# Effect of Testosterone Treatment on Glucose Metabolism in Men With Type 2 Diabetes: A Randomized Controlled Trial

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## OBJECTIVE

**To determine whether testosterone therapy improves glucose metabolism in men with type 2 diabetes (T2D) and lowered testosterone.**

## RESEARCH DESIGN AND METHODS

**We conducted a randomized, double-blind, parallel, placebo-controlled trial in 88 men with T2D, aged 35–70 years with an $HbA_{1c}$ ≤8.5% (69 mmol/mol), and a total testosterone level, measured by immunoassay, of ≤12.0 nmol/L (346 ng/dL). Participants were randomly assigned to 40 weeks of intramuscular testosterone undecanoate (*n* = 45) or matching placebo (*n* = 43). All study subjects were included in the primary analysis. Seven men assigned to testosterone and six men receiving placebo did not complete the study. Main outcome measures were insulin resistance by homeostatic model assessment (HOMA-IR, primary outcome) and glycemic control by $HbA_{1c}$ (secondary outcome).**

## RESULTS

**Testosterone therapy did not improve insulin resistance (mean adjusted difference [MAD] for HOMA-IR compared with placebo −0.08 [95% CI −0.31 to 0.47; *P* = 0.23]) or glycemic control (MAD $HbA_{1c}$ 0.36% [0.0–0.7]; *P* = 0.05), despite a decrease in fat mass (MAD −2.38 kg [−3.10 to −1.66]; *P* < 0.001) and an increase in lean mass (MAD 2.08 kg [1.52–2.64]; *P* < 0.001). Testosterone therapy reduced subcutaneous (MAD −320 $cm^3$ [−477 to −163]; *P* < 0.001) but not visceral abdominal adipose tissue (MAD 140 $cm^3$ [−89 to 369]; *P* = 0.90).**

## CONCLUSIONS

**Testosterone therapy does not improve glucose metabolism or visceral adiposity in obese men with moderately controlled T2D and modest reductions in circulating testosterone levels typical for men with T2D.**


Observational studies consistently show that 30–50% of men with type 2 diabetes (T2D) have lowered circulating testosterone levels, relative to references based on healthy young men (1–3). This association is independent of age and obesity (4,5), and low testosterone levels in men with T2D are independently associated with insulin resistance (3). However, it is not known whether low testosterone levels are a cause or a consequence of T2D or its associated clinical features.

Several lines of evidence lend support to the hypothesis that testosterone treatment decreases insulin resistance. Experimental evidence, reviewed in Grossmann

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et al. (6), suggests that testosterone not only promotes the commitment of pluripotent stem cells into the myogenic lineage and inhibits their differentiation into adipocytes (7), but also regulates the metabolic functions of mature adipocytes and myocytes in ways that reduce insulin resistance. Androgen deprivation therapy in men with prostate cancer leads to insulin resistance (8), and testosterone therapy reduces fat mass and increases lean body mass (9).

There is also evidence for reverse causality, demonstrating that low testosterone may be a consequence of dysglycemia and obesity. In prospective studies, the metabolic syndrome predicts low testosterone (10), and weight gain or development of T2D are major drivers of the age-related decline in testosterone levels (11,12). Moreover, weight loss increases testosterone levels in observational and in intervention studies (13–15).

Testosterone prescribing has increased markedly in the U.S. and globally in recent years (16). However, the effects of testosterone treatment on glucose metabolism and on other important outcomes, such as cardiovascular events, remain uncertain (16). Men with T2D who are frequently obese and commonly present with moderately low testosterone levels constitute a clinically important group. The question arises whether special considerations apply to treating such individuals with testosterone therapy and if testosterone offers specific benefits in improving glucose metabolism in such men.

We therefore conducted a randomized, placebo-controlled clinical trial to test the hypothesis that testosterone therapy decreases insulin resistance and improves glycemic control in men with T2D and lowered circulating testosterone levels. Specifically, we targeted the prevalent population of obese men with established, moderately well-controlled diabetes and moderately lowered testosterone levels. In addition to effects on glucose metabolism, we carefully monitored treatment-related changes in body composition and in individual abdominal fat compartments to dissect their influence on glycemic end points. Intensification of antiglycemic therapy was a strictly enforced protocol violation leading to exclusion from the study.

## RESEARCH DESIGN AND METHODS

### Design Overview

This 40-week, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov NCT00613782) was conducted at a tertiary referral center (Austin Health, Melbourne, Australia) between November 2009 and February 2013 and approved by the Human Research Ethics Committee, Austin Health. Each participant provided written informed consent prior to entering the study.

### Setting and Participants

Study subjects were recruited from specialist diabetes clinics, primary care, and the general community. Men aged 35–70 years of age were eligible to participate in this trial if they had a history of T2D, and the total testosterone (TT) level (averaged from two fasting morning specimens) was ≤12.0 nmol/L (346 ng/dL), as measured by electrochemiluminescence immunoassay (ECLIA). Although TT was measured by both ECLIA and liquid chromatography-tandem mass spectroscopy (LCMS/MS), recruitment was based on ECLIA because the LCMS/MS assay (17) was not available for routine clinical use. Therefore, samples were batched and measured by LCMS/MS at study end.

Exclusion criteria included testosterone treatment within 5 years prior to randomization, established pituitary or testicular disorder, screening TT level of <5.0 nmol/L (144 ng/dL), luteinizing hormone (LH) level >1.5× upper limit of normal, or screening prostate-specific antigen (PSA) level > 4 μg/L, a history of urinary obstruction, prostate cancer, or breast cancer, hematocrit >0.50, uncontrolled hypertension (>160/90 mmHg despite treatment), untreated obstructive sleep apnea, estimated glomerular filtration rate < 30 mL/min, cardiac insufficiency (New York Heart Association score >2), active malignancy, unstable psychiatric disease, weight >135 kg (the weight limit for the dual-energy X-ray absorptiometry [DXA] scanner), current use of glucagon-like peptide-1 agonist therapy or very low-calorie diet, or an $HbA_{1c}$ level >8.5% (69 mmol/mol).

Changes in oral hypoglycemic agents or initiation of insulin therapy constituted a violation of trial protocol, leading to withdrawal from the trial. Changes in insulin dose, antihypertensive, and lipid-lowering therapies were recorded at each study visit. All subjects received written recommendations regarding physical activity, food choices, and glycemic index (http://www.diabetesaustralia.com.au/en/NDSS-Content/Diabetes-Information-Sheets/).

### Randomization and Interventions

Eligible participants were randomly assigned in a concealed 1:1 allocation to either testosterone or placebo using permuted blocks with a block size of 4. The randomization sequence was generated by a statistician and implemented by the Austin Health clinical trials pharmacy. Pharmacists, trial investigators, and participants were blinded to intervention allocation. Intramuscular testosterone undecanoate 1,000 mg or a visually identical placebo injection (both in oily base) was injected into the upper outer quadrant of the buttock at 0, 6, 18, and 30 weeks.

### Outcomes and Follow-up

The primary outcome measure was the change across groups and time from baseline in the homeostasis model assessment index of insulin resistance (HOMA-IR). The secondary outcome measure was the change across group and time in glycemic control as measured by $HbA_{1c}$. Other outcome measures were considered as explanatory variables.

### Schedule of Assessments and Measurements

At 0, 18, and 40 weeks, the following variables were assessed: drug treatment, adverse events, body weight, BMI, waist circumference, blood pressure (BP), $HbA_{1c}$, lipid profile, C-reactive protein (CRP), PSA, and a complete blood count. Baseline and, as per standard clinical practice, weeks 18 and 40 trough TT, sex hormone–binding globulin (SHBG), calculated free testosterone (cFT), and LH levels were measured. All blood samples were collected in the early morning in a fasted state prior to trial medication administration.

In men not on insulin treatment, fasting and post–75-g oral glucose tolerance test (OGTT) glucose and insulin levels (at 0, 90, and 120 min) were assessed at baseline, 18, and 40 weeks. HOMA-IR (3) and OGTT-based Insulin Sensitivity Index (18) were calculated. Oral hypoglycemic drugs were withheld for 48 h

prior to measurement of glucose and insulin levels.

TT was measured by both ECLIA (3) and LCMS/MS (17), SHBG, and LH using ECLIA (3), and free testosterone was calculated according to Vermeulen's formula as described (3). Glucose, insulin, $HbA_{1c}$ (3), and adiponectin (19) were measured as described.

At 0 and 40 weeks, total body mass, fat mass, and lean mass were assessed using DXA (DXA Prodigy, Version 10.51; GE Lunar, Madison, WI) (8). In subjects who had no contraindications to magnetic resonance imaging (MRI) scanning, axial images of the abdominal region were obtained using a three-tesla MRI scanner (Siemens, Erlangen, Germany) and analyzed using the SliceOmatic program software (version 4.2; Tomovision, Montreal, Canada). For each subject and time point, five 10-mm slices were selected for analysis of subcutaneous and visceral adipose tissue volume, with one slice centered at the level of the L4 vertebral superior endplate, three slices distributed at 40-mm intervals superiorly, and one inferiorly. The measured areas (in $mm^2$) were converted into volumes (in $cm^3$). Analyses were performed by a single individual (E.J.G.) blinded to patient identity, date, and study visit. The intraobserver coefficients of variation for visceral and subcutaneous fat area were 3.7 and 2.3%, respectively.

### Sample Size Determination

The trial was designed to have a power of 90% to detect a mean difference in HOMA-IR change from baseline between testosterone treatment and placebo of 1.73 (SD 1) and of an $HbA_{1c}$ of 0.37% (SD 0.4) at 40 weeks based on a crossover trial in men with T2D and lowered serum testosterone treated with intramuscular testosterone (20).

### Statistical Analysis

We used a generalized linear mixed model to compare the primary and secondary outcomes between the treatment and placebo group. The model included the fixed effects of baseline values of the variable assessed, treatment group (testosterone vs. placebo as a categorical variable), repeated measurements taken at the three visits (0, 18, and 40 weeks, used as categorical time points), and the interaction term of visit × treatment group. The random effect was repeated measure by participant. The primary comparison of interest was the change across groups over time represented by the interaction term in the model. The overall *P* value given refers to this comparison. As a quantitative measure, mean adjusted difference (MAD) plus 95% CI between the groups from baseline to week 40 are provided. Following an intention-to-treat protocol, the analysis included all randomized subjects who were enrolled in the trial. A sensitivity analysis was performed first, after imputing missing values by multivariate imputation with chained equations and secondly including only subjects who had completed the study and adhered to the protocol. We also assessed sensitivity of the main outcomes to relevant baseline variables. Separate models with similar characteristics were used to assess other outcome data and safety variables. Comparison of baseline characteristics was based on Wilcoxon rank-sum test or $\chi^2$ test in case of categorical variables. In case of low numbers, the Fisher exact test was used. To compare repeated measurements of variables considered explanatory within groups between two time points, the Wilcoxon signed-rank test was used. Data shown are median plus interquartile range (IQR). All tests were two-tailed with $P < 0.05$ denoting statistical significance. No adjustments were made for multiple comparisons on explanatory variables. Analyses were conducted using R for Mac version 3.01 (21,22) and SPSS version 21 (SPSS Inc., Chicago, IL).

### Role of the Funding Source

Bayer Pharma AG (Berlin, Germany) provided testosterone, placebo, and financial support to conduct investigations, but had no role in trial design, data analysis, or writing the manuscript.

## RESULTS

### Study Subjects

Of 965 men approached, 263 men proceeded to screening investigations, 88 of whom were randomized (testosterone, 45; placebo, 43) and included in the primary analysis. Seventy-five men completed the trial. The most common reason for noncompletion, occurring in 8 out of the 13 men who did not complete the study, was intensification of oral hypoglycemic agents or commencement of insulin therapy, which constituted predefined protocol violations (Supplementary Fig. 1). While changes in insulin dose in the 20% of men receiving insulin therapy (Table 1) was not an exclusion criterion, none of the testosterone-treated men had a reduction in the total daily dose (TDD) of insulin during the study. In addition, patients receiving placebo were not more likely to have an increase in TDD in insulin: three men receiving placebo and three men receiving testosterone treatment had such an increase.

Baseline characteristics were comparable between the groups except that subjects in the testosterone-treated group had lower body weight, lower fasting glucose, and slightly greater insulin sensitivity as measured by the OGTT-based Insulin Sensitivity Index (Table 1).

### Testosterone Levels

TT measured by ECLIA averaged 8.7 nmol/L (251 ng/dL) and 8.5 nmol/L (245 ng/dL) at baseline in the testosterone and placebo groups, respectively ($P = 0.6$) (Table 1). Baseline LCMS/MS-derived TT levels were, as expected (16,23), higher than ECLIA values at 10.6 nmol/L (306 ng/dL) in the testosterone group and 11.0 nmol/L (317 ng/dL) in the placebo group ($P = 0.76$). At 40 weeks, both ECLIA TT and LCMS/MS TT, as well as ECLIA cFT and LCMS/MS cFT, increased significantly in the testosterone group, while there was no significant change in the placebo group (Supplementary Fig. 2). The MADs in change over 40 weeks across the two groups were: LCMS/MS TT, 5.9 nmol/L (170 ng/dL [95% CI 3.9–7.9 (112–228)]; $P < 0.001$) and LCMS/MS cFT, 183 pmol/L (53 pg/mL [138–228 (40–66)]; $P < 0.001$). LH decreased (MAD −5.1 IU/L [95% CI −13 to −2.9]; $P < 0.001$), as did SHBG (MAD −3.7 nmol/L [−5.9 to −1.5]; $P < 0.001$) (Supplementary Fig. 2).

### Changes in Main Outcome Measures

Testosterone treatment did not improve the primary outcome, HOMA-IR over 40 weeks, compared with placebo (MAD −0.08 [95% CI −0.31 to 0.47]; $P = 0.23$) or the secondary outcome, $HbA_{1c}$ (MAD 0.36% [0.0–0.7]; $P = 0.05$) (Table 2).

**Table 1—Baseline characteristics of randomly assigned study participants**

| | Testosterone group ($n$ = 45) | Placebo group ($n$ = 43) | $P$ value |
|---|---|---|---|
| Age, years | 62 (58–68) | 62 (57–67) | 0.75 |
| Duration of diabetes, years | 8 (4–13) | 9 (5–12) | 0.71 |
| Insulin therapy, % | 18 | 23 | 0.71 |
| Metabolic syndrome ATPIII, % | 98 | 95 | 0.97 |
| UKPDS 10-year CV risk, % | 20 (16–29) | 22 (17–27) | 0.64 |
| Weight, kg | 93.0 (85.3–107.7) | 101.5 (93.0–110.8) | 0.04 |
| BMI, kg/m$^2$ | 31.5 (28.3–35.5) | 33.4 (31.4–35.4) | 0.06 |
| Waist circumference, cm | 110.0 (104.0–120.8) | 115.0 (110.0–121.0) | 0.07 |
| SBP, mmHg | 140 (130–150) | 140 (129–150) | 0.98 |
| DBP, mmHg | 72 (70–80) | 80 (70–82) | 0.05 |
| Fat mass, g | 32,040 (26,577–38,284) | 34,077 (29,402–38,380) | 0.34 |
| Lean mass, g | 58,052 (52,871–64,306) | 62,702 (59,489–66,608) | 0.05 |
| TT, nmol/L (ECLIA) | 8.7 (7.1–11.1) | 8.5 (7.2–11.0) | 0.60 |
| TT, nmol/L (LCMS/MS) | 10.6 (9.0–13.0) | 11.0 (8.2–13.3) | 0.76 |
| cFT, pmol/L (ECLIA) | 183 (148–247) | 187 (150–237) | 0.80 |
| cFT, pmol/L (LCMS/MS) | 224 (185–305) | 247 (183–314) | 0.74 |
| SHBG, nmol/L | 28 (23–34) | 28 (23–32) | 0.59 |
| LH, IU/L | 4.5 (3.3–6.5) | 4.5 (3.6–6.4) | 0.61 |
| Fasting glucose, mmol/L | 7.6 (6.5–10.3) | 9.3 (7.7–10.6) | 0.03 |
| Fasting C-peptide, nmol/L | 1.11 (0.89–1.45) | 1.27 (0.95–1.62) | 0.09 |
| Insulin, pmol/L | 103.5 (76.4–138.9) | 124.3 (87.5–188.9) | 0.06 |
| HOMA-IR* ($n$ = 67) | 2.11 (1.69–2.94) | 2.78 (1.76–3.93) | 0.07 |
| OGIS, mL min$^{-1}$ m$^2$* ($n$ = 70) | 483 (423–517) | 419 (380–463) | 0.04 |
| $HbA_{1c}$, % | 6.8 (6.4–7.6) | 7.1 (6.7–7.5) | 0.14 |
| $HbA_{1c}$, mmol/mol | 51 (46–60) | 54 (50–58) | 0.14 |
| Cholesterol, mmol/L | 4.2 (3.8–4.8) | 4.5 (3.6–4.8) | 0.95 |
| LDL, mmol/L | 2.3 (1.7–2.8) | 2.2 (1.8–2.8) | 0.82 |
| HDL, mmol/L | 1.1 (0.9–1.3) | 1.0 (0.8–1.2) | 0.24 |
| Triglycerides, mmol/L | 1.6 (1.1–2.4) | 1.8 (1.3–2.4) | 0.27 |
| CRP, nmol/L | 13.3 (9.5–23.8) | 16.2 (9.5–24.8) | 0.40 |
| Hematocrit | 0.44 (0.41–0.46) | 0.43 (0.41–0.45) | 0.54 |
| Hemoglobin, g/L | 151 (139–157) | 151 (142–156) | 0.93 |
| PSA, μg/L | 0.84 (0.58–1.24) | 0.73 (0.46–1.26) | 0.47 |

Data are median (IQR). $P$ values were calculated for the difference among groups using Wilcoxon, $\chi^2$, or Fisher exact test. $P < 0.05$ was considered significant. ATPIII, Adult Treatment Panel 3; DBP, diastolic BP; OGIS, OGTT-based Insulin Sensitivity Index; SBP, systolic BP; UKPDS CV, UK Prospective Diabetes Study Cardiovascular. *Data from men not on insulin treatment.

### Changes in Explanatory Variables

There was no significant change in OGTT-based Insulin Sensitivity Index, fasting glucose, C-peptide, or insulin levels between the testosterone or placebo group (Table 3). In the men treated with insulin therapy, there was no significant difference in TDD of insulin between the two groups from baseline to 40 weeks ($P$ = 0.32).

While there was no change in body weight, BMI, or waist circumference between groups, testosterone treatment significantly decreased total fat mass (MAD −2,377 g [95% CI −3,096 to −1,658]; $P < 0.001$) and increased lean mass (MAD 2,078 g [1,519–2,637]; $P < 0.001$) (Table 3). There was a significant decrease in abdominal subcutaneous adipose tissue (MAD −320 cm$^3$ [−477 to −163]; $P < 0.001$) but interestingly not in visceral adipose tissue (MAD 140 cm$^3$ [−89 to 369]; $P$ = 0.90) or adiponectin levels (MAD −3.3 μg/mL [−8.2 to 1.6]; $P$ = 0.42) (Table 3).

In subjects with no change in their lipid-lowering agents, testosterone treatment decreased total cholesterol (MAD −0.45 mmol/L [−17.4 mg/dL] [95% CI −0.7 to −0.2 (−27 to 7.7)]; $P < 0.001$), LDL cholesterol (MAD −0.26 mmol/L [−10.0 mg/dL] [−0.46 to −0.06 (−17.8 to −2.3)]; $P$ = 0.01), and HDL cholesterol (MAD −0.11 mmol/L [−4.3 mg/dL] [−0.19 to −0.03 (−7.3 to −1.2)]; $P$ = 0.002). There was no significant between-group change in prevalence of the metabolic syndrome, CRP levels, or, in participants without changes in antihypertensive agents, in BP (Table 3).

### Sensitivity Analyses

Outcomes were essentially unchanged after imputation of missing values or when analyzing participants who adhered to protocol only. MADs were as follows: HOMA-IR, −0.17 (95% CI −0.52 to 0.22), $P$ = 0.25, $n$ = 88; and $HbA_{1c}$, 0.22% (−0.05 to 0.49), $P$ = 0.01; $n$ = 88 in the imputed sample; and in the per-protocol data: HOMA-IR, −0.15 (−0.52 to 0.22), $P$ = 0.40, $n$ = 56; and $HbA_{1c}$, 0.20% (−0.09 to 0.49), $P$ = 0.38, $n$ = 75. Outcomes also remained unchanged when the three men in each group with changes in their TDD of insulin were excluded: HOMA-IR, −0.08 (−0.31 to 0.47), $P$ = 0.23; and $HbA_{1c}$, 0.22% (−0.15 to 0.59), $P$ = 0.32. Further, the change in HOMA-IR and $HbA_{1c}$ over the treatment period was not related to relevant baseline characteristics, such as age, BMI, duration of diabetes, insulin use, or testosterone levels. Moreover, in a post hoc analysis, a higher baseline $HbA_{1c}$ did not predict a better glycemic response ($P$ = 0.42). Similarly, a lower baseline total ($P$ = 0.42) or cFT ($P$ = 0.30) did not predict a better glycemic response. There was no correlation between the change of either TT or free testosterone levels during treatment and measures of glucose metabolism. In contrast, the fat change in testosterone-treated men was related both to the delta (difference between week 40 and week 0) LCMS/MS TT (−0.26; $P < 0.02$) and LCMS/MS TT achieved at week 40 (−0.27; $P < 0.02$), but not to the baseline LCMS/MS TT (−0.01; $P$ = 0.91). Moreover, differences in MAD for HOMA-IR and $HbA_{1c}$ remained nonsignificant if men with a baseline LCMS/MS TT of <12 and ≥12 nmol/L were analyzed separately. By contrast, the MAD for fat mass remained significant in both these two groups (data not shown).

### Adverse Events

The frequency of adverse events is shown in Table 4. Serious adverse

**Table 2—Main outcome measures**

| Parameter | Testosterone group [median (IQR)] | Placebo group [median (IQR)] | MAD[1] (95% CI) | *P* value[2] |
|---|---|---|---|---|
| HOMA-IR* | *n* = 37 | *n* = 30 | | |
| 0 weeks | 2.11 (1.69–2.94) | 2.78 (1.76–3.93) | | |
| 18 weeks | 2.33 (1.60–2.71) | 2.58 (1.66–3.29) | | |
| 40 weeks | 1.75 (1.52–2.37) | 2.64 (1.73–3.65) | −0.08 (−0.31 to 0.47) | 0.23 |
| $HbA_{1c}$, % | *n* = 45 | *n* = 43 | | |
| 0 weeks | 6.8 (6.4–7.6) | 7.1 (6.7–7.5) | | |
| 18 weeks | 6.9 (6.5–7.8) | 7.1 (6.8–7.6) | | |
| 40 weeks | 7.1 (6.5–7.8) | 7.2 (6.9–7.8) | +0.36 (0.0–0.7) | 0.05 |
| $HbA_{1c}$, mmol/mol | *n* = 45 | *n* = 43 | | |
| 0 weeks | 51 (46–60) | 54 (50–58) | | |
| 18 weeks | 52 (48–62) | 54 (51–60) | | |
| 40 weeks | 54 (48–62) | 55 (52–62) | Not applicable^ | |

[1]MAD refers to the change over 40 weeks across groups (mixed model). [2]The *P* value refers to overall significance of the change among groups during follow-up. *Data from men not on insulin treatment. ^Conversion from percentage to mmol/mol values is only valid for $HbA_{1c}$ values between 3 and 20%.

events were few, and incidence was not significantly different between groups.

There was a significant increase in hematocrit (0.04 [IQR 0.02–0.07]; $P < 0.001$) and hemoglobin (14 g/L [IQR 4–19]; $P < 0.001$) in the testosterone-treated patients at 40 weeks, but no change in the placebo group hematocrit (0 [−0.02 to 0.01]; $P = 0.98$) or hemoglobin (−1 g/L [−6 to 3]; $P = 0.23$) (Supplementary Fig. 3). The MADs across groups over 40 weeks were: hematocrit, 0.04 (95% CI 0.03–0.05), $P < 0.001$, and hemoglobin, 14.7 g/L (11.4–18.4), $P < 0.001$ (Table 3). In the testosterone group, three participants (6.6%) developed transient increases in the hematocrit to >0.54. One participant in the testosterone group was withdrawn, as his hematocrit was >0.54 prior to his 30-week injection. There was a significant increase in PSA (0.33 μg/L [IQR 0.11–0.67]; $P < 0.001$) in the testosterone-treated patients at 40 weeks, but no change in the placebo group (0.01 μg/L [IQR −0.04 to 0.13]; $P = 0.39$) (Supplementary Fig. 3). The MAD in PSA levels across groups over 40 weeks was 0.55 μg/L (95% CI 0.25–0.84); $P < 0.001$ (Table 3). There were no significant differences between groups with regard to new diagnosis of ischemic heart disease or significant congestive cardiac failure (Table 4).

## CONCLUSIONS

The hypothesis of the trial that testosterone treatment may confer a specific glycemic benefit to obese men with reasonably well-controlled T2D and moderately lowered testosterone levels was not confirmed in this randomized controlled trial (RCT). Testosterone therapy did not improve measures of basal or dynamic insulin resistance and did not improve glycemic control in such men. These data therefore do not support the addition of testosterone treatment to antidiabetic medications to improve glucose metabolism in such men.

Men enrolled in this RCT had only modestly lowered baseline testosterone levels. As expected (16,23), values measured by LCMS/MS were higher than those obtained by immunoassay. Previous RCTs in men with diabetes (Supplementary Table 1) have measured testosterone only by immunoassay, and baseline levels were similar or higher compared with the immunoassay testosterone levels in our cohort. Profound testosterone deficiency (<1 nmol/L) induced by androgen-deprivation therapy has been shown to induce insulin resistance in observational studies (8). However, current evidence does not support a consistent threshold concentration of circulating testosterone required to maintain insulin sensitivity: in the general population, insulin resistance (24) or prevalence of diabetes (25) was increased in men with circulating testosterone levels <8 nmol/L (24) and <10 nmol/L (25). By contrast, in men with diabetes, the inverse relation between testosterone levels and insulin resistance was present even in men with testosterone levels extending well into the normal range (3). A study of experimentally induced hypogonadism in healthy men showed that reducing testosterone levels to 6.1 nmol/L had no effect on insulin sensitivity (26). Collectively, these data do not exclude the possibility that men with T2D and substantially lowered testosterone levels may derive a glycemic benefit with testosterone therapy. However, marked reductions of testosterone are uncommon in men with diabetes: in meta-analyses, mean pooled differences in TT relative to men without diabetes ranged from −1.61 nmol/L (4) to −2.99 nmol/L (27). Moreover, in our post hoc analyses, lower baseline TT and free testosterone levels did not predict a better glycemic response. Men with unequivocal reductions in their testosterone levels, whether they have T2D or not, should be considered for testosterone treatment irrespective of potential effects on glucose metabolism, given its general benefits in such men (28).

We cannot directly answer the question whether testosterone therapy could be more effective in men with less well-controlled diabetes. We considered this clinically less important given the availability of effective antiglycemic therapies. It can be noted that none of our study subjects required a reduction in their oral antidiabetic medications or insulin doses. A higher baseline $HbA_{1c}$ did not predict a better glycemic response.

Interestingly and somewhat paradoxically, while we did document an expected reduction in fat mass and an increase in lean mass with testosterone therapy, the changes in body composition failed to translate into an improvement in glycemic outcomes. Importantly, the changes in fat mass

**Table 3—Explanatory variables**

| | Testosterone group [median (IQR)] | Placebo group [median (IQR)] | MAD[1] (95% CI) | *P* value[2] |
|---|---|---|---|---|
| OGIS, mL min$^{-1}$ m$^2$* | *n* = 37 | *n* = 33 | | |
| Baseline | 483 (423–517) | 419 (380–463) | | |
| 18 weeks | 461 (408–502) | 441 (399–480) | | |
| 40 weeks | 491 (392–577) | 444 (391–474) | +4.9 (2.5–7.3) | 0.08 |
| Fasting glucose, mmol/L | *N* = 45 | *N* = 43 | | |
| Baseline | 7.6 (6.5–10.3) | 9.3 (7.7–10.6) | | |
| 18 weeks | 8.2 (6.7–10.3) | 9.2 (7.6–10.3) | | |
| 40 weeks | 7.7 (6.5–10.5) | 9.3 (7.7–10.6) | +0.45 (−0.4 to 1.3) | 0.27 |
| C-peptide, nmol/L | *N* = 45 | *N* = 43 | | |
| Baseline | 1.11 (0.89–1.45) | 1.27 (0.95–1.62) | | |
| 18 weeks | 1.23 (0.91–1.44) | 1.24 (0.86–1.61) | | |
| 40 weeks | 1.15 (0.88–1.36) | 1.28 (0.94–1.65) | +0.02 (−0.14 to 0.18) | 0.31 |
| Insulin, pmol/L* | *N* = 37 | *N* = 33 | | |
| Baseline | 103.5 (76.4–138.9) | 124.3 (87.5–188.9) | | |
| 18 weeks | 105.6 (75.7–132.0) | 123.6 (77.1–173.6) | | |
| 40 weeks | 85.4 (67.4–115.3) | 132.0 (80.6–203.5) | −1.46 (−45.14 to 42.36) | 0.053 |
| Weight, kg | *n* = 45 | *n* = 43 | | |
| Baseline | 93.0 (85.3–107.7) | 101.5 (93.0–110.8) | | |
| 18 weeks | 93.7 (83.3–109.5) | 102.4 (95.1–108.8) | | |
| 40 weeks | 91.1 (87.4–108.1) | 99.7 (95.0–108.4) | −0.02 (−1 to 1) | 0.34 |
| BMI, kg/m$^2$ | *n* = 45 | *n* = 43 | | |
| Baseline | 31.5 (28.3–35.5) | 33.4 (31.4–35.4) | | |
| 18 weeks | 31.0 (28.2–36.4) | 33.6 (31.7–35.6) | | |
| 40 weeks | 30.9 (28.2–35.5) | 33.3 (31.6–35.2) | −0.02 (−0.4 to 0.4) | 0.31 |
| WC, cm | *N* = 45 | *N* = 43 | | |
| Baseline | 110.0 (104.0–120.8) | 115.0 (110.0–121.0) | | |
| 18 weeks | 109.5 (103.0–119.9) | 115.0 (110.5–122.0) | | |
| 40 weeks | 111.0 (101.9–119.3) | 117.0 (112.8–123.0) | −1.2 (−2.6 to 0.2) | 0.30 |
| Fat, g | *N* = 45 | *N* = 43 | | |
| Baseline | 32,040 (26,577–38,284) | 34,077 (29,402–38,380) | | |
| 40 weeks | 31,677 (24,721–35,413) | 33,536 (30,181–36,943) | −2,377 (−3,096 to −1,658) | <0.001 |
| Lean, g | *N* = 45 | *N* = 43 | | |
| Baseline | 58,052 (52,871–64,306) | 62,702 (59,489–66,608) | | |
| 40 weeks | 59,644 (55,581–66,188) | 63,674 (58,668–65,875) | +2,078 (1,519–2,637) | <0.001 |
| SAT, cm$^3$# | *N* = 25 | *N* = 27 | | |
| Baseline | 4,095 (3,057–5,593) | 4,661 (3,888–5,320) | | |
| 40 weeks | 3,866 (2,814–4,973) | 4,532 (3,741–5,179) | −320 (−477 to −163) | <0.001 |
| VAT, cm$^3$# | *N* = 25 | *N* = 27 | | |
| Baseline | 3,642 (2,530–4,652) | 4,318 (3,402–5,271) | | |
| 40 weeks | 3,356 (2,381–4,960) | 4,077 (3,462–4,960) | +140 (−89 to 369) | 0.90 |
| Adiponectin, μg/mL | *n* = 45 | *n* = 43 | | |
| Baseline | 15.6 (11.4–28.2) | 14.2 (8.1–28.1) | | |
| 18 weeks | 12.0 (9.6–24.9) | 13.6 (9.9–25.1) | | |
| 40 weeks | 15.1 (9.9–23.5) | 14.6 (9.2–23.1) | −3.3 (−8.2 to 1.6) | 0.42 |
| Cholesterol, mmol/L | *N* = 45 | *N* = 43 | | |
| Baseline | 4.2 (3.8–4.8) | 4.5 (3.6–4.8) | | |
| 18 weeks | 3.9 (3.5–4.6) | 4.3 (3.8–5.0) | | |
| 40 weeks | 3.7 (3.3–4.4) | 4.3 (3.7–5.1) | −0.45 (−0.7 to −0.2) | <0.001 |
| LDL, mmol/L | *N* = 42 | *N* = 41 | | |
| Baseline | 2.3 (1.7–2.8) | 2.2 (1.8–2.8) | | |
| 18 weeks | 2.1 (1.6–2.7) | 2.2 (1.9–3.0) | | |
| 40 weeks | 2.0 (1.7–2.5) | 2.1 (1.8–2.9) | −0.26 (−0.46 to −0.06) | 0.01 |
| HDL, mmol/L | *N* = 45 | *N* = 43 | | |
| Baseline | 1.1 (0.9–1.3) | 1.0 (0.8–1.2) | | |
| 18 weeks | 1.0 (0.9–1.3) | 1.0 (0.8–1.2) | | |
| 40 weeks | 1.2 (0.9–1.3) | 1.1 (0.9–1.3) | −0.11 (−0.19 to −0.03) | 0.002 |
| Triglycerides, mmol/L | *N* = 45 | *N* = 43 | | |
| Baseline | 1.6 (1.1–2.4) | 1.8 (1.3–2.4) | | |
| 18 weeks | 1.6 (1.0–2.0) | 1.8 (1.3–2.6) | | |
| 40 weeks | 1.4 (0.9–1.9) | 1.8 (1.2–2.8) | −0.1 (−0.49 to 0.29) | 0.24 |

*Continued on p. 2104*

**Table 3—Continued**

| | Testosterone group [median (IQR)] | Placebo group [median (IQR)] | MAD[1] (95% CI) | *P* value[2] |
|---|---|---|---|---|
| MetS, % | *n* = 45 | *n* = 43 | | |
| Baseline | 98 | 95 | | |
| 18 weeks | 98 | 95 | | |
| 40 weeks | 92 | 96 | −6% (−2 to 14) | 0.32 |
| CRP, nmol/L | *N* = 44 | *N* = 42 | | |
| Baseline | 13.3 (9.5–23.8) | 16.2 (9.5–24.8) | | |
| 18 weeks | 14.3 (9.5–28.6) | 19.0 (10.5–30.5) | | |
| 40 weeks | 13.3 (9.5–33.3) | 16.2 (10.5–44.8) | −16.2 (−29.5 to −2.9) | 0.051 |
| SBP, mmHg | *N* = 45 | *N* = 42 | | |
| Baseline | 140 (130–150) | 140 (129–150) | | |
| 18 weeks | 140 (130–150) | 142 (132–150) | | |
| 40 weeks | 140 (130–146) | 140 (130–148) | −2 (−7 to 3) | 0.14 |
| DBP, mmHg | *N* = 45 | *N* = 42 | | |
| Baseline | 72 (70–80) | 80 (70–82) | | |
| 18 weeks | 80 (70–81) | 76 (70–80) | | |
| 40 weeks | 73 (70–80) | 76 (70–80) | +2 (−2 to 6) | 0.35 |
| Hematocrit | *N* = 44 | *N* = 43 | | |
| Baseline | 0.44 (0.41–0.46) | 0.43 (0.41–0.45) | | |
| 18 weeks | 0.47 (0.43–0.50) | 0.44 (0.41–0.46) | | |
| 40 weeks | 0.47 (0.43–0.50) | 0.43 (0.41–0.45) | +0.04 (0.03–0.05) | <0.001 |
| Hemoglobin, g/L | *N* = 44 | *N* = 43 | | |
| Baseline | 151 (139–157) | 151 (142–156) | | |
| 18 weeks | 160 (147–171) | 149 (141–158) | | |
| 40 weeks | 164 (148–174) | 149 (139–155) | +14.7 (11.4–18.4) | <0.001 |
| PSA, μg/L | *N* = 44 | *N* = 43 | | |
| Baseline | 0.84 (0.58–1.24) | 0.73 (0.46–1.26) | | |
| 18 weeks | 1.00 (0.72–1.53) | 0.84 (0.49–1.28) | | |
| 40 weeks | 1.15 (0.69–1.73) | 0.79 (0.43–1.34) | +0.55 (0.25–0.84) | 0.001 |

DBP, diastolic BP; MetS, metabolic syndrome; OGIS, OGTT-based Insulin Sensitivity Index; SAT, subcutaneous adipose tissue volume; SBP, systolic BP; VAT, visceral adipose tissue volume; WC, waist circumference. [1]MAD refers to the change over 40 weeks across groups (mixed model). [2]The *P* value refers to overall significance of the change between groups during follow-up. *Data from men not on insulin treatment. #Data from men without contraindications to MRI scanning.

in the testosterone-treated men were related to the testosterone level achieved during treatment, but not to the baseline testosterone level, arguing, consistent with our findings for glucose metabolism, against a testosterone threshold for this biological response. Our finding is consistent with studies in men with experimentally induced hypogonadism (26) and in mice lacking the androgen receptor (29), which also showed that the effects of testosterone on body composition and glucose metabolism can be dissociated. In our study, this dissociation may have occurred because testosterone treatment did not decrease visceral adipose tissue (Table 3),

**Table 4—Incidence of adverse events on treatment**

| Adverse event | Testosterone group (*n* = 45) [*n* (%)]* | Placebo group (*n* = 43) [*n* (%)]* | *P* value |
|---|---|---|---|
| Overall | | | |
| Any adverse event | 8 (18) | 13 (30) | 0.31 |
| Serious adverse event | 4 (9) | 4 (9) | 1.00 |
| Withdrawal due to adverse event | 3 (7) | 1 (2) | 0.62 |
| Physiological system | | | |
| Cardiovascular | 3 (7) | 3 (7) | 1.00 |
| Respiratory | 1 (2) | 2 (5) | 0.61 |
| Hepatobiliary | 0 | 1 (2) | 0.48 |
| Genitourinary | 1 (2) | 3 (7) | 0.36 |
| Hematological | 3 (7) | 0 | 0.24 |
| Psychosexual | 0 | 2 (5) | 0.24 |
| Other | 0 (0) | 2 (5) | 0.24 |

*Study subjects who had at least one adverse event. Serious adverse events included sepsis-related acute myocardial infarction requiring coronary artery bypass grafting (T group; *n* = 1), new-onset congestive cardiac failure (T group; *n* = 1), new diagnosis of severe aortic stenosis and congestive cardiac failure requiring medical treatment (T group; *n* = 1), new diagnosis of ischemic heart disease and congestive cardiac failure requiring coronary artery bypass grafting (P group; *n* = 1), new diagnosis of obstructive sleep apnea (P group, *n* = 2; T group; *n* = 1), and prostatitis requiring hospitalization (P group; *n* = 1). The statistical difference among groups was determined using the Fisher exact test.

the fat compartment most closely associated with insulin resistance. Consistent with this, we did not observe an increase in adiponectin, an insulin-sensitizing adipokine inversely associated with visceral adipose tissue mass in T2D (30). Indeed, our findings are consistent with recent experimental castration studies in men: Finkelstein et al. (31) showed that testosterone add-back prevents gain of subcutaneous but not of visceral fat, although effects on glucose metabolism were not reported. Juang et al. (32) provided evidence, using insulin clamps, that testosterone add-back prevents gain of total fat mass, but does not improve insulin sensitivity, although effects on regional fat mass were not reported. Effects on adiponectin were not measured in either study.

Lack of compliance can be excluded for the negative outcome of the trial because the study drug was administered by intramuscular injection. Failure to achieve adequate testosterone levels with treatment is also unlikely, given an average increase of 5.9 nmol/L (170 ng/L) in circulating trough TT levels and the suppression of trough LH levels in testosterone-treated men (Supplementary Fig. 2). In addition, a robust increase in HCT and PSA levels was observed (Supplementary Fig. 3).

Statistically, it appears also unlikely that the trial may have missed a meaningful testosterone-related improvement in glucose metabolism. The CIs of our analyses make it unlikely ($<$2.5%) that there was an effect of a $>$0.31 decrease in HOMA-IR or an effect of a $>$0.0 decrease in $HbA_{1c}$. Indeed, the CI for $HBA_{1c}$ was favoring placebo, suggesting that the $HbA_{1c}$ may actually have deteriorated slightly in the testosterone-treated group ($P$ = 0.05).

It should be noted that men in the placebo group had a higher body weight compared with men in the testosterone group ($P$ = 0.04), while measures of total, subcutaneous, and visceral abdominal fat mass as well as percent fat and lean mass were not different between groups. In addition, statistical analyses were adjusted for all baseline differences by putting the respective baseline values as a covariate in the mixed model.

Another important variable, change of antidiabetic medication, was closely monitored and resulted in exclusion. Indeed, of the 13 participants who did not complete the trial, 8 were discontinued because intensification of oral hypoglycemic agents or commencement of insulin therapy, which constituted predefined protocol violations.

Consistent with a previous meta-analysis (33), changes in lipid levels or BP, arguably more important cardiovascular risk factors than glycemia, were minor or nonsignificant in this RCT (Table 3).

An increase in hematocrit was the most frequent adverse effect of testosterone therapy, and a significant proportion (6.6%) of men experienced transient increases above 54%, the recommended threshold for testosterone therapy cessation (28). This marked stimulatory effect of testosterone on erythropoiesis is likely because of the older age of our participants, as testosterone has a more pronounced effect on erythropoiesis in older compared with young men (34). Testosterone therapy increased PSA (Table 3) but was not associated with prostate-associated serious adverse events.

Previous RCTs of testosterone therapy in men with diabetes or the metabolic syndrome, summarized in Supplementary Table 1, yielded inconsistent outcomes (20,35–37). The largest RCT, although unpublished, in 180 men with T2D did not report any significant changes in HOMA-IR or $HbA_{1c}$ (accessed at http://www.solvaypharmaceuticals.com/static/wma/pdf/1/3/4/4/2/S176.2.101.pdf). However, limited information regarding this unpublished trial is available, and baseline and on-treatment testosterone levels were not reported. A 12-month RCT of 220 men, 62% of whom had T2D, showed a 15% reduction of HOMA-IR at 6 months with no change in total body fat (37). However, this was measured by bioelectrical impedance, which is less accurate than DXA and abdominal MRI scanning used in our study. After 6 months, adjustments to antiglycemic mediations were allowed, and the improvement in HOMA-IR was maintained until study end (37). Testosterone treatment improved $HbA_{1c}$ at 9 months ($P$ = 0.035), but not at 6 or 12 months. Dropout rates were 29% at 6 months and 46% at 12 months (37). A 30-week RCT of testosterone therapy conducted in 184 men with the metabolic syndrome, 56 of whom had T2D, showed a 31% improvement in HOMA-IR with testosterone treatment, in association with significant weight loss ($-$4.3 kg), although changes in body composition were not assessed (36). The findings in these RCTs are consistent with the possibility that testosterone treatment may have more favorable effects on glucose metabolism in men without established diabetes.

Strengths of our study, compared with the previous RCTs in this population (Supplementary Table 1), include exclusive focus on men with established T2D, the long duration of testosterone treatment, a low dropout rate, and, importantly, the rigorous enforcement of changes in antidiabetic medications as a criterion for withdrawal from the trial. While, similar to previous RCTs, we did not use clamp studies, we assessed glucose metabolism by two different methods that have reasonably good agreement with clamp studies (17,38,39). Importantly, in contrast to previous trials, we rigorously evaluated changes in body composition and assessed the effects of testosterone treatment on abdominal adipose tissue compartments. Indeed, our observation that testosterone treatment did not decrease visceral adipose tissue or increase adiponectin levels provides novel insights into the paradox that testosterone treatment did not improve glucose metabolism, despite metabolically favorable effects on total fat mass (decrease) and lean mass (increase). Given that visceral adipose tissue and adiponectin contribute to cardiovascular risk, the cardiovascular implications of our findings require further study, especially in the light of recent evidence, although controversial, that testosterone treatment may increase cardiovascular events (40).

In conclusion, in this RCT of men with moderately well-controlled diabetes and modest reductions in testosterone levels typical of the majority of men with T2D, testosterone therapy did not improve glucose metabolism. Indications for testosterone therapy in such men should be no different than men without T2D and be reserved for patients with clinically significant symptoms with persistently low testosterone (28,29). Testosterone therapy should not be routinely given to such men until a favorable risk-to-benefit ratio is confirmed by well-conducted clinical

trials. Instead, the first response should focus on the optimization of lifestyle measures and use of established therapies with high-level evidence of outcome benefit.

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## References

1. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 2004;89:5462–5468
2. Kapoor D, Aldred H, Clark S, Channer KS, Jones TH. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. Diabetes Care 2007;30:911–917
3. Grossmann M, Thomas MC, Panagiotopoulos S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab 2008; 93:1834–1840
4. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2006;295:1288–1299
5. Dhindsa S, Miller MG, McWhirter CL, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 2010; 33:1186–1192
6. Grossmann M, Gianatti EJ, Zajac JD. Testosterone and type 2 diabetes. Curr Opin Endocrinol Diabetes Obes 2010;17:247–256
7. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology 2003;144:5081–5088
8. Hamilton EJ, Gianatti E, Strauss BJ, et al. Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. Clin Endocrinol (Oxf) 2011;74:377–383
9. 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;63:280–293
10. Laaksonen DE, Niskanen L, Punnonen K, et al. The metabolic syndrome and smoking in relation to hypogonadism in middle-aged men: a prospective cohort study. J Clin Endocrinol Metab 2005;90:712–719
11. Travison TG, Araujo AB, Kupelian V, O'Donnell AB, McKinlay JB. The relative contributions of aging, health, and lifestyle factors to serum testosterone decline in men. J Clin Endocrinol Metab 2007;92:549–555
12. Wu FC, Tajar A, Pye SR, et al.; European Male Aging Study Group. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. J Clin Endocrinol Metab 2008;93:2737–2745
13. Grossmann M. Low testosterone in men with type 2 diabetes: significance and treatment. J Clin Endocrinol Metab 2011;96:2341–2353
14. Camacho EM, Huhtaniemi IT, O'Neill TW, et al.; EMAS Group. 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;168:445–455
15. Corona G, Rastrelli G, Monami M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol 2013;168:829–843
16. Spitzer M, Huang G, Basaria S, Travison TG, Bhasin S. Risks and benefits of testosterone therapy in older men. Nat Rev Endocrinol 2013;9:414–424
17. Harwood DT, Handelsman DJ. Development and validation of a sensitive liquid chromatography-tandem mass spectrometry assay to simultaneously measure androgens and estrogens in serum without derivatization. Clin Chim Acta 2009;409:78–84
18. Mari A, Pacini G, Murphy E, Ludvik B, Nolan JJ. A model-based method for assessing insulin sensitivity from the oral glucose tolerance test. Diabetes Care 2001;24:539–548
19. Chan DC, Watts GF, Ng TW, et al. Adiponectin and other adipocytokines as predictors of markers of triglyceride-rich lipoprotein metabolism. Clin Chem 2005;51:578–585
20. Kapoor D, Goodwin E, Channer KS, Jones TH. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 2006;154:899–906
21. R Core Team. R: A language and environment for statistical computing [Internet], 2013. Available from http://wwwR-projectorg/. Accessed 30 March 2014
22. Bates D, Maechler M, Bolker M. lme4: Linear mixed-effects models using S4 classes. R package version 0.999999-2 [Internet], 2013. Available from http://CRANR-projectorg/ package=lme4. Accessed 30 March 2014
23. Dandona P, Dhindsa S. Update: Hypogonadotropic hypogonadism in type 2 diabetes and obesity. J Clin Endocrinol Metab 2011;96:2643–2651
24. Tajar A, Huhtaniemi IT, O'Neill TW, et al.; EMAS Group. Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). J Clin Endocrinol Metab 2012;97:1508–1516
25. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006;91:4335–4343
26. Singh AB, Hsia S, Alaupovic P, et al. The effects of varying doses of T on insulin sensitivity, plasma lipids, apolipoproteins, and C-reactive protein in healthy young men. J Clin Endocrinol Metab 2002;87:136–143
27. Corona G, Monami M, Rastrelli G, et al. Type 2 diabetes mellitus and testosterone: a meta-analysis study. Int J Androl 2011;34: 528–540
28. Bhasin S, Cunningham GR, Hayes FJ, et al.; Task Force, Endocrine Society. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2010;95: 2536–2559
29. Rana K, Fam BC, Clarke MV, Pang TP, Zajac JD, MacLean HE. Increased adiposity in DNA binding-dependent androgen receptor knockout male mice associated with decreased voluntary activity and not insulin resistance. Am J Physiol Endocrinol Metab 2011;301:E767–E778
30. Okauchi Y, Kishida K, Funahashi T, et al. Changes in serum adiponectin concentrations correlate with changes in BMI, waist circumference, and estimated visceral fat area in middle-aged general population. Diabetes Care 2009; 32:e122
31. Finkelstein JS, Lee H, Burnett-Bowie SA, et al. Gonadal steroids and body composition, strength, and sexual function in men. N Engl J Med 2013;369:1011–1022
32. Juang PS, Peng S, Allehmazedeh K, Shah A, Coviello AD, Herbst KL. Testosterone with Dutasteride, but Not Anastrazole, Improves Insulin Sensitivity in Young Obese Men: A Randomized Controlled Trial. J Sex Med 2014;11:563–573
33. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560–2575
34. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab 2008; 93:914–919
35. Gopal RA, Bothra N, Acharya SV, et al. Treatment of hypogonadism with testosterone in patients with type 2 diabetes mellitus. Endocr Pract 2010;16:570–576
36. Kalinchenko SY, Tishova YA, Mskhalaya GJ, Gooren LJ, Giltay EJ, Saad F. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in

hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf) 2010;73:602–612
37. Jones TH, Arver S, Behre HM, et al.; TIMES2 Investigators. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 2011;34:828–837
38. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487–1495
39. Matsuda M, DeFronzo RA. Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 1999;22:1462–1470
40. Anawalt BD. Is men's health just a single letter? J Clin Endocrinol Metab 2014;99:70–72