men in the lowest quartile of serum testosterone levels (128).

One interventional study (309), reported that testosterone undecanoate given orally improved angina pectoris in men with coronary heart disease. Testosterone infusion acutely improves coronary blood flow in a canine model and in men with coronary artery disease (310-316). Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease (315). This effect may be related to a direct coronary-relaxing effect. Testosterone replacement has been shown to increase the time to 1-mm ST-segment depression (313). However, in another study, there were no differences among the placebo or testosterone groups in peak heart rate, systolic blood pressure, maximal rate pressure product, perfusion imaging scores, or the onset of ST-segment depression (315). Studies by Yue et al (316) demonstrated testosterone-induced endothelium independent relaxation of rabbit coronary arteries via potassium conductance.

F.1.f. Effects of testosterone supplementation on atherosclerosis progression in animal models of atherogenesis. In a mouse model of atherosclerosis that is LDL-receptor deficient (317) surgical castration accelerated, and testosterone administration retarded the progression of atherosclerosis. The magnitude of testosterone effect on atherosclerosis progression is similar to that observed with estrogen administration. Favorable effects of testosterone on atherosclerosis in this mouse model are antagonized by concomitant administration of an aromatase inhibitor, suggesting that testosterone effects are possibly mediated through its conversion to estrogen in the vessel wall (317). Testosterone effects in retarding atherosclerosis progression were independent of plasma lipids (317). Many, though not all the studies in cholesterol-fed, castrated male rabbits are in agreement that testosterone does not promote atherogenesis (318). Taken together, these data provide evidence that testosterone, through its conversion to estradiol, can retard the progression of atherosclerosis in these animal models.

F.1.g The Effects of Testosterone on Cardiovascular Events. To-date, no randomized trials on the effects of testosterone on cardiovascular-related events have been published (167). Therefore, the published data have been derived necessarily from the analyses of the reported adverse events in randomized clinical trials. The number of cardiovascular-related events reported in randomized testosterone trials has been strikingly low—even lower than that expected for the age and comorbid conditions of the participants (167, 319-320).A randomized trial of testosterone in older men (The TOM Trial) with mobility limitation was stopped early due

to a higher frequency of cardiovascular-related events in men assigned to testosterone than in those assigned to placebo (164), heightening concern about the cardiovascular safety of testosterone in frail older men. In contrast to many other testosterone trials in older men, which recruited relatively healthy older men, the participants in the TOM trial had a high prevalence of chronic conditions, such as heart disease, diabetes mellitus, obesity, hypertension, and hyperlipidaemia (164). Men, 75 years of age or older, and men with higher on-treatment testosterone levels seemed to be at the greatest risk of cardiovascular-related events. The dose of testosterone used in the TOM trial was higher than that used in some previous trials, but not dissimilar from or lower than that used in some other trials.

Several meta-analyses of randomized testosterone trials have been conducted (292, 319-320).However, these meta-analyses are limited by the small size of most trials, heterogeneity of study populations, poor quality of adverse-event reporting, and short treatment duration in many trials. None of the testosterone trials to date was sufficiently powered to adequately assess safety outcomes. The rigor of adverse-event reporting varied greatly among studies. The most recent meta-analysis of randomized testosterone trials included 2,994 men from 27 eligible trials of 12 weeks or longer duration. Randomization to testosterone was associated with an increased the risk of a cardiovascular-related event (odds ratio (OR) 1.54, 95% confidence interval (CI) 1.09 to 2.18) (**Figure 9**) (320). A remarkable finding of this meta-analysis was that the effect of testosterone therapy varied with the source of the trial's funding (320). The risk of a cardiovascular-related event on testosterone therapy was even greater (OR 2.06, 95% CI 1.34 to 3.17) in trials that were not funded by the pharmaceutical industry; in contrast, the trials funded by the pharmaceutical industry did not reveal a significant increase in cardiovascular events. Vigen et al (321) assessed the association between testosterone therapy and all-cause mortality, myocardial infarction (MI), or stroke among male veterans with low testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system between 2005 and 2011. After adjusting for the presence of coronary artery disease, testosterone therapy was associated with increased risk of adverse outcomes (all-cause mortality, myocardial infarction or stroke) (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). It should be noted that a separate retrospective analysis of men in the Veterans Affairs Health Care System reported reduced overall mortality in men receiving testosterone (322).

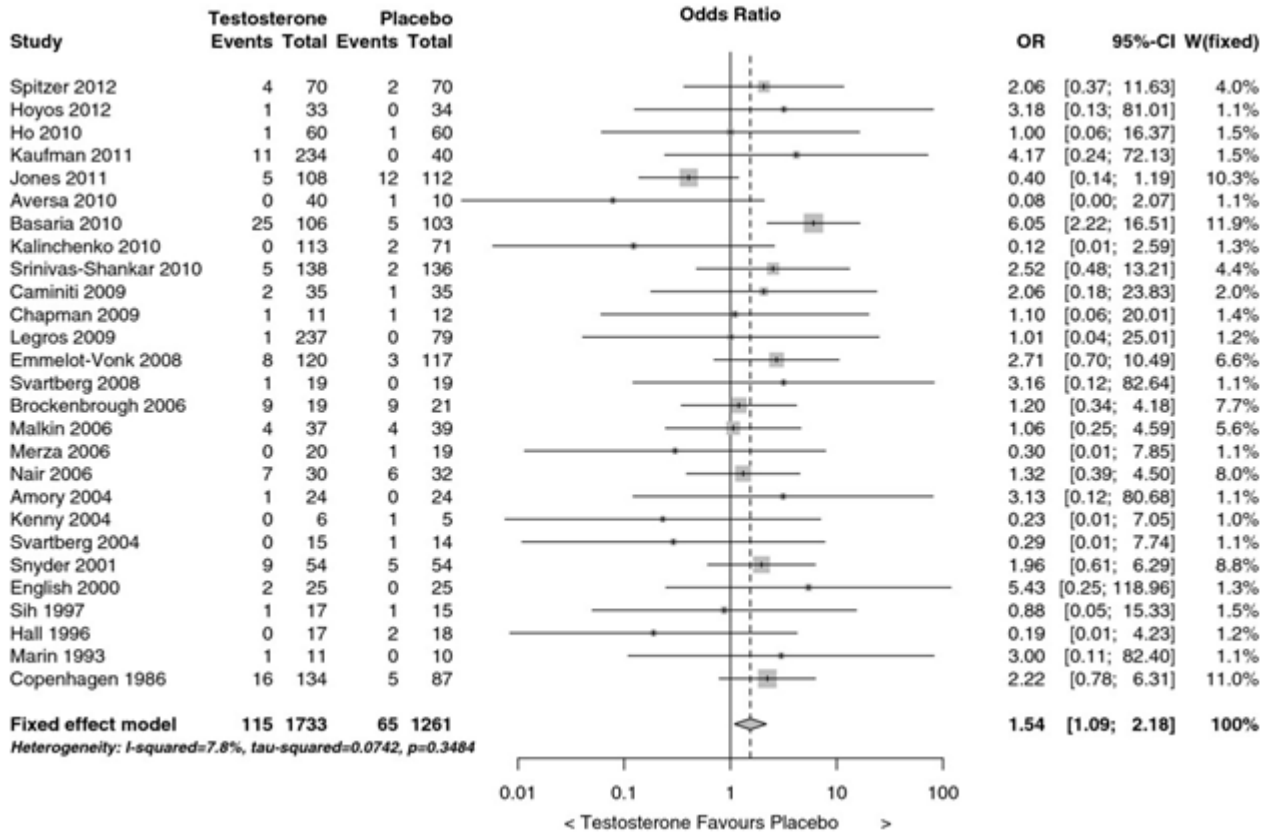


Figure 9. A meta-analysis of cardiovascular events in randomized testosterone trials
In this meta-analysis of cardiovascular-related events in randomized testosterone trials included 2,994 men from 27 eligible trials of 12 weeks or longer duration. Randomization to testosterone was associated with a significantly increased risk of cardiovascular-related event (odds ratio (OR) 1.54 (577). An additional finding of this meta-analysis was that the risk of a cardiovascular-related event on testosterone therapy was even greater (OR 2.06) in trials that were not funded by the pharmaceutical industry; in contrast, the trials funded by the pharmaceutical industry did not reveal a significant increase in cardiovascular events.

Reproduced with permission from Xu et al (577)

The Hormonal Regulators of Muscle and Metabolism in Aging (HORMA) trial reported a significantly greater increase in blood pressure in men treated with testosterone than in those treated with placebo (323). Testosterone administration causes salt and water retention, which can induce edema and worsen pre-existing heart failure. Thus, large prospective randomized trials are needed to determine the effects of testosterone therapy on cardiovascular health.

F.1.h Synopsis of the Effects of Testosterone on Cardiovascular risk. The cohort and cross-sectional studies collectively suggest a neutral or favorable effect of testosterone on coronary heart disease in men, although the evidence is far from conclusive. It is possible that frail elderly men with high burden of chronic diseases and cardiovascular risk factors may be at increased risk of cardiovascular-related adverse events (167). Long term randomized trials of the effects of testosterone replacement on cardiovascular events are needed and are

particularly important because even small changes in incidence rates could have significant public health impact.

F.1.i. Testosterone, Diabetes, and Metabolic Syndrome

Spontaneous (134) and experimentally induced (324) androgen deficiency is associated with increased fat mass, and testosterone replacement decreased fat mass in older men with low testosterone levels (5). In epidemiologic studies, low testosterone levels are associated with higher levels of abdominal adiposity (325-326). Testosterone administration promotes the mobilization of triglycerides from the abdominal adipose tissue in middle-aged men (327). Surgical castration in rats impairs insulin sensitivity; physiologic testosterone replacement reverses this metabolic derangement (328). However, high doses of testosterone impair insulin sensitivity in castrated rats (328), suggesting a biphasic relationship in which both low and high testosterone levels impair insulin resistance. Androgens increase insulin-independent glucose uptake (329) and modulate LPL activity in a region-specific manner (330).

Testosterone levels are lower in men with type 2 diabetes mellitus compared with controls (331-335). Low total testosterone levels have been associated consistently with increased risk of type 2 diabetes mellitus and metabolic syndrome in community dwelling menboth cross-sectionally and longitudinally (336-343). However, the association of free testosterone and type 2 diabetes mellitus has been inconsistent; some studies have reported a weak relationship (336-337, 341) while others have failed to find any relationship (338, 340). Circulating sex hormone binding globulin (SHBG) and some SHBG polymorphisms also have been associated negatively with the risk of type 2 diabetes (336-346). For instance, individuals with the rs6257,rs179994, and rs6259 variants alleles of the SHBG single nucleotide polymorphism (SNP) have lower plasma SHBG levels and a higher risk of type 2 diabetes (342, 344-346). As total testosterone and SHBG levels are highly correlated, we determined whether SHBG is an independent predictor of T2DM.Accordingly, we performed longitudinal analyses of men participating in the Massachusetts Male Aging Study (347), a population-based study of men aged 40-70 years (**Figure 10**). After adjustment for age, body mass index, hypertension, smoking, alcohol intake and physical activity, the hazard ratio (HR) for incident type 2 diabetes was 2.0 for each one SD decrease in SHBG and 1.29 for each one SD decrease in total testosterone (347). Free testosterone was not significantly associated with type 2 diabetes. The strong association of T2DM risk with SHBG persisted even after additional adjustment for free testosterone. Thus, SHBG, but not free testosterone, is an independent predictor of incident type 2 diabetes. Although it is possible that SHBG is a marker of insulin resistance, and low SHBG levels reflect the effects of hyperglycemia or insulin resistance, the association of SHBG polymorphisms with type 2 diabetes suggests an important mechanistic role of SHBG in the pathogenesis of type 2 diabetes.

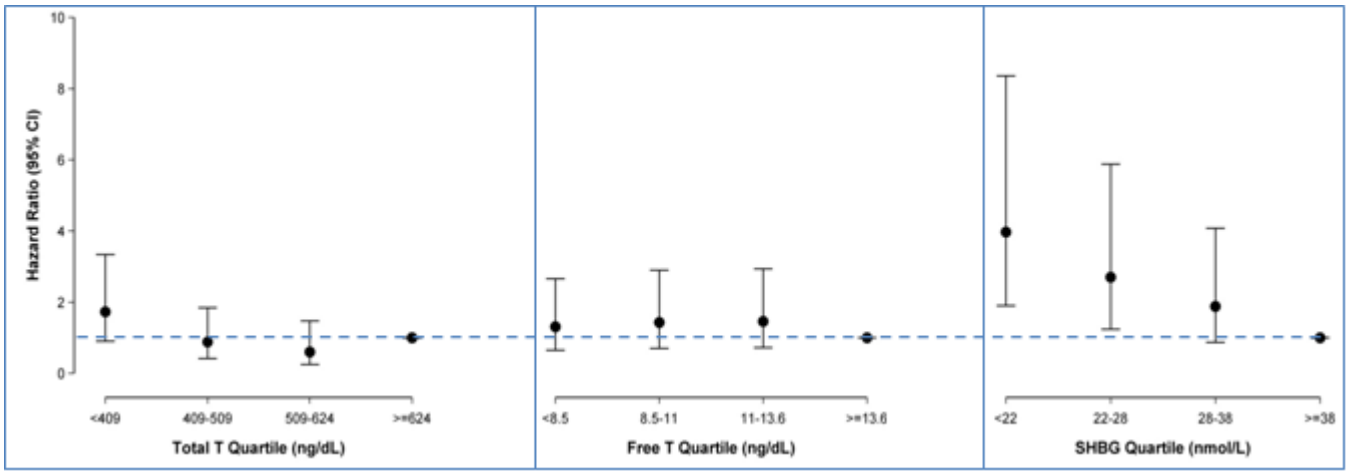


Figure 10. Circulating Concentrations of SHBG, but not total or free testosterone, were associated prospectively with risk of incident diabetes in the Massachusetts Male Aging Study (MMAS). In a prospective analysis of data from the Massachusetts male Aging Study, total testosterone (left panel) and free testosterone (middle panel) were not associated significantly with risk of incident diabetes. Only SHBG concentrations were associated with incident diabetes in longitudinal analysis. Reproduced with permission from Lakshman et al (JAGS).

Interventional trials have yielded inconsistent results. Acute and severe androgen deficiency induced by administration of a GnRH agonist or antagonist worsens measures of insulin sensitivity. Thus, acute withdrawal of testosterone therapy in men with idiopathic hypogonadotropic hypogonadism (348) and administration of androgen deprivation therapy in men with prostate cancer (349) is associated with the development of insulin resistance. The men with prostate cancer who are receiving androgen deprivation therapy are at increased risk of the type 2 diabetes (349). Although several randomized testosterone trials have been conducted in men with type 2 diabetes mellitus, only the results of one such trial have been published (350). In the TIMES2 study (350), the men with type 2 diabetes mellitus and/or metabolic syndrome were randomized to either 2% testosterone gel or placebo gel for 6 months. Randomization to testosterone arm was associated with greater improvements in sexual function and plasma lipid levels than placebo (350). However, the changes in HbA_{1c} levels did not differ between groups (350). Homeostasis model assessment of insulin resistance (HOMA-IR), a marker of insulin resistance, improved modestly in men who were assigned to testosterone compared with placebo (350). Overall, this and other unpublished studies have failed to show improvements in diabetes outcomes or consistent changes in measures of insulin sensitivity (167, 350-353) even though interventional trials have found a consistent reduction in whole body fat as well as abdominal fat (167, 353, 354).

F.2. Testosterone and Prostate Cancer Risk There is no evidence that testosterone administration causes prostate cancer. Also, there is no consistent relationship between endogenous serum testosterone levels and the risk of prostate cancer (5, 355-356). However, there are a number of areas of concern that are discussed below. Prostate cancer is a common,

androgen–dependent tumor, and androgen administration may promote the growth of a pre-existing prostate cancer (356-357). Testosterone administration is absolutely contraindicated in men with history of prostate cancer (5, 355). The prevalence of subclinical, microscopic foci of prostate cancer in older men is high (358-366). There is concern that testosterone administration might make these subclinical foci of cancer grow and become clinically overt. In addition, older men with low testosterone levels may have prostate cancer (367-368). Morgentaler et al (367-368) reported a high prevalence of biopsy-detectable prostate cancer in men with low total or free testosterone levels despite normal PSA levels and normal digital rectal examinations. However, this study did not have a control group, and we do not know whether sextant biopsies of age-matched controls with normal testosterone levels would yield a similarly high incidence of biopsy-detectable cancer. Therefore, this study should not be interpreted to conclude that there is a higher prevalence of prostate cancer in older men with low testosterone levels, or that low testosterone levels are an indication for performing prostate biopsy.

F.2.a. Androgen Levels and Prostate Cancer Risk: Data from Cross-sectional Studies. Overall, in cross-sectional, epidemiological studies, there has not been a consistent association between circulating androgen levels and the occurrence of prostate cancer(369-388). While one meta-analysis found no association between serum testosterone levels and prostate cancer (374), another found a slightly increased risk of prostate cancer in men with the highest testosterone levels (382). A recent meta-analysis of epidemiologic studies concluded that there is no consistent relationship between endogenous testosterone levels and the risk of prostate cancer (356).

F.2.c. Effects of Testosterone Therapy on Prostate Events. None of the testosterone trials in middle-aged or older men has had sufficient power to detect meaningful differences in prostate event rates between testosterone and placebo-treated men. A systematic review of randomized testosterone trials in middle-aged and older men found higher rates of prostate events in testosterone-treated men than in placebo-treated men(**Figure 11**(292). Men treated with testosterone in these trials were at significantly higher risk for undergoing prostate biopsy than placebo-treated men (292). Because of the high prevalence of subclinical prostate cancer in older men, the higher number of prostate biopsies in testosterone-treated men is likely to yield higher detection rates of prostate cancer in comparison with placebo-treated men. Thus, testosterone therapy of middle-aged and older men is associated with a higher risk of prostate biopsy and a bias towards detection of a higher number of prostate events (167, 292).

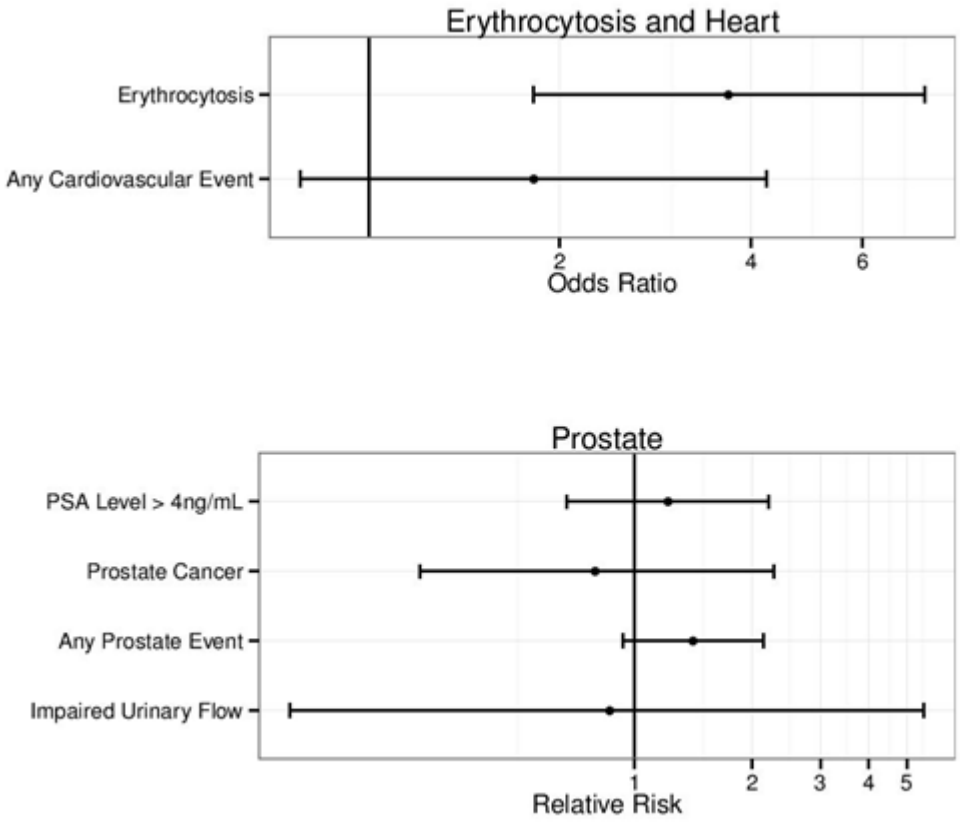


Figure 11. Adverse events associated with testosterone therapy in randomized trials
The odds ratios for erythrocytosis and cardiovascular events in randomized testosterone trials derived from meta-analyses published by Calof et al 2005 and Haddad et al 2007, respectively are shown in the upper panel. The figure was reproduced with permission from Spitzer et al, Nature Reviews in Endocrinology 2013.

The lower panel shows the relative risk of prostate events and the associated 95% confidence intervals in a meta-analysis of randomized testosterone trials. Data were derived from a meta-analysis by Fernandez-Balsells 2010, and the figure reproduced with permission from Spitzer et al, Nature Reviews in Endocrinology 2013.

Administration of exogenous testosterone or suppression of circulating levels of testosterone by administration of a GnRH antagonist is not associated with proportionate changes in intra-prostatic testosterone or DHT concentrations. For instance, in arandomized controlled trial, Marks et al (389) measured intraprostatic testosterone and DHT levels in older men treated with placebo or testosterone. Surprisingly, intraprostatic DHT concentrations were not significantly higher in testosterone-treated men than in placebo-treated men (389). Similarly, the expression levels of androgen-dependent genes in the prostate were not significantly altered by testosterone administration (389). In separate studies, lowering of circulating testosterone levels by administration of a GnRH antagonist was not associated with changes in intraprostatic androgen concentrations (390-391).

F.2.b. Effects of Testosterone Replacement on Serum PSA Levels. Serum PSA levels are lower in androgen–deficient men and are restored to normal following testosterone replacement (5, 392-400). Lowering of serum testosterone concentrations by withdrawal of androgen therapy in young, hypogonadal men is associated with a decrease in serum PSA levels. Similarly, treatment of men with benign prostatic hyperplasia with a 5-alpha reductase inhibitor, finasteride, is associated with a significant lowering of serum and prostatic PSA levels(400-401). Conversely, testosterone supplementation increases PSA levels (393-400). However, serum PSA levels do not increase progressively in healthy hypogonadal men with replacement doses of testosterone. Placebo–controlled trials of testosterone administration in older men have reported either minimal increase or no significant change in serum PSA levels in testosterone–treated men (157-158). The increase in PSA levels during testosterone replacement might trigger evaluation and biopsy in some patients (5, 355).

More intensive PSA screening and follow-up of men receiving testosterone replacement might lead to an increased number of prostate biopsies and the detection of subclinical prostate cancers that would have otherwise remained undetected (5, 355).Serum PSA levels tend to fluctuate when measured repeatedly in the same individual over time (402-404). When serum PSA levels in androgen deficient men on testosterone replacement therapy show a change from a previously measured value, the clinician has to decide whether the change warrants detailed evaluation of the patient for prostate cancer, or whether it is simply due to test–to–test variability in PSA measurement. Therefore, it is important to set criteria for monitoring PSA changes during testosterone supplementation. Criteria that use very low thresholds for performing prostate biopsy relative to test-retest variability will likely result in an excessive number of biopsies with their associated costs, psychological trauma, and morbidity. On the other hand, criteria that use unreasonably high thresholds for performing prostate biopsies may fail to detect clinical prostate cancers at an early stage.

There is considerable test-retest variability in PSA measurements (402-404). Some of this variability is due to the inherent assay variability, and a significant portion of this variability is due to unknown factors. Fluctuations are larger in men with high mean PSA levels. Variability can be even greater if measurements are performed in different laboratoriesthat use dissimilar assay methodology (402-404).

From a clinical perspective, an important issue is what increment in PSA level should warrant a prostate biopsy in older men receiving testosterone replacement. To address this issue, we conducted a systematic review of published studies of testosterone replacement in hypogonadal men (355). This review indicated that the weighted effect size of the change in PSA after testosterone replacement in young, hypogonadal men is 0.68 standard deviation units (95% confidence interval 0.55 to 0.82). This means that the effect of testosterone replacement therapy is to increase PSA levels by an average 0.68 standard deviations over baseline. Because the average standard deviation was 0.47 in this systematic analysis, the standard deviation score of 0.68 translates into an average increase in serum PSA levels of about 0.30 ng/ml in young hypogonadal men (355). There is considerable variability in the magnitude of change in PSA after testosterone supplementation among these studies, in part due to

heterogeneity of study populations, inclusion of older men in some studies but not others, and differences in PSA assays. In addition, many patients who were enrolled in these studies were likely receiving testosterone replacement therapy previously; we do not know whether the washout period was sufficient to return PSA levels to baseline. Therefore, it is possible that because of inadequate washout, the increments in serum PSA levels after testosterone administration might have been under-estimated.

We performed a separate systematic review of data from placebo-controlled trials of testosterone supplementation in older men with low or low normal testosterone concentrations (355). The weighted effect size in six studies of older men was 1.48 standard deviation units, with a 95% confidence interval of 1.21 to 1.75. Thus, on average, older men experience a greater increase in serum PSA concentrations than younger men. The average effect of testosterone replacement in older men is to increase PSA levels by almost 1.5 standard deviations over baseline. There is, however, significant variability in the results among these six studies ($p<0.0001$), and the average standard deviation was skewed by one study, which had a very high standard deviation (355). After excluding this study, the average change in serum PSA levels after testosterone replacement in studies of older men was 0.43 ng/mL.

The data from the Proscar Long-Term Efficacy and Safety Study (PLESS) demonstrated that the 90% confidence interval for the change in PSA values measured 3 to 6 months apart is 1.4 ng/mL (400). Therefore, a change in PSA of >1.4 ng/ml between any two values measured 3 to 6 month apart in the same patient should be verified by a repeat PSA measurement (5, 355). If the repeated measurement confirms a change of >1.4 ng/ml from the previous value, then that patient should be referred for Urologic evaluation.

Carter et al, based on the analysis of PSA data from the Baltimore Longitudinal Study of Aging, reported that PSA velocity, defined as the annual rate of change of PSA, is different in men who develop prostate cancer than in those who do not (405-407). Thus, PSA velocity greater than 0.7 ng/ml/year was unusual in men without prostate cancer whose baseline PSA was between 4 and 10 ng/ml (405-407). However, most men being considered for testosterone replacement will have baseline PSA less than 4 ng/ml. In a subsequent analysis, the same group reported that the PSA velocity in men with baseline PSA between 2 and 4 ng/ml was 0.2 ng/ml/year (407). Because test-to-retest variability in PSA measurement is far greater than this threshold, it is likely that the use of this threshold of 0.2 ng/ml/year to select men for prostate biopsy would lead to many unnecessary biopsies. These considerations of interassay variability and the longitudinal change in PSA led an Endocrine Society Expert Panel to suggest that in men receiving testosterone replacement, a PSA velocity of greater than 0.4 ng/ml/year in men whose baseline PSA is less than 4 ng/ml should lead to urological evaluation (5). Carter et al have emphasized that PSA velocity should not be used for data of less than 2 years duration (405-408).

In eugonadal, young men, administration of supraphysiological doses of testosterone does not further increase serum PSA levels (140, 143, 409). These data are consistent with dose response studies in young men that demonstrate that maximal serum concentrations of

PSA are achieved at testosterone levels that are at the lower end of the normal male range; higher testosterone concentrations are not associated with higher PSA levels (140, 143).

In summary, these data suggest that the administration of replacement doses of testosterone to androgen-deficient men can be expected to produce a modest increment in serum PSA levels. Increments in PSA levels after testosterone supplementation in androgen-deficient men are generally less than 0.5 ng/mL, and increments in excess of 1.0 ng/mL over a 3-6 month period are unusual. Nevertheless, administration of testosterone to men with baseline PSA levels between 2.5 and 4.0 ng/mL will cause PSA levels to exceed 4.0 ng/mL in some men. Increments in PSA levels above 4 ng/mL will trigger a urological consultation and many of these men will be asked to undergo prostate biopsies.

F.2.c. Monitoring PSA Levels in Older Men Receiving Testosterone Replacement (**Tables3 and 6**)Older men considering testosterone supplementation should undergo digital examination of the prostate, evaluation of risk factors for prostate cancer, and a baseline PSA measurement (5). Men with history of prostate cancer should not be given androgen supplementation, and those with palpable abnormalities of the prostate or PSA levels greater than 3 ng/ml should undergo urological evaluation. After initiation of testosterone replacement therapy, PSA levels and digital examination of the prostate should be repeated at 3, 6, and 12 months, and annually thereafter (5). In patients in whom sequential PSA measurements are available for more than two years, PSA velocity criterion can be useful in evaluating change in PSA levels. A PSA velocity of greater than 0.4 ng/ml/year in men with baseline PSA less than 3 ng/ml should be evaluated **(Table 6)**. Although measurements of free PSA and PSA density have been proposed to enhance the specificity of PSA measurement, long term data, especially from studies of testosterone replacement in older men, are lacking.

Table 6. Indications for Urological Consultation in Men Receiving Testosterone Replacement

1. An increase in serum or plasma PSA concentration >1.4 ng/mL within any 12 month period after initiating testosterone treatment
2. A PSA velocity of >0.4 ng/mL/year using the PSA level after 6 months of testosterone administration as the reference* (only applicable if PSA data are available for a period exceeding 2 years)
3. Detection of a prostatic abnormality on digital rectal examination
4. An AUA/IPSS prostate symptom score of >19

*, The recommendation for using PSA velocity threshold of 0.4 ng/ml/year is not based on data, but it takes into consideration the findings of Fang et al (Fang et al. 2002) and those of Smith and Catalona (Smith and Catalona 1994).

Adapted with permission from the Endocrine Society Guideline for the Management of Androgen Deficiency Syndrome in Men in: Bhasin et al J Clin Endocrinol Metab 2010;95(6):2536-59**.**

F.2.d. Testosterone and Benign Prostatic Hypertrophy Testosterone replacement can be administered safely to men with benign prostatic hypertrophy who have mild to moderate symptom scores. The severity of symptoms associated with benign prostatic hypertrophy can be assessed by using either the International Prostate Symptom Score (IPSS) or the American Urological Association (AUA) Symptom questionnaires. Androgen deficiency is associated with decreased prostate volume and androgen replacement increases prostate volumes to those in age–matched controls (389, 392, 396-397). In patients with pre–existing, severe symptoms of benign prostatic hypertrophy, even small increases in prostate volume during testosterone administration may exacerbate obstructive symptoms. In these men, testosterone should either not be administered or administered with careful monitoring of obstructive symptoms.

F.3. Erythrocytosis Testosterone replacement is associated with increased red cell mass and hemoglobin levels (**Figure 9**) (410-414). Therefore, testosterone replacement should not be administered to men with baseline hematocrit of 50% or greater without appropriate evaluation and treatment of erythrocytosis (5) (Table 3). Administration of testosterone to androgen–deficient young men is typically associated with a small increase in hemoglobin levels. Clinically significant erythrocytosis is uncommon in young hypogonadal men during testosterone replacement therapy, but can occur in men with sleep apnea, significant smoking history, or chronic obstructive lung disease. Testosterone administration in older men is associated with more variable and somewhat greater increments in hemoglobin than observed in young, hypogonadal men (415). The magnitude of hemoglobin increase during testosterone therapy appears related to the testosterone dose, the increase in testosterone concentrations during testosterone therapy, and age (415). Testosterone replacement by means of a transdermal system has been reported to produce a lesser increase in hemoglobin levels than that associated with testosterone esters (416).

Testosterone increases hemoglobin and hematocrit by multiple mechanisms (417, 281-283). Testosterone administration stimulates erythropoiesis, suppresses hepcidin transcription by blocking BMP signaling, and increases iron availability for erythropoiesis (417, 281-283). Additionally, testosterone appears to alter the set-point of the relationship between erythropoietin and hemoglobin (281). Testosterone supplementation can correct anemia in older men with anemia of aging and in older mice (281, 283).

F.4. Monitoring Hematocrit During Testosterone Replacement Therapy (Table 3) Hemoglobin levels should be measured at baseline, and 3 and 6 months after institution of testosterone replacement, and every 6 months thereafter. It is not clear what absolute hematocrit level or magnitude of change in hematocrit warrants discontinuation of testosterone administration. Plasma viscosity increases disproportionately as hematocrit rises above 50%. Hematocrit levels above 54% are also associated with increased risk of stroke. Therefore, testosterone dose should be withheld if hematocrit rises above 54%; once hematocrit falls to a safe level, testosterone therapy may be re-initiated at areduced dose (5). Consideration should also be given to switching to a transdermal system, if the men are receiving injectable esters. Periodic phlebotomy is also a reasonable option in men in whom hematocrit rises above this threshold during testosterone supplementation.

F.5. Sleep Apnea Circulating testosterone concentrations are related to sleep rhythm and are generally higher duringsleepthan during waking hours (418-421). Testosteronesecretory peaks coincide with the onset of rapid-eye movement sleep. Aging is associated with decreasedsleep efficiency,reduced numbers of REM sleep episodes, and altered REM sleep latency, which may contribute to lower circulating testosterone concentrations (419-423). The degree of sleep-disordered breathing increases with age, and is associated with reduced overnight plasma bioavailable testosterone. Thus, changes in sleep efficiency and architecture are associated with alterations in testosterone levels in older men (419-423).

Testosterone can induce or exacerbate sleep apnea in some individuals, particularly those with obesity or chronic obstructive lung disease(418-424). This appears to be due to direct effects of testosterone on laryngeal muscles. However, the occurrence of sleep apnea, *de novo,* in healthy older men treated with physiologic testosterone replacement, is very infrequent.

In men with obesity and obstructive sleep apnoea, testosterone administration has been reported to worsen sleep-disordered breathing (421). Testosterone administration depresses hypercapnoeic ventilator drive and induces apnoea in primate infants (423). Short-term administration of high doses of testosteroneshortenssleep duration and worsenssleepapnoea in older men (425) The frequency of sleep apnoea in randomized testosterone trials in older men has been very low (5, 319). Obstructive sleep apnoea is often associated with low testosterone levels (426).

Testosterone should not be given to men with severe obstructive sleep apnea without evaluation and treatment of sleep apnea. Several screening instruments can be used to detect sleep apnea. A history of loud snoring, and daytime somnolence, in an obese individual with hypertension increases the likelihood of sleep apnea.

F.6. Breast Enlargement Testosterone administration can induce breast enlargement due to testosterone conversion to estradiol although this is an uncommon complication. Even with administration of supraphysiological doses of testosterone enanthate, less than 4% of men in a contraceptive trial developed detectable breast enlargement (410). Breast cancer is listed as a contraindication for testosterone replacement therapy primarily because of concern that increased estrogen levels during testosterone treatment might exacerbate breast cancer growth. There are, however, few case reports of breast cancer occurring as a complication of testosterone treatment. Men with Klinefelter's syndrome have a higher risk of breast cancer than general population ().

CHANGES IN THE GAMETOGENIC COMPARTMENT OF THE TESTIS

Women are more fertile below the age of 40, and fertility ceases at the inception of menopause, around age 50. Increasing age in women confers greater risk for infertility, spontaneous abortion, and genetic and chromosomal defects among offspring.In contrast, there is no critical age at which sperm production or function, and fertility cease in men (427-434). Although serum testosterone levels decrease below the normal range in a significant minority of older men, men over the age of 60 years commonly father children; the oldest father on record

was 94-years old(427,429). Even though many older men are fertile, the overall fertility and fecundity declines with aging. The interpretability of data on the effects of aging on male fertility is limited by the small size of the studies and the low overall event rates.

Although there is a positive association between paternal age and incidence of aneuploidy, it has been difficult to dissociate the effect of paternal age from the confounding influence of the advanced maternal age. After accounting for various confounders, there does not appear to be a major independenteffect of increased paternal age on the incidence of autosomal aneuploidies (428-429, 436-437, 439-440).The existence of a paternal age effect on Down syndrome is controversial. Earlier studies from the 1960s and 1970s found no correlation between Down syndrome and paternal age(e.g., 441). However, a study in New York from 1983 to 1997 found a significant greater numbers of mothers and fathers 35 years of age and older, respectively,among parents of patients with Down's syndrome (442). Among the cases of Down syndrome evaluated, paternal age had a significant effect only in mothers 35 years of age or older, and was the greatest in couples greater than 40 years of age where the risk was 6 times the rate of couples younger than 35 years of age (442).

Approximately one third of babies with diseases due to new autosomal dominant mutations are fathered by men aged 40 years or older (443).Paternal age has been associated with a significant increase in the risk of germ line mutations in FGFR2, FGFR3, and RET genes and inherited autosomal dominant diseases, such as Apert's syndrome, achondroplasia, and Costello Syndrome, respectively, in the offspring of older men (434, 439-440, 444-450). These monogenic disorders have been referred to as paternal age effect disorders (PAE). Some other disorders such as schizophrenia and autism have also been linked to paternal age (439-440, 449-450). The rate of de novo mutations increases with paternal age (449), which may contribute to the increase risk of neurodevelopmental diseases such as schizophrenia and autism (449). The accumulation of these de novo germ line mutations with increasing paternal age has been explained by the "selfish spermatogonial selection" hypothesis (445-446). According to this hypothesis, the somatic mutations in male germ cells that enhance the proliferation of germ cells could lead to within-testis expansion of mutant clonal lines (447-448), thus favoring the propagation of germ cells carrying these pathogenic mutations, and increasing the risk of mutations in the offspring of older fathers (447-448).Interestingly, the risk of autism has also been associated with the age of the father as well as the grandparent (450). These concerns have prompted the American Society of Reproductive Medicine to state in their guidelines that semen donors should be younger than 50 years of age so that potential hazards related to aging are diminished (430). More recently, the guidelines lowered the age limit of semen donors to 40 years.

Some cardiac defects have also been attributed to aberrant genetic input from older men. For instance, a case-control study of 4,110 individuals with congenital heart defects born between 1952 and 1973 in British Columbia, found a general pattern of increasing risk with increasing paternal age among cases relative to controls for ventricular septal defects, atrial septal defects and patent ductus arteriosus(443-444). The risk of schizophrenia has also been reported to increase with paternal age (445) and possible loci affecting this risk have been

identified (451). In addition, a modest proportion of preeclampsia, normally associated with increased maternal risk factors including age, might be attributable to an increase in paternal age although no gene loci have been identified (452). These observations need further corroboration.

There are no longitudinal studies in men of any age demonstrating defined changes in the reproductive tract that would explain a decline in fertility. Problems might occur at many levels. Thus aging might affect fertility at the level of the 1) germ cell, decreasing sperm number, sperm DNA integrity, and chromosomal quality; 2) supportive cells, affecting sperm quality and number; 3) accessory glands, affecting sperm motility and function; and 4) deposition of sperm into the vagina, decreasing erectile function, ejaculation and frequency of intercourse.

A. Changes in fertility of older men

A review of studies examining fertility at different ages demonstrated significant age-related differences in fertility rates men, including lower pregnancy rates, increased time to pregnancy, and subfecundity in men older than 50 years (428-429, 438-439, 453). Some changes in fertility rates might be related to age-related decrease in sexual activity. A literature review found no significant change in sperm concentration with aging when comparing men under the age of 30 to those greater than 50 years (433).However, in general, semen volume, sperm motility, and thenumber of morphologically normal sperm decrease with advancing age (Table 7; 428-438, 449, 454). A number of these studies, however, did not control for important confounding variables. Of the 21 studies in which sperm densities were compared among men of different age groups (433), only four studies adjusted for the duration of abstinence, well known to affect sperm concentration. In addition, there is significant heterogeneity in the populations studied; most of the studies examined data from semen of sperm donors while others examined men from infertility clinics. Sperm donors might represent a healthier group of men than the general population; conversely men in infertility clinics might be more likely to have abnormalities of sperm number or function. Even studies that have controlled for abstinence as well as alcohol and tobacco use have shown an age-related decrease in semen volume. In one study of men whose partners had bilateral tubal obstruction or absence of both tubes and who were treated by conventional IVF, the odds ratio of failure to conceive was higher for men 40 years of age or older (455).

Table 7: Changes in Semen Quality and Fertility in Men with Age in a Literature Review by Kidd et al., 2001 (388)

Parameter	Age comparison	Change
Semen volume	30 versus ≥50 years	3-22% decrease
Sperm concentration	Varying	None
Abnormal sperm morphology	≤30 versus ≥ 50 years	4-18% increase
Time to pregnancy	<30-35 versus >30-50	5-20% increase

	years	
Pregnancy rates	<30 versus > 50 years	23-38% decrease
Subfecundity	Varying	11-250% increase

B. Changes in the Germ Cell Compartment

In a comparison of younger men (21-25 years)with older men (>50) referred for andrological evaluation, the ejaculate volume, progressive sperm motility, and sperm morphology were lower in older men than younger menafter adjustment for duration of sexual abstinence, (456). The older men also had a higher frequency of sperm tail defects, suggesting epididymal dysfunction (457). In addition, the fructose content was significantly lower in older men suggesting a defect in the seminal vesicle contribution to semen (457). There were no significant differences in sperm concentration and testicular size between the young and older men in this study.

Necropsies on adult men of different ages have revealed that the testicular volume was lower only in men in the 8th decade of life(458). A recent study examined testicular germ cells obtained by orchidectomy from 36 older men with advanced prostate cancer and by testicular biopsy from 21 younger men with obstructive azoospermia, as controls (459). The ratios of primary spermatocytes, round spermatids, and elongated spermatids to Sertoli cells were significantly decreased in the testes of older men, but the ratio of spermatogonia to Sertoli cell number remained unchanged (459-460). Older men are characterized by lower rates of germ cell apoptosis and cell proliferation compared with younger men, suggesting that germ cell proliferation and apoptosis diminish with aging (460).

Other studies evaluating the fidelity of the germ cell compartment are cross-sectional and depend on analyses of sperm number and semen quality; large-scale chromosomal analyses in healthy community dwelling men are scarce as most data are derived from fertility clinics. A review of studies examining semen quality at different ages demonstrated significant age-related decrease in semen volume and sperm morphology. The change in sperm morphology has been hypothesized to be due to an increase in aneuploidy with age. Härkönen et al (437) found that sperm morphology was directly associated with the number of chromosomes in sperm and that men with higher aneuploidy rates for chromosomes 13, 18, 21, X and Y had lower sperm motility and sperm concentrations. In spite of the changes in sperm morphology and motility from older men, *in vitro* fertilizing capacity of the sperm is well preserved (454-455). In some older men, degenerating germ cells can be observed suggesting loss of germ cells with age.

There are several difficulties in interpreting these data on age-related changes in sperm density and function. The normal range for sperm concentration in men is wide where sperm concentration above 15 million/ml (total sperm per ejaculate > 39 million) is considered normal. Thus, even though average sperm concentrations might decline with aging, they might still be in the normal range (453-454, 459). Furthermore, normal sperm counts might not always correlate with normal sperm function.

Studies in flies demonstrate more germ cells during larval than adult stages suggesting age-related quiescence of the germ line (461). Significant age-related decreases in germ cells and spermatogenesis also have been reported in rodents and primates (462-466). The Brown Norway rat has been studied as a model of aging of the human male reproductive system because in this rodent model, serum testosterone levels decrease with aging, as they do in humans (463-465). Along with changes in hypothalamic-pituitary hormones, alterations in sperm counts, sperm maturation, Sertoli cell number, and progeny outcomes have been observed in this rodent model (**Table 8**; 452, 463-472). Analysis of ribosomal DNA from germ cells of the male brown Norway rat has revealed hypermethylation of ribosomal DNA(466, 473). Alterations in ribosomes have been theorized to promote aging of cells by multiplying errors in protein synthesis which initially might elude gross morphological analysis but eventually might lead to germ cell degeneration (473). Further assessment of spermatogonial stem cell populations is needed. In many animal models of life span extension, there is a trade-off between longer life and fecundity, although there are some exceptions(474).

Table 8. Changes in the reproductive axis in the Brown-Norway rat

Parameter	Change	Reference
GnRH	↓	405-406
FSH	↑	405-406
LH	→	405-406
Testosterone	↓	405-406, 435
Germ Cells	↓	407
Sertoli Cells	↓	406, 436
Spermatogenesis	↓	406, 436
Seminiferous Tubules	↓	406, 436
Seminiferous Tubule Function	altered	436-437
Epididymal function	↓	439-440
Sperm morphology	altered	439
Sperm motility	↓	439
Sperm Count	↓	406
Progeny Outcome	↓	441

C. **Changes in Supportive Cells and Accessory Glands**

Since Sertoli and Leydig cells are crucial to spermatogenesis, changes in these cells could affect sperm number and function. Age-related changes in the supporting structures for sperm maturation have been described in the Brown Norway rat. These changes include reductions in the numbers of Leydig and Sertoli cells, seminiferous tubules, and in epididymal cell number

and function (464-466). Changes in the supporting cells and structures for sperm maturation have been invoked to explain the age-related decrease in sperm number and fecundity in rats. In stallions, the numbers of Sertoli cells decreases with aging but individual Sertoli cells display a remarkable capacity to accommodate greater numbers of developing germ cells(475).

In men, Sertoli cell number has been reported to be lower in men aged 50 to 85 years than in men aged 20 to 48 years (476). The apoptotic rate of primary spermatocytes in aged men was also significantly elevated compared with that of younger men, resulting in a decrease of the number of primary spermatocytes per Sertoli cell (460), leading the authors to suggest that there might be a failure of the Sertoli cells to support spermatogenesis in older men.

Sertoli cells produce inhibin, which regulates gonadotropin expression from the pituitary. Inhibin B has been identified as the physiologically important form of inhibin in men and as a valuable serum marker of Sertoli cell function and spermatogenesis. Higher gonadotropins and lower inhibin levels in older men suggest a decline in Sertoli cell function(476); however changes in circulating inhibin B levels with advancing age have been inconsistent(476-479).Overall, these data suggest a possible decline in Sertoli cell number and function in older men with little affect on spermatogenesis.

Aging is accompanied by a progressive, albeit variable, decline of Leydig cell function with a decrease of mean serum free (or bioavailable) testosterone levels in the population between age 25 and 75 years(480). Total Leydig cell volume and the absolute number of Leydig cells decline with advancing age, although total testis weight does not change substantially with age (480-484). In one study, age accounted for more than a third of the variation in Leydig cell number, and explained more than half the variation in daily sperm production (483). This might in part be explained by a fusion of Leydig cells resulting in fewer but multinucleated Leydig cells with age (484). The functionality of the multinuicleated cells is not known.

II. Conclusion

In male mammals, changes at all levels of the hypothalamic-pituitary-testicular axis, including alterations in the GnRH pulse generator, gonadotropin secretion, and testicular steroidogenesis, in addition to alterations of feed-forward and feed-backrelationships contribute to an age-related decline in circulating testosterone concentrations. The rate of age-related decline in testosterone levels is affected by the presence of chronic illness, adiposity, medication, sampling time, and the methods of testosterone measurement. Epidemiologic surveys reveal an association of low testosterone levels with changes in body composition, physical function and mobility, risk of diabetes, metabolic syndrome, coronary artery disease, and fracture risk. Testicular morphology, semen production, and fertility are maintained up to a very old age in men. There is evidence of a small increase in the risk of specific genetic disorders among the offspring of older men.

Age-related decline in testosterone should be distinguished from classical hypogonadism due to known diseases of the hypothalamus, pituitary and the testis. In young hypogonadal men who have a known disease of the hypothalamus, pituitary and testis, testosterone therapy is generally beneficial and has been associated with a low frequency of adverse events.However,

neither the benefits in improved health outcomes nor the long term risks of testosterone therapy are known in older men with age-related decline in testosterone levels. The clinical consequences of age-related changes in circulating testosterone concentrations and epigenetic changes in sperm DNA are poorly understood.

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