Testosterone Therapy in Men With Hypogonadism Prevents Progression From Prediabetes to Type 2 Diabetes: Eight-Year Data From a Registry Study

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OBJECTIVE

Type 2 diabetes (T2D) is a public health threat. Prediabetes represents a window of opportunity for intervention to prevent T2D. Men with T2D and prediabetes often have low testosterone. Since testosterone improves glycemic control in T2D, we investigated whether testosterone therapy (TTh) in men with hypogonadism and prediabetes prevents progression to T2D.

RESEARCH DESIGN AND METHODS

Three hundred and sixteen men with prediabetes (defined as HbA_{1c} 5.7–6.4%) and total testosterone levels ≤12.1 nmol/L combined with symptoms of hypogonadism were analyzed. Two hundred and twenty-nine men received parenteral testosterone undecanoate (T-group), and 87 men with hypogonadism served as untreated control subjects. Metabolic and anthropometric parameters were measured twice yearly for 8 years.

RESULTS

HbA_{1c} decreased by 0.39 ± 0.03% ($P < 0.0001$) in the T-group and increased by 0.63 ± 0.1% ($P < 0.0001$) in the untreated group. In the T-group, 90% achieved normal glucose regulation (HbA_{1c} <5.7%). In the untreated group, 40.2% progressed to T2D (HbA_{1c} >6.5%). TTh was also associated with significant improvements in fasting glucose, triglyceride:HDL ratio, triglyceride-glucose index, lipid accumulation product, total cholesterol, LDL, HDL, non-HDL, triglycerides, and Aging Males' Symptoms (AMS) scale. Significant deterioration in all these parameters was seen in the untreated group. Mortality was 7.4% in the T-group and 16.1% in the untreated group ($P < 0.05$). The incidence of nonfatal myocardial infarction was 0.4% in the T-group and 5.7% in the untreated group ($P < 0.005$).

CONCLUSIONS

Long-term TTh completely prevents prediabetes progression to T2D in men with hypogonadism and improves glycemia, lipids, and AMS score. TTh holds tremendous potential for the large and growing population of men with prediabetes and hypogonadism.

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Men with hypogonadism, also known as testosterone deficiency, are at increased risk for developing insulin resistance (IR) and type 2 diabetes (T2D) (1,2). Although the relationship between testosterone levels and T2D may be confounded by intra-abdominal (visceral) fat, other data suggest that testosterone deficiency is associated with T2D independently of BMI, waist circumference (a surrogate of visceral fat), and age (3).

The first report of a markedly increased prevalence of hypogonadotropic hypogonadism in men with T2D, irrespective of glycemic control, duration of disease, and obesity, was published in 2004 (4). In a later study, the prevalence of hypogonadism in lean, overweight, and obese men with T2D was significantly higher than in men without T2D (5). In 2018, the American Diabetes Association added to its *Standards of Medical Care in Diabetes* the recommendation to measure testosterone in men with diabetes and signs and symptoms of hypogonadism (6).

The Rancho Bernardo Study showed that men with impaired fasting glucose or impaired glucose tolerance had lower total testosterone than those with normal glucose tolerance, even after adjusting for age and BMI (7). Several studies have reported that men with impaired fasting glucose or impaired glucose tolerance have biochemical evidence of hypogonadism compared with euglycemic peers (3,8,9). Indeed, men with prediabetes are nearly twice as likely to have low total testosterone levels than men with normoglycemia (odds ratio 1.87 [95% CI 1.38–2.54]), regardless of age and after adjusting for BMI, waist circumference, individual metabolic syndrome components, and the metabolic syndrome as an entity (10). Currently, limited information is available regarding the prevalence of hypogonadism in prediabetes; one study found that 41.5% of men with hypogonadism had prediabetes compared with 13% of men without hypogonadism (9).

The lifetime risk of progression from prediabetes to diabetes is as high as 74.0% (8). The prevention strategy is weight loss (10). The American Association of Clinical Endocrinologists/American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients With Obesity strongly recommend that male patients with overweight, obesity, the metabolic syndrome, or prediabetes should aim for a weight loss goal of 10% to prevent progression to diabetes (11). The Guiding Principles for the Care of People With or at Risk for Diabetes published by the National Diabetes Education Program also endorse a weight loss goal of 10% to prevent diabetes (12).

Since long-term testosterone therapy (TTh) in men with hypogonadism results in a marked and sustained weight loss (13), we hypothesized that men with hypogonadism and prediabetes, defined as glycated hemoglobin (HbA_{1c}) 5.7–6.4% (39–46 mmol/mol) according to the American Diabetes Association, would experience a reduced or slower progression to T2D with TTh. Therefore, in this long-term, real-life observational study with 8 years of follow-up, we examined the effect of TTh on prevention of prediabetes progression to overt T2D.

RESEARCH DESIGN AND METHODS

Patients

Patients in this study were pooled from two ongoing urological registries. Ethical guidelines by the German Medical Association for observational studies in patients receiving standard treatment were followed. After receiving an explanation about the nature and the purpose of the study, all subjects consented to be included in the registry and to have their data analyzed. A total of 316 men had prediabetes, defined as HbA_{1c} 5.7–6.4% (39–46 mmol/mol), and total testosterone levels $\leq$12.1 nmol/L ($\sim$350 ng/dL) combined with symptoms of hypogonadism. Two hundred and twenty-nine men received parenteral testosterone undecanoate (TU) 1,000 mg every 12 weeks after an initial 6-week interval (T-group); 87 men with hypogonadism who opted against TTh served as an untreated (control) group. Anthropometric and metabolic parameters were measured over 8 years as described previously (13,14). Measurements were performed at least twice a year, and 8-year data were analyzed.

Assessment

We measured the following parameters: total testosterone, weight, waist circumference, body weight, hemoglobin, hematocrit, fasting glucose, HbA_{1c}, systolic blood pressure (SBP) and diastolic blood pressure (DBP), heart rate, and lipids (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides). We also calculated the following parameters: BMI, non-HDL, triglyceride:HDL ratio, triglyceride-glucose (TyG) index, and lipid accumulation product (LAP).

Non-HDL represents the cholesterol content of all proatherogenic, apo-B–containing lipoproteins (15) and is calculated as total cholesterol minus HDL. Non-HDL levels are elevated in the prediabetes state and positively correlated with HOMA-IR (16).

The triglyceride:HDL ratio is a marker for IR that is significantly related to insulin-mediated glucose disposal (17). A triglyceride:HDL ratio of $>$3.5 provides a simple means of identifying patients with IR and dyslipidemia (17).

The TyG index is calculated as (fasting triglycerides [mg/dL] $\times$ fasting plasma glucose [mg/dL]) / 2 (18). The TyG index represents a marker of IR that correlates with the hyperinsulinemic-euglycemic clamp test (19) and HOMA-IR (18).

LAP is another biomarker of metabolic disorders and is calculated as (waist circumference [cm] $-$ 65) $\times$ triglycerides (mmol/L). LAP is superior to BMI in predicting HOMA-IR (20), fasting glucose, and HbA_{1c} (21) and is negatively correlated with total testosterone and sex hormone–binding globulin in aging men (21). We also assessed quality of life using the Aging Males' Symptoms (AMS) scale.

Statistical Methods

Statistical methods were described in detail previously (14). Briefly, data from both groups were averaged across each year, and yearly data were used to assess differences between the two groups while adjusting for possible confounding. Mean changes over time between groups were compared by a mixed-effects model for repeated measures, with a random effect for intercept and fixed effects for time, group, and their interaction. Changes were adjusted for age, weight, waist circumference, BMI, fasting glucose, SBP and DBP, lipids, and AMS score to account for baseline differences between the two groups.

RESULTS

Table 1 shows the baseline characteristics of the T-group (n = 229) and the untreated group (n = 87). The total follow-up time was 1,993 patient-years. At baseline, the untreated group and T-group exhibited similar BMI and HbA_{1c} values; however, the T-group was

Table 1—Baseline characteristics in the T-group and the untreated group

	T-group (n = 229)	Untreated group (n = 87)	P value between groups
Baseline age (years)	58.2 ± 9.6	66.4 ± 7.2	<0.0001
Mean follow-up (years)	6.6 ± 2.2	5.6 ± 1.6	
Median follow-up (years)	8	6	
Anthropometric parameters			
Weight (kg)	96.5 ± 12.4	92.9 ± 10.4	<0.05
Waist circumference (cm)	104.2 ± 7.0	101.1 ± 9.9	<0.005
BMI (kg/m^2)	30.7 ± 4.1	29.8 ± 3.0	NS
Waist:height ratio	0.58 ± 0.04	0.57 ± 0.05	<0.01
Glycemic control			
HbA_{1c} (%)	5.9 ± 0.2	5.9 ± 0.2	NS
Fasting glucose (mmol/L)	5.3 ± 0.8	4.9 ± 1.3	<0.005
Triglyceride:HDL ratio	6.5 ± 2.7	4.1 ± 2.5	<0.0001
TyG index	9.3 ± 0.4	8.9 ± 0.6	<0.0001
LAP (cm · mmol/L)	110 ± 42.1	79.1 ± 56.5	<0.0001
Lipids			
Total cholesterol (mmol/L)	6.9 ± 1.2	6.4 ± 1.4	<0.0005
HDL cholesterol (mmol/L)	1.1 ± 0.3	1.4 ± 0.4	<0.0001
LDL cholesterol (mmol/L)	4.1 ± 0.7	3.4 ± 0.9	<0.0001
Triglycerides (mmol/L)	2.8 ± 0.9	2.2 ± 1.1	<0.0001
Non-HDL cholesterol (mmol/L)	5.8 ± 1.2	5.0 ± 1.4	<0.0001
SBP (mmHg)	136.9 ± 13.5	129.8 ± 12.7	<0.0001
DBP (mmHg)	81.2 ± 8.9	84.7 ± 6.7	<0.001
Heart rate (beats/min)	76.8 ± 3.6	76.8 ± 5.0	NS
Concomitant medication at baseline			
Statins	31 (13.5)	19 (22.9)	<0.05
Antihypertensives	12 (22.2)	4 (4.8)	<0.01
Quality of life			
AMS score	52.2 ± 9.2	39.3 ± 7.4	<0.0001
International Index of Erectile Function, Erectile Function Domain	11.4 ± 5.6	10.9 ± 5.8	NS
Total testosterone (nmol/L)	8.2 ± 2.1	9.6 ± 2.4	<0.0001

Data are means ± SE or n (%) unless otherwise indicated.

somewhat younger than the untreated group and had larger waist circumference, lower HDL, higher triglycerides, and worse AMS scores. In addition, the mean testosterone level in the T-group was lower (8.2 ± 2.1 nmol/L) than in the untreated group (9.6 ± 2.4 nmol/L; $P < 0.0001$). The prevalence of prediabetes was found to be 50.9% in one of the two registries, comprising 505 men with hypogonadism in whom HbA_{1c} had been measured routinely from the beginning of the study.

TTh resulted in normalization of total testosterone after the first injection. Trough levels measured before the next injection were 16–18 nmol/L (461–519 ng/dL) throughout the 8-year follow-up. In the untreated group, testosterone levels remained in the 9–11 nmol/L (260–317 ng/dL) range (Supplementary Fig. 1).

TTh led to substantial improvements in glycemic parameters. Both fasting blood glucose and HbA_{1c} values were reduced in the T-group but increased in the untreated group (Fig. 1*A* and *B*). At 8 years, HbA_{1c} decreased in the T-group by 0.39 ± 0.03% ($P < 0.0001$) (Fig. 1*B*), whereas it increased by 0.63 ± 0.1% in the untreated group ($P < 0.0001$). The differences in glucose concentrations and HbA_{1c} were substantial and significant between the two groups throughout the entire follow-up period, amounting to a difference in HbA_{1c} of 1.02% at 8 years. At the last observation, all 229 patients in the T-group had an HbA_{1c} of <6.5% (48 mmol/mol), and 205 (90%) achieved normal glucose regulation with an HbA_{1c} <5.7% (39 mmol/mol) (Fig. 1*C*). In the untreated group, only 1 (1%) of the 87 patients had an HbA_{1c} <5.7% (39 mmol/mol), whereas 35 (40.2%) had progressed to frank T2D with an HbA_{1c} >6.5% (48 mmol/mol) (Fig. 1*D*).

At baseline, 161 (51%) patients in the entire cohort were obese, 136 (43%) were overweight, and 19 (6%) were of normal weight. The T-group achieved a weight loss of 8.8 ± 0.4% at 8 years, whereas the untreated group experienced a weight gain of 9.1 ± 1.3% ($P < 0.0001$ for all) (Fig. 2). Body weight decreased by 9.2 ± 0.4 kg in the T-group and increased by 8 ± 1.3 kg in the untreated group (Supplementary Fig. 2*A*). Waist circumference decreased by 6.8 ± 0.3 cm in the T-group and increased by 7.4 ± 1 cm in the untreated group (Supplementary Fig. 2*B*). The waist:height ratio decreased in the T-group and increased in the untreated group (Supplementary Fig. 2*C*). Changes in weight translated into corresponding changes in BMI (Supplementary Fig. 2*D*).

TTh resulted in a reduction in total cholesterol, LDL, and triglyceride levels and an increase in HDL

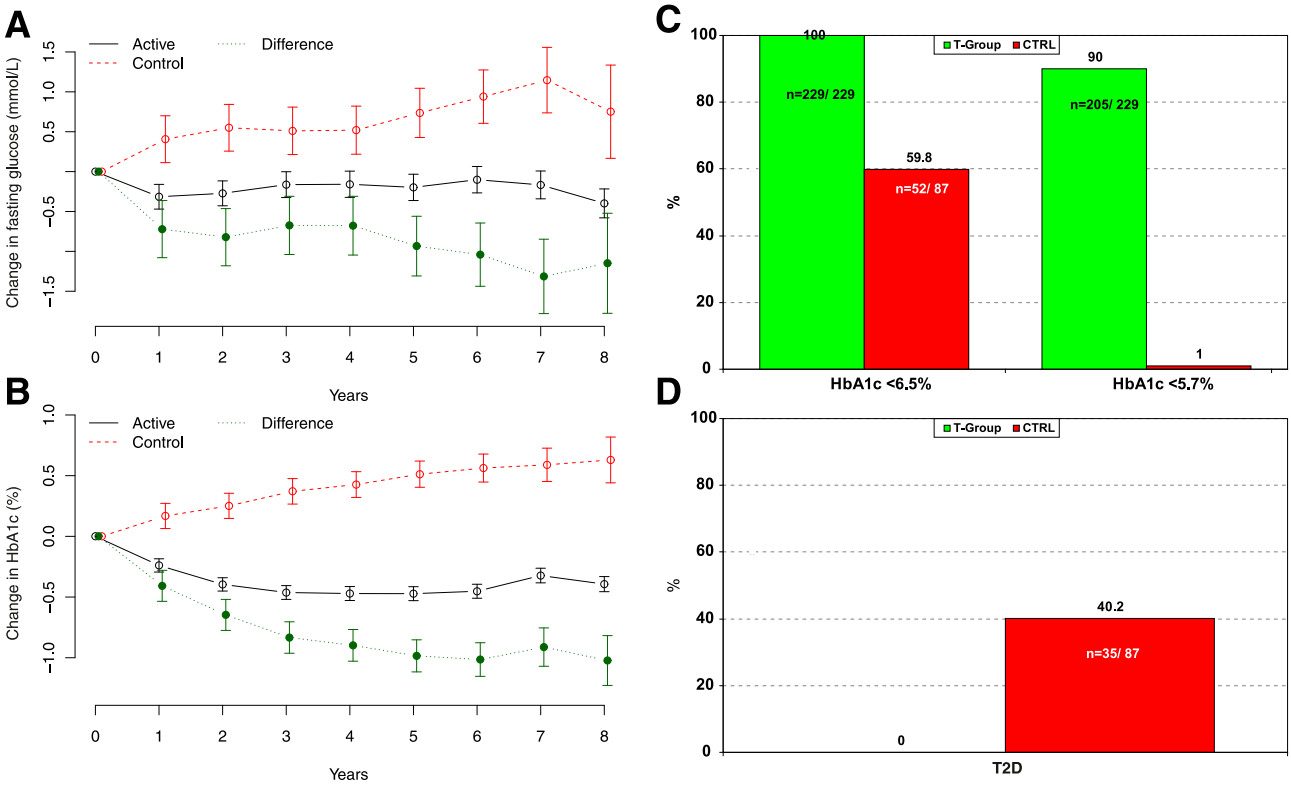

Figure 1—*A* and *B*: Changes in fasting glucose and HbA_{1c} in 229 men with hypogonadism and prediabetes on long-term treatment with TU and 87 untreated control subjects and estimated adjusted differences between groups. Data are least squares means ± SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score. *C*: Proportion of patients achieving an HbA_{1c} <6.5% and normal glucose regulation (HbA_{1c} <5.7%). *D*: Proportion of patients progressing to T2D.

levels (Supplementary Fig. 3*A–D*). The triglyceride:HDL ratio decreased in the T-group by 1.9 ± 0.2 at 8 years ($P <$ 0.0001), whereas it increased by 2.1 ± 0.6 in the untreated group ($P < 0.0001$) (Fig. 3*A*). The TyG index decreased in the T-group by 0.24 ± 0.03 ($P <$ 0.0001), whereas it increased by 0.33 ± 0.1 in the untreated group ($P < 0.0001$) (Fig. 3*B*). LAP decreased in the T-group by 33.3 ± 2.6 cm · mmol/L ($P < 0.0001$), whereas it increased by 41.2 ± 8.4 cm · mmol/L ($P <$ 0.0001) in the untreated group (Fig. 3*C*). Non-HDL decreased in the T-group by 2.2 ± 0.2 mmol/L ($P <$ 0.0001) and increased in the untreated group by 1.7 ± 0.5 mmol/L ($P < 0.0001$) (Fig. 3*D* and Supplementary Table 1).

Supplementary Table 1 summarizes changes from baseline and estimated differences between groups at 8 years adjusted for baseline age, weight, waist circumference, BMI, fasting glucose, lipids, SBP and DBP, and AMS score. The reduction in AMS scores in the T-group was clinically significant and reflects improvements in symptoms of hypogonadism; in the untreated group, AMS scores remained unchanged for the first 2–3 years of follow-up and then gradually worsened over the ensuing years of the study (Supplementary Fig. 4). Testosterone replacement also led to predictable increases in hemoglobin concentration and hematocrit (Supplementary Fig. 5*A* and *B*). The elevations in hemoglobin and hematocrit stayed within the normal range during the entire 8-year-long observation period.

Adverse Events

Two patients in the T-group dropped out because of relocation. Mortality was more than twofold higher in the untreated group (T-group 7.4%, untreated group 16.1%; $P < 0.05$). One (0.4%) patient in the T-group and five patients (5.7%) in the untreated group had a nonfatal myocardial infarction ($P <$ 0.005). No patients in the T-group and one (1.1%) patient in the untreated group had a nonfatal stroke.

CONCLUSIONS

In this observational study of patients treated in real-world clinical venues, we report the effects of long-term TTh for 8 years in men with hypogonadism and prediabetes. Our main finding is that TTh completely prevented the progression of prediabetes to overt T2D as diagnosed on the basis of HbA_{1c} values. Not a single man with hypogonadism and prediabetes who was treated with testosterone progressed to overt T2D. In contrast, 40.2% of untreated men with hypogonadism and with prediabetes developed overt T2D. To our knowledge, this study is the first to show that TTh can completely prevent prediabetes progression to overt T2D. Thus, TTh for hypogonadism fulfills the critical therapeutic goal in patients with prediabetes, which is the prevention of progression to T2D as underscored in the National Diabetes Education Program Guiding Principles for the Care of People With or at Risk for Diabetes (12).

Interventions that aim to prevent prediabetes progression to diabetes ideally

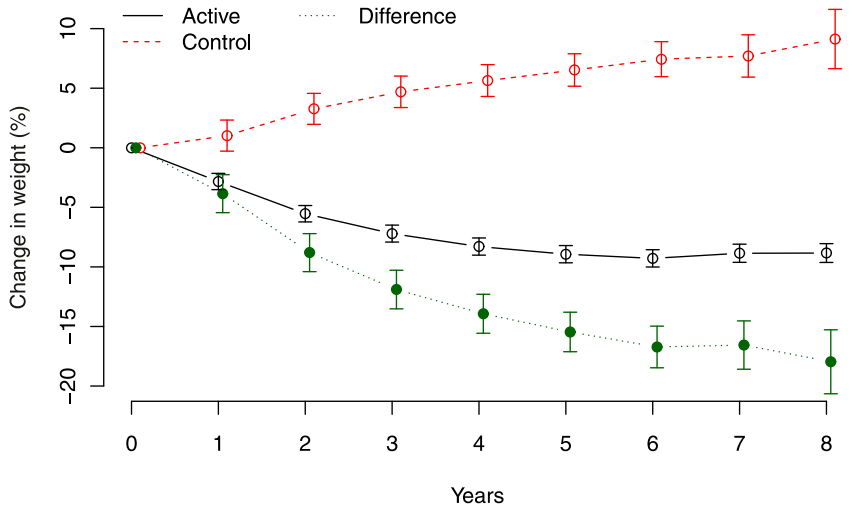

Figure 2—Changes in weight (%) in 229 men with hypogonadism and prediabetes on long-term treatment with TU and 87 untreated control subjects and estimated adjusted differences between groups. Data are least squares means ± SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score.

should restore normoglycemia rather than just maintain the prediabetes state. In this regard, it is particularly notable that 90% of men treated with testosterone achieved regression to normal glucose regulation (HbA_{1c} <5.7% [39 mmol/mol]) and, hence, resolution of prediabetes. A post hoc analysis of the Diabetes Prevention Program (DPP) Outcomes Study (DPPOS) demonstrated a 56% lower risk of diabetes 10 years from randomization among individuals who were able to achieve normal glucose regulation during DPP versus those who remained in the prediabetes state (22).

Our findings are consistent with previous reports of the metabolic benefits of TTh in patients with hypogonadism and diabetes. Long-term TTh with TU for up to 12 years resulted in remission of T2D in 12% of patients (23). In this latter study, mean HbA_{1c} of patients who went into remission dropped from 8.3% (67 mmol/mol) at baseline to 5.7% (39 mmol/mol) at the last measurement (23). This was accompanied by reductions in fasting glucose from 7.8 to 5.4 mmol/L, fasting insulin from 24.7 to 7.6 μU/mL, and HOMA-IR from 8.7 to 1.8. Body weight declined progressively from 107 to 89 kg (17% weight loss) and waist circumference from 108 to 97 cm (23).

As expected, in the current study, TTh resulted in normalization of serum testosterone levels and improvement in symptoms of hypogonadism as assessed by AMS scores. Furthermore, our data show that long-term TTh with injectable TU for 8 years resulted in a sustained and clinically meaningful weight loss of nearly 9%. Notably, this large amount of weight loss was progressive and sustained over the entire treatment period of 8 years (Fig. 2). In a previous study, we showed that >90% of men with hypogonadism are overweight or obese, and almost all of these patients achieved a weight loss of >10% after long-term TTh for up to 8 years (13). Weight loss in response to TTh may be one of the main contributors to the prevention of prediabetes progression to diabetes (10). A weight loss of ~10% appears to maximally prevent future diabetes in patients with prediabetes or the metabolic syndrome (10). Indeed, the American Association of Clinical Endocrinologists/American College of Endocrinology obesity guidelines substantiate that a 10% weight loss can reduce the risk of future T2D by ~80% and that this may represent a threshold above which further weight loss may not result in additional preventive benefits (11). Thus, a residual risk for T2D may exist that cannot be eliminated by weight loss per se. Given the data in our study, it is reasonable to believe that TTh in men with obesity and hypogonadism possibly could reduce this residual risk for T2D.

A weight loss of 10% is notoriously difficult to achieve, and even harder to maintain long term, through diet and exercise interventions (20,21). Clinical trials assessing efficacy of lifestyle interventions as well as pharmacotherapy for obesity are characterized by high attrition rates (22). In our study, attrition was extremely low; only two men in the T-group dropped out, and this was because of relocation. Hence, long-term TTh with TU injections is effective for achieving marked lasting weight loss and prevention of diabetes and feasible long term in real life. Furthermore, our study clearly confirms that long-term TTh is safe and well tolerated; mortality was more than twofold higher in the untreated group, and more nonfatal myocardial infarctions occurred in the untreated group (5 of 87 patients) than the T-group (1 of 229 patients). Support for this comes from other studies that also found a significant reduction in mortality after long-term TTh in men with hypogonadism and T2D (24,25).

Another contributing factor to the prevention of prediabetes progression to diabetes is the consistent increase in lean body mass with TTh (26). Accordingly, several studies showed that a larger muscle mass is associated with higher insulin sensitivity, lower HbA_{1c}, and reduced risk for prediabetes and overt T2D in both older and younger people (27,28). After adjusting for age, ethnicity, sex, obesity, and waist circumference, each 10% increase in muscle mass index (calculated as muscle mass divided by height squared) is associated with a 14% reduction in IR and a 23% reduction in prediabetes risk (27). Vice versa, a lower muscle mass is associated with higher fasting and postprandial blood glucose levels as well as elevated insulin levels (27). We do not have body composition data for our subjects; however, this is predictable on the basis of a meta-analysis of randomized controlled trials showing that TTh results in significant reductions in fat mass and increases in lean (muscle) mass as well as reductions in fasting glycemia and IR (26).

The main mechanism explaining how TTh prevents development of diabetes is likely improvement in insulin sensitivity (29,30). A randomized controlled trial showed that TTh for 24 weeks in men with hypogonadism, obesity, and T2D increased insulin sensitivity (hyperinsulinemic-euglycemic clamp) and lean mass (3.4 kg) while reducing body fat

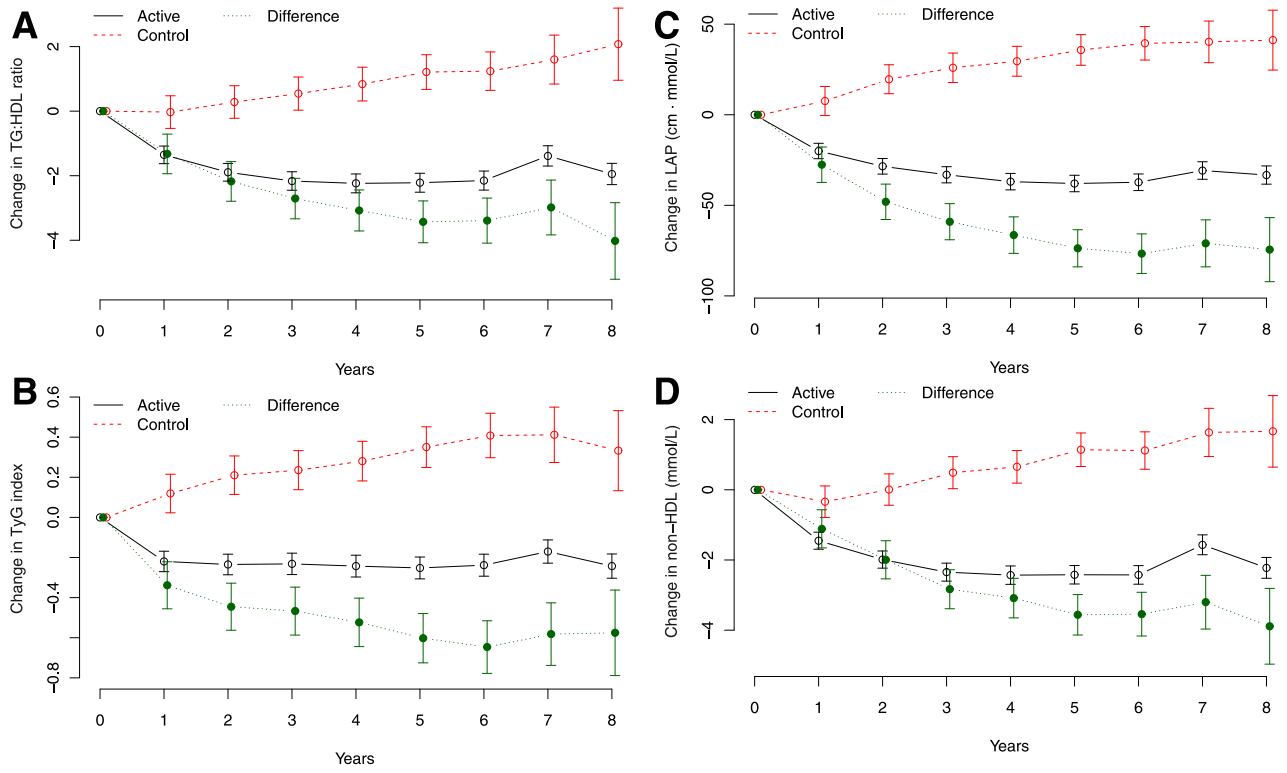

Figure 3—Changes in triglyceride (TG):HDL ratio (*A*), TyG index (*B*), LAP (*C*), and non-HDL cholesterol (*D*) in 229 men with hypogonadism and prediabetes on long-term treatment with TU and 87 untreated control subjects and estimated adjusted differences between groups. Data are least squares means ± SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score.

(−3.3 kg) (5). At the cellular level, TTh has been shown to increase the expression of the glucose carrier GLUT4, the insulin receptor, and the insulin receptor substrate 1, providing an enhanced capacity for insulin-mediated glucose transport (31). Our study shows significant reductions in three lipid parameters that are surrogate measures of IR: triglyceride:HDL ratio, TyG index, and LAP. The marked improvement in the triglyceride:HDL ratio is notable, considering that a high triglyceride:HDL ratio in men is a significant predictor of incident T2D, coronary heart disease, cardiovascular disease (CVD), and all-cause mortality (32).

Non-HDL is more reflective of atherogenicity in the context of elevated triglycerides (33) and has been shown to be a stronger predictor of coronary heart disease death than LDL in people with diabetes (34). Accordingly, several clinical guidelines and medical organizations, such as the International Atherosclerosis Society (33), the European Society of Cardiology/European Atherosclerosis Society (35), and the National Lipid Association (36), stress the importance of non-HDL and recommend that non-HDL replaces LDL as the primary therapeutic target for reducing CVD risk in patients with diabetes. Individuals with prediabetes and/or the metabolic syndrome are considered to be at increased risk for atherosclerotic CVD, and lipid treatment goals for these individuals should be the same as for those with diabetes. In the current study, we show that TTh in men with prediabetes and hypogonadism effectively reduces triglycerides, the triglyceride:HDL ratio, and non-HDL. It is reasonable to hypothesize that these improvements in dyslipidemia contribute to the reduction in mortality and myocardial infarction demonstrated in our study and to the reduction in cardiovascular mortality that has been reported previously in a study of long-term TTh (14). In summary, given the observed improvements in glycemia, IR, body weight, and lipids, our study shows that TTh provides a multifactorial and comprehensive CVD risk reduction in men with hypogonadism and prediabetes.

Although no patient in the T-group developed T2D, in the untreated group, patients with hypogonadism and prediabetes experienced progressive deterioration of fasting glucose, triglycerides, and cholesterol over time, despite the fact that they had better metabolic status at baseline than the men in the T-group. This is in agreement with previous reports demonstrating that the onset of the diabetogenic process starts 10–20 years before the diagnosis of overt T2D (37,38).

In 2017, there were 451 million people (ages 18–99 years) with diabetes worldwide, and 5 million deaths were attributable to diabetes (39). The global health care expenditure incurred by diabetes is in the range of U.S. $850–$1,300 billion (39). Given the common co-occurrence of hypogonadism and dysglycemia, the potential of TTh to prevent development of T2D, and possibly even result in remission of overt T2D, is indeed worthy of large-scale randomized clinical trials. A notable randomized placebo-controlled study is currently under way, the Testosterone for Diabetes Mellitus (T4DM) trial, that is investigating whether TTh combined with lifestyle change can prevent T2D in men who have low testosterone levels and prediabetes (40). Results are expected at the end of 2019 (trial registration ACTRN 12612000287831).

Our study has strengths and limitations. It is not a randomized clinical

trial, and like all observational studies, therefore, it suffers some limitations. This is particularly evident in the differences in baseline clinical characteristics in our real-world registry study. Although baseline BMI and HbA_{1c} values were similar, the T-group was younger and had worse metabolic status in terms of lipids and waist circumference, perhaps contributing to the marked improvement with TTh. The T-group also had higher AMS scores (i.e., worse symptoms) and lower baseline testosterone levels than the untreated group. Among the strengths of this study is that it reflects real-world patient care in outpatient clinics. The study included a large number of patients, a very-long follow-up of 8 years, and 100% adherence to TU treatment because all injections were performed and documented in the offices.

In conclusion, our study shows for the first time that long-term TTh completely prevents progression of prediabetes to overt T2D in men with hypogonadism and prediabetes. It is particularly notable that most of the men in the T-group achieved normoglycemia with an HbA_{1c} <5.7% (39 mmol/mol). This suggests that long-term TTh can achieve resolution of prediabetes. In addition, TTh resulted in a marked reduction of CVD risk by reducing body weight, waist circumference, and glycemia and improving dyslipidemia. Adherence to long-term treatment with TU injections for 8 years was excellent, with no treatment-related dropouts. Testosterone treatment holds tremendous potential for the prevention of diabetes in the rapidly growing population of men with hypogonadism and prediabetes and warrants further investigation in randomized controlled trials as well as replication in additional real-life observational studies conducted in both primary care and specialist practices.

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Author Contributions. A.Y., A.H., and K.S.H. were clinical investigators at the study sites, researched data, and reviewed the manuscript. M.C. and F.S. wrote the manuscript. G.D. performed statistical analyses. W.T.G. participated in data analyses and interpretation and in the writing of the manuscript and contributed to discussion. G.D. and F.S. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented in abstract form at the the 98th Annual Meeting of the Endocrine Society, Boston, MA, 1–4 April 2016; the 77th Scientific Sessions of the American Diabetes Association, San Diego, CA, 9–13 June 2017; the 53rd Annual Meeting of the European Association for the Study of Diabetes, Lisbon, Portugal, 11–15 September 2017; the International Diabetes Federation Congress, Abu Dhabi, United Arab Emirates, 4–8 December 2017; and the 78th Scientific Sessions of the American Diabetes Association, Orlando, FL, 22–26 June 2018.

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