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

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Summary

Background Men who are overweight or obese frequently have low serum testosterone concentrations, which are associated with increased risk of type 2 diabetes. We aimed to determine whether testosterone treatment prevents progression to or reverses early type 2 diabetes, beyond the effects of a community-based lifestyle programme.

Methods T4DM was a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial done at six Australian tertiary care centres. Men aged 50–74 years, with a waist circumference of 95 cm or higher, a serum testosterone concentration of 14·0 nmol/L or lower but without pathological hypogonadism, and impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose 7·8–11·0 mmol/L) or newly diagnosed type 2 diabetes (provided OGTT 2-h glucose ≤15·0 mmol/L) were enrolled in a lifestyle programme and randomly assigned (1:1) to receive an intramuscular injection of testosterone undecanoate (1000 mg) or placebo at baseline, 6 weeks, and then every 3 months for 2 years. Randomisation was done centrally, including stratification by centre, age group, waist circumference, 2-h OGTT glucose, smoking, and first-degree family history of type 2 diabetes. The primary outcomes at 2 years were type 2 diabetes (2-h OGTT glucose ≥11·1 mmol/L) and mean change from baseline in 2-h OGTT glucose, assessed by intention to treat. For safety assessment, we did a masked monitoring of haematocrit and prostate-specific antigen, and analysed prespecified serious adverse events. This study is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12612000287831.

Findings Between Feb 5, 2013, and Feb 27, 2017, of 19 022 men who were pre-screened, 1007 (5%) were randomly assigned to the placebo (n=503) and testosterone (n=504) groups. At 2 years, 2-h glucose of 11·1 mmol/L or higher on OGTT was reported in 87 (21%) of 413 participants with available data in the placebo group and 55 (12%) of 443 participants in the testosterone group (relative risk 0·59, 95% CI 0·43 to 0·80; p=0·0007). The mean change from baseline 2-h glucose was –0·95 mmol/L (SD 2·78) in the placebo group and –1·70 mmol/L (SD 2·47) in the testosterone group (mean difference –0·75 mmol/L, –1·10 to –0·40; p<0·0001). The treatment effect was independent of baseline serum testosterone. A safety trigger for haematocrit greater than 54% occurred in six (1%) of 484 participants in the placebo group and 106 (22%) of 491 participants in the testosterone group, and a trigger for an increase of 0·75 µg/mL or more in prostate-specific antigen occurred in 87 (19%) of 468 participants in the placebo group and 109 (23%) of 480 participants in the testosterone group. Prespecified serious adverse events occurred in 37 (7·4%, 95% CI 5·4 to 10·0) of 503 patients in the placebo group and 55 (10·9%, 8·5 to 13·9) of 504 patients in the testosterone group. There were two deaths in each group.

Interpretation Testosterone treatment for 2 years reduced the proportion of participants with type 2 diabetes beyond the effects of a lifestyle programme. Increases in haematocrit might be treatment limiting. Longer-term durability, safety, and cardiovascular effects of the intervention remain to be further investigated.

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Introduction

Low serum testosterone concentrations, which are common in men who are overweight or obese, are associated with an increased risk of incident type 2 diabetes.[1] In an analysis of longitudinal data from the Florey Adelaide Male Ageing Study, incident diabetes was increased in men with a serum testosterone concentration of less than 16 nmol/L (461 ng/dL).[2] In a systematic review and meta-analysis,[3] men with a serum testosterone concentration greater than 15·5 nmol/L (447 ng/dL) had a

Research in context

Evidence before this study

We searched PubMed and ScienceDirect on Dec 1, 2011, and again on Nov 19, 2019, using the following search terms in various combinations: "testosterone", "type 2 diabetes", "obesity", "metabolic syndrome", "weight loss", "skeletal muscle mass", and "insulin resistance", restricted to the English language. Obesity (with or without insulin resistance and abnormal glucose tolerance) is associated with lowered serum testosterone concentration, which is reversed by weight loss. A low serum testosterone concentration is associated with an increased risk of incident type 2 diabetes. Testosterone treatment decreases fat mass and increases muscle mass in men. In randomised controlled trials, testosterone treatment did not lower HbA_{1c} in men with established type 2 diabetes, but it might improve insulin resistance in men with type 2 diabetes or metabolic syndrome. In a registry-based study, testosterone treatment prevented progression of prediabetes to type 2 diabetes and improved glucose metabolism in people with type 2 diabetes. Weight loss through lifestyle intervention (ie, diet and exercise) prevents the progression of prediabetes to diabetes, including reversal of newly diagnosed type 2 diabetes, but it is not known whether testosterone treatment augments the benefits of a lifestyle intervention.

Added value of this study

The findings of the T4DM trial showed that, among men aged 50–74 years with impaired glucose tolerance or newly diagnosed type 2 diabetes and with a waist circumference of 95 cm or higher, treatment with testosterone significantly reduced the risk of type 2 diabetes (relative risk 0·59) at 2 years compared with placebo, with a between-group difference in mean change from baseline in 2-h glucose (from an oral glucose tolerance test) of –0·75 mmol/L (–1·10 to –0·40). The beneficial effects on glucose metabolism were independent of baseline testosterone concentration. Compared with placebo, testosterone was associated with a greater decrease in fat mass, increase in skeletal muscle mass and strength, and improvement in sexual function. Concerning safety, compared with placebo, treatment with testosterone was not associated with excess cardiovascular or prostate cancer adverse events. However, there were increases in haematocrit and prostate-specific antigen associated with testosterone use. An increase in haematocrit to 54% or higher was flagged in 106 (22%) of 491 testosterone-treated participants, with 25 participants ceasing treatment prematurely as a result.

Implications of all the available evidence

Our findings suggest that testosterone treatment for 2 years, as an adjunct to a lifestyle programme, can prevent or revert type 2 diabetes in overweight men without pathological hypogonadism. This effect compares favourably to that of metformin in the Diabetes Prevention Program and was accompanied by increased muscle mass, grip strength, and sexual function. Increases in haematocrit might be treatment limiting. The minimum dose exposure, duration of treatment, durability of effect, and long-term safety and cardiovascular outcomes of testosterone treatment remain to be determined. We consider it premature to advocate for the widespread use of testosterone for diabetes prevention in men without pathological hypogonadism. Identification of subgroups of men more likely to benefit or most at risk of adverse outcomes might aid treatment decisions, but, if testosterone treatment is considered, there must be a concomitant lifestyle programme and careful monitoring of haematocrit, cardiovascular risk factors, and prostate health.

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42% reduced risk of type 2 diabetes compared with men with a serum testosterone of concentration 15·5 nmol/L or less.[3]

Diet-induced weight loss is reported to prevent the progression of prediabetes to type 2 diabetes[4] and to induce sustained normalisation of glucose tolerance, including in people with recent-onset type 2 diabetes.[5] Diet-induced weight loss is also associated with modest reversal of reduced serum testosterone in men with obesity with no recognised pathological hypothalamo-pituitary-testicular (HPT) disorder.[6] However, adherence to community-based lifestyle programmes can be poor and wanes with time, such that weight loss due to the lifestyle programme after 2 years is typically about 2–4 kg.[7]

In randomised controlled trials, testosterone treatment consistently leads to modest reductions in fat mass and increases in lean mass, body composition changes that are expected to be metabolically favourable.[8] In a registry-based, uncontrolled, observational study[9] of 229 men with a baseline serum testosterone concentration of 12·1 nmol/L (349 ng/dL) or less, 8 years or more of intramuscular testosterone undecanoate treatment prevented progression of prediabetes to type 2 diabetes and improved glucose metabolism in people with type 2 diabetes.

No large-scale, placebo-controlled randomised trial has assessed testosterone treatment for preventing or reversing type 2 diabetes in men who are overweight or obese. We aimed to determine the efficacy and safety of testosterone treatment to prevent progression of impaired glucose tolerance to type 2 diabetes or to reverse newly diagnosed type 2 diabetes beyond the effects of a lifestyle intervention.

Methods

Study design and participants

The Testosterone for Diabetes Mellitus (T4DM) trial was a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial done at six Australian tertiary care centres. The T4DM study sites and steering committee members are listed in appendix 1 (p 2). The detailed T4DM study

See **Online** for appendix 1

See Online for appendix 2

design has been previously reported,[10] and the trial protocol and statistical analysis plan are in appendix 2.

Eligibility was confirmed at the baseline study visit. Eligible participants were men aged 50–74 years, with a waist circumference of 95 cm or more, who had either impaired glucose tolerance (oral glucose tolerance test [OGTT] 2-h glucose ≥7·8 to <11·1 mmol/L [≥140·4 to <199·8 mg/dL]) or newly diagnosed type 2 diabetes (OGTT 2-h glucose ≥11·1 to ≤15·0 mmol/L [≥198·0 to ≤270·0 mg/dL]), for whom the primary intervention could reasonably be a lifestyle programme, and who were willing to participate in such a programme. Additionally, eligible participants were required to have a screening serum total testosterone concentration of 14·0 nmol/L (403·8 ng/dL) or less, as measured by electrochemiluminescent immunoassay (Roche Diagnostics, Indianapolis, IN, USA). The testosterone cutoff was increased from 13·0 nmol/L (374·9 ng/dL) on March 18, 2013, on the basis of a receiver-operating characteristic curve analysis of the relation between serum testosterone concentration and type 2 diabetes risk,[2] and an initial lower limit of 8·0 nmol/L (230·7 ng/dL) was removed from the eligibility criteria on June 26, 2013, provided that an endocrine assessment excluded HPT-axis pathology requiring management. The cutoffs used to define type 2 diabetes on the OGTT have low reproducibility,[11] and ten participants were enrolled with 2-h glucose measurements of 7·7 mmol/L (138·6 mg/dL) after being granted a waiver, in view of the inherent variability of the OGTT. 1 year into the 4-year recruitment period (on Feb 18, 2014), we began including participants with a 2-h glucose of up to 15·0 mmol/L (270·0 mg/dL) who had not previously been diagnosed with type 2 diabetes. A full description of changes to the protocol are in appendix 2 (pp 123–31) and these changes have been previously reported.[12]

Participants were excluded if they were considered at high risk of cardiovascular events, which was defined as having had a stroke or transient ischaemic attack in the past 3 years, a major cardiovascular event in the past 6 months, cardiac failure (New York Heart Association functional classification ≥2), angina, arrhythmias, blood pressure of 160/100 mm Hg or more, personal or family history of thrombophilia, and haematocrit greater than 50%. Other exclusion criteria included testosterone treatment in the past 12 months or when such treatment was indicated for pathology of the HPT axis; use of medication affecting any component of the HPT axis; significant psychiatric disorder; current or previous malignancy besides non-melanomatous skin cancer; chronic viral infection; abnormal liver function (aminotransferase, γ-glutamyltransferase, bilirubin, or alkaline phosphatase ≥3×the upper limit of normal) or renal function (estimated glomerular filtration rate ≤30 mL/min per 1·73m²); previous or planned bariatric surgery; treatment with anti-obesity drugs within the past 6 months; substance abuse in the past 6 months; and previous diagnosis of type 1 or type 2 diabetes. Full eligibility criteria are in appendix 2 (pp 6–7). The screening laboratory investigations were done at a nationally accredited pathology provider (Sonic Healthcare, Sydney, NSW, Australia).

The study received ethics committee approval at each site and all participants provided written informed consent.

Randomisation and masking

Participants were enrolled by a study nurse and randomly assigned (1:1) to the testosterone or placebo treatment groups by a concealed allocation via a centralised web-based randomisation system with dynamic minimisation (Flexetrials version 5.9.4, Sydney, NSW, Australia). Randomisation was stratified by centre, age group (50–59 years or 60–74 years), waist circumference (95–100 cm, 101–115 cm, or >115 cm), 2-h glucose on OGTT (7·8–9·5 mmol/L, 9·6–11·0 mmol/L, or 11·1–15·0 mmol/L), currently smoking (yes or no), and first-degree family history of type 2 diabetes (yes or no). Participants and all study personnel, including nurses administering treatment or doing outcome assessments, were masked to study treatment. There were no requests to unmask any participants and treatment remained masked until the final analysis was done after database lock.

Procedures

Blood collection kits were provided to study sites. The process for collection and the processing requirements were defined in the manual of study procedures provided to site staff during training. Study visits were scheduled in the morning following overnight fasting, and participants were instructed to fast from the midnight before blood collection between 0700 h and 1000 h. Blood for fasting glucose measurement was collected in potassium oxalate tubes and transported within 2 h to a local Sonic Healthcare laboratory, where OGTT samples were also analysed. All participants were enrolled in a 2-year lifestyle programme provided by WW (formerly Weight Watchers), established to be acceptable to men and effective for prevention of type 2 diabetes.[13] The programme provided an interactive website and weekly group meetings; participants were encouraged to engage in both. The interactive website provided diet and activity guidelines and self-monitoring tools that allowed the participants to log their food, physical activity, and weigh-in details. Adherence was assessed categorically (yes or no) at each clinic visit (since previous visit: used website, attended meetings, or both) by participant report.

Testosterone undecanoate (Reandron, Bayer, Allschwil, Switzerland; 1000 mg [4 mL]) or matching placebo were administered by deep intramuscular injection slowly into the upper outer quadrant of the gluteal muscle by the study centre nurse after the completion of other study

procedures at baseline, 6 weeks, and thereafter every 3 months for 2 years. Blood samples were obtained before each dose was given. There was no provision for adjustment of dose or dose interval.

To assess physical activity, we used a validated Active Australia Survey,[14] which comprises eight questions that assess participation in various types of activity, including duration and intensity. From the questionnaire, we determined whether a participant did what we termed sufficient exercise (≥150 min exercise per week) at 2 years, which was the amount needed to obtain a health benefit. The quantity was calculated by summing the reported time of walking and moderate activity, and adding twice the time of vigorous activity.[14]

Pre-screening data were collected via a bespoke, web-based application (developed in Java version 1.7, Oracle Corporation, Redwood Shores, CA, USA) and stored in the central data system (Flexetrials). Screening and on-study pathology testing results were captured by data linkage to the pathology provider. Other clinical data were entered by the study nurses into an electronic data capture system (OpenClinica version 3.3.1, Waltham, MA, USA). Questionnaires were paper-based and read into comma-separated value files by use of data capture software (Teleform version 10.4.1, OpenText, Waterloo, ON, Canada) by staff at the central coordinating centre (National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Camperdown, NSW, Australia). Records in the central data system, the electronic data capture system, and the questionnaire response files were linked via unique participant identifiers. All databases were managed by the central coordinating centre.

Outcomes

The two primary outcomes were the incidence of type 2 diabetes at 2 years (OGTT 2-h glucose ≥11·1 mmol/L [199·8 mg/dL]) and the mean change in the 2-h glucose on OGTT at 2 years compared with baseline. The results would be deemed positive if either of the primary outcomes was met. The primary outcomes were based on an OGTT because, despite its shortcomings, it remains generally accepted as the gold standard.[15] The second primary outcome (mean change in the 2-h glucose on OGTT) was introduced with the changes to the protocol (appendix 2 pp 123–31).

Secondary outcomes at 2 years included normalisation of 2-h glucose on OGTT (<7·8 mmol/L [140·4 mg/dL]), initiation of pharmacotherapy for diabetes, adherence to the lifestyle programme, sufficient exercise, and the following changes at 2 years from baseline: fasting glucose and HbA_{1c} (measured by Sonic Healthcare), bodyweight, waist circumference, body composition (skeletal muscle mass, and total and abdominal fat mass measured by dual x-ray absorptiometry), and non-dominant hand-grip strength (measured by hand-grip dynamometer). Sex steroids (total testosterone, dihydrotestosterone, oestrone, and oestradiol) were measured by a validated liquid chromatography–tandem mass spectrometry (LC-MS) method,[16] and the remaining assays (luteinising hormone [LH], follicle stimulating hormone [FSH], and sex hormone-binding globulin [SHBG]) by platform chemiluminescent-based methods.[12] Free testosterone was calculated (appendix 1 pp 15–16). Sexual function was assessed by the International Index of Erectile Function subscales, and lower urinary tract symptoms by the International Prostate Symptom Score.[12] Psychosocial secondary outcome measures,[12] including health-related quality of life, are detailed in appendix 1 (p 17). Of the remaining prespecified secondary outcomes, lipids and biomarkers have not yet been assayed because of budget constraints and health-care expenditure has not yet been analysed; we plan to report these outcomes elsewhere.

Prespecified subgroup analyses for type 2 diabetes at 2 years were planned according to whether the participant had prediabetes or was newly diagnosed with type 2 diabetes at baseline (ie, baseline OGTT <11·1 mmol/L *vs* ≥11·1 mmol/L [199·8 mg/dL]), and according to baseline testosterone concentrations (<11·0 nmol/L *vs* ≥11·0 nmol/L [317·3 ng/dL], by LC-MS). This testosterone concentration was selected as being closest to the cutoff of 300 ng/dL, below which the US Endocrine Society indicates treatment with testosterone might be considered.[17] An additional post-hoc exploratory analysis was done according to baseline testosterone quintiles, to investigate the relation between baseline testosterone and treatment effects; this post-hoc analysis was also done for calculated free testosterone quintiles.

Prespecified serious adverse events of interest were cardiovascular-related, prostate-related, depression-related, and cancer-related events, any other events deemed significant by the investigator, and death from any cause. Because investigators were masked to assigned treatment and any study parameters that could lead to unmasking, on-study haematocrit level (every 6 months) and prostate-specific antigen (PSA; at week 30 and 2 years) were monitored centrally. Haematocrit of more than 54% was flagged to the study site, to be repeated in a non-fasting state; if it was again greater than 54%, treatment was permanently ceased, but participants were asked to remain on the study for follow-up. Any increase in PSA of 0·75 µg/mL or more was flagged and the measurement repeated by the study site; if it was greater than the age-specific upper limit, the participant was referred to a urologist, on whose advice further study treatment was based. In men with type 2 diabetes, HbA_{1c} was monitored every 3 months and, if it was 7·5% (58·5 mmol/mol) or more, or increased by 0·5% (5·5 mmol/mL) or more at 6 months or longer after type 2 diabetes diagnosis, then metformin was commenced or titrated upwards.

An independent drug safety monitoring committee (appendix 1 p 3) met about every 6 months to review safety and serious adverse events data. The committee met four times and did not recommend any changes to the protocol.

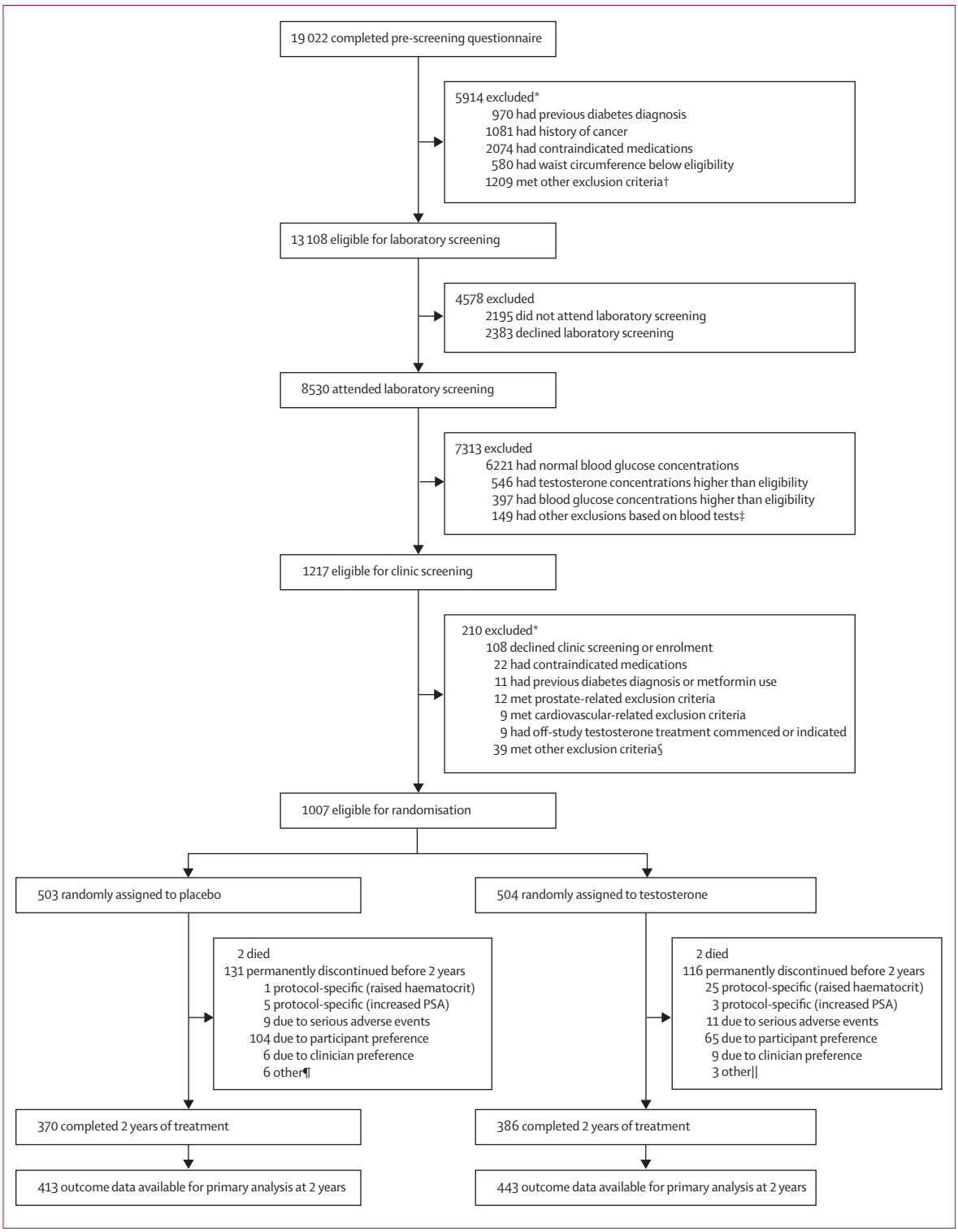

Figure 1: **Trial profile**

Note that the full cohorts were included in the safety analysis for serious adverse events. PSA=prostate-specific antigen. *Participants were counted only once according to the first ineligibility criterion met; therefore, numbers of participants with each exclusion criterion are likely to be underestimates. †Other exclusion criteria met were history of cardiovascular disease, bariatric surgery, tumour or abnormality of the pituitary or hypothalamus, HIV positive, and planning to father a child. ‡Blood test exclusions were based on haematocrit, alanine transferase, alkaline phosphatase, aspartate transferase, γ-glutamyltransferase, bilirubin, PSA, and epidermal growth factor receptor. §Other exclusion criteria met were clinician's diagnosis of significant medical conditions, including abnormal prostate examination, participating in a competing trial, or previous use of testosterone. ¶Other reasons for discontinuation were moved overseas, extended holiday, and lost to follow-up. ||Other reasons for discontinuation were moved interstate, extended holiday, lost to follow-up, and health reasons.

	Placebo group (n=503)	Testosterone group (n=504)
Clinical characteristics		
Baseline 2-h glucose		
Normal (<7·8 mmol/L)*	3 (1%)	7 (1%)
Prediabetes (≥7·8 to <11·1 mmol/L)	400 (80%)	397 (79%)
Type 2 diabetes (≥11·1 to <15 mmol/L)	100 (20%)	100 (20%)
Screening testosterone, nmol/L	10·0 (2·5)	9·9 (2·5)
Low (<8·0 nmol/L)	101 (20%)	101 (20%)
Medium (8·0 to <11·0 nmol/L)	201 (40%)	218 (43%)
High (≥11·0 to ≤14·0 nmol/L)	201 (40%)	185 (37%)
Baseline testosterone, nmol/L	13·9 (4·6; n=478)	13·4 (4·1; n=481)
Low (<8·0 nmol/L)	45/478 (9%)	27/481 (6%)
Medium (8·0 to <11·0 nmol/L)	82/478 (17%)	126/481 (26%)
High (≥11·0 nmol/L)	351/478 (73%)	328/481 (68%)
Haematocrit, %	46% (3)	45% (2)
HBA_{1c}, %	5·7 (0·5)	5·7 (0·5)
Sex hormone-binding globulin, nmol/L	37·8 (13·8; n=476)	37·4 (13·6; n=479)
Waist circumference, cm	117·8 (11·6)	118·4 (12·6)
Bodyweight, kg	107·9 (17·2)	107·8 (17·3)
Height, cm	176·5 (6·4)	175·9 (6·3)
BMI, kg/m²	34·6 (5·1)	34·8 (5·1)
Normal (18·50 to 24·99 kg/m²)	3 (1%)	6 (1%)
Overweight (25·00 to 29·99 kg/m²)	99 (20%)	79 (16%)
Obese (30·00 to 34·99 kg/m²)	179 (36%)	199 (39%)
Severely obese (35·00 to 39·99 kg/m²)	146 (29%)	147 (29%)
Very severely obese (≥40 kg/m²)	76 (15%)	73 (14%)
Body surface area, m²	2·3 (0·2)	2·3 (0·2)
Family medical history		
Type 2 diabetes	192 (38%)	207 (41%)
Prostate cancer	59/502 (12%)	57 (11%)
Angina, heart attack, bypass graft, or stent	218/502 (43%)	248 (49%)
Heart failure	80/502 (16%)	105 (21%)
High blood pressure	249/502 (50%)	227 (45%)
Demographic characteristics		
Age, years	59·6 (6·4)	59·8 (6·3)
Aboriginal or Torres Strait Islander descent	4 (1%)	4/503 (1%)
(Continued from previous column)		
Country of birth		
Australia or New Zealand	357 (71%)	357/503 (71%)
Europe	80 (16%)	78/503 (16%)
Asia	13 (3%)	13/503 (3%)
Other	53 (11%)	55/503 (11%)
Selective serotonin reuptake inhibitors use	29 (6%)	35 (7%)
Current smoker	26 (5%)	27/503 (5%)
Relationship status		
Married or de facto married	425 (84%)	432/503 (86%)
Separated or divorced	44 (9%)	42/503 (8%)
Widowed	8 (2%)	6/503 (1%)
Single	26 (5%)	23/503 (5%)
Occupational status		
Employed	267 (53%)	248 (49%)
Self-employed	91 (18%)	98 (19%)
Working without pay in family business	3 (1%)	2 (<0·5%)
Retired or on pension	125 (25%)	130 (26%)
Unemployed	17 (3%)	26 (5%)
Current shift worker	49/502 (10%)	42 (8%)
Age when left school, years	16·6 (1·3; n=498)	16·6 (1·3; n=502)
Study centre†		
Concord Hospital	114 (23%)	111 (22%)
The Austin Hospital	93 (18%)	93 (18%)
Queen Elizabeth Hospital	92 (18%)	94 (19%)
Keogh Institute for Medical Research	71 (14%)	69 (14%)
Princess Alexandra Hospital	60 (12%)	63 (13%)
Fiona Stanley Hospital	47 (9%)	48 (10%)
Fremantle Hospital	20 (4%)	18 (4%)
Prince Henry's Research Institute	6 (1%)	8 (2%)

Data are n (%), mean (SD), or n/N (%). Totals with data available and denominators are shown when different from the total number of participants in the treatment group. *Ten participants were enrolled with a screening 2-h glucose of 7·7 mmol/L after being granted a waiver. †Fremantle participants were transferred to Fiona Stanley Hospital, and Prince Henry's Research Institute participants were transferred to The Austin Hospital, giving a total of six study centres.

Table 1: **Baseline characteristics**

Statistical analysis

The original sample size estimate was for 1490 participants to give 80% power (with 5% significance) to detect a 35% relative risk (RR) reduction in type 2 diabetes events (from 16·1% in the placebo group to 10·5% in the testosterone group), allowing for 15% attrition and 5% non-adherence.[12] This calculation was based on findings from the Diabetes Prevention Program, in which metformin decreased type 2 diabetes by 30%[4] with the same outcome measure, and therefore this effect size was considered a clinically important difference.

	Placebo group (n=413)	Testosterone group (n=443)	Treatment effect in the primary analysis (unadjusted)*	Treatment effect adjusted for baseline testosterone*	Treatment effect adjusted for baseline risk factors*
2-h glucose on OGTT ≥11·1 mmol/L	87 (21%)	55 (12%)	0·59 (0·43 to 0·80; p=0·0007)	0·61 (0·45 to 0·84; p=0·0018)	0·65 (0·50 to 0·86; p=0·0091)
Mean change from baseline in 2-h glucose on OGTT (mmol/L)	−0·95 (2·78)	−1·70 (2·47)	−0·75 (−1·10 to −0·40; p<0·0001)	−0·69 (−1·05 to −0·33; p=0·0002)	−0·71 (−1·07 to −0·35; p=0·0001)

Data are n (%) or mean change (SD), unless otherwise indicated. OGTT=oral glucose tolerance test. *Treatment effect for 2-h glucose ≥11·1 mmol/L (categorical outcome) is relative risk (95% CI; p value); treatment effect for mean change from baseline in 2-h glucose (continuous outcome) is mean difference (95% CI; p value). Adjusted for centre, age group (50–59 and 60–74 years), waist circumference (95–100, >100–115, or >115 cm), baseline 2-hr glucose (7·8–9·5, >9·5–11·0, or >11·0–15·0 mmol/L), baseline smoking status, whether they have first-degree family history of type 2 diabetes, weight at baseline, baseline testosterone groups (≤8·0, 8·0 to <11·0, or ≥11·0 nmol/L), and the use of selective serotonin reuptake inhibitors at baseline.

Table 2: **Primary outcomes at 2 years**

Following the change in protocol to include participants with a 2-h OGTT of 15·0 mmol/L (270·0 mg/dL) or less, we calculated that a sample size of 1000 participants would have at least 80% power to detect a change in the proportion of participants with an OGTT of 11·1 mmol/L (199·8 mg/dL) or higher at 2 years (from 16·1% in the control group to 9·0% in the testosterone group), based on a significance level of 3·5%. To maintain a type 1 error rate of 5%, the significance level of each primary endpoint was estimated on the basis of an anticipated correlation of 0·75, with a lower significance level given to the categorical outcome. Additionally, this revised sample size had at least 88% power to detect a between-group difference of 0·6 mmol/L (10·8 mg/dL) in the change in OGTT 2-hour glucose from baseline to 2 years, based on an SD of 2·42 mmol/L (43·56 mg/dL) and a significance level of 2·5%. This sample size allowed for non-adherence of 5% and attrition of 15%. The trial would be deemed positive if either of the primary outcomes was met.

The primary outcomes were analysed in accordance with the intention-to-treat principle, including data for all participants with an OGTT at 2 years (21–27 months). This set included participants who discontinued trial treatment or started medication for diabetes but still completed an OGTT at 2 years. Similarly, secondary outcomes included patients with data available for that outcome. A multiple imputation analysis was done as a post-hoc sensitivity analysis, to assess whether the effect of treatment was unbiased.

A statistical analysis plan was agreed before any analyses were done (appendix 2 pp 139–68). Primary analyses were done unadjusted by use of χ^2 tests for the categorical primary outcome and two-sample independent *t* tests for the continuous primary outcome. Adjusted analyses (including subgroup analyses with tests for interaction) were done via binominal regression with a log-link function (to obtain RRs and 95% CIs) or linear regression. Risk factors for adjusted analyses included stratification factors and baseline bodyweight, baseline serum testosterone concentration (≤8·0, 8·0 to <11·0, or ≥11·0 nmol/L), and baseline use of selective serotonin reuptake inhibitors. Secondary outcomes were analysed in the same manner as the primary outcomes, both unadjusted and adjusted. An additional adjusted analysis was done for the primary outcomes, adjusted for baseline testosterone only. For secondary outcomes with censored data, two analyses were done: setting the censored values to the limit (0·01) or setting the values to zero, and then calculating the change. A multiple imputation analysis[10] using RR regression was done for the categorical primary outcome with the same baseline risk factors listed previously but excluding baseline testosterone, which had no interaction with treatment (appendix 1 p 4). Harms are presented as the numbers and proportions of patients who had a serious adverse event or safety trigger of interest, and 95% CIs are given for proportions of participants who had events.

For all secondary outcomes, two-sided p values less than 0·05 were considered to indicate statistical significance. We did not make any adjustment for multiple comparisons. Statistical analyses were done with SAS version 9.4 and R version 3.6.3.

This study is registered with the Australian New Zealand Clinical Trials Registry, ACTRN12612000287831.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Of 19 022 men who underwent internet-based or telephone-based pre-screening, 1217 (6%) were eligible after laboratory screening and 1007 (5%) were enrolled and randomly assigned between Feb 5, 2013, and Feb 27, 2017 (figure 1), with 503 allocated to placebo and 504 allocated to testosterone. Baseline characteristics were similar in the placebo and testosterone groups (table 1). The final follow-up visit was on May 21, 2019. OGTT outcome data at 2 years were available for 413 (82%) of 503 participants in

	At baseline		At 2 years from baseline*		Treatment effect (95% CI; p value)†
	Placebo group (n=503)	Testosterone group (n=504)	Placebo group (n=503)	Testosterone group (n=504)	
Categorical outcomes					
Normalised blood glucose (ie, 2-h glucose <7·8 mmol/L)	3/413 (1%)	7/443 (2%)	179/413 (43%)	230/443 (52%)	1·20 (1·04 to 1·38; p=0·012)
Reported use of antidiabetes drugs	0/503	0/504	16/503 (3%)	20/504 (4%)	1·25 (0·65 to 2·38; p=0·50)
Adherent to lifestyle programme	0/471	0/480	132/471 (28%)	144/480 (30%)	1·07 (0·88 to 1·31; p=0·50)
Achieved sufficient weekly exercise‡	229/395 (58%)	253/431 (59%)	280/398 (70%)	293/434 (68%)	0·96 (0·88 to 1·05; p=0·38)
Voiding function problems‡	101/395 (26%)	112/432 (26%)	133/396 (34%)	133/433 (31%)	0·91 (0·75 to 1·11; p=0·38)
Storage function problems‡	148/395 (37%)	163/432 (38%)	169/396 (43%)	187/433 (43%)	1·01 (0·86 to 1·18; p=0·88)
Continuous outcomes					
Fasting glucose, mmol/L	6·1 (0·9; n=404)	6·1 (0·9; n=435)	−0·07 (0·86; n=404)	−0·24 (0·85; n=435)	−0·17 (−0·29 to −0·06; p=0·0036)
HbA_{1c}, %	5·7 (0·5; n=419)	5·7 (0·5; n=450)	−0·03 (0·38; n=419)	−0·05 (0·36; n=450)	−0·02 (−0·07 to 0·03; p=0·42)
Bodyweight, kg	107·1 (16·8; n=410)	107·2 (17·2; n=439)	−3·53 (7·79; n=410)	−4·45 (6·36; n=439)	−0·92 (−1·87 to 0·04; p=0·060)
Waist circumference, cm	117·4 (11·3; n=410)	117·9 (12·2; n=440)	−4·85 (7·06; n=410)	−6·99 (6·61; n=440)	−2·14 (−3·06 to −1·22; p<0·0001)
Total muscle mass, kg	64·6 (8·1; n=388)	64·5 (8·7; n=415)	−1·32 (2·84; n=388)	0·39 (2·88; n=415)	1·71 (1·32 to 2·11; p<0·0001)
Total fat mass, kg	37·5 (10·2; n=388)	37·4 (10·1; n=415)	−1·89 (5·81; n=388)	−4·60 (4·80; n=415)	−2·71 (−3·44 to −1·97; p<0·0001)
Abdominal fat mass, %	44·5 (6·7; n=382)	44·9 (6·6; n=409)	−1·21 (4·82; n=382)	−3·55 (4·99; n=409)	−2·34 (−3·03 to −1·66; p<0·0001)
Arm muscle mass, kg	7·7 (1·2; n=388)	7·6 (1·3; n=415)	−0·06 (0·78; n=388)	0·30 (0·77; n=415)	0·36 (0·25 to 0·47; p<0·0001)
Muscle strength for non-dominant hand, kg	42·1 (9·2; n=398)	41·6 (9·2; n=432)	−0·45 (6·44; n=398)	1·74 (6·87; n=432)	2·19 (1·28 to 3·10; p<0·0001)
Testosterone, nmol/L	13·9 (4·6; n=364)	13·4 (4·1; n=404)	0·76 (4·59; n=364)	3·41 (6·26; n=404)	2·65 (1·86 to 3·43; p<0·0001)
Dihydrotestosterone, nmol/L	1·1 (1·1; n=330)	1·0 (0·5; n=360)	−0·06 (1·13; n=330)	0·36 (0·76; n=360)	0·42 (0·28 to 0·56; p<0·0001)
Oestrone, pmol/L	138·5 (63·6; n=364)	135·9 (59·2; n=404)	−2·38 (46·55; n=364)	19·11 (59·21; n=404)	21·5 (13·9 to 29·1; p<0·0001)
Oestradiol, pmol/L	202·2 (104·1; n=364)	201·5 (99·8; n=404)	−0·92 (109·4; n=364)	29·06 (125·7; n=404)	30·0 (13·2 to 46·8; p=0·0005)
LH, IU/L (limit) §¶	5·4 (2·7; n=363)	5·2 (2·5; n=402)	0·42 (2·29; n=363)	−4·18 (2·87; n=402)	−4·60 (−4·97 to −4·23; p<0·0001)
LH, IU/L (zero)¶	5·4 (2·7; n=363)	5·2 (2·5; n=402)	0·42 (2·30; n=363)	−4·25 (2·87; n=402)	−4·67 (−5·04 to −4·30; p<0·0001)
FSH, IU/L (limit)§¶	7·1 (5·4; n=363)	6·9 (5·0; n=402)	0·74 (2·97; n=363)	−5·18 (4·93; n=402)	−5·92 (−6·50 to −5·33; p<0·0001)
FSH, IU/L (zero)¶	7·1 (5·4; n=363)	6·9 (5·0; n=402)	0·74 (2·97; n=363)	−5·18 (4·93; n=402)	−5·92 (−6·50 to −5·33; p<0·0001)
SHBG, nmol/L	37·5 (13·6; n=363)	37·4 (13·6; n=402)	4·74 (10·81; n=363)	0·79 (9·11; n=402)	−3·94 (−5·36 to −2·53; p<0·0001)
Erectile function score	16·7 (10·8; n=390)	17·4 (11·0; n=425)	−0·95 (8·77; n=390)	1·16 (7·99; n=425)	2·10 (0·95 to 3·26; p=0·0004)
Orgasmic function score	6·8 (3·8; n=389)	6·8 (3·9; n=425)	−0·57 (3·77; n=389)	0·28 (3·64; n=425)	0·85 (0·34 to 1·36; p=0·0012)
Sexual desire score	6·0 (2·1; n=390)	6·0 (2·1; n=420)	0·15 (1·94; n=390)	0·70 (1·91; n=420)	0·56 (0·29 to 0·82; p<0·0001)
Intercourse satisfaction score	6·8 (5·1; n=384)	6·9 (5·1; n=425)	−0·63 (4·51; n=384)	0·71 (4·01; n=425)	1·33 (0·75 to 1·92; p<0·0001)
Overall sexual satisfaction score	5·9 (2·8; n=389)	5·8 (2·8; n=419)	−0·12 (2·57; n=389)	0·51 (2·43; n=419)	0·63 (0·29 to 0·98; p=0·0003)
Total lower urinary tract symptoms score	5·8 (4·8; n=395)	5·4 (4·7; n=432)	0·89 (4·30; n=395)	1·35 (4·60; n=432)	0·46 (−0·15 to 1·07; p=0·14)

Data are n/N (%) or mean (SD; number with data available), unless otherwise indicated; denominators for percentage calculations are the numbers with data available. These results are unadjusted. Adjusted results are in appendix 1 (pp 9–10). LH=luteinising hormone. FSH=follicle stimulating hormone. SHBG=sex hormone-binding globulin. *For categorical outcomes, numbers at 2 years are shown; for continuous outcomes, the mean change from baseline at 2 years is shown. †Treatment effect for categorical outcomes is relative risk (95% CI; p value); treatment effect for continuous outcomes is mean difference in change from baseline (95% CI; p value). ‡Some participants had missing data at baseline. §For FSH, a total of 17 (2%) of 765 participants were censored at 2 years (none censored at baseline); for LH, seven (1%) of 765 participants were censored at baseline and 246 (32%) were censored at 2 years, with one censored at both timepoints. ¶Limit denotes a *t* test with values at the limit set to the detectable limit (0·1) and zero denotes a t-test with values at the limit set to zero.

Table 3: **Secondary outcomes**

the placebo group and 443 (88%) of 504 participants in the testosterone group (figure 1, appendix 1 pp 5–6). Of these 856 men, 172 (20%) had type 2 diabetes at baseline.

All participants received at least one dose of study medication, and 847 (84%) of 1007 participants were adhering to treatment at 1 year (appendix 1 p 6). 131 (26%) of 503 participants in the placebo group discontinued treatment before 2 years, as did 116 (23%) of 504 participants in the testosterone group, mostly due to participant preference (104 [79%] of 131 for placebo *vs* 65 [56%] of 116 for testosterone) or a protocol-specified rise in haematocrit (one [1%] *vs* 25 [22%]). Additional medications taken during the study are shown in appendix 1 (p 7). Off-protocol testosterone treatment was started by five (1%) of 503 participants in the placebo group and one (<1%) of 504 participants in the testosterone group. Medication for diabetes was initiated by 16 (3%) participants in the placebo group and 20 (4%) participants in the testosterone group, of whom two (13%) in the placebo group and four (20%) in the

testosterone group were due to trial protocol HbA_{1c} safety triggers, and the remainder were off-protocol treatments initiated by the patients' general practitioners. The medications were metformin (34 [94%] of 36 participants), dapagliflozin (one [3%]), dulaglutide (one [3%]), empagliflozin (one [3%]), and glibenclamide (one [3%]). Two participants reported use of more than one medication for diabetes over the course of the study (appendix 1 p 7).

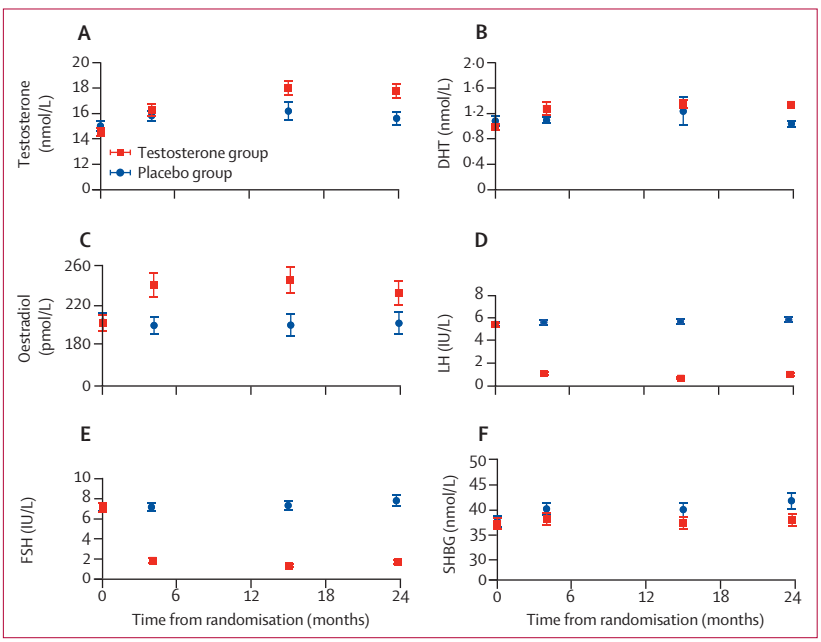

Figure 2: **Mean changes from baseline in testosterone (A), DHT (B), oestradiol (C), LH (D), FSH (E), and SHBG (F)**
Error bars show 95% CIs. DHT=dihydrotestosterone. LH=luteinising hormone. FSH=follicle stimulating hormone. SHBG=sex hormone-binding globulin.

At 2 years, the first primary outcome of 2-h glucose of 11·1 mmol/L or higher was reported in 87 (21%) of 413 participants in the placebo group and 55 (12%) of 443 participants in the testosterone group (RR 0·59, 95% CI 0·43 to 0·80; p=0·0007; table 2). The second primary outcome of mean change from baseline in 2-h glucose on OGTT was –0·95 mmol/L (SD 2·78) in the placebo group and –1·70 mmol/L (SD 2·47) in the testosterone group (mean difference –0·75 mmol/L, –1·10 to –0·40; p<0·0001). The observed correlation between the two outcomes was 0·75 (0·72 to 0·78). In adjusted analyses, treatment effects were largely unchanged (table 2). To account for missing data at 2 years in 90 (18%) of 503 participants in the placebo group and 61 (12%) of 504 participants in the testosterone group, a multiple imputation sensitivity analysis was done for 2-h glucose OGTT of 11·1 mmol/L or higher, which resulted in an RR of 0·62 (0·47 to 0·82; p=0·0015). An additional analysis excluding the ten participants who were enrolled with a screening 2-h OGTT glucose of 7·7 mmol/L showed similar results (data not shown).

Regarding secondary outcomes, there were no significant differences in adherence to the lifestyle programme or sufficient exercise (table 3). A higher proportion of participants in the testosterone group had normalised 2-h glucose at 2 years from baseline, but

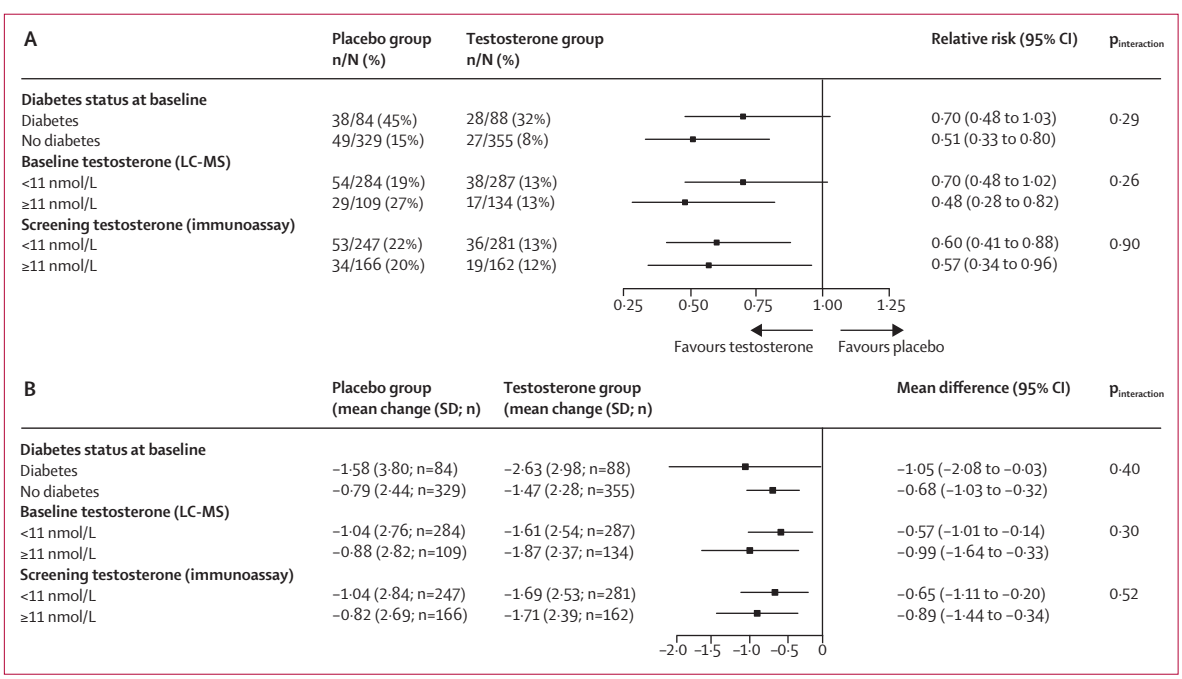

Figure 3: **Effect of treatment within subgroups for the primary outcomes of OGTT 2-h glucose at 2 years ≥11·1mmol/L (A) and change from baseline in OGTT 2-h glucose at 2 years (B)**
OGTT=oral glucose tolerance test. LC-MS=liquid chromatography–tandem mass spectrometry.

HbA_{1c} was similar in the two groups (table 3). 32 (8%) of 419 participants in the placebo group and 37 (8%) of 450 participants in the testosterone group had HbA_{1c} of 6·5% (48 mmol/mol) or higher at 2 years (p=0·75). However, compared with the placebo group, the testosterone group had greater decreases in fasting glucose, waist circumference, total fat mass, and abdominal fat mass, and greater increases in total muscle mass, arm muscle mass, and hand-grip strength (table 3). Compared with the placebo group, the testosterone group had significant improvements in the International Index of Erectile Function subscales (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction). There was no evidence of a between-group difference in lower urinary tract symptoms (table 3). Adjusted results are given in appendix 1 (pp 9–10) and average sex steroid concentrations over time are shown in figure 2. There was no evidence of a treatment difference in any of the psychosocial outcome measures (appendix 1 p 17).

The treatment effect was consistent across the subgroups of baseline 2-h glucose and serum testosterone concentrations for both the categorical primary outcome and the continuous primary outcome (figure 3). There was no association between baseline testosterone concentrations (in quintiles) and the treatment effect of testosterone at 2 years (appendix 1 pp 12–13).

Concerning safety measures, there were no significant between-group differences in the change at 2 years for systolic or diastolic blood pressure, or alanine transferase (appendix 1 p 11). However, compared with placebo, there were increases in the change at 2 years in haematocrit (4%, 95% CI 3 to 4) and PSA (0·3 ng/mL, 0·2 to 0·4; both p<0·0001; appendix 1 p 11). At least one safety trigger occurred for 93 (19%) of 485 participants in the placebo group and 185 (38%) of 492 participants in the testosterone group, including triggers for haematocrit of 54% or higher (six [1%] of 484 in the placebo group *vs* 106 [22%] of 491 in the testosterone group) and an increase in PSA of 0·75 µg/mL or more (87 [19%] of 468 *vs* 109 [23%] of 480; table 4). Prespecified serious adverse events occurred in 37 (7·4%, 95% CI 5·4 to 10·0) of 503 patients (total 41 events) in the placebo group and 55 (10·9%, 8·5 to 13·9) of 504 patients (total 55 events) in the testosterone group (table 5, appendix 1 p 14), including arrhythmias (three [1%] in the placebo group *vs* eight [2%] in the testosterone group), ischaemic heart disease (13 [3%] *vs* seven [1%]), cerebrovascular disease (three [1%] *vs* four [1%]), benign prostatic hyperplasia (three [1%] *vs* eight [2%]), prostate cancer (five [1%] *vs* four [1%]), other cancers (four [1%] *vs* ten [2%]), depression (three [1%] *vs* one [<0·5%]) and venous thrombotic events (none *vs* two [<0·5%]. There were two deaths in each group: one by suicide in each group, one by stroke in the placebo group, and one by sudden cardiac death in the testosterone group (appendix 1 p 15).

	Placebo group (n=503)	Testosterone group (n=504)
Total participants who experienced any trigger*	93/485 (19%)	185/492 (38%)
Total participants who experienced haematocrit ≥54%†	6/484 (1%)	106/491 (22%)
Total participants who experienced an increase in PSA of ≥0·75 µg/mL‡	87/468 (19%)	109/480 (23%)

Data are n/N (%). PSA=prostate-specific antigen. *Denominators are numbers of participants who had at least one haematocrit measurement during the study or at least two PSA measurements during the study. †Denominators are numbers of participants who had at least one haematocrit measurement during the study. This trigger led to the cessation of treatment for 26 participants (25 in the testosterone group). The remaining 86 participants either did not have raised haematocrit confirmed when repeated in a non-fasting state or they had already received their final study treatment injection at the time the haematocrit trigger occurred. ‡Denominators are numbers of participants who had at least two PSA measurements during the study. This trigger led to the cessation of treatment for 8 participants (5 in testosterone group). The remaining 188 participants either did not have increased PSA confirmed on repeat, were permitted to remain on treatment based on urologist advice, or had already received their final study treatment injection at the time the PSA trigger occurred.

Table 4: **Safety triggers**

	Placebo group (n=503)	Testosterone group (n=504)
Participants with at least one event (%, 95% CI)	37 (7·4%, 5·4–10·0)	55 (10·9%, 8·5–13·9)
Participants with at least one cardiovascular event (%, 95% CI)	21 (4·2%, 2·3–6·3)	26 (5·2%, 3·5–7·5)
Participants with at least one prostate event (%, 95% CI)	8 (1·6%, 0·8–3·1)	12 (2·4%, 1·4–4·1)
Participants with at least one other event (%, 95% CI)	11 (2·2%, 1·2–3·9)	17 (3·4%, 2·1–5·3%)
Total serious adverse events	41	55
Cardiovascular adverse events		
Arrythmia	3	8
Cardiac failure (cardiomyopathy)	1	1
Cardiac valvular disease	2	1
Cerebrovascular disease	3	4
Hypertension	0	1
Ischaemic heart disease	13	7
Syncope or collapse	0	2
Venous thromboses	0	2
Prostate adverse events		
Benign prostate hyperplasia-related hospital admissions	3	8
Prostate cancer	5	4
Other adverse events		
Cancers other than prostate cancer	4	10
Non-cardiac chest pain or chest pain of uncertain cause	2	4
Depression	2	0
Suicide	1	1
Other*	2	2

Data are number of events; no particpant had more than one event of the same sub-event category. *Other adverse events were dizziness with no cause (placebo; n=1)), benign positional vertigo (placebo; n=1), and syncope with no cause found (testosterone; n=2).

Table 5: **Serious adverse events**

Discussion

In men at high risk of, or with newly diagnosed, type 2 diabetes, who are enrolled in a lifestyle programme,

testosterone treatment at standard physiological replacement doses for 2 years significantly reduced the proportion of participants with type 2 diabetes, based on a standard OGTT (RR 0·59, 95% CI 0·43 to 0·80), with a between-group difference in mean change from baseline in 2-h glucose of –0·75 mmol/L (–1·10 to –0·40). The rates seen for the categorical primary outcome at 2 years were higher than anticipated in the sample size calculation, but the relative effect size was similar to what was expected (RR 0·56). Similarly, the absolute difference in the change in 2-h glucose at 2 years was larger than the expected value of 0·60 mmol/L, but the 95% CI was consistent with the expected value. Compared with placebo, testosterone treatment also produced a greater decrease from baseline to 2 years in fasting serum glucose concentration, but there was no significant difference in HbA_{1c}. The discrepancy between HbA_{1c} and blood glucose is consistent with other studies of testosterone treatment.[18,19] HbA_{1c} is linearly related to blood glucose and erythrocyte longevity. At any given average blood glucose, shortened red cell survival decreases HbA_{1c} and lengthened survival increases HbA_{1c}.[20] To our knowledge, the effect of testosterone on red cell survival is not known, but an increase in red cell survival could plausibly explain the discrepancy between our blood glucose and HbA_{1c} findings, warranting further investigation.

Baseline risk factors were well balanced between treatment groups. During the trial, medication use for diabetes, lifestyle programme engagement, and maintenance of sufficient exercise were similar between the groups. A sensitivity analysis accounting for missing outcome data revealed minimal change in the effect of treatment (RR 0·62, 95% CI 0·47–0·82).

Enrolment was based on a screening serum testosterone concentration of less than 14·0 nmol/L (403·8 ng/dL), as measured by immunoassay.[12] The use of immunoassay for initial screening and recruitment was a pragmatic decision because it is the standard assay offered by the network of laboratories that were easily accessible to participants and it remains in routine use worldwide. The use of a threshold of testosterone of 14·0 nmol/L was not because of any syndromic association of low testosterone with non-specific symptoms suggestive of hypogonadism, but because it is the concentration below which the risk of type 2 diabetes rises steeply.[2] Baseline serum testosterone concentrations, measured by LC-MS immediately before the first dose of testosterone was given, ranged from 4·0 to 33·1 nmol/L, consistent with well known discrepancies between these methods.[21] However, we identified no relation between either screening or baseline serum total testosterone or calculated free testosterone concentration and the testosterone treatment effect, suggesting a pharmacological action of testosterone in the T4DM trial.

In the placebo group, in response to the lifestyle programme alone, bodyweight was decreased by 3·53 kg at 2 years, despite declining participation in WW (on average 28% attended WW groups or used the website over the 2 years). Improvements in diet might be sustained despite decreased engagement in WW groups and website use. The magnitude of bodyweight change was in accordance with the 2-year outcomes of other clinical trials with a structured weight loss component.[7,22] The testosterone group showed a non-significantly greater weight loss of 0·92 kg compared with the placebo group; the absence of a significant effect on bodyweight can be at least partly explained by the greater reductions in total and abdominal fat mass being offset by increases in lean body mass, which is consistent with other studies of testosterone treatment.[23,24] A decrease in skeletal muscle mass (and concomitant decrease in hand grip strength), as seen in the placebo group, is an established consequence of weight loss induced by lifestyle interventions,[22] which can only be partly abrogated by an increase in physical activity.[22]

Although testosterone treatment improved sexual function, in accordance with results from the T Trials[23] and a subsequent meta-analysis of 14 testosterone treatment trials,[25] there were no differences in health-related quality of life or other psychosocial outcomes between the treatment groups.

The safety profile of the study was reassuring, with 41 serious adverse events recorded in the placebo group and 55 in the testosterone group, and no difference in incident cardiovascular events or prostate cancer. The increase in benign prostate hyperplasia-related hospital admissions with testosterone treatment compared with placebo (eight *vs* three) is consistent with the label information for testosterone products, which indicates a risk for acute urinary retention. Testosterone labels also indicate a risk for worsening lower urinary tract symptoms; however, we did not identify between-group differences in the mean International Prostate Symptom Score or in the category of lower urinary tract symptoms. Findings from a recent meta-analysis[26] suggested that testosterone treatment had no effect on lower urinary tract symptoms.

Although there were almost twice as many non-prostate cancers in the testosterone group than in the placebo group, the clinical significance of this finding is unclear because there were only one or two cases of each type of cancer. There were two instances of venous thrombotic complications, both in participants in the testosterone group. An association between treatment with testosterone and venous thrombosis has been reported.[27] However, incidence in the current study was lower than in other studies with similar populations in terms of risk profile in which treatment with testosterone was not provided.[28] The data from this study provide some reassurance regarding 2-year cardiovascular safety and are in accordance with a recent meta-analysis[29] indicating the cardiovascular safety of testosterone treatment.

The strengths of our study include the 2-year duration, high retention of participants, inclusion of a standardised

lifestyle programme that has been established as effective for diabetes prevention in men,[13] administration of study treatment directly by nurses at the time of clinic visits, and two primary outcomes that are based on an OGTT rather than relying on fasting glucose and HbA_{1c}. Although OGTT results can vary widely in clinical practice, we applied rigorous standards to limit this variability. We chose OGTT for our primary outcomes in line with the most widely cited clinical trial for diabetes prevention, the Diabetes Prevention Program trial, which compared lifestyle changes with metformin.[4]

The 15% attrition rate is low compared with trials of a 2-year duration involving weight-loss pharmacotherapy,[30] and is similar to the attrition seen in the T Trials, which had 89% retention at 1 year.[4] Participants who discontinued treatment continued to be followed up. The effect of treatment discontinuation would probably have been to attenuate the treatment effect, as confirmed in our multiple imputation analysis.

The study has some limitations. We excluded men who had pathological hypogonadism, but it is well established that such men benefit from treatment with testosterone including for body composition. Physical activity and adherence with the WW programme were self-reported, but they were similar across treatment groups and the magnitude of effect on bodyweight was consistent with studies of lifestyle interventions of similar duration.[7,30] No formal adjustments were made for multiple comparisons. However, we have followed the approach of Schulz and Grimes[31] and interpreted the patterns and consistency of results across related outcomes rather than focusing on statistical significance alone. No interim assessments were done before 2 years and, accordingly, only participants who had the OGTT at 2 years had primary outcome data that could be assessed. Some participants discontinued testosterone during the study and still had the final OGTT. These participants were included in the analysis under the intention-to-treat principle and thus there is no bias in this respect. We used multiple imputation to explore whether there was any obvious sign in the missing outcomes that would suggest completer bias. This is in effect a sensitivity analysis, the results of which provide reassurance with respect to the primary results of the trial.

A treatment-limiting increase in haematocrit to 54% or higher, a prespecified safety trigger, was flagged in 106 (22%) of 491 participants treated with testosterone. This proportion is within the range of treatment-limiting increases in haematocrit (2·5–40%) in other studies of testosterone treatment.[32,33] This trigger led to the cessation of treatment for 26 participants (25 in the testosterone group). The remaining 86 participants either did not have raised haematocrit confirmed when repeated in a non-fasting state, or they had already received their final study treatment injection at the time the haematocrit trigger occurred. We did not titrate the dose or dose interval of testosterone undecanoate, because in a previous smaller study,[24] the same dose of testosterone undecanoate was given every 10 weeks for 56 weeks with only one instance of treatment-limiting polycythaemia. Additionally, based on the predicted pharmacokinetics in the study population, we anticipated that dose exposure would be adequate without being excessive.[34] Accordingly, mean serum testosterone concentrations, which represent trough levels 3 months after an injection, were 2·7 nmol/L (76·4 ng/dL) higher in the testosterone group than in the placebo group. The adequacy of the dose is evident from the suppression of serum LH, FSH, and SHBG, and the increase in haematocrit. One possible explanation for the frequency of increased haematocrit is the probable prevalence of about 25% of moderate-to-severe obstructive sleep apnoea in the T4DM study population.[35] We did not screen for or exclude men with obstructive sleep apnoea because any deleterious effect of testosterone on the condition has been found to be transient[36] and there was an anticipated benefit from the lifestyle intervention.[37]

The magnitude of effect of testosterone to prevent type 2 diabetes was greater than that seen for metformin in the Diabetes Prevention Program,[4] which did not include an intensive lifestyle component. By contrast with metformin, testosterone increased skeletal muscle mass, grip strength, and sexual function. However, metformin has been shown to have cardiovascular benefit.[38] Despite a recent meta-analysis[29] showing neither cardiovascular benefit nor risk for testosterone treatment, controversy remains. An increase in non-calcified plaque volume of uncertain clinical significance was reported in older men (aged 65 years and older) after 12 months of transdermal testosterone treatment in the cardiovascular study of the T Trials.[39] However, in another study,[40] 3·8 years of long-acting testosterone undecanoate injections in men with established type 2 diabetes was associated with reduced mortality despite no improvement in conventional cardiovascular risk factors.

Neither benefit nor safety can be generalised beyond the relatively low-risk population enrolled, the concurrent introduction of a lifestyle programme, and the relatively frequent monitoring and support. Furthermore, in view of the frequency of treatment-induced increased haematocrit, screening for pre-existing increase of haematocrit or risk factors for such an increase would be prudent before considering testosterone treatment. Although these data might inform decisions about testosterone as a pharmacotherapy for diabetes prevention, the minimum dose exposure, duration of treatment, durability of effect, and long-term safety remain to be determined. For now, we consider it premature to treat men who do not have pathological hypogonadism with testosterone, for whom the primary approach should be assessment and management of physical and psychological conditions and risk factors known to be causally associated with functional hypogonadism.

Contributors

All authors were involved in the study design, applications for funding, and conduct of the study. All authors had input into and approved the statistical analysis plan. All authors accessed and verified the data in the study. KPR did the statistical analyses. All authors had input into the interpretation of the data and writing of the report. GW wrote the first draft of the report. All authors contributed to the revision of the report and approved the submitted version.

Declarations of interests

GW, KB, KPR, MG, BBY, BS, AC, WI, RM, CA, DJ, MNTF, WH, AJ, VG, and AK report grants from the Australian National Health and Medical Research Council (NHMRC), grants and non-financial support with the testosterone and matching placebo used in the study from Bayer, grants from Eli Lilly, and non-financial support (ie, free access to the lifestyle programme for study participants) from WW (formerly Weight Watchers), related to the present study. GW also reports grants from the Freemasons Centre for Male Health and Wellbeing at the University of Adelaide, related to the conduct of the present study, as well as grants and honoraria from Lawley Pharmaceuticals and Elsevier, and speaker fees from Bayer and Besins, unrelated to the present study. DJH reports grants from the NHMRC, grants and non-financial support from Bayer (testosterone and matching placebo used in this study), and non-financial support from WW (ie, free access to the lifestyle programme for study participants), related to the present study. DJH also reports grants from Besins and Lawley Pharmaceuticals, unrelated to the present study, and has provided expert testimony to anti-doping and professional standards tribunals and testosterone tort litigation. BBY also reports conference support and honoraria from, and an advisory role for Eli Lilly and Besins; conference support and honoraria from Bayer; research grants and research support from, and an advisory role for Lawley Pharmaceuticals; and honorarium from and an advisory role for Ferring, unrelated to the present study. BS also reports speaker honoraria from Besins, unrelated to the present study. CA also reports being on an advisory panel for Ferring and speaker's bureau from Besins, unrelated to the present study. DJ also reports honoraria from Eli Lilly, Merck, and Boehringer Ingelheim, unrelated to the present study. MG also reports grants and consultancy fees as an advisory board member from Otsuka and speaker fees from Besins, unrelated to the present study. AJ also reports grants from Abbott, non-financial support (provision of trial drug and placebo, unrelated to the present study) from Mylan, grants from the NHMRC, grants and non-financial support (provision of devices for a study unrelated to the present study) from Medtronic, grants from JDRF, grants from the Leona M and Harry B Helmsley Charitable Trust, being an honorary board member for Insulin for Life, grants from the International Diabetes Federation (IDF), and being an honorary board member for the IDF Western Pacific Region Executive Council, unrelated to the present study. AK also reports honoraria and research funding from, and being an advisory board member for Amgen; grants, honoraria, and support for educational activity from Mylan and Novartis; honoraria from, and being on an advisory board for AstraZeneca, Sanofi, and Bayer; sitting fees from Kowa; and hororaria from Pfizer, unrelated to the present study. MD declares no competing interests.

Data sharing

Deidentified data are available for sharing. To request data, please contact the corresponding author to be provided with a data access request form. Requests will be reviewed by the study statistician and steering committee. Applications from investigators with the academic capability and credibility to undertake the work proposed will be considered. The scientific merit of the proposal, including the appropriate methods, analysis, and publication plan will be assessed. Consideration will be taken of any overlap with analyses already undertaken or planned to be undertaken by the study team. If a proposal is approved, a signed data transfer agreement will be required before data sharing.

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