Testosterone Supplementation Therapy for Older Men: Potential Benefits and Risks

David A. Gruenewald, MD†‡, and Alvin M. Matsumoto, MD*†‡*

Serum testosterone levels decline gradually and progressively with aging in men. Many manifestations associated with aging in men, including muscle atrophy and weakness, osteoporosis, reduced sexual functioning, and increased fat mass, are similar to changes associated with testosterone deficiency in young men. These similarities suggest that testosterone supplementation may prevent or reverse the effects of aging. A MEDLINE search was performed to identify studies of testosterone supplementation therapy in older men. A structured, qualitative review was performed of placebo-controlled trials that included men aged 60 and older and evaluated one or more physical, cognitive, affective, functional, or quality-of-life outcomes. Studies focusing on patients with severe systemic diseases and hormone deficiencies related to specific diseases were excluded.

In healthy older men with low-normal to mildly decreased testosterone levels, testosterone supplementation increased lean body mass and decreased fat mass. Upper and lower body strength, functional performance, sexual functioning, and mood were improved or unchanged with testosterone replacement. Variable effects on cognitive function were reported, with improvements in some cognitive domains (e.g., spatial, working, and verbal memory). Testosterone supplementation improved exercise-induced coronary ischemia in men with coronary heart disease, whereas angina pectoris was improved or unchanged. In a few studies, men with low testosterone levels were more likely to experience improvements in lumbar bone mineral density, self-perceived functional status, libido, erectile function, and exercise-induced coronary ischemia with testosterone replacement than men with less marked testosterone deficiency. No major unfavorable effects on lipids were reported, but hematocrit and prostate specific antigen levels often increased.

Based on these results, testosterone supplementation cannot be recommended at this time for older men with normal or low-normal testosterone levels and no clinical manifestations of hypogonadism. However, testosterone replacement may be warranted in older men with markedly decreased testosterone levels, regardless of symptoms, and in men with mildly decreased testosterone levels and symptoms or signs suggesting hypogonadism. The long-term safety and efficacy of testosterone supplementation remain uncertain. Establishment of evidence-based indications will depend on further demonstrations of favorable clinical outcomes and symptomatic, functional, and quality-of-life benefits in carefully performed, long-term, randomized, placebo-controlled clinical trials. **J Am Geriatr Soc 51:101–115, 2003.**

Key words: testosterone; aging; hormone replacement therapy; androgens; hypogonadism

In cross-sectional and longitudinal studies, aging in men is associated with a gradual and progressive decline in serum total testosterone concentrations as a result of primary testicular and secondary hypothalamic-pituitary dysfunction.[1–8] A substantial proportion of older men (ranging from 20% of 60-year-old to 50% of 80-year-old men) exhibit serum total testosterone levels below the normal range for younger men.[8] Because concentrations of sex hormone-binding globulin (SHBG), the main circulating binding protein for testosterone, increase with age, the age-related decline in serum free or bioavailable (non-SHBG-bound) testosterone is greater than that of total testosterone, and a larger proportion of older men have levels of free or bioavailable testosterone below the normal range for younger men. When low total testosterone levels occur in healthy older men, the level is usually mildly decreased (e.g., 2.5–3.0 ng/mL) and associated with symptoms such as erectile dysfunction, loss of libido, and muscle weakness. In frail older men in rehabilitation units or living in nursing homes, low testosterone levels are more

From the *Geriatric Research, Education, and Clinical Center, Veterans Affairs Puget Sound Health Care System, and †Division of Gerontology and Geriatric Medicine, Department of Medicine, and ‡Population Center for Research in Reproduction, University of Washington School of Medicine, Seattle, Washington.

This work was supported by Department of Veterans Affairs Medical Research Funds.

Address correspondence to David A. Gruenewald, MD, Veterans Affairs Puget Sound Health Care System, S-182-GRECC, 1660 South Columbian Way, Seattle, WA 98108. E-mail: david.gruenewald@med.va.gov.

0002-8614/03/$15.00

prevalent than in community-dwelling men of the same age,[9,10] and average free testosterone levels are usually below the normal range for healthy young men.[10,11] Testosterone levels are often low in a number of chronic medical illnesses (e.g., renal failure, malignancy) and with the use of certain medications (e.g., glucocorticoids, opiates) in older men. Furthermore, clinical findings suggesting hypogonadism are extremely common in these men.

In hypogonadal young men, the manifestations of androgen deficiency are fully or partially reversible with testosterone replacement, including decreased libido and energy, inability to concentrate, erectile dysfunction, weakness, and decreased muscle and bone mass. Because apparently healthy men often experience similar changes in association with reductions in serum testosterone levels with aging, testosterone supplementation has been proposed as a potential approach to prevent or reverse these conditions. For example, aging is associated with alterations in body composition, including decreased muscle mass and strength, increased fat mass, and decreased bone mineral density (BMD). These alterations in body composition contribute to overall frailty and an increased risk of falls and fractures. The anabolic effects of testosterone are well known. In young men, testosterone supplementation increases lean body mass and strength not only in men with hypogonadism, but also in men with normal testosterone levels receiving supraphysiological doses of testosterone.[12] Moreover, uncontrolled studies have demonstrated an increase in BMD with testosterone treatment in hypogonadal men[13–15] and eugonadal middle-aged and older men with idiopathic osteoporosis.[16] Low testosterone concentrations are associated with an increased risk of low-trauma hip fracture.[17–19] However, the goal of therapy in older men is not only to improve age-related changes in body composition, but also to effect meaningful changes in strength, fall and fracture risk, and functional status.

Disorders of mood, sexual functioning, and cognition are common in older and hypogonadal young men, but the effects of testosterone on these conditions have not been evaluated extensively in older men. In hypogonadal young men, testosterone is required for the maintenance of normal libido and sexual functioning.[20] Androgen levels are positively correlated with spatial ability in hypogonadal young men,[21] and improvement in sexual function, mood, perceived well-being, and ability to concentrate have been reported with testosterone supplementation.[22–28] In older men, lower testosterone levels are associated with depressed mood and reduced cognitive function.[29–31]

The role of testosterone in the development of coronary heart disease (CHD) in men is controversial. Men have a higher incidence of CHD than women of similar age, and it has been suggested that testosterone may predispose to the development of CHD. However, in men referred for coronary angiography, low testosterone levels were associated with an increased risk of coronary atherosclerosis.[32] In fact, most epidemiological studies suggest a favorable or neutral rather than an adverse effect of testosterone on CHD in men.[33] Furthermore, testosterone was found to induce relaxation of coronary arteries and increase coronary blood flow in animal models.[34,35] Nevertheless, the clinical significance of these observations is unclear.

Several important trials of testosterone supplementation in older men have been published over the past few years. As a result, there is now more and better information on which to base an assessment of its potential benefit. A number of reviews of testosterone replacement therapy have been published recently (e.g.,[1,36–38,88,89,90]), but, because none of these reviews used a systematic approach to the literature review and study selection process, they may be subject to bias in their conclusions. To the authors' knowledge, this is the first review of testosterone replacement therapy in older men to describe a structured methodology, including a comprehensive literature search strategy and predefined study selection criteria. Given the potential for a strong placebo effect for many endpoints in studies of hormone supplementation, it seemed appropriate to limit the review to evidence from placebo-controlled trials.

METHODS

A MEDLINE search (Ovid Web Gateway) was performed from January 1966 through October 31, 2001, inclusive, using explosions of the medical subject headings (MeSH) testosterone and androgens and limiting the search to documents in which the subject heading was the major point of the article. The search was also limited to MeSH of middle age (45–64), aged (≥65), or aged (≥80), and (1) prospective studies, placebos, random allocation, double-blind method, or (2) publication type, clinical trial. There was no language limitation. Search results were supplemented with articles from bibliographies of review articles and source articles. In addition, the Proceedings of the Endocrine Society and American Society of Andrology Annual Meetings for the years 1992 through 2001 and American College of Cardiology Annual Meetings for 1999 to 2001 were manually searched for abstracts indexed by the search terms "testosterone" and "androgens." Abstracts were not included if study data were subsequently published in a peer-reviewed journal. If the search identified more than one abstract for the same study, only the abstract with the most recent update was included.

To assess the full spectrum of potential clinical applications of testosterone, an inclusive approach was taken rather than limiting the review to specific outcome measures such as body composition measurements. Accordingly, a qualitative review was performed. Both authors and a trained research assistant independently assessed study design and quality of the methods used in each trial. Trial methodology was assessed according to the method of Jadad et al.,[39] using a quality scale to assess randomization, double blinding, and description of withdrawals and dropouts. One point was given for each of the following: (1) the study was described as randomized, (2) the study was described as double-blind, and (3) there was a description of withdrawals and dropouts. An additional point was given for each of the following: (1) the method of randomization was described and was appropriate and (2) the method of double blinding was described and was appropriate. A point was deducted for each of the following: (1) the method of randomization was described and was inappropriate and (2) the method of double blinding was described and was inappropriate. (Criteria for determining appropriateness were as defined by Jadad et al.[39]) The quality score of abstracts was based only on information provided in the abstract and may therefore have underestimated (or

overestimated) actual study quality. Disagreements regarding inclusion of articles and quality scores were resolved by discussion.

Placebo-controlled trials were included if they involved participants who were male and aged 60 and older and the treatment intervention was a preparation of testosterone. However, to ensure that the review remained focused on older people, trials involving study populations with a mean age of less than 50 were excluded. As a result, several studies that involved subjects aged 60 and older but also had a high proportion of young adult subjects were excluded from consideration (e.g.,[25,27,28,40,41]). Peer-reviewed studies and trials published in abstract form with a quality score less than two were excluded. In addition, because of the decreased opportunity for peer review and the relative lack of methodological detail, trials published as letters or abstracts were included only if the study was clearly identified as a double-blind, placebo-controlled study. For studies published in peer-reviewed journals, trials clearly identified as nonrandomized and trials without a placebo control group were excluded from consideration, although studies with a crossover design and studies without a statement of randomization were allowed and noted as such in the tables. Studies whose purpose was dose finding rather than treatment were excluded. Moreover, trials intended primarily to study subjects with severe or unstable systemic illnesses such as burns, advanced cancer, and human immunodeficiency virus infection or subjects with hormone deficiencies due to specific diseases (e.g., Klinefelter's syndrome) rather than "normal" human aging were excluded. Finally, the authors received no financial support other than Veterans Affairs medical research funds for any portion of the data collection, analysis, or interpretation, nor did a funding organization exert any control over the approval of this manuscript for publication.

RESULTS

Twenty-nine studies met the criteria for inclusion and exclusion, four of which were published only in abstract form, with sample sizes ranging from six to 108 and study durations ranging from single-dose administration to 3 years (Table 1). Mean baseline circulating testosterone levels in subjects participating in these studies ranged from normal to moderately below the lower end of the normal range for young adult men and typically increased into the middle of the normal young adult range with supplementation. Many studies, including all trials of more than 3 months of supplementation save one,[61] required study subjects to have baseline testosterone levels below a specified value (e.g., 1 standard deviation below the mean for young men) or below the reference range for young adult men.[42–50,52–54,58,62,67,69,70,76,77] The remaining trials enrolled subjects with a wide range of baseline levels, but only a few studies enrolled subjects with mean total testosterone levels well below the reference range for young men.[58,68,70,75] Moreover, only one study stratified its subjects by baseline testosterone level before random treatment group allocation.[44,53]

Body Composition

All but three trials[51,56,57] evaluating body composition and muscle strength limited enrollment to subjects with baseline testosterone levels below a specified value. In general, lean body mass increased and fat mass decreased with testosterone administration,[42–50] although these changes were not significant in all cases[42,45,51] (Table 2). These effects on body composition were more consistently observed in studies with a long duration of testosterone supplementation[42,44–47,49,50,54] than in studies of 3 months' duration or less.[43,51,52] However, relatively few studies of shorter duration evaluated parameters of body composition. Visceral fat mass decreased in men with abdominal obesity.[45] Despite these effects, body circumference measurements in testosterone-treated subjects were unchanged compared with placebo or from pretreatment baseline.[42,43,46,52]

Bone Mineral Density

Testosterone supplementation for 1 year prevented bone loss at the femoral neck[49] and increased BMD of the lumbar spine[50] in older men with total testosterone levels below the normal range for younger men. In another study, BMD increased in both placebo- and testosterone-treated subjects over a 3-year period, but the increase was not significantly greater in subjects treated with testosterone.[53] However, linear regression analysis of those data suggested that testosterone supplementation did increase lumbar spine bone density in men with the lowest baseline testosterone levels. A 6% increase in bone density would be expected in men with testosterone levels of 2.0 ng/mL, whereas bone density would not change in men with testosterone levels of 4.0 ng/mL.[53] Biochemical indices of bone turnover decreased in a shorter-term (3-month) study,[43] but bone turnover was unchanged in 1-year[49] and 3-year[53] studies.

Muscle Strength and Functional Ability

In healthy older men receiving testosterone, hand-grip strength increased[42,56] or was unchanged,[43,44,52] whereas knee extension and flexion strength was unaffected.[44,49–52] Hand-grip strength increased in studies involving both short[56] and relatively long[42] durations of testosterone supplementation, although testosterone treatment for 3 years did not affect hand-grip strength in another study.[44]

Testosterone administration for 3 years did not improve timed walking or timed stair climbing.[44] However, in a preliminary study, timed walking and stair climbing improved in older men treated with testosterone for 1 month.[51] Self-assessment of physical functioning did not change over 3 years of testosterone treatment, but a decline was observed in placebo-treated men, becoming significantly worse than in treated subjects by the end of the study.[44] Using regression analysis of these data, the greatest effect of testosterone on perception of physical functioning occurred in subjects with the lowest baseline testosterone levels. Aerobic capacity was not significantly improved after 6 months of testosterone supplementation, although a positive effect of combined testosterone and growth hormone administration on aerobic capacity was greater than with growth hormone alone.[54] In men undergoing total knee or hip arthroplasty, administration of supraphysiological testosterone doses for 4 weeks preoperatively did not significantly affect postoperative functional status, but there was a trend toward improvement in some measures of functional independence in men receiving testosterone treatment.[55]

Table 1. Placebo-Controlled Trials of Testosterone (T) Supplementation in Older Men

Study	Quality Score	Design	T Dose	Duration	Subjects' Age, Number	Baseline T level, ng/mL, Mean ± SD (Reference Range)		T Level with Supplementation, ng/mL, Mean ± SD		Comments
						Total T	FT or BT	Total T	FT or BT	
T supplementation longer than 3 months										
Studies enrolling only subjects with baseline T below specified value										
Kenny et al., 2001[49]	4	Randomized, double-blind trial	Transdermal T 5 mg daily	1 year	Healthy men aged 65–87, n = 44	3.9 ± 1.7 (NR)	BT 0.9 ± 0.3 (1.3–4.3)	6.4 ± 3.2	1.6 ± 1.0	Drop-outs: 10/34 T group and 13/33 placebo
Marin et al., 1993[45]	4	Randomized, double-blind trial	Topical T 125 mg gel daily	9 months	Men with abdominal obesity aged 57.7 ± 2.1, n = 31	4.5 ± 0.7 (NR)		5.2 ± 1.7		
Sih et al., 1997[42]	4	Randomized, double-blind trial	TC 200 mg IM/2 weeks	1 year	Healthy men aged 51–79, n = 32	2.9 ± 0.3 (3.0–10.0)	BT 0.4 ± 0.05 (0.7–2.5)	3.7 ± 0.9	0.7 ± 0.3	
Snyder et al., 1999a/b, 2000[44,53,87]	4	Randomized, double-blind trial	Scrotal T 6 mg daily	3 years	Healthy men with low BMD, mean age 73, n = 108	3.7 ± 0.8 (NR)	FT 0.05 ± 0.02 (NR)	6.3 ± 2.5	0.1 ± 0.04	Drop-outs: 4/54 T group and 8/54 placebo
Munzer et al., 2001[46] Blackman et al., 1999[48] Christmas et al., 1999[67] Edmond et al., 1999[54] Harman et al., 2000[76] Ivey et al., 1999[47]	3	Randomized, double-blind trial	TE 100 mg IM/2 weeks	6 months	Healthy men with low T levels, 65–88, n = 32	4.4 ± 0.2 (NR)		5.9 ± 0.5		Effects on abdominal fat published in peer-reviewed journal[46]; other data published only as abstracts
Bebb et al., 2001[50]	2	Randomized, double-blind trial	Oral TU 80 mg three times daily	1 year	Men with low T levels 49–75, n = 40	* (NR)		*		Abstract
Drinka et al., 1995[77]	2	Randomized, double-blind trial	T 150 mg/70 kg BW IM/2 weeks	6 months	Male nursing home residents aged 60–90, n = 8	<3.2* (NR)	FT <0.012* (NR)	*	*	
Marin et al., 1995[69]	2	Randomized trial	Topical T 125 mg gel daily	9 months	Men with abdominal obesity, aged 40–65, n = 27	<5.8* (NR)		*		
Studies without upper limit on baseline T levels										
Holmang et al., 1993[61]	3	Randomized, double-blind trial	Oral TU 80 mg twice daily	8 months	Men with mild/moderate obesity, aged 40–65, n = 23	4.6 ± 1.2 (2.3–9.2)		*		
T supplementation 1 week to 3 months										
Studies enrolling only subjects with baseline T below specified value										
Clague et al., 1999[52]	4	Randomized, double-blind trial	TE 200 mg IM/2 weeks	12 weeks	Healthy men aged >60, n = 14	3.3 ± 0.5 (NR)		5.6 ± 1.4		
Tenover, 1992a/b[43,62]	3	Double-blind crossover study	TE 100 mg IM/week	3 months	Healthy men aged 57–76, n = 13	3.4 ± 0.1 (3.5–10.0)	BT 0.2 ± 0.03 (0.46–?)	5.7 ± 0.2	0.6 ± 0.1	12/13 subjects correctly guessed active treatment
Nankin et al., 1986[58]	2	Double-blind crossover study	TC 200 mg IM/2 weeks	12 weeks	Men with erectile dysfunction aged 51–74, n = 10	3.2 ± 0.8 (4.7–11.4)	FT 0.10 ± 0.02 (0.159–0.250)	3.8 ± 1.0	0.118 ± 0.033	

Studies without upper limit on baseline T levels

Cherrier et al., 2001[65]	5	Randomized, double-blind trial	TE 100 mg IM/week†	6 weeks	Healthy cognitively normal men age 50–80, n = 25	5.8 ± 1.8 (5.2–7.5)		12.7 ± 1.4†		
Bakhshi et al., 2000[56]	4	Randomized, double-blind trial	TE 100 mg IM/week	Until discharge (8 weeks max.)	Men admitted to GEM unit for rehab aged 60–90, n = 15	*		*		
English et al., 2000[72]	4	Randomized, double-blind trial	Transdermal T 5 mg nightly	12 weeks	Men with coronary artery disease aged 62 ± 2, n = 46	3.9 ± 0.2 (2.2–10.7)	FT 0.01 ± 0.001 (0.011–0.040)	5.4 ± 0.3	0.021 ± 0.002	
Jaffe, 1977[73]	4	Randomized, double-blind trial	TC 200 mg IM/week†	8 weeks	Men with postexercise ST depression aged 35–71, n = 50	*		*†		
Benkert et al., 1979[59]	3	Randomized, double-blind trial	Oral TU 80 mg in a.m., 40 mg in p.m.	8 weeks	Men with erectile dysfunction aged 45–75, n = 29	5.8 ± 1.9 (NR)		4.4 ± 2.1		
Gentili et al., 2000[57]	3	Phase 1: crossover, double-blind study	Phase I: TE 100 mg IM/week	Phase I: 3 weeks	"Older" men, age and health status unspecified, n = 8	*		*		Abstract
		Phase 2: crossover, double-blind study	Phase II: TE 200 mg IM/week†	Phase II: 3 weeks				\ Phase II†		
Janowsky et al., 1994[63]	3	Randomized, double-blind trial	Scrotal T 15 mg daily	3 months	Healthy men aged 60–75, n = 56		FT 16±1 (NR)			peak levels ↑ 50%, but trough levels ↓
Schiavi et al., 1997[60]	3	Double-blind crossover study	TE 200 mg IM/2 weeks	6 weeks	Men with erectile dysfunction aged 46–67, n = 12	4.1 ± 0.5 (NR)		3.2 ± 0.7		
Amory et al., 2001[55]	2	Double-blind; group assignment not stated to be random	TE 600 mg IM/week†	4 weeks preoperatively	Men undergoing knee or hip replacement surgery aged 70 ± 5, n = 36	3.5 ± 1.2 (NR)		25.6 ± 5.2†		Abstract 4 drop-outs in placebo group, reasons unspecified
Brill et al., 2000[51]	2	Double-blind crossover study	Transdermal T 5 mg daily	1 month	Healthy men aged 68 ± 2.5, n = 10		FT 0.012 (SD NR) (NR)		0.022 (SD NR)	Abstract
Janowsky et al., 2000[64]	2	Randomized, double-blind trial	TE 150 mg IM/week	1 month	Healthy men aged 61–75, n = 19		FT 0.012 (SD NR) (0.016–0.043)		0.045† (SD NR)	
Sigler, 1943[74]	2	Single-blind crossover study	T propionate 25 mg IM twice a week	6–8 weeks	Men with angina pectoris aged 42–64, n = 6	*	*			
Uyanik et al., 1997[68]	2	Nonrandomized trial	Oral TU 120 mg daily	2 months	Healthy men aged 53–89, n = 37	2.2 ± 0.4 (2.9–10.1)	FT 0.02 ± 0.005 (0.052–0.280)	4.0 ± 1.7	0.023 ± 0.003	

(*continued*)

Table 1. (Continued)

Study	Quality Score	Design	T Dose	Duration	Subjects' Age, Number	Baseline T level, ng/mL, Mean ± SD (Reference Range)		T Level with Supplementation, ng/mL, Mean ± SD		Comments
						Total T	FT or BT	Total T	FT or BT	
Single-dose T supplementation										
Studies enrolling only subjects with baseline T below specified value										
Webb, 1999[70]	3	Double-blind crossover study	T 2.3 mg IV†	One-time dose	Men with coronary artery disease aged 35–75, n = 14	1.5 ± 0.1 (3.2–12.7)		33.7 ± 4.3†		
Studies without upper limit on baseline T levels										
Rosano, 1999[71]	4	Randomized, double-blind trial	T 2.5 mg IV†	One-time dose	Men with coronary artery disease aged 45–66, n = 14	9.75 ± 1.76 (9–?)		527 ± 342†		
Ong et al., 2000[75]	3	Study 1: Double-blind crossover study	Study 1: T 2.3 mg IV†	Both studies: one-time dose	Study 1: men with coronary artery disease aged 58 ± 8, n = 11	Study 1: 2.2 ± 1.0		Study 1: 222 ± 109†		
		Study 2: Double-blind crossover study	Study 2: T 23–46 mcg IV		Study 2: men with coronary artery disease aged 66 ± 8, n = 11	Study 2: 2.4 ± 1.3 (3.2–12.7)		Study 2: 6.9 ± 3.0		
Wolf et al., 2000[66]	2	Nonrandomized, double-blind trial	TE 250 mg IM†	One-time dose	Healthy men, mean aged 67–69, n = 30	3.8 ± 0.3 Mean 5.0 ± 0.3 Young controls	FT 0.01 ± 0.001 Mean 0.02 ± 0.002 Young controls	16.5 ± 5.5†	0.069±0.015†	

Note: Trials grouped by duration of therapy. Within groups, trials subgrouped based on requirement of baseline T level below specified value. Within subgroups, listed in order of quality score. Within quality score, listed alphabetically.
*T levels not specified.
†Supraphysiological supplementation.
SD = standard deviation; NR = not reported; IM = intramuscular; GEM = Geriatric Evaluation and Management; BW = body weight; BMD = bone mineral density; TE = testosterone enanthate; TC = testosterone cypionate; TU = testosterone undecanoate; FT = free testosterone; BT = bioavailable testosterone; IV = intravenous.

Only one trial evaluated the effects of testosterone supplementation on function and strength in frail, debilitated older men. In subjects undergoing rehabilitation on an inpatient geriatric evaluation and management (GEM) unit, grip strength and functional status improved with testosterone administration,[56] but length of stay on the inpatient unit was unaffected.

A preliminary study found that 3 weeks of supraphys-

Table 2. Potential Effects of Testosterone (T) Supplementation on Body Composition, Strength, Function, and Quality of Life in Older Men

Study	Lean Body Mass and Muscle Strength	Body Fat	Bone	Function and Quality of Life
T supplementation longer than 3 months				
Studies enrolling only subjects with baseline T below specified value				
Kenny et al., 2001[49]	↑ LBM ↔ LE strength	↓ fat mass	Prevented femoral neck bone loss ↔ markers of bone turnover	↔ physical activity
Marin et al., 1993[45]	↔ LBM ↑ glucose disposal rate	↓ visceral fat	NA	NA
Sih et al., 1997[42]	↑ hand-grip strength	↓ fat mass trend	NA	NA
Snyder et al., 1999a/b[44,53]	↑ LBM ↔ hand-grip strength ↔ LE strength	↓ fat mass	↔ BMD ↑ lumbar BMD in subjects with ↓ T ↔ markers of bone turnover	↔ timed walk, stair climb Prevented ↓ perceived physical function ↔ other QOL endpoints
Munzer et al., 2001[46] Blackman et al., 1999[48] Ivey et al., 1999[47] Edmond et al., 1999[54]	↑ LBM ↑ thigh muscle area	↓ total body fat ↓ thigh fat area ↓ abdominal sc fat ↔ abdominal visceral fat	NA	↔ aerobic capacity
Bebb et al., 2001[50]	↑ LBM ↔ LE strength	↓ fat mass	↑ lumbar BMD	NA
Marin et al., 1995[69]	NA	↓ TG uptake ↓ LPL activity in abdominal but not femoral fat	NA	NA
T supplementation 1 week to 3 months				
Studies enrolling only subjects with baseline T below specified value				
Clague et al., 1999[52]	↔ LBM ↔ hand-grip and LE strength	↔ triceps skinfold thickness	NA	↔ maximum step height
Tenover, 1992a/b[43,62]	↑ LBM ↔ hand-grip strength	↔ fat mass	↓ urine hydroxyproline	NA
Studies without upper limit on baseline T levels				
Bakhshi et al., 2000[56]	↑ hand-grip strength	NA	NA	↑ FIM score ↔ duration rehabilitation
Gentili et al., 2000[57]*	↑ Growth hormone with high- but not low-dose T	NA	NA	NA
Amory et al., 2001[55]*	NA	NA	NA	Improved FIM standing POD 3 trend ↔ length hospital stay
Brill et al., 2000[51]	↔ LE strength	↔ fat mass	NA	↑ timed stair-climb ↑ timed walk trend ↔ flexibility

Note: Trials grouped by duration of therapy. Within groups, trials subgrouped based on requirement of baseline T level below specified value. Within subgroups, listed in order of quality score. Within quality score, listed alphabetically.

*Supraphysiological supplementation.

↑ = increased; ↓ = decreased; ↔ = unchanged; NA = not assessed/not reported; LPL = lipoprotein lipase; TG = triglyceride; LBM = lean body mass; BMD = bone mineral density; LE = lower extremity; sc = subcutaneous; FIM = Functional Independence Measure; QOL = quality of life; POD = postoperative day.

iological testosterone supplementation increased growth hormone secretion in older but not in young men, whereas low-dose testosterone supplementation did not increase growth hormone in either group[57] (Table 2).

Sexual Function and Mood

Testosterone's effects on sexual functioning and mood were variable and not clearly related to duration of treatment (Table 3). Testosterone treatment improved or tended to improve libido in studies in which it was assessed.[43,58,60–62] Testosterone improved erectile function in some[58] but not all[59,60] studies of older men with preexisting erectile dysfunction. In the study that showed a beneficial effect of testosterone on erectile dysfunction, mean baseline testosterone levels were significantly below the normal reference range.[58] By comparison, mean testosterone levels were higher in the two studies that found no effect on erectile function,[59,60] but reference ranges were not provided in either study. Some healthy older men reported increased feelings of well-being, energy,[43,45,61] and frequency of sexual activity[60,62] during treatment, but energy,[44] mood[42,59,60,63,64] and sexual functioning[44,50] were unchanged in other studies of healthy men treated for up to 3 years. Scores on the Geriatric Depression Scale improved in frail, debilitated older men.[56]

Cognitive Function

Testosterone's effects on cognitive function were mixed. Some studies involving physiological[63] to mildly supraphysiological[64,65] supplementation reported improvement in spatial cognition,[63,65] spatial and verbal memory,[65] and working memory (the ability to hold and manipulate information in short-term memory before responding),[64] but other investigators found no effect of testosterone treatment on memory, recall, or verbal fluency.[42] In addition, in contrast to placebo-treated subjects, verbal fluency failed to improve with practice in subjects treated with mildly supraphysiological doses of testosterone,[66] suggesting that testosterone supplementation may adversely affect some cognitive functions in older men. Only one study assessing cognitive endpoints involved more than 3 months of testosterone treatment,[42] therefore differences between

Table 3. Other Potential Benefits of Testosterone (T) Supplementation in Older Men

Study	Sexual Function	Well-Being And Mood	Cognition
T supplementation greater than 3 months			
Studies enrolling only subjects with baseline T below specified value			
Marin et al., 1993[45]	NA	↑ well-being, energy	NA
Sih et al., 1997[42]	NA	↔ mood	↔ memory, recall, verbal fluency
Snyder et al., 1999a/b[44,53]	↔ sexual function	↔ energy	NA
Bebb et al., 2001[50]	↔ sexual function	NA	NA
Studies without upper limit on baseline T levels			
Holmang et al., 1993[61]	↑ libido (trend)	↑ energy (trend)	NA
T supplementation 1 week to 3 months			
Studies enrolling only subjects with baseline T below specified value			
Tenover, 1992a/b[43,62]	↑ libido, frequency sexual activity	↑ well-being	NA
Nankin et al., 1986[58]	↑ libido, erectile function	NA	NA
Studies without upper limit on baseline T levels			
Cherrier et al., 2001[65]*	NA	NA	↑ spatial/verbal memory, spatial ability
Bakhshi et al., 2000[56]	NA	↓ depression	NA
Benkert et al., 1979[59]	↔ erectile function	↔ mood, somatic complaints	NA
Janowsky et al., 1994[63]	NA	↔ mood	↑ spatial cognition
Schiavi et al., 1997[60]	↑ libido (trend) ↑ ejaculation frequency ↔ erectile function, sexual satisfaction	↔ mood	NA
Janowsky et al., 2000[64]	NA	↔ mood	↑ working memory
T supplementation single dose			
Studies without upper limit on baseline T levels			
Wolf et al., 2000[66]*	NA	NA	Prevented ↑ verbal fluency with practice

*Supraphysiological supplementation.
↑ = increased; ↓ = decreased; ↔ = unchanged; NA = not assessed/not reported.

Table 4. Potential Benefits of Testosterone (T) Supplementation on Coronary Artery Disease in Older Men

Study	Cardiac Ischemia	Angina Pectoris	Quality of Life
T supplementation 1 week to 3 months			
Studies without upper limit on baseline T levels			
English et al., 2000[72]	↑ time to exercise-induced ST depression 24%	↔ angina frequency	↑ quality of life
Jaffe, 1977[73]*	↓ ST depression	NA	↔ exercise capacity
Sigler, 1943[74]	NA	↓ angina	↑ exercise tolerance
T supplementation single dose			
Studies enrolling only subjects with baseline T below specified value			
Webb, 1999[70]*	↑ time to exercise-induced ST depression 22%	↔ angina	↔ exercise capacity
Studies without upper limit on baseline T levels			
Rosano, 1999[71]*	↑ time to exercise-induced ST depression 23% ↓ ST depression/recovery time	Exertional angina in 12 subjects after placebo, 8 subjects after T	↑ exercise capacity (total exercise time)
Ong et al., 2000[75]*	↑ brachial artery diameter (high-dose T only)	NA	NA

*Supraphysiological supplementation.
↑ = increased; ↓ = decreased; ↔ = unchanged; NA = not assessed/not reported.

short-term and long-term effects of testosterone on cognition could not be assessed.

Lipids and Cholesterol

Regardless of the baseline testosterone level and duration of testosterone therapy, total and low density lipoprotein (LDL) cholesterol levels were reduced[43,45,67,68] or unchanged,[42,52,87] whereas high density lipoprotein (HDL) cholesterol levels were unchanged.[42,43,45,67,68,87] Testosterone inhibited triglyceride uptake and lipoprotein lipase activity in abdominal but not in femoral subcutaneous fat, suggesting that testosterone may regulate the proportion of fat deposited in central and peripheral locations.[69]

Coronary Heart Disease

In five studies of older men with established CHD, improvements in exercise-induced ST-segment depression on electrocardiography were observed after acute[70,71] and chronic[72–74] testosterone administration and with physiological[72] and supraphysiological[70,71,73] doses (Table 4). The beneficial effects of testosterone on ST-segment depression were observed in men with low-normal[71,72] and more markedly decreased[70] baseline levels of testosterone. No effects on time to onset of angina pectoris during exercise testing or anginal frequency were reported in studies of a single dose or 12 weeks of testosterone,[70,72] but angina pectoris decreased and exercise tolerance improved in other subjects receiving testosterone for 6 to 8 weeks.[74] In addition, subjects with angina pectoris who received testosterone for 3 months reported a significant improvement in all quality of life domains assessed by the SF-36 health survey questionnaire, especially pain perception and role limitation resulting from physical problems.[72] Finally, brachial artery caliber increased after acute testosterone infusion in men with CHD, suggesting that the effects of testosterone on the heart may be due to a vasodilatory effect on the coronary arteries.[75] None of these studies were of sufficient size or duration to allow an assessment of the effects of testosterone on overall cardiovascular morbidity and mortality.

Prostate Gland

In studies reporting effects of testosterone on the prostate, none reported an increase in voiding symptoms, prostate examination abnormalities, or postvoid residual urine volumes during treatment,[42,43,45,49,50,53,55,61,76] but prostate size increased 12% in one study.[61] Although five studies reported no effect of testosterone therapy on prostate specific antigen (PSA) levels,[45,50,61,72,76] the PSA increased slightly but significantly in four others[43,49,53,65] after as little as 6 weeks of treatment.[65] This increase in PSA occurred irrespective of the baseline testosterone level. In studies reporting PSA levels,[42,43,49,52,53,65] the average baseline PSA ranged from 1.0 to 2.4 ng/mL, with an increment of 0.6 to 1.0 ng/mL during treatment. However, PSA levels remained within the normal range, except for one subject whose PSA increased from 3.5 ng/mL at baseline to 4.1 ng/mL during testosterone supplementation.[65]

Erythrocytosis

In most studies, the mean hematocrit increased during treatment from 2.5% to 5% over baseline values, and between 6% and 25% of study subjects developed hematocrit elevations above the normal range.[42,43,52,53,73,76,77] No significant change in the hematocrit was observed in some[49,72] but not all[53] trials that used transdermal testosterone supplementation.

Table 5. Potential Risks of Testosterone (T) Supplementation in Older Men

Study	Erythrocytosis	Increased PSA	Prostate DRE	BPH Symptoms	Cholesterol	Other
T supplementation greater than 3 months						
Studies enrolling only subjects with baseline T below specified value						
Kenny et al., 2001[49]	↔	PSA 2.0→2.6	↔	↔	NA	↑ rash with induration
Marin et al., 1993[45]	NA	↔	NA	↔ prostate volume ↔ urine flow rate	↓ TC, TG ↔ HDL-C	Breast tenderness (1 subject)
Sih et al., 1997[42]	HGB 15.0→16.0 HCT >51 in 4/17 subjects	PSA 1.0→1.9 (NS)	↔	NA	↔ TC, LDL-C ↔ HDL-C, TG	
Snyder et al., 1999a/b, 2000[44,53,87]	HCT 43.1→45.6 HCT >51 in 3/54 subjects	PSA 1.6→2.2	↔	↔ urine flow rate, PVR	↔ TC, LDL-C ↔ HDL-C, TG	↔ sleep apnea, hypopnea ↔ cardiovascular events
Christmas et al., 1999[67]	HCT ↑ 5.5% (trend)	↔	NA	↔	↓ TC, LDL-C	
Harman et al., 2000[76]	No HCT >55 in any subject				↔ HDL-C, TG	
Bebb et al., 2001[50]	NA	↔	NA	↔	NA	
Drinka et al., 1995[77]	HCT >51 in 2/8 subjects	NA	NA	NA	NA	
Studies without upper limit on baseline T levels						
Holmang et al., 1993[61]	NA	↔	↔	↔ urine flow rate ↑ prostate size 12%	NA	
T supplementation 1 week to 3 months						
Studies enrolling only subjects with baseline T below specified value						
Clague et al., 1999[52]	HCT 43→47	PSA 2.4→3.4 (NS)	NA	NA	↔ TC	
Tenover, 1992a/b[43,62]	HCT 43.1→46.7 HCT >51 in 1/13 subjects	PSA 2.1→2.7	↔	↔ prostate size, PVR	↓ TC, LDL-C ↔ HDL-C	No acne, gynecomastia
Studies without upper limit on baseline T levels						
Cherrier et al., 2001[65]*	NA	↑ (3.5→4.1 in 1 subject)	NA	NA	NA	
Bakhshi et al., 2000[56]	No erythrocytosis	None >4.5	NA	↔	NA	1 unexpected ?cardiac death
English et al., 2000[72]	↔	↔	NA	NA	"no change" lipids	↑ skin irritation from T patch
Jaffe, 1977[73]*	HCT 46→51	NA	NA	NA	NA	Edema in 3/25 subjects
Uyanik et al., 1997[68]	NA	NA	NA	↔	↓ TC, LDL-C ↔ HDL-C	No acne, gynecomastia

*Supraphysiological supplementation.

↑ = increased; ↓ = decreased; ↔ = unchanged; NA = not assessed/not reported; PSA = prostate specific antigen (ng/mL); DRE = digital rectal examination; HCT = hematocrit; HGB = hemoglobin; BPH = benign prostatic hyperplasia; PVR = postvoid residual urine volume; NS = not significant versus placebo group; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglyceride.

Sleep Apnea

In the one study that formally assessed sleep apnea, sleep studies did not reveal a change in the occurrence of sleep apneas or hypopneas in men receiving testosterone treatment[53]

Effect of Quality Score and Baseline Testosterone

The effects of testosterone supplementation did not differ systematically for any endpoint based on whether studies had a higher or a lower quality score (data analysis not shown).

Finally, the effects of testosterone supplementation were compared between studies enrolling subjects with baseline testosterone levels below a specified value[42–50,52–54,58,62,67,69,70,76,77] and those with no upper limit on testosterone levels (Tables 2–5). It was hypothesized that studies enrolling only men with levels below a cutoff value would be more likely to show a favorable effect of testosterone supplementation than studies without this restriction. Erectile function improved in a study enrolling only older men with low baseline testosterone levels,[58] whereas two studies without this limitation did not find an improvement in erectile function with testosterone administration.[59,60] One study limiting enrollment to men with low testosterone levels reported an improvement in subjective well-being in some subjects,[43] whereas only one[56] of five studies without this limitation reported an improvement in mood. No other systematic differences were observed based on whether study enrollment was limited to men with testosterone levels below a given level.

DISCUSSION

This review found evidence from placebo-controlled trials that testosterone supplementation increases lean body mass and decreases fat mass in healthy older men with low-normal or mildly decreased testosterone levels. Furthermore, lumbar spine bone density appeared to increase and bone loss at the femoral neck was prevented in men with circulating testosterone levels below normal values for young men. Testosterone's effects on strength and function were more mixed, but some studies found an increase in upper extremity strength and improved performance of some functional tasks. Self-perceived physical functioning, like bone density, was more likely to improve in subjects with the lowest baseline testosterone levels.

Sexual functioning, energy, mood, libido and subjective well-being were improved or unchanged with testosterone therapy. Testosterone therapy more consistently caused an activation in sexual behavior and libido than an improvement in erectile function. Testosterone improved aspects of spatial ability and spatial, working, and verbal memory in some studies. However, supraphysiological testosterone appeared to worsen cognition in another study by blocking the practice effect on verbal fluency. In fact, most of these effects on memory and verbal fluency were observed in subjects receiving mildly supraphysiological testosterone supplementation. By comparison, physiological supplementation improved spatial cognition but had no effect on other cognitive domains in one study,[63] whereas another reported no effect on memory and verbal fluency.[42]

In contrast to the HDL-suppressive effects of testosterone replacement in severely hypogonadal younger men[78] or supraphysiological testosterone treatment,[79] in older men testosterone generally had little effect on HDL cholesterol, and total and LDL cholesterol levels were decreased or unchanged. In men with CHD, testosterone consistently improved electrocardiographic evidence of exercise-induced coronary ischemia, regardless of whether testosterone supplementation was physiological or supraphysiological, or whether baseline testosterone levels were low-normal or more markedly decreased. Effects on angina pectoris were more variable.

Testosterone therapy was generally well tolerated, although abnormal elevations in the hematocrit occurred in many subjects, especially those receiving high-dose parenteral testosterone. PSA levels often increased slightly but significantly, mostly within the normal range (<4 ng/mL).

Taken together, these findings suggest that testosterone replacement in mildly androgen-deficient older men may have potentially beneficial effects on body composition, muscle strength, sexual functioning, subjective well-being, and manifestations of CHD. In addition, there is evidence for short-term improvement in some functional measures of physical performance. However, it is unclear whether these effects will result in long-term improvements in clinical outcomes such as prevention of frailty, fractures, and coronary events, and it is unknown whether the long-term benefits outweigh the potential risks.

Only one study identified in this review demonstrated an improvement in quality of life outcomes with testosterone supplementation,[72] although others reported improvement in energy, mood, and other factors that may enhance quality of life. However, most studies of testosterone supplementation were insufficiently powered to demonstrate absence of efficacy of testosterone on mood and other quality of life–related endpoints. In addition, the "generic" instruments used in these studies to assess quality of life may not have been sensitive to change. The Androgen Deficiency in Aging Males questionnaire, a screening tool for symptoms of testosterone deficiency, includes questions that are condition specific and relevant to quality of life (e.g., decrease in libido and erections, lack of energy).[91] It represents a step toward the development of a quality-of-life assessment instrument that is specific for men with age-related androgen deficiency. It may be difficult to demonstrate improved function and quality of life in men who are healthy and living independently, as were most of the subjects enrolled in these studies. Testosterone supplementation may have a greater effect on functional status in frail, functionally dependent older men, based on the high prevalence of hypogonadism and catabolic states in this population. One small trial performed in a GEM unit milieu suggests that such patients may benefit functionally from testosterone replacement,[56] but the merits of testosterone therapy in debilitated older men remain largely unexplored.

It is unknown whether long-term testosterone supplementation in older men will lead to an increase in diseases such as clinically significant prostate cancer, benign prostatic hyperplasia, and cardiovascular disease. Given their high prevalence rates in older men, even a small unfavorable effect of testosterone on these conditions may outweigh the potential long-term benefits of treatment. The apparent absence of unfavorable effects on the lipid profile in these studies is noteworthy, but a significant undetected adverse lipid effect cannot be completely excluded because of the relatively small number of study subjects (n = 328

in studies reporting lipid profiles) and the possibility of a beta error. Moreover, the increases in hematocrit and PSA levels in many subjects indicate that close monitoring is necessary in men receiving testosterone replacement. Erythrocytosis is less likely to develop when low-dose testosterone replacement regimens are used (e.g., patches or low-dose injections). These regimens minimize the stimulation of erythropoiesis associated with supraphysiological peak circulating testosterone levels,[1,36,88–90] although erythrocytosis may still occur in some men.[53] Studies in hypogonadal men have implicated testosterone replacement in the development or worsening of obstructive sleep apnea.[80] No differences in the occurrence of sleep apneas and hypopneas were reported in testosterone compared with placebo-treated subjects over 3 years,[53] but a clinically important effect of testosterone on sleep apnea in some individuals is still possible. Therefore, symptoms suggesting sleep apnea (e.g., daytime somnolence, excessive snoring) should be monitored in men receiving testosterone.

There is increasing agreement among andrologists that testosterone replacement therapy is indicated in older men with total testosterone levels consistently below 2.0 ng/mL, regardless of whether symptoms are present.[81] Consistent with this view, some studies included in this review found that older men with low testosterone levels were more likely to experience improvements in lumbar BMD, self-perceived functional status, libido, erectile function, and exercise-induced coronary ischemia than men with less marked testosterone deficiency.[44,53,58,59,71,72]

Based on this evidence that the benefits of testosterone administration may be greatest in more severely androgen-deficient older men, this review attempted to group studies for analysis by baseline testosterone levels. However, several problems were encountered in this analysis, and meaningful overall conclusions could not be made. First, only a few studies enrolled subjects with mean testosterone levels well below the normal range,[58,68,70,75] whereas most studies included subjects with levels ranging from low-normal to mildly decreased. Second, only one trial stratified its subjects by baseline testosterone levels.[44,53] Third, studies employed different methods of assessing baseline testosterone levels, including total, bioavailable, and free testosterone levels. Fourth, reference ranges were not included for comparison in a number of studies. Finally, when testosterone reference ranges were disclosed, there was significant variation between studies, reflecting differences in methodology.

Although it was impossible to analyze study results by baseline testosterone level, this review found that trials enrolling subjects with baseline testosterone levels below a specified value were more likely to report an improvement in erectile function and mood than studies with no upper limit on testosterone levels. However, these observations were based on data from a small number of subjects. Clearly, further studies are needed to determine the effects of testosterone supplementation in older men with markedly decreased testosterone levels. In addition, trials with sufficient numbers of subjects should stratify participants according to baseline testosterone level before randomization.

This review of testosterone replacement therapy in older adults has a number of inherent limitations. Its scope was intentionally broad, to assess the range of potential clinical applications of testosterone in older men. Broad-based narrative reviews may be the most appropriate method of describing current developments in fields where existing research is preliminary and there is a limited number of high-quality studies,[82,83] but traditional narrative reviews may offer inappropriate clinical recommendations based on a biased sampling of the literature or "expert opinion" that is not evidence based. In an attempt to minimize bias and to provide evidence-based conclusions, a comprehensive literature search was performed, a priori criteria were specified for study selection, these criteria were rigorously applied, and the quality of the articles included in this review was assessed. In addition, symposium proceedings were searched for appropriate abstracts, to minimize potential publication bias in the event that studies showing a positive treatment effect were more likely to be published than "negative" studies.[84]

Despite the broad scope of this review, some potential applications of testosterone in older men were not addressed. Studies primarily intended to evaluate hormone deficiencies due to specific diseases (e.g., Klinefelter's or Kallmann's syndromes) were excluded, thereby limiting the generalizability of the findings to older men in good health or with testosterone deficiency related to acute or chronic disease. In addition, the exclusion of trials that were not placebo controlled undoubtedly resulted in omission of a number of well-performed studies. Some of these studies may suggest other potential clinical applications or provide additional insight into the potential benefits and risks of testosterone replacement. However, on balance, this review was stronger and less subject to bias because of the structured approach to article selection. Finally, androgenic preparations other than testosterone may be reasonable alternatives to testosterone for supplementation in older men. For example, a recent randomized, placebo-controlled study of dihydrotestosterone gel treatment for 3 months in mildly androgen-deficient older men demonstrated decreased fat mass, decreased total and LDL cholesterol without a change in HDL cholesterol, and an increase in some measures of lower extremity strength without apparent adverse effects.[85] The relative merits of testosterone versus dihydrotestosterone supplementation in older men remain to be clarified.

It is possible that the inclusion of preliminary studies published only in abstract form could have biased the conclusions of this review. In addition, random group allocation could not be confirmed in four peer-reviewed studies and one abstract.[55,58,66,68,74] The likelihood of bias was minimized by requiring a minimum quality score of two for peer-reviewed studies and preliminary reports published in abstract form.[39,86] Furthermore, quality scores for abstracts arguably would have been upgraded more often than downgraded if additional information on study methods had been available.

A detailed discussion of the clinical evaluation and management of low testosterone levels in older men is beyond the scope of this review, and the reader is referred to several recent reviews.[1,36,38,88–90]

Determining the long-term safety and efficacy of testosterone supplementation therapy will be a formidable challenge. By analogy to estrogen replacement therapy in postmenopausal women, a full assessment of the benefits

and risks of testosterone replacement would require large-scale, long-term, randomized, controlled trials to evaluate its effects on cardiovascular and prostate disease morbidity and mortality. Unfortunately, well-controlled trials of this magnitude are unlikely to be completed in the near future. In the interim, studies may identify subsets of older men most likely to benefit from testosterone supplementation. For example, such studies may provide further support for a reduction in fracture risk in older men with osteoporosis, for functional improvement in frail men living in nursing homes, and for a reduction in cardiovascular morbidity.

In conclusion, current data from placebo-controlled clinical trials do not support testosterone supplementation in healthy, asymptomatic older men with normal to low-normal testosterone levels outside of controlled clinical studies. However, this review found evidence for potentially beneficial effects of testosterone in men with decreased testosterone levels and symptoms and signs suggesting hypogonadism (e.g., decreased bone density, muscle mass, strength and libido; impaired sexual function; increased adiposity; and symptomatic CHD), especially if severe. Based on these findings, a trial of testosterone replacement therapy is reasonable in such men, if contraindications (e.g., prostate or breast cancer, polycythemia, or untreated sleep apnea) are absent. In addition, testosterone supplementation may be beneficial in older men with markedly decreased testosterone levels regardless of symptoms. To our knowledge, no randomized, controlled trials of testosterone replacement therapy extending more than 3 years have been performed in older men. Therefore, the long-term benefits and risks of testosterone treatment in older men remain unknown. Nevertheless, if additional well-controlled studies confirm important functional, symptomatic, or quality-of-life benefits of testosterone replacement, the potential long-term risks of supplementation may be acceptable for many older men.

ACKNOWLEDGMENTS

The authors wish to thank Edward Boyko and Eric Whitsel for reviewing the manuscript, Mia Hannula for her assistance with the MEDLINE search, and Rory Shields for assisting with the literature assessment.

REFERENCES

1. Tenover JL. Male hormone replacement therapy including “andropause”. Endocrinol Metab Clin North Am 1998;27:969–987.
2. Swerdloff RS, Wang C. Androgen deficiency and aging in men. West J Med 1993;159:579–585.
3. Tenover JS. Male hormonal changes with aging. In: Morley JE, Korenman SG, eds. Endocrinology and Metabolism in the Elderly. Cambridge, MA: Blackwell Scientific Publications, 1992, pp 243–261.
4. Vermeulen A, Rubens R, Verdonck L. Testosterone secretion and metabolism in male senescence. J Clin Endocrinol Metab 1972;34:730–735.
5. Gray A, Berlin JA, McKinlay JB et al. An examination of research design effects on the association of testosterone and male aging: Results of a meta-analysis. J Clin Epidemiol 1991;44:671–684.
6. Zmuda JM, Cauley JA, Kriska A et al. Longitudinal relation between endogenous testosterone and cardiovascular risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am J Epidemiol 1997;146:609–617.
7. Morley JE, Kaiser FE, Perry HM III et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. Metabolism 1997;46:410–413.
8. Harman SM, Metter EJ, Tobin JD et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724–731.
9. Rudman D, Mattson DE, Nagraj HS et al. Plasma testosterone in nursing home men. J Clin Epidemiol 1988;41:231–236.
10. Kosasih JB, Abbasi AA, Rudman D. Serum insulin-like growth factor-I and serum testosterone status of elderly men in an inpatient rehabilitation unit. Am J Med Sci 1996;311:169–173.
11. Binkley N, Drinka PJ, Schultz S et al. Clinical prediction of testosterone deficiency in male nursing home residents. Nurs Home Med 1995;3:295–299.
12. Bhasin S, Storer TW, Berman N et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335:1–7.
13. Snyder PJ, Peachey H, Berlin JA et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670–2677.
14. Behre HM, Kliesch S, Leifke E et al. Long-term effect of testosterone therapy on bone mineral density in hypogonadal men. J Clin Endocrinol Metab 1997;82:2386–2390.
15. Katznelson L, Finkelstein JS, Schoenfeld DA et al. Increase in bone density and lean body mass during testosterone administration in men with acquired hypogonadism. J Clin Endocrinol Metab 1996;81:4358–4365.
16. Anderson FH, Francis RM, Faulkner K. Androgen supplementation in eugonadal men with osteoporosis-effects of 6 months of treatment on bone mineral density and cardiovascular risk factors. Bone 1996;18:171–177.
17. Stanley HL, Schmitt BP, Poses RM et al. Does hypogonadism contribute to the occurrence of a minimal trauma hip fracture in elderly men? J Am Geriatr Soc 1991;39:766–771.
18. Jackson JA, Riggs MW, Spiekerman AM. Testosterone deficiency as a risk factor for hip fractures in men: A case-control study. Am J Med Sci 1992; 304:4–8.
19. Abbasi AA, Rudman D, Wilson CR et al. Observations on nursing home residents with a history of hip fracture. Am J Med Sci 1995;310:229–234.
20. Tenover JS. Testosterone and the aging male. J Androl 1997;18:103–106.
21. Gouchie C, Kimura D. The relationship between testosterone levels and cognitive ability patterns. Psychoneuroendocrinology 1991;16:323–334.
22. O’Carroll R, Shapiro C, Bancroft J. Androgens, behaviour and nocturnal erection in hypogonadal men: The effects of varying the replacement dose. Clin Endocrinol (Oxf) 1985;23:527–538.
23. Burris AS, Banks SM, Carter CS et al. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. J Androl 1992;13:297–304.
24. Cappa SF, Guariglia C, Papagno C et al. Patterns of lateralization and performance levels for verbal and spatial tasks in congenital androgen deficiency. Behav Brain Res 1988;31:177–183.
25. Davidson JM, Camargo CA, Smith ER. Effects of androgen on sexual behavior in hypogonadal men. J Clin Endocrinol Metab 1979;48:955–958.
26. Skakkebaek NE, Bancroft J, Davidson DW et al. Androgen replacement with oral testosterone undecanoate in hypogonadal men: A double blind controlled study. Clin Endocrinol (Oxf) 1981;14:49–61.
27. Kwan M, Greenleaf WJ, Mann J et al. The nature of androgen action on male sexuality: A combined laboratory-self-report study on hypogonadal men. J Clin Endocrinol Metab 1983;57:557–562.
28. Wang C, Swerdloff RS, Iranmanesh A et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab 2000;85:2839–2853.
29. Morley JE, Kaiser F, Raum WJ et al. Potentially predictive and manipulable blood serum correlates of aging in the healthy human male: Progressive decreases in bioavailable testosterone, dehydroepiandrosterone sulfate, and the ratio of insulin-like growth factor 1 to growth hormone. Proc Natl Acad Sci U S A 1997;94:7537–7542.
30. Barrett-Connor E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: The Rancho Bernardo Study. J Clin Endocrinol Metab 1999;84:573–577.
31. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. J Clin Endocrinol Metab 1999;84: 3681–3685.
32. Phillips GB, Pinkernell BH, Jing TY. The association of hypotestosteronemia with coronary artery disease in men. Arterioscler Thromb 1994;14:701–706.
33. Alexandersen P, Haarbo J, Christiansen C. The relationship of natural androgens to coronary heart disease in males: A review. Atherosclerosis 1996; 125:1–13.
34. Yue P, Chatterjee K, Beale C et al. Testosterone relaxes rabbit coronary arteries and aorta. Circulation 1995;91:1154–1160.
35. Chou TM, Sudhir K, Hutchison SJ et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. Circulation 1996; 94:2614–2619.

36. Bhasin S, Bagatell CJ, Bremner WJ et al. Issues in testosterone replacement in older men. J Clin Endocrinol Metab 1998;83:3435–3448.
37. Bross R, Javanbakht M, Bhasin S. Anabolic interventions for aging-associated sarcopenia. J Clin Endocrinol Metab 1999;84:3420–3430.
38. Tenover JL. Experience with testosterone replacement in the elderly. Mayo Clin Proc 2000;75(Suppl.):S77–S82.
39. Jadad AR, Moore RA, Carroll D et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996;17:1–12.
40. Dobs AS, Hoover DR, Chen MC et al. Pharmacokinetic characteristics, efficacy, and safety of buccal testosterone in hypogonadal males: A pilot study. J Clin Endocrinol Metab 1998;83:33–39.
41. O'Carroll R, Bancroft J. Testosterone therapy for low sexual interest and erectile dysfunction in men: A controlled study. Br J Psychiatry 1984;145: 146–151.
42. Sih R, Morley JE, Kaiser FE et al. Testosterone replacement in older hypogonadal men: A 12-month randomized controlled trial. J Clin Endocrinol Metab 1997;82:1661–1667.
43. Tenover JS. Effects of testosterone supplementation in the aging male. J Clin Endocrinol Metab 1992;75:1092–1098.
44. Snyder PJ, Peachey H, Hannoush P et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. J Clin Endocrinol Metab 1999;84:2647–2653.
45. Marin P, Holmang S, Gustafsson C et al. Androgen treatment of abdominally obese men. Obesity Res 1993;1:245–251.
46. Munzer T, Harman SM, Hees P et al. Effects of GH and/or sex steroid administration on abdominal subcutaneous and visceral fat in healthy aged women and men. J Clin Endocrinol Metab 2001;86:3604–3610.
47. Ivey FM, Harman SM, Hurley BF et al. Effects of GH and/or sex steroid administration on thigh muscle and fat by magnetic resonance imaging (MRI) in healthy elderly men and women [Abstract]. In: Proceedings of the Endocrine Society 81st Annual Meeting, June 12–15, 1999. San Diego, CA. Bethesda, MD: Endocrine Society Press, 1999, p 390.
48. Blackman MR, Christmas C, O'Connor KG et al. Effects of growth hormone and/or sex steroid administration on body composition in healthy elderly women and men [Abstract]. In: Proceedings of the Endocrine Society 81st Annual Meeting, June 12–15, 1999. San Diego, CA. Bethesda, MD: Endocrine Society Press, 1999, p 391.
49. Kenny AM, Prestwood KM, Gruman CA et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. J Gerontol A Biol Sci Med Sci 2001;56A:M266–M272.
50. Bebb R, Anawalt B, Wade J et al. A randomized, double blind, placebo controlled trial of testosterone undecanoate administration in aging hypogonadal men: Effects on bone density and body composition [Abstract]. In: Proceedings of the Endocrine Society 83rd Annual Meeting, June 20–23, 2001. Denver, CO. Bethesda, MD: Endocrine Society Press, 2001, pp 100–101.
51. Brill K, Weltman A, Gentili A et al. Single and joint impact of one month of transdermal testosterone (T) and/or recombinant human growth hormone (rhGH) supplementation on body composition, strength, balance, function, and muscle IGF-I and androgen gene expression in healthy older men: A prospective randomized double-blind crossover study [Abstract]. In: Proceedings of the Endocrine Society 82nd Annual Meeting, June 21–24, 2000. Toronto, Canada. Bethesda, MD: Endocrine Society Press, 2000, p 398.
52. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. Int J Androl 1999;22:261–265.
53. Snyder PJ, Peachey H, Hannoush P et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. J Clin Endocrinol Metab 1999;84:1966–1972.
54. Edmond J, Busby-Whitehead MJ, Harman SM et al. Effects of growth hormone and/or sex steroid administration on aerobic capacity in healthy elderly women and men [Abstract]. In: Proceedings of the Endocrine Society 81st Annual Meeting, June 12–15, 1999. San Diego, CA. Bethesda, MD: Endocrine Society Press, 1999, p 392.
55. Amory JK, Chansky HC, Anawalt BD et al. Supraphysiologic androgen administration in elderly men undergoing joint replacement surgery [Abstract]. In: J Androl (Suppl.). Proceedings of the 7th International Congress of Andrology. June 15–19, 2001. Montreal, Canada. Lawrence, KS: Allen Press, 2001, p 175.
56. Bakhshi V, Elliott M, Gentili A et al. Testosterone improves rehabilitation outcomes in ill older men. J Am Geriatr Soc 2000;48:550–553.
57. Gentili A, Mulligan T, Godschalk M et al. Testosterone supplementation increases growth hormone secretion in older men [Abstract]. In. Proceedings of the Endocrine Society 82nd Annual Meeting, June 21–24, 2000. Toronto, Canada. Bethesda, MD: Endocrine Society Press, 2000, p 470.
58. Nankin HR, Lin T, Osterman J. Chronic testosterone cypionate therapy in men with secondary impotence. Fertil Steril 1986;46:300–307.
59. Benkert O, Witt W, Adam W et al. Effects of testosterone undecanoate on sexual potency and the hypothalamic-pituitary-gonadal axis of impotent males. Arch Sex Behav 1979;8:471–479.
60. Schiavi RC, White D, Mandeli J et al. Effect of testosterone administration on sexual behavior and mood in men with erectile dysfunction. Arch Sex Behav 1997;26:231–241.
61. Holmang S, Marin P, Lindstedt G et al. Effect of long-term oral testosterone undecanoate treatment on prostate volume and serum prostate-specific antigen concentration in eugonadal middle-aged men. Prostate 1993;23: 99–106.
62. Tenover JS. Effect of testosterone (T) and 5-alpha-reductase inhibitor (5-ARI) administration on the responses to a sexual function questionnaire in older men [Abstract]. J Androl 1992;13:50.
63. Janowsky JS, Oviatt SK, Orwoll ES. Testosterone influences spatial cognition in older men. Behav Neurosci 1994;108:325–332.
64. Janowsky JS, Chavez B, Orwoll E. Sex steroids modify working memory. J Cogn Neurosci 2000;12:407–414.
65. Cherrier MM, Asthana S, Plymate S et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. Neurology 2001;57: 80–88.
66. Wolf OT, Preut R, Hellhammer DH et al. Testosterone and cognition in elderly men: A single testosterone injection blocks the practice effect in verbal fluency, but has no effect on spatial or verbal memory. Biol Psychiatry 2000; 47:650–654.
67. Christmas C, Harman SM, Munzer T et al. Effects of growth hormone and/or sex steroid administration on serum lipid profiles in healthy elderly women and men [Abstract]. In: Proceedings of the Endocrine Society 81st Annual Meeting, June 12–15, 1999. San Diego, CA. Bethesda, MD: Endocrine Society Press, 1999, p 394.
68. Uyanik BS, Ari Z, Gumus B et al. Beneficial effects of testosterone undecanoate on the lipoprotein profiles in healthy elderly men. A placebo controlled study. Jpn Heart J 1997;38:73–82.
69. Marin P, Oden B, Bjorntorp P. Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue in vivo in men: Effects of androgens. J Clin Endocrinol Metab 1995;80:239–243.
70. Webb CM, Adamson DL, de Zeigler D et al. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. Am J Cardiol 1999;83:437–439.
71. Rosano GM, Leonardo F, Pagnotta P et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation 1999;99:1666–1670.
72. English KM, Steeds RP, Jones TH et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina. Circulation 2000;102:1906–1911.
73. Jaffe MD. Effect of testosterone cypionate on postexercise ST segment depression. Br Heart J 1977;39:1217–1222.
74. Sigler LH, Tulgan J. Treatment of angina pectoris by testosterone propionate. N Y State J Med 1943;43:1424–1428.
75. Ong PJL, Patrizi G, Chong WCF et al. Testosterone enhances flow-mediated brachial artery reactivity in men with coronary artery disease. Am J Cardiol 2000;85:269–272.
76. Harman SM, Pabst KM, Munzer T et al. Adverse effects observed in healthy women and men over 65 years of age treated with GH and sex steroid hormone replacement [Abstract]. In: Proceedings of the Endocrine Society 82nd Annual Meeting, June 21–24, 2000. Toronto, Canada. Bethesda, MD: Endocrine Society Press, 2000, p 395.
77. Drinka PJ, Jochen AL, Cuisinier M et al. Polycythemia as a complication of testosterone replacement therapy in nursing home men with low testosterone levels. J Am Geriatr Soc 1995;43:899–901.
78. Bagatell CJ, Knopp RH, Vale WW et al. Physiologic testosterone levels in normal men suppress high-density lipoprotein cholesterol levels. Ann Intern Med 1992;116:967–973.
79. Bagatell CJ, Heiman JR, Matsumoto AM et al. Metabolic and behavioral effects of high-dose, exogenous testosterone in healthy men. J Clin Endocrinol Metab 1994;79:561–567.
80. Matsumoto AM, Sandblom RE, Schoene RB et al. Testosterone replacement in hypogonadal men. Effects on obstructive sleep apnea, respiratory drives, and sleep. Clin Endocrinol (Oxf) 1985;22:713–721.
81. Swerdloff RS, Bhasin S, Blackman MR et al. Summary of the Consensus Session From the 1st Annual Andropause Consensus 2000 Meeting; 28–30 April, 2000 Beverly Hills, CA. Bethesda, MD. Endocrine Society Press, 2000, pp. 1–6.
82. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews. Synthesis of best evidence for clinical decisions. Ann Intern Med 1997;126:376–380.
83. McAlister FA, Clark HD, van Walraven C et al. The medical review article revisited: Has the science improved? Ann Intern Med 1999;131:947–951.
84. Rosenfeld RM. How to systematically review the medical literature. Otolaryngol Head Neck Surg 1996;115:53–63.

85. Ly LP, Jiminez M, Zhuang TN et al. A double-blind, placebo-controlled, randomized clinical trial of transdermal dihydrotestosterone gel on muscular strength, mobility, and quality of life in older men with partial androgen deficiency. J Clin Endocrinol Metab 2001;86:4078–4088.
86. Khan KS, Daya S, Jadad AR. The importance of quality of primary studies in producing unbiased systematic reviews. Arch Intern Med 1996;156:661–666.
87. Snyder PH, Peachey H, Berlin JA et al. Effect of transdermal testosterone treatment on serum lipid and apolipoprotein levels in men more than 65 years of age. Am J Med 2001;111:255–260.
88. Bhasin S, Buckwalter JG. Testosterone supplementation in older men: A rational idea whose time has not yet come. J Androl 2001;22:718–731.
89. Vermeulen A. Androgen replacement therapy in the aging male—a critical evaluation. J Clin Endocrinol Metab 2001;86:2380–2390.
90. Matsumoto AM. Andropause: Clinical implications of the decline in serum testosterone levels with aging in men. J Gerontol A Biol Sci Med Sci 2002; 57A:M76–M99.
91. Morley JE, Charlton E, Patrick P et al. Validation of a screening questionnaire for androgen deficiency in aging males. Metabolism 2000;49:1239–1242.

MANUSCRIPT ADDENDUM

Following the acceptance of this manuscript for publication, seven additional studies were published that met inclusion criteria (summarized below).[92–98] Five involved cohorts already included in this review,[92, 94–96, 98] although one included additional subjects.[95]

Subphysiological testosterone supplementation for 6 months did not affect BMD or biochemical markers of bone turnover in healthy men.[92] Physiological to slightly supraphysiological testosterone for 6 months increased lean body mass, muscle volume, strength, and muscle insulin-like growth factor-I (IGF-I) levels, whereas muscle protein catabolism and total body fat decreased.[93] Supraphysiological but not physiological testosterone for 3 weeks increased growth hormone and IGF-I secretion in older men.[94]

In men undergoing knee replacement, supraphysiological testosterone administration for 4 weeks preoperatively improved ability to stand and tended to improve other functional status measures postoperatively.[95]

Supplemental testosterone for one year in healthy men improved Trailmaking B cognitive scores versus baseline, but the change in score was not significantly different from placebo. Testosterone did not affect perceived health status.[96]

Acute physiological or moderately supraphysiological intravenous testosterone did not affect myocardial perfusion imaging scores or onset of ST depression during stress testing in men with stable CHD.[97] Brachial artery reactivity was unaffected by one year of testosterone in healthy men, whereas HDL cholesterol decreased.[98]

PSA levels, prostate volume and urinary flow rates were unchanged after 6 months of physiological to mildly supraphysiological testosterone.[93] Hematocrit increased within normal limits in two studies.[93, 95]

These findings are generally consistent with other data reported in this review. Nevertheless, it is noteworthy that testosterone was not found to affect vascular reactivity,[98] or cardiac ischemia in CHD patients.[97]

REFERENCES

92. Christmas C, O'Connor KG, Harman SM et al. Growth hormone and sex steroid effects on bone metabolism and bone mineral density in healthy aged women and men. J Gerontol Biol Sci Med Sci 2002;57A:M12–M18.
93. Ferrando AA, Sheffield-Moore M, Yeckel CW et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. Am J Physiol Endocrinol Metab 2002;282:E601–E607.
94. Gentili A, Mulligan T, Godschalk M et al. Unequal impact of short-term testosterone repletion on the somatotropic axis of young and older men. J Clin Endocrinol Metab 2002;87:825–834.
95. Amory JK, Chansky HA, Chansky KL et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. J Am Geriatr Soc 2002;50:1698–1701.
96. Kenny AM, Bellantonio S, Gruman CA et al. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. J Gerontol Biol Sci Med Sci 2002;57A:M321–M325.
97. Thompson PD, Ahlberg AW, Moyna NM et al. Effect of intravenous testosterone on myocardial ischemia in men with coronary artery disease. Am Heart J 2002; 143:249–256.
98. Kenny AM, Prestwood KM, Gruman CA et al. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. J Gerontol Biol Sci Med Sci 2002;57A:M460–M465.