University Library



A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Grossmann, M;Anawalt, BD;Yeap, BB

Title:
Testosterone therapy in older men: clinical implications of recent landmark trials

Date:
2024

Citation:
Grossmann, M., Anawalt, B. D. & Yeap, B. B. (2024). Testosterone therapy in older men: clinical implications of recent landmark trials. European Journal of Endocrinology (EJE), 191 (1), pp.R22-R31. https://doi.org/10.1093/ejendo/lvae071.

Persistent Link:
https://hdl.handle.net/11343/351701

License:
CC BY

European Journal of Endocrinology, 2024, **191**, R22–R31
https://doi.org/10.1093/ejendo/lvae071
Advance access publication 26 June 2024
Invited Review

Testosterone therapy in older men: clinical implications of recent landmark trials

Mathis Grossmann,[1,2,*†] Bradley D. Anawalt,[3,†] and Bu B. Yeap[4,5,†]

[1]Department of Medicine (Austin Health), The University of Melbourne, Heidelberg, Victoria 3084, Australia
[2]Department of Endocrinology, Austin Health, Heidelberg, Victoria 3084, Australia
[3]Department of Medicine, University of Washington School of Medicine, Seattle, WA 98195, United States
[4]Medical School, University of Western Australia, Perth, Western Australia 6009, Australia
[5]Department of Endocrinology and Diabetes, Fiona Stanley Hospital, Murdoch, Western Australia 6150, Australia

*Corresponding author: Department of Medicine (Austin Health), Austin Health, Studley Road, Heidelberg, Victoria 3084, Australia.
Email: mathisg@unimelb.edu.au

Abstract

Testosterone therapy for men with hypogonadism due to identifiable hypothalamic-pituitary-testicular (HPT) pathology is uncontroversial. However, the risks and benefits of testosterone for men with clinical features of hypogonadism in the absence of identifiable HPT axis pathology have been uncertain. Recent landmark placebo-controlled trials assessed the benefits and risks of testosterone therapy (≤3 years) for middle-aged and older men with symptoms and possible signs of hypogonadism or end-organ androgen deficiency, low or low-normal serum testosterone concentrations, but no HPT pathology: Testosterone therapy (1) had modest—but clinically significant—benefits on average self-reported energy and mood, sexual function, and satisfaction; (2) in conjunction with a lifestyle programme, reversed or reduced incident type 2 diabetes mellitus (T2D) in men at high risk of or newly diagnosed with T2D; (3) modestly improved objectively assessed muscle strength and timed walking distance; (4) increased bone density and strength, but did not reduce falls or typical osteoporotic fractures and surprisingly increased the risk of fractures typically attributable to trauma; and (5) did not significantly increase the risk of myocardial infarction, stroke, or prostate cancer. These landmark trials help to inform clinical decision-making about testosterone therapy for men.

Keywords: testosterone, hypogonadism, androgen deficiency, aging men, testosterone therapy

Significance

In men older than 40 years, a low serum testosterone in the absence of identifiable hypothalamic-pituitary-testicular axis pathology is common. Many of these men have symptoms and signs of possible androgen deficiency. Four landmark randomised placebo-controlled clinical trials of testosterone therapy given to such men have been published in recent years. In this narrative review, we discuss the salient findings of these trials and provide our perspective on how they inform "personalized decision-making" about testosterone therapy in middle-aged and older men with possible hypogonadism but no identifiable cause.

Introduction

As men enter their fourth or fifth decade, their serum testosterone typically declines, and they might develop symptoms consistent with hypogonadism (eg, low libido, fatigue, and low mood), signs of hypogonadism (eg, reduced physical function, reduced bone density, unexplained anaemia, and diabetes mellitus), and changes of body composition and metabolism (increased total boy and visceral fat and decreased muscle mass and insulin sensitivity) that are associated with type 2 diabetes mellitus (T2D).[1,2] About 2% of men over age 40 have low or low-normal serum testosterone concentrations, typically normal serum gonadotropins, symptoms, and signs of possible androgen deficiency and no identifiable hypothalamic-pituitary-testicular (HPT) axis pathology (a scenario sometimes referred to as "functional" or "late onset hypogonadism").[3,4] This might be due to obesity, poor health, or medications (reverse causality), and potentially reversible by addressing these factors.[5] Therefore, whether low serum testosterone is a causal contributor or is solely a marker of poor health (eg, eugonadal sick syndrome[6]) can only be determined by randomised controlled clinical trials. Moreover, should benefits outweigh risk, testosterone therapy might benefit men with low serum testosterone with potential androgen-sensitive, end-organ target deficits, irrespective of symptoms suggestive of hypogonadism.

Four landmark studies of testosterone therapy in men with late onset hypogonadism have been published in recent years (Table 1). Of note, men with identifiable pathology of the HPT axis (ie, classical hypogonadism) were excluded from these trials because there is general consensus that such men should receive testosterone replacement irrespective of age. In this review, we will use the term testosterone therapy as

† M.G., B.D.A., and B.B.Y. contributed equally.

Received: February 5, 2024. **Revised:** April 23, 2024. **Editorial Decision:** May 23, 2024. **Accepted:** June 20, 2024
© The Author(s) 2024. Published by Oxford University Press on behalf of European Society of Endocrinology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

Table 1. Key characteristics of recent large placebo-controlled clinical trials.

Trial	Participants (men)	Intervention	Primary outcome
TEAAM	$N = 308 \geq 60$ years Serum total T 3.47-13.9 nmol/L	T 75 mg transdermal gel vs placebo gel daily for 3 years with dosage adjusted to maintain total T 17.4-31.2 nmol/L	Carotid artery intimal thickness and coronary artery calcium scores
T-Trials	$N = 790 \geq 65$ years Serum total T ≤ 9.5 nmol/L + symptoms or signs of T deficiency	T 50 mg transdermal gel vs placebo gel daily with dosage adjusted to keep the serum T concentration within the normal range for 1 year	Seven sub-studies with different primary outcomes: 1. Sexual activity (men with impaired sexual function, $N = 459$); 2. Distance walked in 6 min (men with mobility limitations $N = 390$); 3. Vitality (men with low vitality, $N = 474$); 4. Cognitive function (men with age-associated memory impairment, $N = 493$); 5. Increase in haemoglobin (men with anaemia, $N = 126$); 6. Volumetric bone mineral density of the spine ($N = 211$); and 7. Non-calcified coronary artery plaque volume ($N = 138$).
T4DM	$N = 1007$ 50-74 years Serum total T ≤ 14 nmol/L Impaired glucose tolerance or newly diagnosed type 2 diabetes by oral glucose tolerance test	Intramuscular T undecanoate 1000 mg vs placebo at 0 weeks and 6 weeks, then every 3 months for 2 years on the background or a community-based lifestyle programme administered by Weight Watchers (WW)	Prevention or reversion of type 2 diabetes as defined by a 2-year serum 2 h glucose of ≥ 11.1 mmol/L on oral glucose tolerance test
TRAVERSE	$N = 5246$ 45-80 years Serum total T > 3.5-$\leq$10.4 nmol/L + symptoms or signs of T deficiency	T gel with dosage adjusted to maintain serum total T concentrations between 12.1 nmol/L and 26.0 nmol/L and to maintain a haematocrit of $\leq$54%) vs placebo gel daily up to 4 years (mean = 22 months)	Composite of major cardiovascular adverse event (non-fatal myocardial infarction, non-fatal stroke, or cardiovascular-related death)

Men with medical disease of the HPT axis who require T replacement therapy were excluded from these trials.
Abbreviation: T, testosterone.

an umbrella term because in the randomised clinical trials enrolling men without identifiable HPT axis pathology, it is not certain whether testosterone therapy was given as replacement (ie, correction of a physiologic deficit) or as pharmacotherapy. We review here the major findings and clinical implications of the benefits and risks of testosterone therapy of these recent trials that were large (enrolling at least 300 men), placebo-controlled, and had at least 1 year of therapy with assessment of clinically important outcomes (Tables 1-5).

Effects of testosterone therapy on vitality/energy, mood, and cognitive function

In TEAAM,[7] testosterone therapy had no effect on health-related quality of life measured by the full SF-36 questionnaire that includes questions regarding vitality, emotional well-being, and social functioning. In the larger T-Trials that used a lower serum testosterone threshold than TEAAM as an entry criterion, testosterone therapy had no significant effects on vitality and mood in the primary outcome analysis, but the subgroup of men with baseline low vitality and mood had a significantly improved a SF-36 vitality score ($P = .03$), a trend towards improved vitality on the FACIT-fatigue scale ($P = .06$), and improved mood scores in the PANAS affect and PHQ9 depression questionnaires.[8] In secondary analyses of all men in the T-Trials, the men randomised to testosterone reported, on average, a small benefit to vitality and mood, and they were more likely to report an increase in energy vs placebo ($P < .001$).[8] In T4DM, testosterone therapy had no effect on measures of health-related quality of life (using SF-36).[9] In TRAVERSE, for men with significant depressive symptoms ($n = 2643$) and for all randomised participants ($n = 5204$), testosterone therapy caused modest but significant improvements in mood and energy, but not in sleep quality.[10] In summary, the studies that enrolled solely men with low serum testosterone concentrations (T-Trials ≤ 9.8 nmol/L; TRAVERSE ≤ 10.4 nmol/L) demonstrated that testosterone therapy improved vitality and mood whereas 2 studies that included men with low-normal serum testosterone concentrations (TEAAM ≤ 13.9 nmol; T4DM ≤ 14.0 nmol/L) showed no change in these clinical outcomes.

In the T-Trials Cognitive Function substudy, testosterone therapy did not improve memory or cognitive function of men with self-reported, age-related memory impairment; a broad range of cognitive instruments were used. In an exploratory analysis, there was a significant improvement of executive function when all men in the T-Trials were included (not just the men with age-related memory impairment).[11] Executive function is important for maintaining focus, following directions, and completing daily tasks. This finding could be important, but it would require confirmation. In TEAAM[12] and TRAVERSE,[10] there were no detectable clinically significant effects of testosterone therapy on cognitive function. Neither of these studies required evidence of cognitive dysfunction as an entry criterion, and the cognitive function testing was less extensive and sophisticated than the T-Trials. T4DM did not assess cognitive function.

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

Table 2. Change in serum testosterone and key beneficial outcomes (compared to placebo) of T therapy in recent large clinical trials.

Domain	TEAAM	T-Trials	T4DM	TRAVERSE
Serum total T (baseline and treatment)	Mean baseline: 10.6 nmol/L Median treatment (month 36): 19.5 nmol/L	Mean baseline: 8.4 nmol/L Mean treatment (months 3-12): ~17.4 nmol/L	Mean baseline: 13.4 nmol/L Mean treatment trough (months 4-24): ~16-18 nmol/L	Median baseline: 8 nmol/L Median treatment trough: (months 2-36) 11.3-13.4 nmol/L
Vitality/energy, mood, sexual function, and cognition	Vitality and mood not measured: No effect on health-related quality of life assessed with SF-12 Sexual function: No effect on sexual desire, erectile function, overall sexual function scores Cognitive function: No effect on cognition	Vitality: No effect in primary outcome (change in FACIT-fatigue score of at least 4), but a trend towards a small increase of vitality (change in FACIT-fatigue 1.2; $P = .06$); greater increase of T from baseline = greater increase of FACIT-fatigue score; there was a significant but modest improvement of SF-36-vitality score Mood: Statistically significant but small improvements in mood and depressive symptoms on PANAS and PHQ-9 questionnaires Sexual function: Significant, but modest increases of libido, sexual activity, satisfaction, increase in erectile function (+2.64 in IEEF) Cognitive function: There was no effect on cognition.	Vitality and mood not measured: No effect on health-related quality of life (assessed with SF-12 questionnaire) Sexual function: Small, but significant increases of libido and overall sexual satisfaction Modest improvement of erectile function score: +2.10 (95% CI 0.95 to 3.26; $P = .0004$) Cognitive function: Cognitive function was not assessed.	Vitality and mood: Improvement in haemoglobin in T-treated men was associated with a small improvement in energy scores. Mood modestly improved in men with and without depressive symptoms. Sexual function: Significant improvement of sexual desire, but not erectile function Significantly greater improvement in self-reported sexual activities. Note that sexual activities were broadly defined: Sexual daydreams, anticipation of sex, sexual interactions with partner, flirting by you, flirting towards you, orgasm, ejaculation, intercourse, masturbation, night spontaneous erection, day spontaneous erection, and erection in response to sexual activity. Treatment effect was maintained at 24 months. Cognitive function: No improvement of cognitive function or change in sleep quality in men with or without depressive symptoms
Glucose and lipid metabolism	No effect on fasting glucose and lipid profile	Significant decrease of fasting insulin (adjusted mean difference, −1.7 µIU/mL; $P = .02$) and homeostatic model assessment-insulin resistance (adjusted mean difference, −0.6; $P = .03$). No change in plasma fasting glucose. Decreased serum total cholesterol (−0.16 mmol/L; $P < .001$), high-density lipoprotein cholesterol (adjusted mean difference, −0.05 mmol/L; $P < .001$), and low-density lipoprotein cholesterol (adjusted mean difference, −0.06 mmol/L; $P = .051$). No change in serum triglycerides	55 (12%) of participants in the T group and 87 (21%) in the placebo group had diabetes (defined as a 2 h glucose of 11.1 mmol/L or higher on OGTT) (relative risk 0.59, 95% CI 0.43 to 0.80; $P = .0007$). Greater decreases in fasting glucose in T vs placebo group No effect on HbA1c	Over a mean follow-up of 32 months, T therapy compared to placebo did not reduce rates of progression of prediabetes (defined as a HbA1c between 5.7% and 6.4% or 1 or more fasting glucose between 5.6 and 6.9 mmol/L) to diabetes (defined as an HbA1c > 6.5%, initiation of diabetes medications or 2 consecutive fasting glucose concentrations of >6.9 mmol/L) with progression rates ranging from 0.7% at 6 months in the testosterone group and 1.4% in the placebo group to 13.4% at 48 months in the testosterone group and 15.7% in the placebo group (omnibus test $P = .49$ after adjusting for pre-existing cardiovascular disease. The rates of diabetes remission (defined as HbA1c < 6.5% or 2 consecutive fasting glucose concentrations of ≤6.9 nmol/L) among participants with diabetes at baseline were not different between testosterone and placebo groups (omnibus test $P = .95$, hazard ratio 1.15, 95% CI 0.87-1.53).
Muscle strength and physical function	Testosterone-treated men had significantly greater improvement of chest press strength and power, leg press power, and stair-climbing power compared to placebo at the end of the 36-month treatment.	No significant difference in proportions of men with increase in walking distance ≥ 50 m in 6 min walk test in men with limitation in mobility but increased walking distance and increased walking distance ≥ 50 m in 6 min walk test and improvements in	Greater increases in total muscle mass + 1.71 kg [95% CI 1.32 to 2.11] $P < .0001$, arm muscle mass + 0.36 kg [0.25 to 0.47] $P < .0001$, and hand-grip strength + 2.19 kg [1.28 to 3.10] $P < .0001$ in T vs placebo group	Not reported

(*continued*)

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

Table 2. Continued

Domain	TEAAM	T-Trials	T4DM	TRAVERSE
		self-reported walking ability in all participants; no difference in falls compared to placebo group		
Bone health	Not reported	Significant volumetric bone mineral density and strength of lumbar spine bone (6.8%; $P < .001$ compared to placebo)	Significant increase of tibial cortical volumetric bone mineral density (3.1%) and of total tibial cortical bone (1.3%) compared to placebo). T, compared to placebo, increased areal bone mineral density at the lumbar spine (3.3%), total hip (1.9%) and femoral neck (1.7%)	See Table 3.
Haematological parameters	Not reported	Significantly more patients with unexplained anaemia had resolution of anaemia. Improved haemoglobin concentration (of those with unexplained anaemia); 54% in the T group vs 15% in the placebo group had a significant increase in haemoglobin concentration ≥ 1.0 g/dL	Not reported	~15% and 5% more men receiving T vs *P* had resolution of anaemia at 6 months and 48 months, respectively. In addition, incidence of new anaemia was lower in fewer men receiving T (absolute difference of incident anaemia was ~3% compared to *P*).

Comparisons are always compared to placebo.
Abbreviation: T, testosterone.

Overall, in men with serum testosterone concentrations (≤10.4 nmol/L) and symptoms of hypogonadism, testosterone therapy modestly improves vitality (energy) and mood, but has no effect on cognitive function. The modest improvement of vitality and mood seems generally too small to constitute the sole criterion for initiation of testosterone therapy. The effects of testosterone therapy on sense of well-being and cognition merit further study, and methods and instruments specific for the effects of sex steroids on mood and cognition should be developed.

Effects of testosterone therapy on sexual function

TEAAM reported no effect of testosterone therapy on sexual function measures.[7] The lack of improvement in sexual function in TEAAM is surprising and not in line with other evidence; lack of testosterone treatment dose adjustment could be 1 potential reason for this unexpected outcome. Moreover, the inclusion of men with baseline normal serum total testosterone concentrations in the TEAAM trial might have attenuated the average effect of testosterone therapy on sexual function. In the T-Trials, in the primary analysis of men with self-reported low libido, testosterone therapy increased sexual activity during the first 9 months of the study, but this effect tended to decline in the last 3 months.[8] In more detailed analyses,[13] testosterone therapy improved 10 of 12 measures in sexual activity (including sexual desire, activity, and overall satisfaction) with standardised mean differences (SMD) up to 0.45 (SMDs of 0.2-0.5 represent a modest effect). The effect on erectile function (2.64 mean increase in the erectile function domain of the International Index of Erectile Function [IIEF] score) was below what has been used as a clinically significant threshold of ~4.0 for effectiveness studies of phosphodiesterase inhibitors for erectile dysfunction[14] (TEAAM, T-Trials, T4DM, and TRAVERSE did not include erectile dysfunction as an entry criterion). In T4DM, testosterone therapy similarly improved erectile dysfunction (2.1 increase of mean IIEF score), sexual desire, and overall sexual satisfaction.[9] In TRAVERSE, which recruited men with high risk at or with pre-existing cardiovascular disease, testosterone therapy improved sexual activity and libido among the subgroup of men with self-reported low libido ($n = 1161$), but had no effect on erectile function.[15]

In summary, testosterone improves libido and most aspects of sexual function in men with low libido in the presence of low testosterone, but men with erectile dysfunction due to cardiovascular or neurovascular disease are more likely to respond to phosphodiesterase 5 inhibitors. Low libido, but not erectile dysfunction, is a primary indication for testosterone therapy in hypogonadal men.

Effects of testosterone therapy on body composition and glucose metabolism

Testosterone therapy reduces fat mass by about 1-4 kg and increases lean mass by about 1.5 to 5 kg[16,17]—changes in body composition that are expected to be metabolically favourable for the prevention and therapy of T2D. In TEAAM that included 15% with baseline diabetes, there was no effect of testosterone therapy on fasting blood glucose concentrations.[7] However, in a secondary analysis of the T-Trials, 37% of whom had baseline T2D, testosterone slightly but significantly decreased fasting insulin (adjusted mean difference,

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

Table 3. Key potential risks of T therapy in recent large clinical trials.

Domain	TEAAM	T-Trials	T4DM	TRAVERSE
Cardiovascular health	No differences in progression of carotid intimal thickness or coronary artery calcium scores; 7 men in T group vs 2 in *P* group had a MACE; another 5 vs 2 underwent coronary revascularisation.	Increase in non-calcified plaque volume (from median 204 mm^3 to 232 mm^3 in T group, and from 317 mm^3 to 325 mm^3 in *P* group; $P = .003$; 7 men in T group and 7 men in *P* group had a MACE.	12 men in T group vs 17 in *P* group experienced a MACE; another 8 vs 3 had arrhythmia, 1 vs 1 cardiac failure, 1 vs 2 cardiac valvular disease, and 2 vs 0 syncope/collapse.	The only significant differences in cardiovascular events were increased non-fatal cardiac arrhythmias (mostly atrial fibrillation. 182 (7%) men in T group vs 190 (7.3%) in *P* group experienced the primary MACE safety endpoint. 269 (10.4%) men in T group vs 264 (10.1%) in *P* group experienced the secondary endpoint (MACE or coronary revascularization). 144 (5.5%) men in T group vs 148 (5.7%) in *P* group died from any cause. Non-fatal arrhythmias that warranted intervention occurred in 134 (5.2%) of men in T group vs 87 (3.3%) in *P* group; and atrial fibrillation in 91 (3.5%) vs 63 (2.3%) men, respectively.
Haematologic parameters and venous thromboembolism (VTE)	13 men in T group experienced haematocrit > 54% vs none in *P* group; no VTE reported.	Seven men in T group vs none in *P* group developed a haemoglobin > 17.5 g/dL; 2 men in the T group vs 3 men in the *P* group experienced venous thromboembolism.	106 (22%) men in T group and 6 (1%) men in *P* group experienced a haematocrit > 54%; 2 men in T group vs none in *P* group had venous thromboses.	24 (0.9%) men in the T group vs 12 (0.5%) in the *P* group experienced pulmonary embolism; 16 vs 13 deep venous thrombosis; and 11 vs 12 other peripheral venous thrombosis. Pulmonary embolism was a tertiary outcome with a very low event; formal statistical analysis was precluded.
Prostate health	Four participants in the T group, but none in the *P* group, experienced PSA levels greater than 4 ng/dL. Fourteen men in the T group vs 2 in the *P* group had an IPSS score higher than 21. Very low incidence of newly diagnosed prostate cancer; no significant difference compared to placebo.	Mean serum PSA increased significantly more (0.46 vs 0.06 ng/mL) in placebo group; 5% and 2.5% of the T-treated men had an increase of ≥1.7 and ≥3.6 ng/mL, respectively. 27 men in T group and 26 in *P* group develop severe LUTS with an IPSS score higher than 19. Very low incidence of newly diagnosed prostate cancer; no significant difference compared to placebo.	109 (23%) of participants in the T group and 87 (19%) in the *P* group experienced an increase of 0.75 µg/mL or more in PSA. 8 T-treated men vs 3-placebo-treated men developed LUTS. Very low incidence of newly diagnosed prostate cancer; no significant difference compared to placebo.	Increase of PSA from baseline was greater in T vs *P* group (0.20 ± 0.61 ng/mL vs 0.08 ± 0.90 ng/mL, $P < .001$); Prostate cancer occurred in 12 patients (.5%) in the T group and in 11 patients (0.4%) in the *P* group ($P = .87$). There was no difference in BPH with LUTS, but there was a trend towards increased in incident urinary retention (50 vs 34). Very low incidence of newly diagnosed prostate cancer; no significant difference compared to placebo.
Bone health	Not reported.	See Table 2.	See Table 2.	Increased incidence of clinical fracture in the T group 91/2601 (3.50%) vs 64/2603 (2.46%) in the placebo group; Ankle and rib fractures accounted for most excess fractures in the T group, with no significant difference in the incidence of major osteoporotic fractures of the spine, hip, humerus, and wrist fractures.

Comparisons are always compared to placebo.
Abbreviations: LUTS, lower urinary tract symptoms; IPSS, International Prostate Symptoms Score; MACE, major adverse cardiovascular events; PSA, prostate specific antigen; T, testosterone; VTE, venous thromboembolism.

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

Table 4. Summary of the 4 recent major testosterone and major beneficial patient outcomes.

Vitality/ energy	Mood	Sexual function	Cognitive function	Insulin sensitivity	Diabetes mellitus prevention	Walking speed	Falls	Chest, hand, leg strength, and power	Bone density and strength	Major osteoporotic fractures	Resolution or prevention of unexplained anaemia
↑↑	↑↑	↔↑↑↑	↔↔	↑↑	↑↔	↑	↔	↑↑	↑↑	↔	↑↑

TEAAM = blue arrows. T-Trials = green arrows. T4DM = purple arrows. TRAVERSE = red arrows.

Table 5. Summary of the 4 recent major testosterone and major detrimental patient outcomes.

MACE[a]	VTE[a]	Pulmonary embolism	↑ PSA > 4 (increasing CaP assessment)	BPH with lower urinary tract symptoms	Urinary retention	Overall fractures	Erythrocytosis
↔ ↔ ↔ ↔	↔ ↔ ↔ ↔	↑?	↑↑	↑?	↑?	↑	↑↑↑↑

TEAAM = blue arrows. T-Trials = green arrows. T4DM = purple arrows. TRAVERSE = red arrows.
Abbreviations: BPH, benign prostatic hyperplasia; CaP, prostate cancer; LUTS, lower urinary tract symptoms; MACE, major adverse cardiovascular events; VTE, venous thromboembolism.
[a]Only 1 study, TRAVERSE, was specifically designed to examine the relationship between testosterone therapy and MACE (as a primary outcome) and testosterone therapy and VTE (as a secondary outcome).

21.7 mIU/mL; $P = .02$) and homeostatic model assessment-insulin resistance (adjusted mean difference, 20.6; $P = .03$).[18]

In T4DM, testosterone therapy plus lifestyle changes (Weight Watchers; WW) reduced fasting glucose by 0.17 nmol/L and the absolute incidence of T2D in men at high risk of T2D by 8.6% (55/443, 12.4% vs 87/413, 21%).[9] Interestingly, there was no effect of testosterone on HbA1c in T4DM, a finding that confirmed a 2015 meta-analysis of 7 small studies (total $n = 833$ men).[19] Serum HbA1c might not be an ideal metric to assess glycaemic effects of testosterone therapy, partially due its effects on red blood cell kinetics. The glycaemic benefit of testosterone therapy is mediated by predominantly by changes in fat mass with possible contributions by changes in skeletal muscle mass, grip strength, SHBG, and oestradiol.[20] In contrast to T4DM in the TRAVERSE Diabetes study, testosterone treatment did not affect glycaemic outcomes[21]; this might be due to the fact that a daily transdermal rather than a 3-monthly deep intramuscular formulation of testosterone was used, and/or that TRAVERSE Diabetes did not include a lifestyle programme. Moreover, in contrast to T4DM, changes in diabetic medications were not recorded in TRAVERSE Diabetes, and it is possible that this might have affected the results of this substudy. Finally, HbA1c might be less sensitive than the OGTT which was used to assess glycaemia in T4DM.

Overall, the data from TEAAM, T-Trials, and T4DM suggest that testosterone therapy might be effective if given early (eg, to high-risk men with insulin resistance due obesity) to prevent or revert early T2D, but it would not benefit men with longstanding T2D who have irreversible beta islet cell dysfunction.

Effects of testosterone therapy on muscle and physical function

Increased lean mass (by about 1.6 to 4.7 kg) is one of the most consistent effects of testosterone therapy.[16,17] Increased lean body mass might be clinically important, particularly for prevention of hip fractures, because of increased protective padding around the hips. In older men with mobility limitations, testosterone improved leg-press strength and stair-climbing power.[22] In TEAAM, testosterone-treated men had significantly greater improvement of chest press strength and power, leg press power, and stair-climbing power at the end of the 36-month treatment.[23] In the T-Trials,[8] testosterone therapy did not improve self-reported walk or gait speed in a 6 min walking test in men who were frail in the Physical Function substudy (defined as self-reported difficulty with walking or climbing stairs and gait speed < 445 m in a 6 min walking test), but there was an improvement in self-reported walking and the 6 min walk test for all men enrolled in the T-Trials. However, testosterone therapy had no effect on incident falls.[24] In the TEAAM study, testosterone resulted in significantly increased strength,[23] and there have been no muscle strength, power, or physical function published from TRAVERSE.

Based on these data, testosterone therapy improves muscle strength and certain aspects of physical function that are clinically significant such as self-reported ability to ascend stairs and walking speed. The lack of effect on falls suggests that strength and gait might not translate into decreased major osteoporotic fracture (see bone section below). Alternatively, men who have low serum testosterone concentrations might feel better early in the first year of testosterone therapy and engage in behaviour associated with greater risk of falls and trauma before the full musculoskeletal benefits have occurred. Although the data suggest that there is likely a benefit, there is insufficient evidence to recommend testosterone therapy in men with androgen deficiency solely to improve physical function.

Effects of testosterone therapy on bone health

Testosterone therapy consistently increases bone density and estimated bone strength in men with low- to low-normal serum testosterone. In the T-Trials Bone Study ($n = 211$), testosterone therapy for 12 months increased volumetric BMD (measured by standard resolution quantitative CT) at the trabecular spine (+6.8% [4.8-8.7]) and total hip (+1.3% [0.8-1.7]) and increased estimated spine trabecular bone strength (+8.5% [6.0-10.9], all $P < .001$.[25] In the T4DM bone substudy (T4Bone; $n = 600$), testosterone therapy for 2

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

years increased areal BMD of the lumbar spine (3.3%; 95% CI 2.7, 3.9%), total hip (1.9%; 95% CI 1.2, 2.7), and femoral neck (1.7%; 95% CI 0.8%, 2.7%), P values all $< .001$.[26] Moreover, in a subset of 177 men of T4Bone, testosterone therapy significantly increased total and cortical volumetric BMD assessed by high resolution-peripheral quantitative CT (HR-pqCT) with standardised effect sizes of 1.3%-3.1%. These results mirror results of studies using HR-pqCT in postmenopausal women with low BMD (T scores < -2.5) treated with drugs with proven anti-fracture benefits. Men in these 2 studies were not selected based on low bone density or osteoporosis,[25,26] and the effects of testosterone therapy on bone architecture, bone strength, or incident fracture have not been systematically studied in men with low serum testosterone concentrations at high risk of fracture.

Of note, a recent analysis of the TRAVERSE cohort reported that testosterone therapy surprisingly was associated with an increased risk of overall clinical fractures (3.50% [91/2601] vs 2.46% [64/2603]; testosterone and placebo groups, respectively).[27] Fracture curves diverged early, suggesting that the increased risk might be due to behavioural effects of testosterone therapy.[28] This hypothesis is supported by the observation that ankle and rib fractures—typically associated with trauma—accounted for the majority of the excess fractures.[27]

Although the TRAVERSE fracture data require confirmation, the clinical implication of the findings are that men at high risk of fragility fracture should be offered drug therapy with proven anti-fracture benefit independent of decisions about testosterone therapy.

Effect of testosterone therapy on haematologic parameters

Testosterone stimulates erythropoiesis via direct effects on bone marrow, stimulation of erythropoietin, and changes in iron transport that is regulated by hepcidin. In the T-Trials, 16% of participants had baseline anaemia, and 7.9% had unexplained anaemia.[29] At the end of the 12-month-treatment period, 52% of testosterone-treated men with anaemia of known cause and 58% of testosterone men with unexplained anaemia had normal serum haemoglobin concentrations compared to 19% and 22% of placebo-treated men, respectively; none become erythrocytotic. In men with unexplained anaemia, haemoglobin increased by $\geq$1.0 g/dL in 54% of testosterone-treated compared to 15% of placebo-treated men (adjusted mean difference 0.82 g/dL; 95% CI 0.48-1.39; $P = .002$). Similar results were observed in men with anaemia of known cause.[29] In the TRAVERSE trial, 15.6% of the 5204 men were categorised as anaemic.[30] Anaemia resolved in a greater proportion of testosterone-treated than placebo-treated men (treatment months 6 and 48: 41.0% vs 27.5% and 44.6% vs 39.2% in the testosterone and placebo groups, respectively; $P < .05$); increased haemoglobin was associated with increased energy.[30] In TRAVERSE, a smaller fraction of testosterone-treated developed anaemia (7.2% vs 10.4% in the placebo group; $P < .05$).[30] Improvement in blood haemoglobin and haematocrit would benefit many men with unexplained anaemia and could be a factor in the decision whether to prescribe testosterone.

Erythrocytosis is generally a contraindication to the initiation of testosterone therapy in clinical practice or trials.[31] Erythrocytosis due to testosterone therapy can generally be managed by reducing the dosage of testosterone and switching to a non-injectable formulation. Clinically significant, persistent erythrocytosis that required stopping testosterone was uncommon in TEAAM, T-Trials, and TRAVERSE where a transdermal testosterone formulation was used, but it was more common in the T4DM trial that used a long-acting intramuscular formulation. In TEAAM, testosterone caused erythrocytosis in 0.8% of testosterone-treated men, 0.2% of the testosterone-treated men withdrew from the study due to erythrocytosis, and there was no erythrocytosis in the placebo group.[7] In the T-Trials, testosterone therapy resulted in erythrocytosis in 1.5% of participants who had no baseline anaemia.[29] In the TRAVERSE trial, only 0.15% men in the testosterone group and 0.08% in the placebo group stopped the study because of persistent erythrocytosis.[30] However, in T4DM, 22% and 1% of the testosterone and placebo groups became erythrocytotic, respectively, leading to cessation of therapy in 0.5% of the testosterone group.[9]

Effects of testosterone therapy on cardiovascular health

In TEAAM, men randomised to testosterone therapy had similar increases in carotid intima-media thickness and coronary calcium scores compared to placebo-treated men.[7] In a T-Trials substudy of 73 testosterone and 65 placebo-treated men, testosterone therapy was associated with greater increases in non-calcified and total coronary atheroma plaque volume, but the groups were unbalanced for baseline plaque volumes making the results difficult to interpret.[32] Changes in coronary calcium scores were similar in both groups. In TEAAM,[7] the T-Trials,[8] and T4DM,[9] rates of major adverse cardiovascular events (MACE) were low and similar between men randomised to testosterone or placebo therapy, but these studies were underpowered to detect a difference.

In TRAVERSE, the sole study designed and powered to study testosterone therapy and MACE outcomes,[33] similar proportions of men in each group experienced the primary outcome of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke (7.0% and 7.3% in the testosterone and placebo groups, respectively, mean treatment duration = 22 months; $P < .001$ for noninferiority). There was likewise no difference in overall mortality (5.5% vs 5.7% in the testosterone and placebo groups). There was an excess of non-fatal arrhythmia (primarily atrial fibrillation) warranting intervention in the testosterone group, (5.2% vs 3.3%; $P = .001$).[33] One of the limitations of TRAVERSE was the relatively high treatment discontinuation rate, 61.4% in the testosterone and 61.7% in the placebo group; nevertheless the study was powered for short term cardiovascular safety of testosterone treatment.

In these 4 major testosterone trials, there was no overall safety signal for venous thromboembolism (VTE). There were no VTE events reported in TEAAM.[7] In the T-Trials, 0.5% and 0.8% of men had VTE in the testosterone and placebo groups, respectively.[33] In T4DM, 2 testosterone-treated men had VTE vs none of the placebo-treated men.[9] In TRAVERSE, there was a similar incidence of VTE in both groups (1.7% vs 1.2% in the testosterone and placebo groups; HR 1.46; CI 0.92-2.32).[33] The VTE events consisted of 24 pulmonary emboli in testosterone-treated men vs 12 in placebo-treated men; and 16 deep venous thromboses and 11 other peripheral venous thromboses (confirmed by

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

imaging, including calf, portal, subclavian, or mesenteric veins) in the testosterone group vs 13 and 12 in the placebo group, respectively.[33] Although the small excess of pulmonary embolism events in testosterone-treated men in TRAVERSE is intriguing, numbers were small and precluded formal statistical analysis of significance. Overall, these 4 major trials indicate that testosterone therapy is unlikely to confer significant benefit or risk for major cardiovascular events in high-risk men for up to 4 years after the initiation of testosterone therapy. Testosterone therapy does not seem to be associated with increased risk of deep venous thrombosis or other peripheral venous thrombosis. These results might not apply to men with underlying coagulation disorders. Because of the small safety signal in the TRAVERSE trial, the risk of pulmonary embolism should be factored in the decision-making for men at higher risk of pulmonary embolism—particularly those who are not on effective anti-thrombotic therapy or have compromised cardiopulmonary function.

Effects of testosterone therapy on prostate health

The principal trophic hormone of the prostate is dihydrotestosterone that is derived by local prostatic production via 5-alpha reduction of testosterone. Thus, testosterone therapy consistently increases serum prostate specific antigen (PSA) in men with testosterone deficiency. In TEAAM, PSA increased more in the testosterone group than in the placebo group (model-estimated mean difference, 0.28 ng/mL; 95% CI, 0.06-0.49; $P = .01$).[7] In the T-Trials,[34] after 12 months of therapy, 1.9% of the testosterone group and 0.3% of the placebo group had serum PSA ≥ 4.0 ng/mL.[8] In T4DM,[9] 23% of testosterone and 19% of placebo treatment men experienced an increase of >0.75 ng/mL in PSA. In TRAVERSE, the change from baseline in PSA was greater in testosterone-treated compared placebo-treated men (0.20 ± 0.61 vs 0.08 ± 0.90 ng/mL, $P < .001$).[33] Prostate cancer incidence was low in all trials (testosterone vs placebo-treated participants: Not reported in TEAAM, 3 vs 1 in the T-Trials, 5 vs 4 in T4DM, 12 vs 11 in TRAVERSE). However, men at high risk for prostate (eg, baseline PSA > 4 ng/mL and history of prostate cancer abnormal digital rectal exam) were excluded. The true differential prostate cancer incidence in these trials is unknown because prostate biopsies were not equally and systematically performed in the testosterone and placebo groups.

Lower urinary tract symptoms (LUTS) did not differ significantly between testosterone and placebo groups in these trials, but men with severe benign prostatic hyperplasia (BPH) and LUTS (baseline International Prostate Symptom Score [IPSS] > 19) were excluded. In TEAAM and the T-Trials, the mean end-of-therapy change of IPSS score did not differ between the groups.[7,33] Of note, more testosterone-treated men in TEAAM had severe LUTS (IPSS > 21; 14 vs 2 in placebo) at the end of therapy.[7] In T4DM, incident BPH with LUTS was reported in 8 testosterone-treated vs 3 placebo-treated men. There was no difference in incident BPH with LUTS in TRAVERSE (45 vs 46; $P = .92$, but there was a trend towards increased incident urinary retention (50 vs 34 testosterone- and placebo-treated men, respectively; ($P = .08$). In TRAVERSE, acute kidney injury was slightly more common in the testosterone group (60 vs 40 men, $P = .04$), an unexpected finding that might have been due to chance.[9]

Overall, the data from these trials do not indicate that testosterone therapy increases the risk of *de novo* prostate cancer or promotes BPH with LUTS. However, the data suggest that men should be advised that testosterone therapy increases the risk of an evaluation for prostate cancer due to increased serum PSA. Furthermore, men with moderate or severe BPH with LUTS should be advised and monitored for possible increased risk of urinary retention.

Conclusions and outlook

In summary, testosterone therapy modestly improves vitality and depressive symptoms, improves libido and most aspects of sexual dysfunction, improves insulin sensitivity and with a lifestyle programme reduces T2D risk, modestly improves some aspects physical function without effect on falls risk, and improves bone structure, bone density and volumetry, and bone strength. TRAVERSE did not demonstrate a reduction of major osteoporotic fracture (and surprisingly reported increased fractures likely attributable to trauma[27]), but this study did not recruit men at high risk of fragility fractures and had other limitations.[28] Testosterone improves anaemia and in the short term does not increase the risk of MACE, but the effects on the risk of arrhythmias (eg, atrial fibrillation) and VTE require further study. In men without high risk of prostate cancer or BPH, effects on prostate health are reassuring although longer-term studies are needed. Of note, some effects of testosterone treatment discussed in this review are secondary rather than primary trial outcomes; clinicians should exercise caution when making conclusions based on secondary analyses. Moreover, the trials included in this review were ≤4 years duration, some potential outcomes of testosterone treatment (eg, major cardiovascular events and prostatic disease) require further study with longer-term clinical trials. As expected from large randomised clinical trials, baseline characteristics that might affect outcomes (such as for example age, body mass index, and diabetes status for cardiovascular outcomes) were, by virtue of the randomisation procedure, generally well balanced between the groups and it is unlikely that primary outcomes reported in these landmark trials were confounded by baseline differences. However secondary outcomes in subgroup analyses have to be interpreted with caution; for example, in the T-Trials atheroma substudy of 73 testosterone and 65 placebo-treated men, discussed above the groups were unbalanced for baseline plaque volumes making the greater increases in non-calcified and total coronary atheroma plaque volume in the testosterone-treated participants difficult to interpret.

These data help inform "personalized decision-making" about testosterone therapy in middle-aged and older men with possible hypogonadism but no identifiable cause and allow the clinician to target patients with maximal potential benefit or benefits that exceed risks and to advise on adverse risks with small absolute risk (eg, pulmonary embolism and risk or traumatic fractures). For example, a 55-year-old man with reproducibly low serum testosterone measured by a good quality assay, low energy, low libido, unexplained anaemia, a body mass index of 29 kg/m^2, coronary artery disease, impaired fasting glucose, moderate lower urinary tracts symptoms (eg, IPSS = 17), PSA of 3.2 ng/dL, high risk of fragility fracture and no identifiable cause of HPT axis dysfunction should be prescribed effective therapy for osteoporosis, advised on lifestyle changes, and considered for a trial of testosterone therapy for 1-2 years with a focus on the above outcomes. He should be advised about lifestyle changes and

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

offered reassurance about the evidence of cardiovascular and prostate safety. However, his clinician should advise the man of the significant risk that his PSA might exceed 4.0 ng/dL with testosterone treatment and review the possibility of a small absolute risk of pulmonary embolism and urinary retention.

The recent large randomised clinical trials of testosterone therapy are pivotal contributions which advance our understanding of testosterone and men's health. These trials lay the foundation for future large-scale clinical trials to comprehensively determine the benefits vs risks of testosterone pharmacotherapy, particularly in men aged >70 years where biochemical evidence of Leydig cell impairment appears.[35] Future trials should explore other key outcomes related to aging, such as loss of independence and risk of incident dementia.[36] Pending further studies, a holistic approach to men's health, including encouragement of healthy lifestyle behaviours, and assessment and attention to risk factors and disease, should remain the universal approach.

Funding

This work did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Conflict of interest: M.G. has received research funding from Bayer and Otsuka, and speaker's honoraria from Besins Health Care and Novartis. B.D.A. is funded as a co-investigator by NIH-NICHD (HHSN275000251). B.D.A. is also a consultant for the United States Anti-Doping Agency, and he serves on the board of directors of Biozen. B.B.Y. has received speaker honoraria and conference support from Bayer, Lilly, and Besins Healthcare, research support from Bayer, Lilly, and Lawley Pharmaceuticals, and participated in advisory roles for Lilly, Besins Healthcare, Ferring, and Lawley Pharmaceuticals. Co-author M.G. is on the editorial board of EJE. He is not involved in the review or editorial process for this paper, on which he is listed as an author.

Authors' contributions

Mathis Grossmann (Conceptualization [equal], Methodology [equal], Writing—original draft [equal], Writing—review & editing [equal]), Bradley D. Anawalt (Conceptualization [equal], Methodology [equal], Writing—original draft [equal], Writing—review & editing [equal]), and Bu B. Yeap (Conceptualization [equal], Methodology [equal], Writing—original draft [equal], Writing—review & editing [equal])

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

References

1. Shi Z, Araujo AB, Martin S, O'Loughlin P, Wittert GA. Longitudinal changes in testosterone over five years in community-dwelling men. *J Clin Endocrinol Metab*. 2013;98(8):3289-3297. https://doi.org/10.1210/jc.2012-3842
2. Camacho EM, Huhtaniemi IT, O'Neill TW, *et al*. Age-associated changes in hypothalamic-pituitary-testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study. *Eur J Endocrinol*. 2013;168(3):445-455. https://doi.org/10.1530/EJE-12-0890
3. Wu FC, Tajar A, Beynon JM, *et al*. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010;363(2):123-135. https://doi.org/10.1056/NEJMoa0911101
4. Anawalt BD, Matsumoto AM. Aging and androgens: physiology and clinical implications. *Rev Endocr Metab Disord*. 2022;23(6):1123-1137. https://doi.org/10.1007/s11154-022-09765-2
5. Grossmann M, Matsumoto AM. A perspective on middle-aged and older men with functional hypogonadism: focus on holistic management. *J Clin Endocrinol Metab*. 2017;102(3):1067-1075. https://doi.org/10.1210/jc.2016-3580
6. Grossmann M, Jayasena CN, Anawalt BD. Approach to the patient: the evaluation and management of men ≥ 50 years with low serum testosterone concentration. *J Clin Endocrinol Metab*. 2023;108(9):e871-e884. https://doi.org/10.1210/clinem/dgad180
7. Basaria S, Harman SM, Travison TG, *et al*. Effects of testosterone administration for 3 years on subclinical atherosclerosis progression in older men with low or low-normal testosterone levels: a randomized clinical trial. *JAMA*. 2015;314(6):570-581. https://doi.org/10.1001/jama.2015.8881
8. Snyder PJ, Bhasin S, Cunningham GR, *et al*. Effects of testosterone treatment in older men. *N Engl J Med*. 2016;374(7):611-624. https://doi.org/10.1056/NEJMoa1506119
9. Wittert G, Bracken K, Robledo KP, *et al*. Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. *Lancet Diabetes Endocrinol*. 2021;9(1):32-45. https://doi.org/10.1016/S2213-8587(20)30367-3
10. Bhasin S, Seidman S, Travison TG, *et al*. Depressive syndromes in men with hypogonadism in the TRAVERSE trial: response to testosterone replacement therapy. *J Clin Endocrinol Metab*. 2024;109(7):1814-1826. https://doi.org/10.1210/clinem/dgae026
11. Resnick SM, Matsumoto AM, Stephens-Shields AJ, *et al*. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA*. 2017;317(7):717-727. https://doi.org/10.1001/jama.2016.21044
12. Huang G, Wharton W, Bhasin S, *et al*. Effects of long-term testosterone administration on cognition in older men with low or low-to-normal testosterone concentrations: a prespecified secondary analysis of data from the randomised, double-blind, placebo-controlled TEAAM trial. *Lancet Diabetes Endocrinol*. 2016;4(8):657-665. https://doi.org/10.1016/S2213-8587(16)30102-4
13. Cunningham GR, Stephens-Shields AJ, Rosen RC, *et al*. Testosterone treatment and sexual function in older men with low testosterone levels. *J Clin Endocrinol Metab*. 2016;101(8):3096-3104. https://doi.org/10.1210/jc.2016-1645
14. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. *Eur Urol*. 2011;60(5):1010-1016. https://doi.org/10.1016/j.eururo.2011.07.053
15. Pencina KM, Travison TG, Cunningham GR, *et al*. Effect of testosterone replacement therapy on sexual function and hypogonadal symptoms in men with hypogonadism. *J Clin Endocrinol Metab*. 2024;109(2):569-580. https://doi.org/10.1210/clinem/dgad484
16. Isidori AM, Giannetta E, Greco EA, *et al*. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)*. 2005;63(3):280-293. https://doi.org/10.1111/j.1365-2265.2005.02339.x
17. Sinclair M, Grossmann M, Hoermann R, Angus PW, Gow PJ. Testosterone therapy increases muscle mass in men with cirrhosis and low testosterone: a randomised controlled trial. *J Hepatol*. 2016;65(5):906-913. https://doi.org/10.1016/j.jhep.2016.06.007
18. Mohler ER III, Ellenberg SS, Lewis CE, *et al*. The effect of testosterone on cardiovascular biomarkers in the testosterone trials. *J Clin Endocrinol Metab*. 2018;103(2):681-688. https://doi.org/10.1210/jc.2017-02243
19. Grossmann M, Hoermann R, Wittert G, Yeap BB. Effects of testosterone treatment on glucose metabolism and symptoms in men with type 2 diabetes and the metabolic syndrome: a systematic review

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024

and meta-analysis of randomized controlled clinical trials. *Clin Endocrinol (Oxf)*. 2015;83(3):344-351. https://doi.org/10.1111/cen.12664
20. Robledo KP, Marschner IC, Handelsman DJ, *et al.* Mediation analysis of the testosterone treatment effect to prevent type 2 diabetes in the Testosterone for Prevention of Type 2 Diabetes Mellitus trial. *Eur J Endocrinol*. 2023;188(7):613-620. https://doi.org/10.1093/ejendo/lvad074
21. Bhasin S, Lincoff AM, Nissen SE, *et al.* Effect of testosterone on progression from prediabetes to diabetes in men with hypogonadism: a substudy of the TRAVERSE randomized clinical trial. *JAMA Intern Med*. 2024;184(4):353-362. https://doi.org/10.1001/jamainternmed.2023.7862
22. Travison TG, Basaria S, Storer TW, *et al.* Clinical meaningfulness of the changes in muscle performance and physical function associated with testosterone administration in older men with mobility limitation. *J Gerontol A Biol Sci Med Sci*. 2011;66(10):1090-1099. https://doi.org/10.1093/gerona/glr100
23. Storer TW, Basaria S, Traustadottir T, *et al.* Effects of testosterone supplementation for 3 years on muscle performance and physical function in older men. *J Clin Endocrinol Metab*. 2017;102(2):583-593. https://doi.org/10.1210/jc.2016-2771
24. Bhasin S, Ellenberg SS, Storer TW, *et al.* Effect of testosterone replacement on measures of mobility in older men with mobility limitation and low testosterone concentrations: secondary analyses of the testosterone trials. *Lancet Diabetes Endocrinol*. 2018;6(11):879-890. https://doi.org/10.1016/S2213-8587(18)30171-2
25. Snyder PJ, Kopperdahl DL, Stephens-Shields AJ, *et al.* Effect of testosterone treatment on volumetric bone density and strength in older men with low testosterone: a controlled clinical trial. *JAMA Intern Med*. 2017;177(4):471-479. https://doi.org/10.1001/jamainternmed.2016.9539
26. Ng Tang Fui M, Hoermann R, Bracken K, *et al.* Effect of testosterone treatment on bone microarchitecture and bone mineral density in men: a 2-year RCT. *J Clin Endocrinol Metab*. 2021;106(8):e3143-e3158. https://doi.org/10.1210/clinem/dgab149
27. Snyder PJ, Bauer DC, Ellenberg SS, *et al.* Testosterone treatment and fractures in men with hypogonadism. *N Engl J Med*. 2024;390(3):203-211. https://doi.org/10.1056/NEJMoa2308836
28. Grossmann M, Anawalt BD. Breaking news—testosterone treatment and fractures in older men. *N Engl J Med*. 2024;390(3):267-268. https://doi.org/10.1056/NEJMe2313787
29. Roy CN, Snyder PJ, Stephens-Shields AJ, *et al.* Association of testosterone levels with anemia in older men: a controlled clinical trial. *JAMA Intern Med*. 2017;177(4):480-490. https://doi.org/10.1001/jamainternmed.2016.9540
30. Pencina KM, Travison TG, Artz AS, *et al.* Efficacy of testosterone replacement therapy in correcting anemia in men with hypogonadism: a randomized clinical trial. *JAMA Netw Open*. 2023;6(10):e2340030. https://doi.org/10.1001/jamanetworkopen.2023.40030
31. Ponce OJ, Spencer-Bonilla G, Alvarez-Villalobos N, *et al.* The efficacy and adverse events of testosterone replacement therapy in hypogonadal men: a systematic review and meta-analysis of randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2018;103(5):1745-1754. https://doi.org/10.1210/jc.2018-00404
32. Budoff MJ, Ellenberg SS, Lewis CE, *et al.* Testosterone treatment and coronary artery plaque volume in older men with low testosterone. *JAMA*. 2017;317(7):708-716. https://doi.org/10.1001/jama.2016.21043
33. Lincoff AM, Bhasin S, Flevaris P, *et al.* Cardiovascular safety of testosterone-replacement therapy. *N Engl J Med*. 2023;389(2):107-117. https://doi.org/10.1056/NEJMoa2215025
34. Cunningham GR, Ellenberg SS, Bhasin S, *et al.* Prostate-specific antigen levels during testosterone treatment of hypogonadal older men: data from a controlled trial. *J Clin Endocrinol Metab*. 2019;104(12):6238-6246. https://doi.org/10.1210/jc.2019-00806
35. Marriott RJ, Murray K, Adams RJ, *et al.* Factors associated with circulating sex hormones in men: individual participant data meta-analyses. *Ann Intern Med*. 2023;176(9):1221-1234. https://doi.org/10.7326/M23-0342
36. Marriott RJ, Murray K, Flicker L, *et al.* Lower serum testosterone concentrations are associated with a higher incidence of dementia in men: the UK Biobank prospective cohort study. *Alzheimers Dement*. 2022;18(10):1907-1918. https://doi.org/10.1002/alz.12529

Downloaded from https://academic.oup.com/ejendo/article/191/1/R22/7698939 by University of Melbourne user on 03 October 2024