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Testosterone supplementation in the aging male: Which questions have been answered?

WALTER KRAUSE¹, ULRICH MUELLER², & ALLAN MAZUR³

¹Department of Andrology, University Hospital, School of Medicine, Philipp University, Marburg, Germany, ²Institute of Medical Sociology and Social Medicine, School of Medicine, Philipp University, Marburg, Germany, and ³Maxwell School, Syracuse University, Syracuse, USA

Abstract

Purpose: There is no consensus on possible benefits and risks of testosterone supplementation. Here we review various controlled studies of testosterone supplementation in aging males.

Methods: We performed a PubMed search using the terms “testosterone/therapeutic use” with the limits “> 65 years of age”, “randomized controlled clinical trials”, and “male gender”, starting in 1999.

Results: Forty-three articles have been published since 1999. Some of these studies also included patients in middle-age or younger. Findings reported in these articles were not entirely consistent. After weighting studies by the number of patients, hints are found that testosterone supplementation increases bone mass, lean body mass, muscle mass and hematopoiesis, and improves sexual functioning and perhaps mood, but does not affect serum lipids, cardiovascular parameters, prostate-specific antigen level, or cognition. Considering studies including only men older than 65 years, and in which testosterone supplements were compared with placebo treatment, slightly different results are obtained. In these patient groups, testosterone does not improve sexual function or mood.

Conclusion: The overall benefit of testosterone supplementation for the aging male remains unclear. Any supplementation in men with age-normal testosterone levels only on grounds of subjective symptoms is not advisable.

Keywords: Testosterone, aging male, substitution, organ functions

Introduction

Numerous publications of the last years speculate on possible benefits and risks of testosterone supplementation in the aging male. Testosterone is responsible for a number of clinical effects in different organs of aging men (Table I). The effects of testosterone deficiency may be mimicked by other pathogenic mechanisms.

Tenover [1], one of the first authors to present a controlled randomized trial on this problem, concluded that “targets of interest are body composition (muscle mass, fat mass, strength), bone, sexual function, cognition and mood, sleep, prostate, erythropoiesis, [and] cardiovascular factors (lipoproteins, hemostasis, fluid volume)”. Tenover [2] stated again in 1999, “The decline in testosterone with age often parallels unfavorable changes in organs upon which androgens act, and the goal of male HRT would be to prevent, stabilize or even reverse some of these detrimental target-organ changes”. Two other reviews [3,4] of the same year essentially agreed that more scientific work is needed before general replacement of “falling hormones” and warned against the hormo-

nal supplementation in older males outside the content of a clinical trial.

With growing interest in problems of aging, one might expect that knowledge about testosterone supplementation would increase as rapidly. However, later reviews repeated the theme of insufficient understanding. Juul and Skakkebaek [5] concluded, “In the future, testosterone therapy may prove beneficial in some elderly males with low-normal testosterone levels. However, at this point in time, widespread use of testosterone in an elderly male population outside controlled clinical trials seems inappropriate”. Morley and Perry [6] wrote of the need for research on the long-term efficacy and safety of testosterone replacement in older persons.

We must consider important ambiguities in evaluating testosterone replacement. First, there is no certain diagnosis of testosterone deficiency in elderly men. Most experts agree that diagnosis should be based on a combination of symptoms and dysfunctions, as summarized in Table I, and a low serum testosterone level. However, the reference range is defined only in young men. Vermeulen [7] proposes that “low” testosterone levels in the aging

Table I. Clinical effects of testosterone (based on Oddens and Vermeulen [19])

Organ	Effect of physiologic doses	Consequence of deficiency
Genital organs	Growth, masculinization	Shrinking of testis (?)
Bone	Growth, improved mineralization	Osteoporosis
Larynx	Growth	No change of voice(?)
Skin	Growth of terminal hairs, improved sebum production	Alopecia, dryness
Kidney	Improved erythropoietin production	Lower level of EPO
Lipid metabolism	Dissociation of lipoproteins	Cardiovascular risk (?)
Cardiovascular system	Vascular dilation	?
Fatty tissue	Decrease of visceral fat	Decrease of lean body mass
Bone marrow	Stimulation of erythropoiesis	Anemia (?)
Muscles	Increase of muscle mass	Sarcopenia
Testis	Maintenance of spermatogenesis	Infertility
Prostate	Improved growth and function	BPH, carcinoma (?)
Mammary gland	Growth inhibition	Gynecomastia
Psychosexual functions	Sexual stimulation	Decreased libido
Cognition	Improvement	Decreased spatial memory
Mood	improvement (?)	Depression (?)

male may be taken as anything below the lowest 1% of levels in young healthy males, but obviously this is arbitrary.

Also, the best method for administering testosterone is unclear. Different testosterone (T) delivery systems are currently on the market or in phase II/III trials [8] (the latter are marked with superscript a), including oral and buccal modes of application (T, buccal T, bioadhesive buccal T^a, T cyclodextrin^a, T undecanoate, specific androgen receptor modulators [SARMs]), injectables (T enanthate, -cypionate, undecanoate^a, buciclate^a, decanoate^a, microspheres^a), transdermals (patches, gels, DHT gel^a), and implants (T, 7 α -methyl nor-testosterone [MENT]^a). Comparative studies of different delivery systems are rarely available, and Tenover's statement [9], "All methods of T replacement are probably efficacious if adequate serum T levels are achieved", is an assumption, but not based on correctly designed studies. In contrast, Wu and Eckardstein [10] assume that the effects of exogenous testosterone on cardiovascular risk factors differ considerably in clinical studies according to the route of administration as well as the dose.

Recently Tenover [9] optimistically suggested, "The data that are available give support to the hypothesis that ART should have a number of beneficial effects for some older men and that its adverse effects may not be so severe as to overwhelm efficacy". But is this optimism justified?

Material and methods

Studies that compare the clinical characteristics of (i) aging men with low versus normal testosterone levels, or of (ii) hypogonadal young men versus normal young men, are not suited to answer questions about the efficacy of testosterone supplementation. We do not include them in evaluations of treatment, limiting ourselves to experimental studies.

To locate recent reports of this kind, we conducted a PubMed search on "testosterone/therapeutic use" with the limits "> 65 years of age", "randomized controlled clinical trials", and "male gender".

Results

The PubMed search produced 43 studies published from 1999 through 2003. Their findings are compiled in Table II. As may be seen in the column labeled "Change", these results are often inconsistent, even for the same organ function. When the study results were weighted according to the number of patients included, the following effects of testosterone supplementation are supported: increase of bone mass, no change in serum lipids and cardiovascular parameters, increase in lean body mass, increase in hematopoiesis, increase in muscle mass, no change in PSA level, improvement in sexual functioning, no change in cognition, and improvement in mood.

Some studies found in the search included men of middle age or younger, and not all studies compared testosterone administration with a placebo. Table III is limited to studies of patients older than 65 years, and where testosterone was compared to placebo. The results in Table II are grossly repeated in Table III, including some inconsistency in findings. Generally speaking, men over 65 who received testosterone placement (by diverse means), for periods ranging from 3 weeks to 3 years, showed at the end of treatment (compared to controls) increases in bone mass, in lean body mass, in muscle mass, and in hematopoiesis, while cardiovascular parameters, serum lipids, sexual function, cognition and mood were unchanged. Also, the PSA level remained unchanged in controlled testosterone supplementation. A functional decrease was observed only in breathing characteristics.

Discussion

One can read from Tables III and IV evidence for the improvement or steadiness of several parameters by testosterone supplementation in the aging male. The most reliable effects of testosterone replacement, found consistently in three or more studies, were increases in lean body mass and muscle mass, and no change in cognition. A functional deterioration was seen in the quality of breathing, based on a study of only 17 patients.

Table III reports the various organ functions simply as "improvement", "unchanged", or "deterioration", without considering the strength of effects. Although most studies quoted the effects in a quantitative manner, the instruments used for measurement, and the doses, durations, and means of delivering testosterone were so varied that a more precise meta-analysis could not be compiled.

While some effects of testosterone supplementation appear to be clear and secure, there is still uncertainty about clinical implications. Authors of several of the recent papers expressed hesitation. Concerning bone mass, Swerdloff and Wang [8] noted that "testosterone replacement results in increases in BMD in all reported studies, but there are no available data on a decrease in fracture risk". Testosterone may be responsible for the improvement in bone metabolism only after its conversion to estradiol [11]. Concerning serum lipids and cardiovascular system, Gooren [12] concluded, "Many more studies are needed to examine whether raising T levels will lead to an improvement of the cardiovascular and diabetogenic risk factors". Crook [13] remained similarly cautious, stating, "It is an important but unanswered question whether there are real symptomatic or functional benefits or decreased cardiovascular mortality from testosterone treatment". The increase in muscle mass that is observed in these studies is not necessarily associated with an increase in muscle strength, as Swerdloff and Wang [8] state: "Muscle mass is correlated with T levels in elderly men, whereas data on muscle strength are not conclusive".

Other investigators have been more positively assertive. Kaufman [14] concluded, "No evidence of increased risk for clinical prostate cancer or symptomatic BPH has been found in trials of androgen replacement therapy lasting up to 3 years". Still, there have not been many studies of the effect of testosterone replacement on the elderly prostate, and the important question of long-term prostatic risk is unaddressed.

Swerdloff and Wang [8] comment, "There is also epidemiologic evidence linking serum T and bio T with sexual activity", but this was not supported by other studies. However, the authors

also considered that "Erectile dysfunction may not be corrected by testosterone therapy alone". In this respect, the study of Aversa et al. [15] is of interest, in which sildenafil for erectile dysfunction had a better effect in men with normalized testosterone levels, thus indicating the importance of normal testosterone levels for normal functioning of androgen-related structures.

While there was no effect of testosterone supplementation on cognitive ability or only small effects restricted to a few test parameters ("these studies suggest that T administration may improve spatial or verbal memory, particularly for older males who have age-related decreases in endogenous T levels" [16]), the effect on mood appeared to be clear from earlier but uncontrolled studies. This is, however, not supported by Seidman et al. [17] who stated that "although exogenous testosterone is currently being used for refractory depression, this was the first systematic study of testosterone in depressed men, and efficacy was not supported". On the other hand, Pope et al. [18] came to the conclusion that "testosterone gel, added to the subjects existing antidepressant regimens, proved significantly superior to placebo in reducing scores on the Hamilton Depression Rating Scale". This again gives evidence for the necessity of normal testosterone levels for normal functioning of androgen-related structures.

Conclusions and recommendations for future research

Overall, in spite of the recent publication of well-conducted studies with clear effects on certain parameters, the benefits and risks of testosterone supplementation for the aging male remain unclear. Thus, for the time being, testosterone supplementation should be performed only in controlled clinical studies, in which effects and risks are thoroughly recorded, and any undesirable developments can be dealt with at an early stage, starting with short-term efficacy trials [47]. The short duration of initial trials will allow for review and reconceptualization as the effects of testosterone therapy are established. However, given the sobering results of the large Women's Health Initiative studies (published from 2003 onwards, mostly in the *Journal of the American Medical Association*) on the effects of long-term steroid supplementation in the aging female, for which initially a much stronger point could be made, controlled studies on the effect of exogenous testosterone supplementation in large samples of normal aging males are difficult to imagine in the foreseeable future. Since clinical signs may have various causes, any supplementation in men with age-normal testosterone levels only on grounds of subjective symptoms is not advisable.

Table II. Effects on organ functions quoted in the literature

Organ function	Change	Active treatment	Comparison	N	Patients	Duration of treatment	Ref.
Bladder function	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
Bone mass	→	DHT gel	HCG	33	> 60 yr	3 mo	[21]
	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]
	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[24]
Breathing	↓	T injection-	Placebo	17	> 65 yr, community dw.	3 wk	[25]
Cardiovascular	↑	T injection + sildenafil	Sildenafil alone	20	Sildenafil non-responder	1 mo	[15]
	↑	T patch	Placebo	46	Stable angina	12 wk	[27]
	→	T patch	Placebo	44	65–87 yr	12 mo	[26]
	→	T patch	Placebo	108	> 65 yr	36 mo	[28]
Glucose metab.	↑	T injection	GH	10	68 yr	1 mo	[29]
	→	T injection	No treatment	48	Type 2 diabetes	3 mo	[30]
Serum lipids	↑	Oxymetholone	Placebo	31	65–80 yr	12 wk	[32]
	→	Before treatment	After treatm.	15	Elderly men	3 wk	[31]
	→	DHT gel	HCG	33		3 mo	[21]
	→	T patch	Placebo	44	65–87 yr	12 mo	[26]
	→	T patch	Placebo	46	Stable angina	12 wk	[27]
	→	T patch	Placebo	108	> 65 yr	36 mo	[28]
	→	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
Lean body mass	↑	T injection	Placebo	12	> 60 yr, PSA < 4 ng/ml	3 mo	[35]
	↑	T injection	Placebo	17	> 65 yr, community dw.	3 wk	[25]
	↑	T gel	T patch	27	19–68 yr, multicenter	6 mo	[33]
	↑	Oxymetholone	Placebo	31	65–80 yr	12 wk	[32]
	↑	T injection	Placebo	43	On prednisone	12 mo	[36]
	↑	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	TU oral	Placebo	76	> 60 yr	12 mo	[37]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]
	↑	T gel	T patch	208	31–80 yr, multicenter	3 mo	[38]
	↑	T gel or T patch	Placebo	406	20–80 yr, multicenter	3 mo	[39]
	→	T injection	GH	10	68 yr	1 mo	[29]
	→	T injection	No treatment	48	Type 2 diabetes	3 mo	[30]
	→	T injection	Placebo	?	?	12 wk	[34]
Hematopoiesis	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	→	T patch	Placebo	46	Stable angina	12 wk	[27]
	↑	TU oral	Placebo	76	> 60 yr	12 mo	[37]
	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
Muscle mass ^a	↑	T gel or T patch	Placebo	406	20–80 yr, multicenter	3 mo	[39]
	↑	T injection	Placebo	12	> 60 yr, PSA < 4 ng/ml	3 mo	[35]
	↑	Oxymetholone	Placebo	31	65–80 yr	12 wk	[32]
	↑	T injection	Placebo	43	On prednisone	12 mo	[36]
	↑	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]

(continued)

Table II. (continued)

Organ function	Change	Active treatment	Comparison	N	Patients	Duration of treatment	Ref.
Prostate (PSA)	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
	→	DHT gel	HCG	33	> 60 yr	3 mo	[21]
	→	T injection	GH	10	68 yr, muscle biopsy	1 mo	[29]
	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	→	T patch	Placebo	46	Stable angina	12 wk	[27]
	→	TU-oral	Placebo	76	> 60 yr	12mo	[37]
Cognition	→	PIN+	PIN–	75	Not given	12	[40]
	↑	T injection	Placebo	25	Healthy volunteers	6 wk	[41]
	→	T injection	Placebo	11	Elderly men	12 wk	[42]
	→	T injection	Placebo	30	Elderly men	Single inj.	[43]
	→	T patch	Placebo	44	65–87 yr	12 mo	[44]
Mood	↑	T patch	Placebo	46	Stable angina	12 wk	[27]
	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
	↑	T gel	Placebo	22	30–65 yr, depression	8 wk	[18]
	→	T injection	GH	10	68 yr	1 mo	[29]
Sexual function	→	T injection 100 mg	200 mg T	16	Major depression	8 wk	[45]
	→	T injection	Placebo	22	> 65 yr	8 wk	[46]
	→	T injection	Placebo	32	Depression and low T	6 wk	[17]
	→	T patch	Placebo	44	65–87 yr	12 mo	[44]
	→	T injection	GH	10	68 yr	1 mo	[29]
	↑	T inj. + sildenafil	Sildenafil	20	Sildenafil non-respond.	1 mo	[15]
	↑	T injection	No treatment	48	type 2 diabetes	3 mo	[30]
	↑	T gel	T patch	208	31–80 yr, multicenter	3 mo	[38]
	↑	T gel	T patch	227	19–68 yr, multicenter	6 mo	[33]
	↑	T gel or T patch	Placebo	406	20–80 yr, multicenter	3 mo	[39]

^aUsually, muscle mass is calculated as the difference between total body mass and fat body mass. An increase in muscle mass is not identical to an increase in muscle strength.

Table III. Extract from Table II in which only placebo-controlled studies including only men > 65 years of age are summarized

Organ function	Change	Active treatment	Comparison	N	Patients	Duration of treatment	Ref.
Bladder function	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
Bone	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]
Breathing	↓	T injection	Placebo	17	> 65 yr, community dw.	3 we	[25]
Cardiovascular	→	T patch	Placebo	44	65–87 yr	12 mo	[26]
	→	T patch	Placebo	108	> 65 yr	36 mo	[28]
Serum lipids	↑	Oxymetholone	Placebo	31	65–80yr	12 we	[32]
	→	T patch	Placebo	44	65–87 yr	12 mo	[26]
	→	T patch	Placebo	108	> 65 yr	36 mo	[28]
Lean body mass	↑	T injection	Placebo	12	> 60 yr, PSA < 4 ng/ml	3 mo	[35]
	↑	T injection	Placebo	17	> 65 yr, community dw.	3 we	[25]
	↑	Oxymetholone	Placebo	31	65–80 yr	12 we	[32]
	↑	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	TU oral	Placebo	76	> 60 yr	12 mo	[37]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]
Hematopoiesis	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	TU oral	Placebo	76	> 60 yr	12 mo	[37]
Muscle mass	↑	T injection	Placebo	12	> 60 yr, PSA < 4 ng/ml	3 mo	[35]
	↑	Oxymetholone	Placebo	31	65–80 yr	12 we	[32]
	↑	T patch	Placebo	44	65–87 yr	12 mo	[20]
	↑	T patch	Placebo	108	> 65 yr	36 mo	[22,23]
Prostate (PSA)	→	T patch	Placebo	44	65–87 yr	12 mo	[20]
	→	TU oral	Placebo	76	> 60 yr	12mo	[37]
Cognition	→	T injection	Placebo	11	Elderly men	12 we	[42]
	→	T injection	Placebo	30	Elderly men	Single inj.	[43]
	→	T patch	Placebo	44	65–87 yr	12 mo	[44]
Mood	→	T injection	Placebo	22	> 65 yr	8 we	[46]
	→	T patch	Placebo	44	65–87 yr	12 mo	[44]
Sexual function	→	T injection	GH	10	68 yr	1 mo	[29]

The figures give the number of men included in the study. Abbreviations: See Table II.

Table IV. Summary of Table III

Organ function	↑	→	↓	Summary
Bladder function		44		→
Bone	108	44		↑
Breathing			17	↓
Cardiovascular		152		→
Serum lipids	31	152		→
Lean body mass	300			↑
Hematopoiesis	76	44		↑
Muscle	207			↑
Prostate (PSA)		120		→
Sexual function		10		→
Cognition		85		→
Mood		66		→

The figures give the number of men included in the study.

References

1. Tenover JL. In: Oddens B, Vermeulen A, editors. Androgens and the aging male. Parthenon Publishing; 1995.
2. Tenover JL. Testosterone replacement therapy in older adult men. *Int J Androl* 1999;22(5):300–306.
3. Janssens H, Vanderschueren DM. Endocrinological aspects of aging in men: is hormone replacement of benefit? *Eur J Obstet Gynecol Reprod Biol* 2000;92(1):7–12.
4. Hermann M, Berger P. Hormone replacement in the aging male? *Exp Gerontol*. 1999;34(8):923–933.
5. Juul A, Skakkebaek NE. Androgens and the ageing male. *Hum Reprod Update* 2002;8(5):423–433.
6. Morley JE, Perry HM 3rd. Andropause: an old concept in new clothing. *Clin Geriatr Med* 2003;19(3):507–528.
7. Vermeulen A. Diagnosis of partial androgen deficiency in the aging male. *Ann Endocrinol (Paris)* 2003;64(2):109–114.
8. Swerdloff RS, Wang C. Androgens an the aging male. In: Lunenfeld B, Gooren L, editors. *Textbook of men's health*. Parthenon Publishing; 2002.
9. Tenover JL. Androgens in older men. In: Bagatell CJ, Bremner WJ, editors. *Androgens in health and disease*. New Jersey: Humana Press; 2003.
10. Wu FC, Eckardstein A. Androgens and coronary artery diseases. In: Bagatell CJ, Bremner WJ, editors. *Androgens in health and disease*. New Jersey: Humana Press; 2003.

11. Szulc P, Claustrat B, Marchand F, Delmas PD. Increased risk of falls and increased bone resorption in elderly men with partial androgen deficiency: the MINOS study. *J Clin Endocrinol Metab* 2003;88(11):5240–5247.
12. Gooren L. Visceral obesity, androgens and the risks of cardiovascular disease and diabetes mellitus. In: Lunenfeld B, Gooren L, editors. *Textbook of men's health*. Parthenon Publishing; 2002.
13. Crook D. Atherosclerotic risk assessment of androgen therapy in aging men. In: Lunenfeld B, Gooren L, editors. *Textbook of men's health*. Parthenon Publishing; 2002.
14. Kaufman JM. The effect of androgen supplementation therapy on the prostate. *Aging Male* 2003;6:166–174.
15. Aversa A, Isidori AM, Spera G, Lenzi A, Fabbri A. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. *Clin Endocrinol (Oxf)*. 2003;58(5):632–638.
16. Cherrier MM, Craft S. Androgens and cognition. In: Bagatell CJ, Bremner WJ, editors. *Androgens in health and disease*. New Jersey: Humana Press; 2003.
17. Seidman SN, Spatz E, Rizzo C, Roose SP. Testosterone replacement therapy for hypogonadal men with major depressive disorder: a randomized, placebo-controlled clinical trial. *J Clin Psychiatry* 2001;62(6):406–412.
18. Pope HG Jr, Cohane GH, Kanayama G, Siegel AJ, Hudson JL. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry* 2003;160(1):105–111.
19. Oddens B, Vermeulen A, editors. *Androgens and the aging male*. New York/London: Parthenon Publishing; 1996.
20. Kenny AM, Prestwood KM, Gruman CA, Marcello KM, Raisz LG. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2001;56(5):M266–M2672.
21. Ng MK, Liu PY, Williams AJ, Nakhla S, Ly LP, Handelsman DJ, Celermajer DS. Prospective study of effect of androgens on serum inflammatory markers in men. *Arterioscler Thromb Vasc Biol* 2002;22(7):1136–1141.
22. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Holmes JH, et al. Effect of testosterone treatment on bone mineral density in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84(6):1966–1972.
23. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA, 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(8):2647–2653.
24. Wang C, Swerdloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Effects of transdermal testosterone gel on bone turnover markers and bone mineral density in hypogonadal men. *Clin Endocrinol (Oxf)* 2001;54(6):739–750.
25. Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. *J Clin Endocrinol Metab* 2003;88(8):3605–3613.
26. Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G. Effects of transdermal testosterone on lipids and vascular reactivity in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2002;57(7):M460–M465.
27. English KM, Steeds RP, Jones TH, Diver MJ, Channer KS. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind, placebo-controlled study. *Circulation* 2000;102(16):1906–1911.
28. Snyder PJ, Peachey H, Berlin JA, Rader D, Usher D, Loh L, 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(4):255–260.
29. Brill KT, Weltman AL, Gentili A, Patrie JT, Fryburg DA, Hanks JB, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. *J Clin Endocrinol Metab* 2002;87(12):5649–5657.
30. Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male* 2003;6(1):1–7.
31. Herbst KL, Amory JK, Brunzell JD, Chansky HA, Bremner WJ. Testosterone administration to men increases hepatic lipase activity and decreases HDL and LDL size in 3 wk. *Am J Physiol Endocrinol Metab* 2003;284(6):E1112–E1118.
32. Schroeder ET, Singh A, Bhasin S, Storer TW, Azen C, Davidson T, et al. Effects of an oral androgen on muscle and metabolism in older, community-dwelling men. *Am J Physiol Endocrinol Metab* 2003;284(1):E120–E128.
33. Wang C, Swedloff RS, Iranmanesh A, Dobs A, Snyder PJ, Cunningham G, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. Testosterone Gel Study Group. *J Clin Endocrinol Metab* 2000;85(8):2839–2853.
34. Lambert CP, Sullivan DH, Freeling SA, Lindquist DM, Evans WJ. Effects of testosterone replacement and/or resistance exercise on the composition of megestrol acetate stimulated weight gain in elderly men: a randomized controlled trial. *J Clin Endocrinol Metab* 2002;87(5):2100–2106.
35. Ferrando AA, Sheffield-Moore M, Yeckel CW, Gilkison C, Jiang J, Achacosa A, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol Endocrinol Metab* 2002;282(3):E601–E607.
36. Crawford BA, Liu PY, Kean MT, Bleasel JF, Handelsman DJ. Randomized placebo-controlled trial of androgen effects on muscle and bone in men requiring long-term systemic glucocorticoid treatment. *J Clin Endocrinol Metab* 2003;88(7):3167–3176.
37. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol A Biol Sci Med Sci* 2003;58(7):618–625.
38. McNicholas TA, Dean JD, Mulder H, Carnegie C, Jones NA. A novel testosterone gel formulation normalizes androgen levels in hypogonadal men, with improvements in body composition and sexual function. *BJU Int* 2003;91(1):69–74.
39. Steidle C, Schwartz S, Jacoby K, Sebre T, Smith T, Bachand R. North American AA2500 T Gel Study Group. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. *J Clin Endocrinol Metab* 2003;88(6):2673–2681.
40. Rhoden EL, Morgentaler A. Testosterone replacement therapy in hypogonadal men at high risk for prostate cancer: results of 1 year of treatment in men with prostatic intraepithelial neoplasia. *J Urol* 2003;170(6 Pt 1):2348–2351.
41. Cherrier MM, Asthana S, Plymate S, Baker L, Matsumoto AM, Peskind E, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001;57(1):80–88.
42. Kenny AM, Fabregas G, Song C, Biskup B, Bellantonio S. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci* 2004;59(1):75–78.
43. Wolf OT, Preut R, Hellhammer DH, Kudielka BM, Schurmeyer TH, Kirschbaum C. 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(7):650–654.

44. Kenny AM, Bellantonio S, Gruman CA, Acosta RD, Prestwood KM. Effects of transdermal testosterone on cognitive function and health perception in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2002;57(5):M321–M325.
45. Perry PJ, Yates WR, Williams RD, Andersen AE, MacIndoe JH, Lund BC, et al. Testosterone therapy in late-life major depression in males. *J Clin Psychiatry* 2002;63(12):1096–1101.
46. Reddy P, White CM, Dunn AB, Moyna NM, Thompson PD. The effect of testosterone on health-related quality of life in elderly males – a pilot study. *J Clin Pharm Ther* 2000;25(6):421–426.