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Effect of Testosterone on Progression From Prediabetes to Diabetes in Men With Hypogonadism

A Substudy of the TRAVERSE Randomized Clinical Trial

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IMPORTANCE The effect of testosterone replacement therapy (TRT) in men with hypogonadism on the risk of progression from prediabetes to diabetes or of inducing glycemic remission in those with diabetes is unknown.

OBJECTIVE To evaluate the efficacy of TRT in preventing progression from prediabetes to diabetes in men with hypogonadism who had prediabetes and in inducing glycemic remission in those with diabetes.

DESIGN, SETTING, AND PARTICIPANTS This nested substudy, an intention-to-treat analysis, within a placebo-controlled randomized clinical trial (Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men [TRAVERSE]) was conducted at 316 trial sites in the US. Participants included men aged 45 to 80 years with hypogonadism and prediabetes or diabetes who were enrolled in TRAVERSE between May 23, 2018, and February 1, 2022.

INTERVENTION Participants were randomized 1:1 to receive 1.62% testosterone gel or placebo gel until study completion.

MAIN OUTCOMES AND MEASURES The primary end point was the risk of progression from prediabetes to diabetes, analyzed using repeated-measures log-binomial regression. The secondary end point was the risk of glycemic remission (hemoglobin A_{1c} level <6.5% [to convert to proportion of total hemoglobin, multiply by 0.01] or 2 fasting glucose measurements <126 mg/dL [to convert to mmol/L, multiply by 0.0555] without diabetes medication) in men who had diabetes.

RESULTS Of 5204 randomized participants, 1175 with prediabetes (mean [SD] age, 63.8 [8.1] years) and 3880 with diabetes (mean [SD] age, 63.2 [7.8] years) were included in this study. Mean (SD) hemoglobin A_{1c} level in men with prediabetes was 5.8% (0.4%). Risk of progression to diabetes did not differ significantly between testosterone and placebo groups: 4 of 598 (0.7%) vs 8 of 562 (1.4%) at 6 months, 45 of 575 (7.8%) vs 57 of 533 (10.7%) at 12 months, 50 of 494 (10.1%) vs 67 of 460 (14.6%) at 24 months, 46 of 359 (12.8%) vs 52 of 330 (15.8%) at 36 months, and 22 of 164 (13.4%) vs 19 of 121 (15.7%) at 48 months (omnibus test $P = .49$). The proportions of participants with diabetes who experienced glycemic remission and the changes in glucose and hemoglobin A_{1c} levels were similar in testosterone- and placebo-treated men with prediabetes or diabetes.

CONCLUSIONS AND RELEVANCE In men with hypogonadism and prediabetes, the incidence of progression from prediabetes to diabetes did not differ significantly between testosterone- and placebo-treated men. Testosterone replacement therapy did not improve glycemic control in men with hypogonadism and prediabetes or diabetes. These findings suggest that TRT alone should not be used as a therapeutic intervention to prevent or treat diabetes in men with hypogonadism.

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Visual Abstract
Editor's Note
Supplemental content

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Nearly 35% of adults in the US have prediabetes.[1] Prediabetes is associated with increased risk of progression to type 2 diabetes, cardiovascular disease (CVD), chronic kidney disease, and all-cause mortality.[2-6] Low testosterone levels are associated with increased risk of prediabetes and type 2 diabetes in men.[7-12] Experimental or therapeutic induction of testosterone deficiency in men is associated with increased fat mass, insulin resistance, and type 2 diabetes.[13-16]

Testosterone replacement therapy (TRT) in men with hypogonadism reduces whole body and visceral fat mass, increases muscle mass, and improves insulin sensitivity.[17-19] Testosterone-induced increases in muscle mass may secondarily improve metabolic outcomes.[20,21] An uncontrolled registry study reported a decrease in hemoglobin A_{1c} level and a lower rate of progression from prediabetes to diabetes in testosterone-treated men than in a separate group of untreated men with hypogonadism.[22] However, to our knowledge, a randomized clinical trial of the effects of TRT without concurrent lifestyle intervention on the progression from prediabetes to diabetes in middle-aged and older men with hypogonadism has not been conducted. This issue is clinically important because men with prediabetes and diabetes have a high prevalence of hypogonadism,[23,24] and a substantial proportion of men receiving TRT have diabetes or prediabetes. Information on testosterone's efficacy in preventing progression from prediabetes to diabetes or in inducing glycemic remission would be useful to clinicians and men with hypogonadism who are weighing the potential benefits and risks of TRT.

The Testosterone Replacement Therapy for Assessment of Long-Term Vascular Events and Efficacy Response in Hypogonadal Men (TRAVERSE) trial (NCT03518034) evaluated the effect of TRT and placebo on major adverse cardiovascular events (MACE) in men with hypogonadism.[25,26] The TRAVERSE Diabetes Study was a prespecified efficacy study nested within the TRAVERSE trial in which the primary aim was to compare the efficacy of TRT and placebo in preventing progression from prediabetes to diabetes in middle-aged and older men with hypogonadism. We hypothesized that TRT for men with hypogonadism and prediabetes would be associated with a significantly lower rate of progression to diabetes. A secondary aim was to assess the efficacy of TRT in inducing glycemic remission among participants with diabetes at baseline. The study also evaluated the effect of TRT on fasting glucose and hemoglobin A_{1c} levels.

Key Points

Question Does testosterone replacement therapy (TRT) prevent progression from prediabetes to diabetes or induce glycemic remission in middle-aged and older men with hypogonadism?

Findings In this randomized clinical trial of 5204 participants aged 45 to 80 years with hypogonadism and prediabetes (n = 1175) or diabetes (n = 3880), the risk of progression from prediabetes to diabetes did not differ significantly between a group that received TRT and a placebo group and TRT did not improve glycemic control in men with prediabetes or diabetes.

Meaning This study did not provide evidence of TRT's efficacy in preventing progression from prediabetes to diabetes or improving glycemic control in men with hypogonadism.

Methods

This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The TRAVERSE trial's design and MACE results have been previously published.[25,26] This placebo-controlled randomized clinical trial was conducted at 316 sites in the US and, from May 23, 2018, to January 19, 2023, enrolled men aged 45 to 80 years with 2 fasting morning testosterone concentrations less than 300 ng/dL (to convert to nmol/L, multiply by 0.0347) measured using liquid chromatography-tandem mass spectrometry (LC-MS/MS), 1 or more symptoms of hypogonadism, and preexisting CVD or increased risk of CVD.[25] Men with contraindications for TRT, such as erythrocytosis, history of prostate cancer, or severe lower urinary tract symptoms, were excluded.[25] The trial protocol (Supplement 1) was approved by the participating national and local institutional review boards for human participant research. All participants provided written informed consent. A data and safety monitoring committee reviewed unblinded safety data every 6 months. TRAVERSE site investigators are listed in the eAppendix in Supplement 2.

The protocol for the parent TRAVERSE trial has been previously published.[25] The Diabetes Substudy protocol and statistical analysis plan are included in Supplement 1. The TRAVERSE Diabetes Study was nested within the parent TRAVERSE trial and included 2 subpopulations: those with prediabetes or diabetes at baseline. The participants included in the diabetes substudy met the eligibility criteria for the parent trial. In addition, randomized participants included in the analysis of progression from prediabetes to diabetes had prediabetes defined by a hemoglobin A_{1c} level between 5.7% and 6.4% (to convert to proportion of total hemoglobin, multiply by 0.01) or 1 or more fasting glucose level measurement between 100 and 125 mg/dL (to convert to mmol/L, multiply by 0.0555). Secondary analyses of glycemic remission of diabetes included all randomized participants with diabetes at baseline, defined by a hemoglobin A_{1c} level greater than or equal to 6.5% or 2 fasting glucose level measurements greater than 125 mg/dL before randomization, current diagnosis of diabetes, or current use of diabetes medication.

Fasting plasma glucose in samples collected in tubes containing sodium fluoride) and hemoglobin A_{1c} (assayed using ion exchange high-pressure liquid chromatography) levels at baseline and during months 6, 12, 24, 36, and 48 and at the end of study were measured by LabCorp, Inc. Serum testosterone, dihydrotestosterone, and estradiol levels were measured by LabCorp, Inc, using LC-MS/MS methods certified by the Hormone Standardization Program of the Centers for Disease Control and Prevention.

Race and ethnicity were ascertained by self-report. Race categories included Black or African American, White, and other (American Indian or Alaska Native, Asian, Native Hawaiian, Pacific Islander, and multiracial). Ethnicity categories were Hispanic or Latino and not Hispanic or Latino.

Intervention and Randomization

Patients were randomized 1:1 to receive 1.62% testosterone gel or placebo gel until study completion. Patients were randomized in a 1:1 ratio with stratification for preexisting cardiovascular disease using Interactive Response Technology to receive 1.62% testosterone gel or matching placebo gel until study completion. The participant, the study staff, and those assessing outcomes were blinded. As described previously,[26] testosterone dose was titrated centrally based on serum on-treatment testosterone levels and hematocrit to maintain serum on-treatment testosterone levels between 350 and 750 ng/dL.

Study Outcomes

The primary end point of the TRAVERSE Diabetes Study was the risk of progression from prediabetes to diabetes (defined as hemoglobin A_{1c} level ≥6.5%, initiation of diabetes medication, or 2 consecutive fasting glucose level measurements >125 mg/dL) assessed at all available postrandomization time points in participants with prediabetes at baseline. A secondary end point was the risk of glycemic remission in participants with diabetes at baseline, defined as hemoglobin A_{1c} level less than 6.5% or 2 consecutive fasting glucose level measurements less than 126 mg/dL without current use of antidiabetic medications. Additionally, changes from baseline in fasting glucose and hemoglobin A_{1c} levels were evaluated separately in men who had prediabetes or diabetes.

Statistical Analyses

End-of-study assessments were completed on January 19, 2023. The intention-to-treat analysis of the primary efficacy end point, progression from prediabetes to diabetes, included all randomized participants (full analysis set) who had prediabetes at baseline (statistical analysis plan in Supplement 1). The risk ratio of progression to diabetes in the TRT vs placebo group was estimated by repeated-measures log-binomial generalized estimating equations regression with fixed effects for treatment, visit, treatment-visit interaction, and preexisting CVD and an unstructured working correlation matrix (or compound symmetric where explicitly stated) to account for repeated measures at multiple visits. The estimates of the relative risk associated with TRT compared with placebo, 95% CIs, and an associated generalized score statistic *P* value testing the null hypothesis of no difference between the TRT and placebo groups across all time points were derived from the model.

The risk ratio of glycemic remission associated with TRT compared with placebo was estimated using a model similar to that used for the primary analysis. Analyses for change from baseline in glucose level, hemoglobin A_{1c} level, body weight, and sex hormones used a linear mixed-effects model controlling for baseline value and preexisting CVD, assuming an unstructured covariance matrix. Sensitivity analyses estimated the intervention effect on progression to diabetes and glycemic remission using a discrete-time proportional hazards regression model[27] with event-time intervals based on scheduled visits. Supportive analyses in which follow-up time was censored at 30 and 365 days after the last dose of study medication were also performed.

Subgroup analysis by race was performed because racial differences in body weight and composition, diet, and insulin sensitivity are associated with glycemic response.[28] As genetic variants are associated with hemoglobin A_{1c} levels,[29,30] especially in Black individuals in the US,[30] prespecified analyses using discrete-time proportional hazards regression models were performed in participants who self-identified as Black or African American and in whom prediabetes was defined by 2 fasting glucose level measurements between 100 and 125 mg/dL and diabetes was defined by 2 consecutive fasting glucose level measurements greater than 125 mg/dL, current diagnosis of diabetes, or current use of antidiabetic medications. Glycemic remission in participants with diabetes by this modified definition was defined by 2 consecutive fasting glucose level measurements less than 126 mg/dL without current use of antidiabetic medications.

The sample size in the TRAVERSE trial was guided by estimated numbers of MACE, and sample size in the diabetes substudy was defined by the number of randomized participants who had prediabetes or diabetes at baseline. It was estimated that a sample size of 6000 men in the parent trial would provide 90% power to detect a 25% difference in the incidence of progression from prediabetes to diabetes.[26]

Data analyses were conducted in SAS, version 9.4 (SAS Institute Inc) and R, version 4.2.1 (R Foundation for Statistical Computing). Two-sided $P < .05$ was considered significant. No adjustments in *P* values or 95% CIs were made for multiplicity.

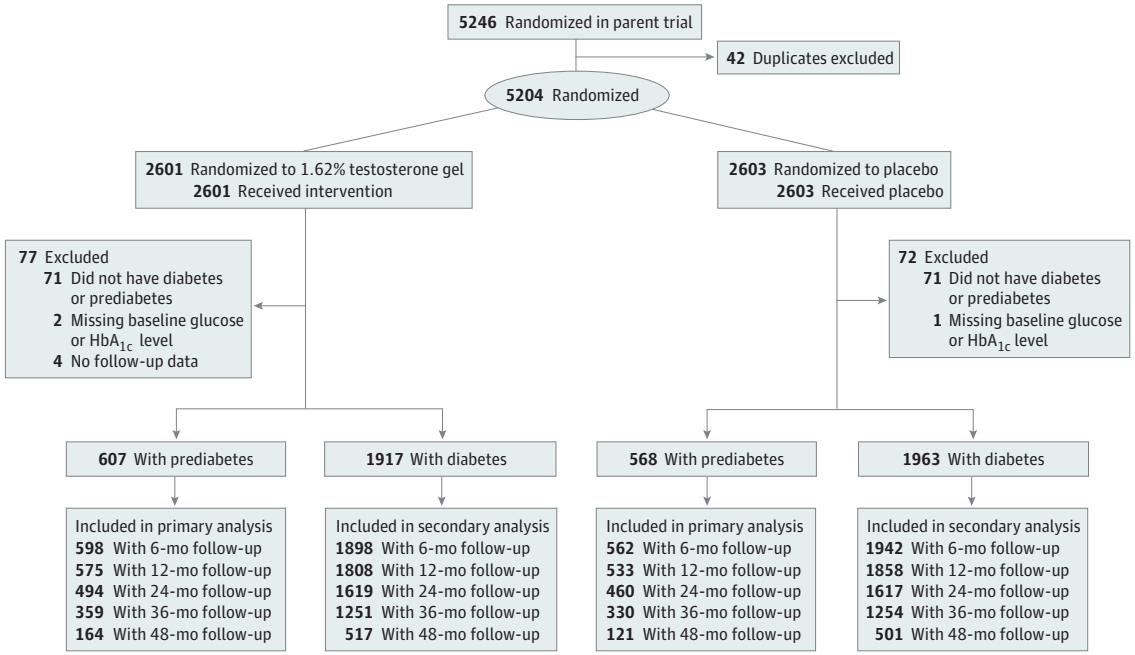
Results

A total of 5246 individuals were randomized in the TRAVERSE trial.[26] After exclusion of 42 participants with identification numbers attributed to duplicate enrollment, the full analysis set for the present study included 5204 participants, of whom 2601 were in the TRT group and 2603 in the placebo group. Among these participants, 1175 had prediabetes (607 randomized to testosterone and 568 randomized to placebo) (**Figure 1**) and 3880 had diabetes (1917 randomized to testosterone and 1963 randomized to placebo).

Baseline characteristics were similar between the testosterone- and placebo-treated men who had prediabetes or diabetes (**Table**). Mean (SD) age of participants with prediabetes was 63.8 (8.1) years, mean (SD) fasting glucose level was 109.4 (13.8) mg/dL, and mean (SD) hemoglobin A_{1c} level was 5.8% (0.4%). Mean (SD) age of participants with diabetes was 63.2 (7.8) years, mean (SD) fasting glucose level was 164.5 (60.3) mg/dL, and mean (SD) hemoglobin A_{1c} level was 7.6% (1.3%). Of the 5204 total participants, 877 (16.9%) were Black or African American; 848 (16.3%), Hispanic or Latino; 4353 (83.6%), not Hispanic or Latino; 4154 (79.8%), White; and 173 (3.3%), other race. The frequency of use of various diabetes medications was similar between the TRT and placebo groups.

Of 1175 participants with prediabetes, 1160 (98.7%) were followed up for at least 6 months, 1108 (94.3%) for 1 year, 954 (81.2%) for 2 years, 689 (58.6%) for 3 years, and 285 (24.3%) for 4 years (Figure 1). The mean (SD) follow-up duration was 32.1 (12.2) months and 31.5 (12.4) months in the TRT and placebo groups, respectively. Of 3880 participants with diabe-

Figure 1. CONSORT Diagram Showing the Flow of Study Participants Through Different Phases of the Study



All participants who were classified as having prediabetes or diabetes at baseline and who had at least 1 postbaseline value were included in the analyses. Because this was an event-driven trial, the randomized participants were followed up until accrual of at least 256 major adverse cardiovascular events. Thus, the follow-up duration varied for different participants. HbA_{1c} indicates hemoglobin A_{1c}.

tes, 3840 (99.0%) were followed up for at least 6 months, 3666 (94.5%) for 1 year, 3326 (83.4%) for 2 years, 2505 (64.6%) for 3 years, and 1018 (26.2%) for 4 years; mean (SD) follow-up duration was 33.5 (11.9) months and 33.3 (11.9) months in the TRT and placebo groups, respectively.

Progression From Prediabetes to Diabetes

The relative risk of progression from prediabetes to diabetes did not differ significantly between testosterone and placebo groups: 4 of 598 (0.7%) vs 8 of 562 (1.4%) at 6 months, 45 of 575 (7.8%) vs 57 of 533 (10.7%) at 12 months, 50 of 494 (10.1%) vs 67 of 460 (14.6%) at 24 months, 46 of 359 (12.8%) vs 52 of 330 (15.8%) at 36 months, and 22 of 164 (13.4%) vs 19 of 121 (15.7%) at 48 months (omnibus test $P = .49$ after adjusting for preexisting CVD) (**Figure 2**). Supportive analyses using the discrete-time proportional hazards regression model showed similar results (hazard ratio [HR], 0.78; 95% CI, 0.58-1.06).

Glycemic Remission Among Those With Diabetes

The risk of glycemic remission among participants with diabetes at baseline did not differ significantly between the testosterone and placebo groups: 7 of 1898 (0.4%) vs 5 of 1942 (0.3%) at 6 months, 78 of 1808 (4.3%) vs 74 of 1858 (4.0%) at 12 months, 82 of 1619 (5.1%) vs 70 of 1617 (4.3%) at 24 months, 64 of 1251 (5.1%) vs 61 of 1254 (4.9%) at 36 months, and 24 of 517 (4.6%) vs 23 of 501 (4.6%) at 48 months (omnibus test $P = .95$ after adjusting for preexisting CVD) (**Figure 3**). The discrete-time proportional hazards regression model showed similar results (HR, 1.15; 95% CI, 0.87-1.53).

Fasting Glucose and Hemoglobin A_{1c} Levels and Prespecified Subgroup Analyses

The change from baseline in fasting glucose or hemoglobin A_{1c} (**Figure 4**) concentrations did not differ between testosterone and placebo groups in participants with either prediabetes or diabetes at baseline. The findings of prespecified subgroup analyses by baseline testosterone level (<250 or ≥250 ng/dL), preexisting CVD (yes or no), self-identified race (Black or African-American or White), and age (<65 or ≥65 years) did not show significant differences between testosterone and placebo groups for either progression from prediabetes to diabetes or glycemic remission (eFigures 1 and 2 in Supplement 2).

Sensitivity Analyses

Of the 877 randomized participants self-identifying as Black or African American, 178 were classified as having prediabetes and 682 as having diabetes at baseline by the standard definition; by the modified definition that did not consider hemoglobin A_{1c} level, 168 had prediabetes and 660 had diabetes. The discrete-time proportional hazards regression model of progression from prediabetes to diabetes (HR, 2.47; 95% CI, 0.48-12.76) and glycemic remission (HR, 2.71; 95% CI, 1.07-6.87) using the modified definitions of prediabetes and diabetes yielded results similar to those using the standard definition.

Post hoc sensitivity analyses of the primary and secondary events occurring within 30 days or within 365 days after stopping treatment yielded results similar to the those of the primary analyses (eFigures 3 and 4 in Supplement 2). In men

Table. Baseline Characteristics of Study Participants in the Full Analysis Set and of Randomized Participants With Diabetes or Prediabetes[a]

Variable	Overall participants		Participants with diabetes		Participants with prediabetes	
	TRT (n = 2601)	Placebo (n = 2603)	TRT (n = 1917)	Placebo (n = 1963)	TRT (n = 607)	Placebo (n = 568)
Age, mean (SD), y	63.3 (7.9)	63.3 (7.9)	63.2 (7.8)	63.2 (7.8)	64.1 (8.1)	63.5 (8.0)
Age group, y						
45 to <65	1360 (52.3)	1392 (53.5)	1023 (53.4)	1077 (54.9)	292 (48.1)	279 (49.1)
≥65	1241 (47.7)	1211 (46.5)	894 (46.6)	886 (45.1)	315 (51.9)	289 (50.9)
Race						
Black or African American	445 (17.1)	432 (16.6)	346 (18.0)	336 (17.1)	89 (14.7)	89 (15.7)
White	2070 (79.6)	2084 (80.1)	1501 (78.3)	1555 (79.2)	504 (83.0)	467 (82.2)
Other[b]	86 (3.3)	87 (3.3)	70 (3.7)	72 (3.7)	14 (2.3)	12 (2.1)
Ethnicity						
Hispanic or Latino	409 (15.7)	439 (16.9)	316 (16.5)	333 (17.0)	77 (12.7)	93 (16.4)
Not Hispanic or Latino	2191 (84.3)	2162 (83.1)	1600 (83.5)	1629 (83.0)	530 (87.3)	474 (83.6)
Missing	1 (<0.1)	2 (<0.1)	1 (<0.1)	1 (<0.1)	0	1 (0.2)
Body mass index, mean (SD)[c]	35.0 (5.7)	34.8 (6.0)	35.4 (5.6)	35.2 (5.9)	34.0 (5.7)	34.1 (5.9)
Preexisting CVD	1410 (54.2)	1437 (55.2)	978 (51.0)	1038 (52.9)	386 (63.6)	352 (62.0)
CVD risk factors	1191 (45.8)	1166 (44.8)	939 (49.0)	925 (47.1)	221 (36.4)	216 (38.0)
Prior testosterone use	5 (0.2)	10 (0.4)	4 (0.2)	7 (0.4)	1 (0.2)	2 (0.4)
Hypertension	2423 (93.2)	2402 (92.3)	1811 (94.5)	1835 (93.5)	545 (89.8)	504 (88.7)
Dyslipidemia	2344 (90.1)	2332 (89.6)	1752 (91.4)	1793 (91.3)	527 (86.8)	482 (84.9)
Aspirin use	1570 (60.4)	1546 (59.4)	1170 (61.0)	1180 (60.1)	360 (59.3)	325 (57.2)
Metformin use	1346 (51.7)	1348 (51.8)	1345 (70.2)	1348 (68.7)	0	0
Systolic blood pressure, mean (SD), mm Hg[d]	132.8 (15.9)	132.5 (15.4)	133.2 (15.7)	133.0 (15.7)	131.7 (16.1)	131.1 (14.3)
Diastolic blood pressure, mean (SD), mm Hg[d]	79.1 (9.7)	79.3 (9.6)	78.6 (9.6)	79.1 (9.6)	80.2 (9.7)	79.8 (9.6)
Testosterone level, mean (SD), ng/dL[d]	220.5 (47.0)	220.1 (48.1)	219.3 (47.2)	219.1 (47.8)	223.0 (46.6)	222.8 (48.8)
Dihydrotestosterone level, mean (SD), ng/dL[e]	16.1 (7.9)	16.3 (8.5)	15.2 (7.5)	15.4 (8.1)	18.3 (8.1)	18.8 (9.4)
Estradiol level, mean (SD), pg/mL[f]	21.0 (8.2)	21.0 (8.4)	21.3 (8.1)	21.1 (8.2)	20.4 (8.6)	20.6 (8.7)
Hemoglobin A_{1c} level, mean (SD), %[g]	7.1 (1.4)	7.2 (1.4)	7.6 (1.3)	7.6 (1.4)	5.8 (0.4)	5.8 (0.3)
Fasting glucose level, mean (SD), mg/dL[h]	149.7 (57.5)	150.4 (58.6)	164.4 (59.9)	164.5 (60.7)	110.9 (13.6)	108.8 (14.0)
Diabetes medication						
Any	1699 (65.3)	1735 (66.7)	1698 (88.6)	1735 (88.4)	0	0
Metformin	1346 (51.7)	1348 (51.8)	1345 (70.2)	1348 (68.7)	0	0
Any GLP-1 agonist	275 (10.6)	306 (11.8)	274 (14.3)	306 (15.6)	0	0
Any SGLT-2 inhibitor	265 (10.2)	296 (11.4)	265 (13.8)	296 (15.1)	0	0
Other	244 (9.4)	259 (10.0)	244 (12.7)	259 (13.2)	0	0

Abbreviations: CVD, cardiovascular disease; GLP-1, glucagon-like peptide 1; SGLT-2, sodium-glucose transporter 2; TRT, testosterone replacement therapy.

SI conversion factors: To convert dihydrotestosterone to nmol/L, multiply by 0.0344; estradiol to pmol/L, multiply by 3.671; glucose to mmol/L, multiply by 0.0555; hemoglobin A_{1c} to proportion of hemoglobin, multiply by 0.01; and testosterone to nmol/L, multiply by 0.0347.

[a] Data are presented as number (percentage) of participants unless otherwise indicated.

[b] Other includes American Indian or Alaska Native, Asian, Native Hawaiian, Pacific Islander, or multiracial.

[c] Calculated as weight in kilograms divided by height in meters squared. In the overall TRT group, n = 2595; overall placebo, n = 2602; and diabetes TRT, n = 1916.

[d] In the overall TRT group, n = 2596, and overall placebo, n = 2602.

[e] In the overall TRT group, n = 2487; overall placebo, n = 2498; diabetes TRT, n = 1838; diabetes placebo, n = 1880; prediabetes TRT, n = 582; and prediabetes placebo, n = 551.

[f] In the overall TRT group, n = 2470; overall placebo, n = 2494; diabetes TRT, n = 1822; diabetes placebo, n = 1879; prediabetes TRT, n = 582; and prediabetes placebo, n = 547.

[g] In the overall TRT group, n = 2586; overall placebo, n = 2599; diabetes TRT, n = 1911; diabetes placebo, n = 1961; prediabetes TRT, n = 604; and prediabetes placebo, n = 567.

[h] In the overall TRT group, n = 2590; overall placebo, n = 2593; diabetes TRT, n = 1912; and diabetes placebo, n = 1955.

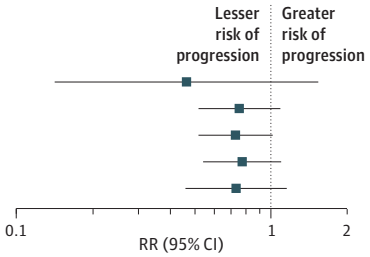
with prediabetes and diabetes at baseline, body weight decreased significantly more in the TRT group than in the placebo group (eTable 1 in Supplement 2).

Hormone Levels and Safety

Serum total testosterone, dihydrotestosterone, and estradiol concentrations increased significantly more in the testosterone-treated men than in the placebo-treated men with prediabetes or diabetes (eTable 2 in Supplement 2). Testosterone replacement therapy was associated with higher incidence of venous thromboembolism, atrial fibrillation, and acute kidney injury in the parent trial,[26] but there did not appear to be any additional between-group differences by diabetes or prediabetes status (eTable 3 in Supplement 2).

Figure 2. Progression From Prediabetes to Diabetes Among Participants Who Had Prediabetes at Baseline

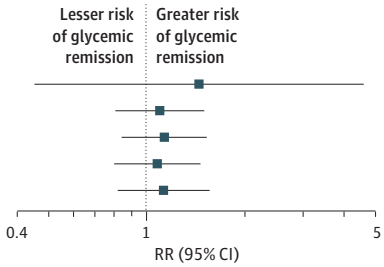
Month	Participants with events, No./total No. (%) TRT	Placebo	RR (95% CI)
6	4/598 (0.7)	8/562 (1.4)	0.47 (0.14-1.55)
12	45/575 (7.8)	57/533 (10.7)	0.76 (0.52-1.10)
24	50/494 (10.1)	67/460 (14.6)	0.73 (0.52-1.02)
36	46/359 (12.8)	52/330 (15.8)	0.78 (0.55-1.11)
48	22/164 (13.4)	19/121 (15.7)	0.74 (0.46-1.16)



The risk ratio of progression to diabetes in the testosterone replacement therapy (TRT) vs placebo group was estimated by repeated-measures log-binomial generalized estimating equations regression with fixed effects for treatment, visit, treatment-visit interaction, and preexisting cardiovascular disease and an unstructured correlation matrix to account for repeated measures. A simpler compound symmetric matrix was used due to the algorithm's inability to estimate the covariance function needed for the omnibus test when an unstructured matrix was assumed. The omnibus test *P* value was .49 for a test of the null hypothesis of no difference between TRT and placebo groups across all time points. RR indicates relative risk.

Figure 3. Glycemic Remission Among Men Who Had Diabetes at Baseline by Treatment Group and Time Point

Month	Participants with events, No./total No. (%) TRT	Placebo	RR (95% CI)
6	7/1898 (0.4)	5/1942 (0.3)	1.44 (0.46-4.53)
12	78/1808 (4.3)	74/1858 (4.0)	1.10 (0.80-1.49)
24	82/1619 (5.1)	70/1617 (4.3)	1.13 (0.84-1.52)
36	64/1251 (5.1)	61/1254 (4.9)	1.08 (0.80-1.46)
48	24/517 (4.6)	23/501 (4.6)	1.13 (0.82-1.55)



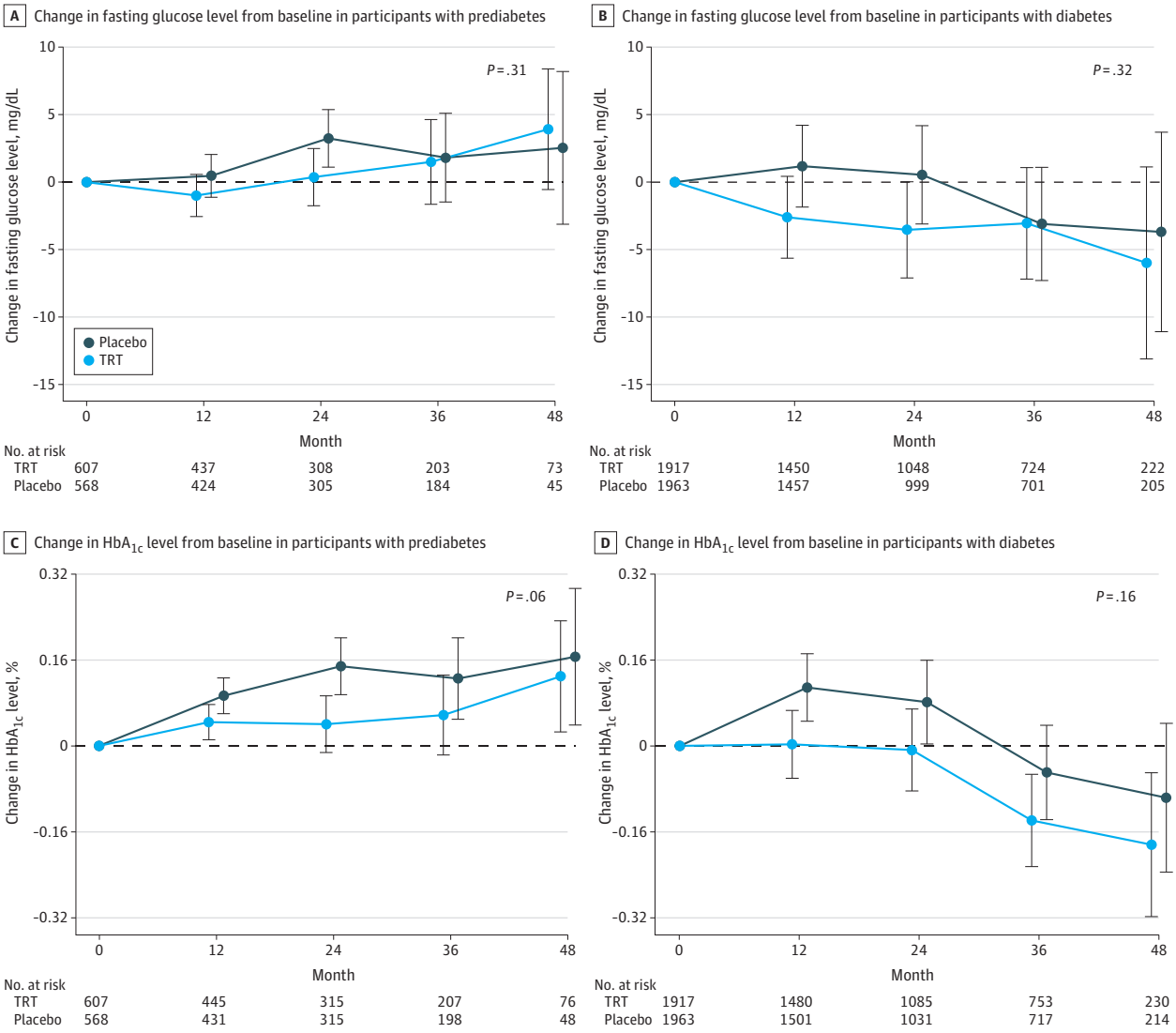
The risk of glycemic remission in the testosterone replacement therapy (TRT) vs placebo group was estimated by repeated-measures log-binomial generalized estimating equations regression with fixed effects for treatment, visit, treatment-visit interaction, and preexisting cardiovascular disease and an unstructured correlation matrix to account for repeated measures. The omnibus test *P* value was .95 for a test of the null hypothesis of no difference between TRT and placebo groups across all time points. RR indicates relative risk.

Discussion

The TRAVERSE Diabetes Study is, to our knowledge, the largest placebo-controlled randomized clinical trial to date to evaluate the efficacy of TRT without a lifestyle intervention in preventing progression from prediabetes to diabetes in men with hypogonadism and in inducing glycemic remission in men with hypogonadism and diabetes. In this study, TRT was not superior to placebo in preventing progression from prediabetes to diabetes; consistent with these findings, fasting glucose and hemoglobin A_{1c} levels did not change significantly in either group and did not differ significantly between the 2 study groups. These findings were further corroborated by sensitivity analyses using discrete-time proportional hazards regression models in which the events were censored 30 and 365 days after the last dose. The risk of glycemic remission also was similar between testosterone- and placebo-treated participants who had diabetes at baseline; between-group differences in the changes in fasting glucose or hemoglobin A_{1c} levels were neither statistically significant nor clinically meaningful, corroborating the findings of no significant effect on glycemic remission. Other, smaller trials of TRT in men with hypogonadism also found no significant improvements in hemoglobin A_{1c} or fasting glucose level.[31,32] The findings of this study suggest that TRT alone should not be used as a therapeutic intervention to prevent or treat diabetes in men with hypogonadism.

Testosterone's known effects on body composition and metabolism would be expected to improve insulin sensitivity and retard progression from prediabetes to diabetes. Testosterone treatment increases skeletal muscle mass, reduces whole body and visceral fat mass,[19,33,34] and modestly improves insulin sensitivity.[31,32] Muscle is an important regulator of metabolism,[35] and testosterone-induced increases in muscle mass might be expected to secondarily improve insulin sensitivity. Induction of severe testosterone deficiency by administration of a gonadotropin-releasing hormone agonist to healthy men or men with prostate cancer or by cessation of TRT in men with hypogonadism is associated with the development of insulin resistance and an increased risk of diabetes.[14-16] However, the present study found no meaningful improvements in either fasting glucose or hemoglobin A_{1c} levels. The TRAVERSE participants had mild to moderate testosterone deficiency; it is possible that greater improvements in insulin sensitivity may be observed in men with severe testosterone deficiency. However, most men with hypogonadism receiving TRT today have mild testosterone deficiency.[36] Testosterone levels during treatment in this study were lower than in some

Figure 4. Estimated Changes From Baseline in Fasting Glucose and Hemoglobin A_{1c} (HbA_{1c}) Levels for Participants Who Had Prediabetes or Diabetes at Baseline



A linear mixed model was fit with fixed effects for treatment, visit, and treatment-visit interaction, baseline value, and preexisting cardiovascular disease and a random per-participant repeated-measures effect with an unstructured covariance matrix. Omnibus test *P* values were derived separately for participants with prediabetes and diabetes from a test of the null hypothesis of no difference between the testosterone replacement therapy (TRT) and placebo groups across all time points. To convert glucose to mmol/L, multiply by 0.0555; and hemoglobin A_{1c} to proportion of hemoglobin, multiply by 0.01. Error bars indicate 95% CIs.

other testosterone trials; testosterone levels in TRAVERSE were measured 24 hours after gel application, and nadir levels are lower than the 24-hour time-averaged concentrations. In the Testosterone for Diabetes Mellitus (T4DM) trial,[37] testosterone treatment plus lifestyle intervention in men with overweight or obesity was associated with a lower incidence of 2-hour glucose level greater than or equal to 200 mg/dL on an oral glucose tolerance test compared with lifestyle intervention alone. However, not all men in the T4DM trial had hypogonadism, and testosterone was administered along with a lifestyle intervention that may have augmented the effects of testosterone on muscle and fat mass.[38,39] Similar to the findings of the current study, the T4DM trial also did not find significant changes in hemoglobin A_{1c} levels.[37]

The TRAVERSE participants were selected on the basis of preexisting or increased risk of CVD and had high rates of prediabetes and diabetes at baseline. Epidemiologic studies, surveys of men receiving TRT, and randomized clinical trials have also found high prevalence of diabetes and prediabetes in men with hypogonadism.[24,40,41]

Lifestyle modification, metformin, acarbose, pioglitazone, and glucagon-like peptide 1 analogs reduce the incidence of progression from prediabetes to diabetes.[42,43] The findings of this study do not support the use of TRT alone to

prevent or to treat diabetes in men with hypogonadism. The trial's findings may be useful in weighing the potential benefits of TRT in middle-aged and older men with hypogonadism who have prediabetes or diabetes.

Strengths and Limitations

The TRAVERSE trial has some notable strengths. The participants were required to have 2 fasting morning testosterone level measurements using an LC-MS/MS assay certified by the Hormone Standardization Program of the Centers for Disease Control and Prevention and 1 or more symptoms of hypogonadism in conformity with the Endocrine Society's guideline.[44] We used fasting glucose and hemoglobin A_{1c} levels to ascertain prediabetes and diabetes; the combined use of fasting glucose and hemoglobin A_{1c} testing has better predictive value than either test alone for progression to diabetes[45] and for assessing glycemic control. It was not deemed to be feasible to perform a 2-hour oral glucose tolerance test given participant burden and cost in the context of a large trial. There is substantial overlap in pathophysiological mechanisms in persons diagnosed with prediabetes or diabetes by any of the 3 tests, although the pathophysiology of hyperglycemia in some individuals diagnosed by oral glucose tolerance test may differ from those diagnosed by fasting glucose or hemoglobin A_{1c} testing.[45,46] Neither fasting glucose nor hemoglobin A_{1c} levels changed significantly with TRT in men with prediabetes or diabetes, supporting the findings of the primary analyses. Factors other than glucose concentrations can influence hemoglobin A_{1c} levels, especially in Black individuals in the US,[30] but sensitivity analyses using only fasting glucose testing confirmed the findings of the primary analyses.

The study has some limitations. The findings should not be extrapolated to men who do not have hypogonadism or to women. The association of testosterone with risk of diabetes is sexually dimorphic,[12] and sex and gender differences in response to testosterone have not been studied. The sample size of the TRAVERSE trial was guided by estimated numbers of MACE, and the sample size of the diabetes substudy was defined by the number of randomized participants who had prediabetes and diabetes at baseline. However, the lack of meaningful change in fasting glucose and hemoglobin A_{1c} levels using more statistically powerful analyses of continuous outcomes supports the findings of the primary and secondary analyses of prespecified binary end points. As reported previously,[26] the incidence of early discontinuation of the trial regimen while continuing trial assessments (61.6%) and early withdrawal from the trial and having no further assessments (39.0%) was relatively high but was similar in the 2 trial groups. These rates were high but not dissimilar from that in real-life clinical practice[47,48] and in randomized clinical trials of other symptomatic conditions.[49-51] Nonretention rates were similar in the 2 groups, and sensitivity analyses of events censored 30 and 365 days after treatment discontinuation yielded similar results.

Conclusions

In middle-aged and older men with hypogonadism and prediabetes in the TRAVERSE Diabetes Study, the incidence of progression from prediabetes to diabetes did not differ significantly between testosterone- and placebo-treated men. Testosterone replacement therapy did not improve glycemic control in men with hypogonadism and prediabetes or diabetes.

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