



ORIGINAL ARTICLE

Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study

Karim Sultan Haider MD¹  | Ahmad Haider MD¹ | Farid Saad DVM^{2,3}  |
Gheorghe Doros PhD⁴ | Markolf Hanefeld MD^{5,6} | Sandeep Dhindsa MD⁷ |
Paresh Dandona MD^{8,9} | Abdulmageed Traish PhD¹⁰

¹Private Urology Practice, Bremerhaven, Germany

²Consultant to Medical Affairs Andrology, Bayer AG, Berlin, Germany

³Research Department, Gulf Medical University School of Medicine, Ajman, United Arab Emirates

⁴Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, Massachusetts

⁵Zentrum für klinische Studien, GWT-TU Dresden GmbH, Dresden, Germany

⁶Medizinische Klinik 3, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

⁷Division of Endocrinology, Diabetes and Metabolism, Saint Louis University, St. Louis, Missouri

⁸Division of Endocrinology, Diabetes and Metabolism, State University of New York at Buffalo, New York

⁹Internal Medicine - Endocrinology, Kaleida Health, Buffalo, New York

¹⁰Department of Urology, Boston University School of Medicine, Boston, Massachusetts

Correspondence

Abdulmageed Traish, Professor Emeritus of Biochemistry and Urology, Boston University School of Medicine, Boston, MA 02118, USA. Email: atraish@bu.edu

Funding information

The work described in this paper received partial financial support for data entry and statistical analyses from Bayer AG, Berlin, Germany, the manufacturer of the testosterone preparation used in this study

Abstract

Aims: To investigate whether testosterone therapy (TTh) in men with hypogonadism and type 2 diabetes mellitus (T2DM) improves glycaemic control and insulin sensitivity, and results in remission of T2DM.

Material and Methods: A total of 356 men who had total testosterone levels ≤ 12.1 nmol/L (350 ng/dL) and symptoms of hypogonadism were included in the study and followed up for 11 years. All patients received standard diabetes treatment and 178 patients additionally received parenteral testosterone undecanoate 1000 mg every 12 weeks following an initial 6-week interval. A control group comprised 178 hypogonadal patients who opted not to receive TTh.

Results: Patients with hypogonadism and T2DM treated with testosterone had significant progressive and sustained reductions in fasting glucose, glycated haemoglobin (HbA1c) and fasting insulin over the treatment period. In the control group, fasting glucose, HbA1c and fasting insulin increased. Among the patients treated with testosterone 34.3% achieved remission of their diabetes and 46.6% of patients achieved normal glucose regulation. Of the testosterone-treated group, 83.1% reached the HbA1c target of 47.5 mmol/mol (6.5%) and 90% achieved the HbA1c target of 53.0 mmol/mol (7%). In contrast, no remission of diabetes or reductions in glucose or HbA1c levels were noted in the control group. There were fewer deaths, myocardial infarctions, strokes and diabetic complications in the testosterone-treated group.

Conclusions: Long-term TTh in men with T2DM and hypogonadism improves glycaemic control and insulin resistance. Remission of diabetes occurred in one-third of the patients. TTh is potentially a novel additional therapy for men with T2DM and hypogonadism.

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2020 The Authors. *Diabetes, Obesity and Metabolism* published by John Wiley & Sons Ltd.

Peer Review

The peer review history for this article is available at <https://publons.com/publon/10.1111/dom.14122>.

KEYWORDS

endocrine therapy, insulin resistance, observational study, type 2 diabetes, weight control

1 | INTRODUCTION

Reduced testosterone concentrations are commonly encountered in men with type 2 diabetes mellitus (T2DM). Dhindsa et al.¹ first described the syndrome of hypogonadotropic hypogonadism (HH) in men with T2DM. This syndrome occurs in approximately one-third of patients with diabetes and is associated with obesity, but not with severity or duration of diabetes, or age.² Obesity, without diabetes, was associated with HH in approximately 25% of patients.³ Patients with HH also exhibited an inflammatory state, beyond that experienced by eugonadal patients with T2DM and had significantly greater insulin resistance than eugonadal patients with T2DM.^{4,5} Testosterone therapy (TTh) reduced insulin resistance in such patients, according to homeostatic model assessment of insulin resistance (HOMA-IR).^{6,7} Men with T2DM and hypogonadism have more fat mass and a 36% lower glucose infusion rate during hyperinsulinaemic-euglycaemic clamps than eugonadal men, as well as reduced insulin signalling at the cellular level in adipose tissue.^{5,8-11}

Testosterone deficiency (TD), also termed "hypogonadism", contributes to reduced glucose disposal, increased insulin resistance and onset of T2DM.¹²⁻¹⁴ Androgen deprivation therapy for prostate cancer is associated with significantly increased risk of incident diabetes.^{15,16} TTh in men with TD and T2DM increases insulin sensitivity and induces greater expression of insulin receptor- β , insulin receptor substrate-1, AKT-2 and GLUT-4 in adipose tissue, thus providing a mechanistic explanation for the increased insulin sensitivity.^{5,17} We have previously shown that long-term TTh halted the progression of prediabetes to overt diabetes.¹³

The primary objectives of this registry study were, firstly, to examine the effect of TTh on the course of glucose intolerance, with glycated haemoglobin (HbA1c) and insulin secretion as target variables, and, secondly, to assess the impact of TTh on weight control and major cardiovascular risk factors (lipids, blood pressure, inflammation). In the present paper, we report the results of long-term TTh (11 years) in men with hypogonadism and T2DM and compare the outcomes with data derived from a parallel group of patients who remained untreated (control) during the entire follow-up period.

2 | METHODS

2.1 | Patients

In a prospective registry study, patients were examined in a single urological practice clinic for the past 11 years. The ethical guidelines as formulated by the German "Ärztammer" (the German Medical Association) for observational studies in patients receiving standard

treatment were followed. After receiving a detailed and informative explanation regarding the nature and the purpose of the study, all participants provided written consent. A total of 356 patients with T2DM who had total testosterone levels ≤ 12.1 nmol/L (350 ng/dL) and symptoms of hypogonadism according to the Guidelines of the European Association of Urology were included in the study.¹⁸ All patients with diabetes were managed by the same local diabetes centre and received standard diabetes treatment, which includes mandatory educational courses and materials. In addition, 178 patients were treated with parenteral testosterone undecanoate 1000 mg every 12 weeks following an initial 6-week interval (testosterone group); 178 hypogonadal patients opted against TTh and served as a control group. Patients opting against TTh did so for a variety of reasons, the most common being advice against TTh by their general practitioners, acceptance of hypogonadal symptoms as part of ageing, or financial reasons due to cost of medication. All patients were followed-up for a duration exceeding 11 years. There were five patients with primary hypogonadism (including one patient with Klinefelter's syndrome) in the testosterone group and six in the control group. Most of the patients had HH, consistent with their T2DM.

2.2 | Patient educational support

Patients received standard diabetes treatment in a diabetes centre and were enrolled onto a mandatory disease management educational programme for diabetes, which encompasses a certified educational course on diabetes including information regarding lifestyle changes in order to prevent further progression of the disease. To further encourage lifestyle improvements, patients received a pamphlet from our urological office with options for physical exercise. The pamphlet also included some options for dietary changes, with advice on how to reduce fatty foods and consume more vegetables and an encouragement to initiate the changes now without further delay. All patients were encouraged to continue to visit the diabetologist regularly. Patients who did not achieve the target HbA1c after approximately 2 to 3 years were encouraged to participate in the educational courses again. Whenever a change in medication was necessary, educational materials and support were also provided to those patients who were undergoing medication changes. Patients who encountered a secondary disease or comorbidity as a result of their diabetes were provided with educational materials and support regarding these comorbidities.

2.3 | Assessment and follow-up

We measured the following variables: height; weight; waist circumference; blood pressure; haemoglobin; haematocrit; fasting glucose and HbA1c; insulin; systolic and diastolic blood pressure; heart rate; lipids

TABLE 1 Baseline characteristics in the testosterone-treated group and untreated hypogonadal controls

	Testosterone group (n = 178)	Control (n = 178)	P value between groups
Baseline age, years	61.5 ± 5.4	63.7 ± 4.9	<0.0001
Mean follow-up, years	7.7 ± 3.0	8.7 ± 2.6	
Median follow-up, years	8	10	
Anthropometric variables			
Weight, kg	114.1 ± 13.9	102.8 ± 14.2	<0.0001
Waist circumference, cm	116.8 ± 14.3	116.9 ± 13.6	NS
BMI, kg/m ²	36.5 ± 4.5	33.4 ± 5.3	<0.0001
Waist:height ratio	0.66 ± 0.08	0.66 ± 0.08	NS
Glycaemic control			
HbA1c, mmol/mol (%)	79 ± 16 (9.4 ± 1.4)	62 ± 8 (7.8 ± 0.7)	<0.0001
Fasting glucose, mmol/L	7.8 ± 1.2	6.3 ± 0.7	<0.0001
Fasting insulin, µU/mL ^a	28.6 ± 4.0	24.9 ± 2.9	<0.0001
Insulin dose, U/d ^b	37.8 ± 13.4	31.3 ± 6.2	<0.0005
HOMA-IR ^a	9.8 ± 2.0	7.1 ± 1.3	<0.0001
HOMA-β ^a	71.8 ± 15.0	75.3 ± 10.8	NS
Duration of diabetes, years	2.5 ± 2.3	2.0 ± 1.2	<0.01
Lipids			
Total cholesterol, mmol/L	8.3 ± 1.1	7.1 ± 1.2	<0.0001
HDL cholesterol, mmol/L	1.0 ± 0.4	1.1 ± 0.5	NS
LDL cholesterol, mmol/L	4.7 ± 0.9	4.1 ± 1.4	<0.0001
Triglycerides, mmol/L	3.5 ± 0.6	3.1 ± 0.6	<0.0001
Non-HDL cholesterol, mmol/L	7.3 ± 1.2	6.0 ± 1.4	<0.0001
Remnant cholesterol, mmol/L	2.6 ± 1.0	2.0 ± 1.0	<0.0001
Blood pressure and heart rate			
Systolic blood pressure, mmHg	163.0 ± 13.3	145.6 ± 14.6	<0.0001
Diastolic blood pressure, mmHg	97.6 ± 10.8	84.8 ± 10.3	<0.0001
Heart rate, bpm	79.1 ± 4.0	77.1 ± 4.6	<0.0001
Pulse pressure, mmHg	65.1 ± 7.9	60.8 ± 7.4	<0.0001
Renal function			
Creatinine, mg/dL	0.95 ± 0.16	1.00 ± 0.14	<0.005
Glomerular filtration rate	82.3 ± 12.8	77.0 ± 12.1	<0.0001
Inflammatory markers			
hsCRP, mg/dL	4.4 ± 5.2	1.5 ± 1.4	<0.0001
Concomitant medication at baseline			
Antidiabetics, %	100	99.4	NS
Statins, %	73.6	69.7	NS
Anti-hypertensives, %	84.3	48.3	<0.0001
Quality of life			
AMS	54.7 ± 9.3	40.0 ± 5.7	<0.0001
IIEF-EF	16.1 ± 6.1	19.1 ± 3.8	<0.0001
Testosterone			
Total testosterone, nmol/L	9.3 ± 1.7	9.8 ± 1.1	<0.005
Comorbidities			
Prior cardiovascular disease, %	38.8	39.3	NS
Erectile dysfunction, %	94.9	98.9	<0.005

Abbreviations: AMS, Aging Males' Symptoms scale; BMI, body mass index; hsCRP, high-sensitive C-reactive protein; HOMA-β, homeostatic model assessment of β-cell function; HOMA-IR, homeostatic model assessment of insulin resistance; IIEF-EF, International Index of Erectile Function – Erectile Function domain; NS, non-significant.

Note: Data are mean ± SD, unless otherwise indicated.

^aIn patients who never received insulin (n = 91 in testosterone group and n = 89 in control group).

^bIn patients receiving insulin (n = 87 in testosterone group and n = 69 in control group).

(total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides); high-sensitive C-reactive protein; and total testosterone. We also assessed quality of life using the Aging Males' Symptoms scale (AMS) and erectile function using the International Index of Erectile Function - Erectile Function Domain (IIEF-EF). Assessment of clinical variables was performed at least twice a year, and 11-year data were analysed.

2.4 | Statistical methods

Statistical methods were described in detail previously.¹⁹ Briefly, in the treated group, patients returned quarterly for testosterone undecanoate injections, whereas in the control group, patients returned two to four times for a visit. Data in both treated and untreated groups have been averaged across each year of patients participating in the study. Thus, obtained yearly data were used to assess differences between the two groups while adjusting for possible confounders. 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, fasting glucose, blood pressure, lipids and AMS score to account for baseline differences between the treated and untreated groups.

3 | RESULTS

Table 1 describes the baseline characteristics, comorbidities and concomitant medications of all patients (treated or untreated) and, for some variables, in patients who never received insulin and in patients who did receive insulin. The mean age of the testosterone group was 61.5 ± 5.4 years, and for the control group it was 63.7 ± 4.9 years. The mean follow-up was 7.7 ± 3.0 years in the testosterone group and 8.7 ± 2.6 years in the control group. In the testosterone group, baseline testosterone prior to treatment was 9.3 ± 1.7 nmol/L, and in the control group it was 9.8 ± 1.1 nmol/L. Fasting glucose was 7.8 ± 1.2 mmol/L in the treated group at baseline and 6.3 ± 0.7 mmol/L in the control group. HbA1c concentration was 79 ± 16 mmol/mol ($9.4 \pm 1.4\%$) in the testosterone group versus 62 ± 8 mmol/mol ($7.8 \pm 0.7\%$) in the control group. Body weight and body mass index (BMI) were also higher in the testosterone group, as compared with the control group.

3.1 | Effects of TTh on fasting blood glucose levels in men with TD and T2DM

Figure 1A shows the changes over time in fasting blood glucose (mmol/L) in the testosterone group ($n = 178$) and the control group ($n = 178$). Patients with TD and T2DM in the testosterone group had significant gradual reductions in fasting blood glucose (estimated adjusted difference between groups at 11 years: -3.6 mmol/L). The

reductions in blood glucose were progressive for the first 2 years and were sustained throughout the follow-up observation period. In the control group, fasting blood glucose levels were fairly stable during the first 6 years, but a rise was noted thereafter.

3.2 | Effects of TTh on HbA1c concentrations

As shown in Figure 1B, hypogonadal patients with T2DM receiving TTh had significant sustained and gradual reductions in HbA1c over the course of the treatment period (estimated adjusted difference between groups at 11 years: -73 mmol/mol (-6.7%) (95% confidence interval [CI] -78 ; -68 ; $P < 0.0001$). Statistically significant progressive decreases were observed with long-term TTh over the entire observation time. In contrast, a gradual increase in HbA1c was observed in the control group. The unadjusted mean HbA1c declined from 79 ± 16 mmol/mol ($9.4 \pm 1.4\%$) to 39 ± 3 mmol/mol ($5.8 \pm 0.3\%$) in the testosterone group and increased from 62 ± 8 mmol/mol ($7.8 \pm 0.7\%$) to 91 ± 15 mmol/mol ($10.5 \pm 1.4\%$) in the untreated group. The decrease in HbA1c in the testosterone group was statistically significant compared to baseline from year 1 onward ($P < 0.0001$) and statistically significant compared to the previous year for the first 7 years. Figure S1A shows adjusted absolute HbA1c values.

3.3 | Effects of TTh on fasting insulin concentrations

Figure 1C illustrates the changes in fasting insulin ($\mu\text{U/mL}$) in patients with TD and T2DM who were never treated with exogenous insulin ($n = 91$) in the testosterone group and for those who did not receive exogenous insulin in the control group ($n = 89$). In the testosterone group, a gradual and statistically significant decrease in insulin concentrations was recorded. In the control group, insulin concentrations increased over the entire follow-up period. The estimated adjusted difference between groups at 11 years was -28.9 $\mu\text{U/mL}$ ($P < 0.0001$).

3.4 | Effects of TTh on HOMA-IR

Figure 1D depicts the changes in HOMA-IR in patients with TD and T2DM who had never been treated with exogenous insulin in the testosterone group ($n = 91$) and in patients who did not receive exogenous insulin in the control group ($n = 89$). A marked and sustained reduction in HOMA-IR was observed beginning in year 1 of TTh and the decrease was progressive throughout the entire follow-up period. In the control group, there was a rise in HOMA-IR, which was demonstrable after the first few years. The estimated adjusted difference between groups at 11 years was -11.0 ($P < 0.0001$). We also calculated the updated HOMA-IR (HOMA2-IR), which showed similar results (Figure S1B).

3.5 | Effects of TTh on achieving diabetes remission, or HbA1c targets of 47.5 or 53.0 mmol/mol

Figure 2 summarizes the proportion of patients in each group who achieved remission of T2DM or normal glucose regulation, that is, HbA1c <39 mmol/mol (5.7%), and those achieving HbA1c targets of 47.5 or 53.0 mmol/mol (6.5% or 7.0%). Remission was defined

as HbA1c <47.5 mmol/mol (6.5%) and discontinuation of all anti-diabetic agents, including metformin. Among patients in the testosterone group, 34.3% achieved remission of their diabetes. Of these patients, 22 had been on insulin at baseline. The mean time to discontinuation of diabetes medications was 8.6 ± 2.9 years. The mean time following remission was 2.5 ± 2.3 years. There were no relapses.

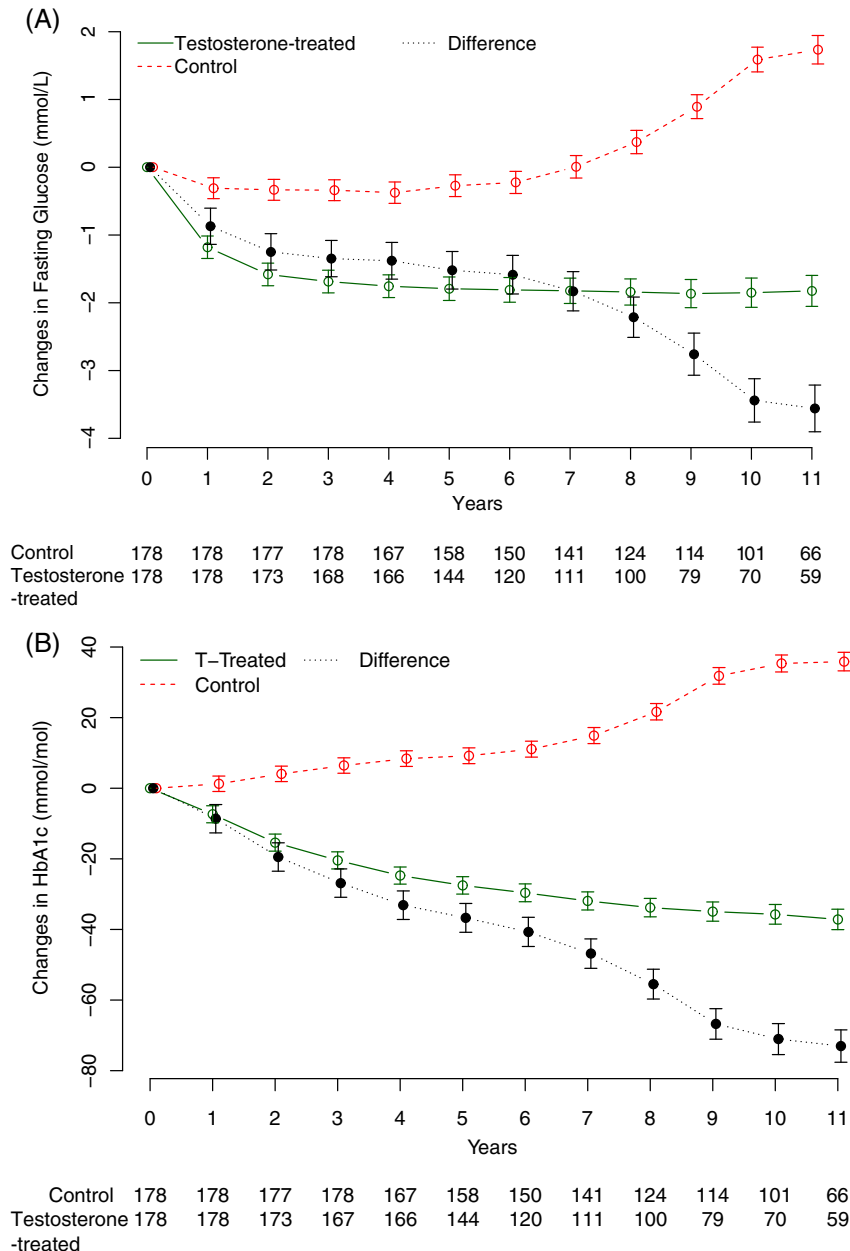


FIGURE 1 Changes in fasting glucose, glycated haemoglobin (HbA1c), fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) in men with hypogonadism and type 2 diabetes. Numbers below the graphs are numbers of patients per group in each year. **A**, Changes in fasting glucose (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term testosterone therapy (TTh). **B**, Changes in HbA1c (%) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **C**, Changes in fasting insulin ($\mu\text{U}/\text{mL}$) in patients who never received insulin treatment, with ($n = 91$) or without ($n = 89$) long-term TTh. **D**, Changes in HOMA-IR in patients who never received insulin treatment, with ($n = 91$) or without ($n = 89$) long-term TTh. Data are shown as least squares means after adjustment for age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Aging Males' Symptoms scale quality-of-life score. * $P < 0.0001$ between groups

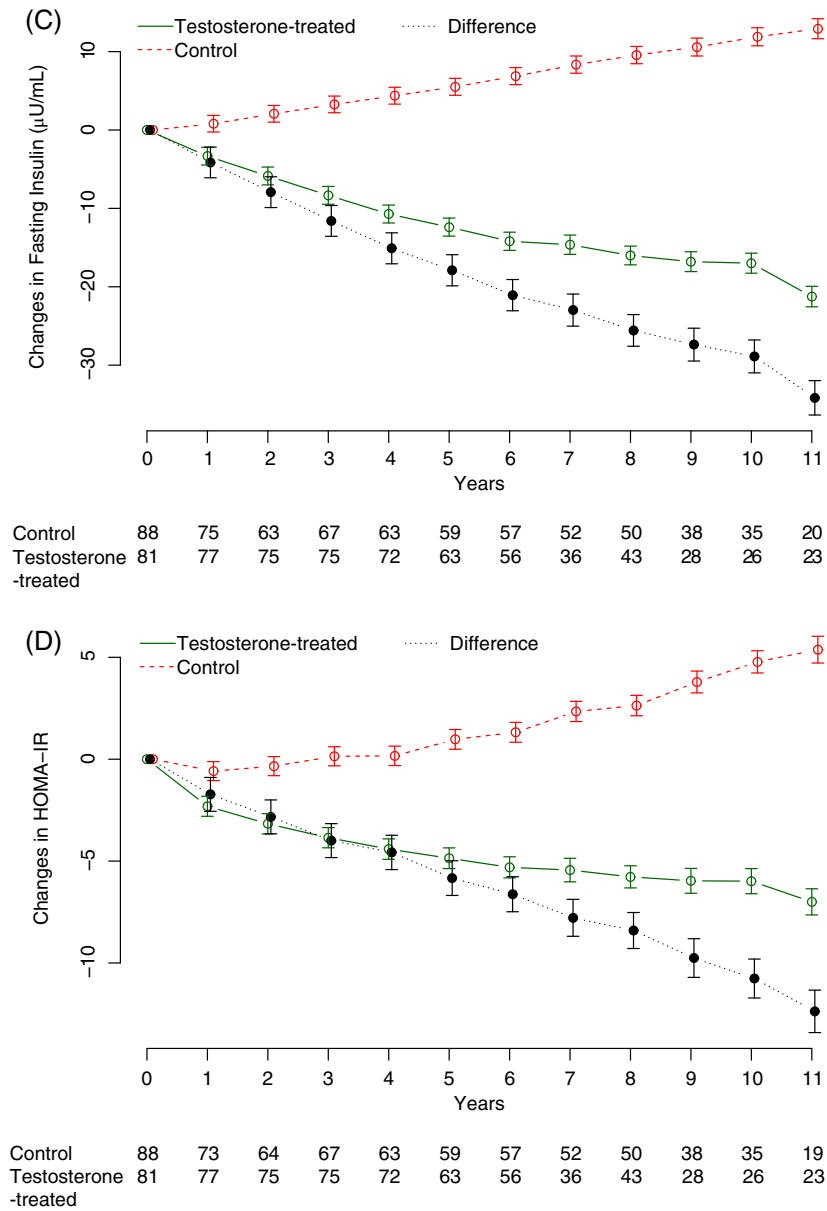


FIGURE 1 (Continued)

In the testosterone group, 46.6% of patients achieved normal glucose regulation and 83.1% achieved HbA1c values of 47.5 mmol/mol and 91% achieved HbA1c values of 53.0 mmol/mol. In contrast, no remission of diabetes or reduction in glucose or HbA1c levels were noted in the untreated group.

3.6 | Effects of TTh on lipid profiles, anthropometric variables, glomerular filtration rate and insulin dose requirement

Testosterone therapy resulted in significant improvements in lipid profile (Table 2). Total cholesterol (Figure 3A), LDL cholesterol (Figure 3C) and triglyceride levels (Figure 3D) decreased in the testosterone

group and increased in the control group. HDL cholesterol (Figure 3B) increased in the testosterone group and decreased in the control group. Non-HDL cholesterol (Figure 3E) decreased in the testosterone group by 3.3 ± 0.1 mmol/L ($P < 0.0001$) and increased in the untreated group by 1.4 ± 0.1 mmol/L ($P < 0.0001$). Remnant cholesterol (Figure 3F) decreased in the testosterone group by 1.4 ± 0.1 mmol/L ($P < 0.0001$) and increased in the control group by 0.5 ± 0.1 mmol/L ($P < 0.0001$).

Testosterone therapy produced a progressive and sustained decrease in body weight (in kg and % change). Over 11 years, there was a 22.1 kg (19.3%) reduction in body weight in the testosterone group, while the control group gained weight (Figures S2A and S2B). TTh also resulted in a progressive and sustained decrease in waist circumference, with an increase of waist circumference in the control

group (Figure S2C). The estimated adjusted difference between groups at 11 years was -20.4 cm (95% CI -21.7 ; -19.1 ; $P < 0.0001$ [Table 2]). In parallel, we noted significant reductions in BMI and waist-to-height ratio in the testosterone group, with increases of these variables in the control group (Figure S2D,E).

We also observed marked improvements in the estimated glomerular filtration rate (eGFR), calculated by the Modification of Diet in Renal Disease formula, in the testosterone group as compared to the control group (Table 2 and Figure S3). Since diabetic nephropathy is a major concern with regard to progression of kidney disease, these observations suggest that there was a profound improvement in kidney function in patients with T2DM who received TTh.

Patients in the testosterone group who had been on insulin at baseline had a reduction in insulin dose requirement compared with the control group, suggesting improvements in β -cell function (Figure S4). Twenty patients in the control group were started on insulin therapy during the observation time.

Total testosterone levels in the testosterone group increased significantly into the physiological range, while they remained low and decreased over time in the control group (Figure S5).

3.7 | Effects of TTh on quality of life and erectile function

As shown in Table 2, quality of life, assessed by the AMS questionnaire, and erectile function, as assessed by the IIEF-EF, improved significantly in the testosterone group and declined in the control group.

3.8 | Adverse events

Adverse events are reported in Table S1. There were 13 deaths (7.3%) in the testosterone group and 52 (29.2%) in the control group. All-cause mortality data from the testosterone group and the untreated control group were used to obtain Kaplan–Meier plots (Figure 4). We also recorded more strokes, myocardial infarctions, and diabetic complications in the control group as compared with the testosterone group (Table S1).

4 | DISCUSSION

Our findings show that, in patients with TD and T2DM, TTh significantly reduced fasting blood glucose by more than 1.5 mmol/L, even after adjustments for baseline variables, including age, waist circumference, weight, systolic and diastolic blood pressure, total cholesterol and triglycerides. The reductions in blood glucose in response to TTh were sustained throughout the treatment period. In contrast, no significant reductions in blood glucose were noted in the untreated patients. In fact, we observed an increase in blood glucose with extended follow-up periods in the untreated patients. It is not clear if

this rise in glucose implies worsening insulin resistance or insulin secretion.

We observed a significant reduction in HbA1c, exceeding 9 mmol/mol (3%), in patients with hypogonadism and T2DM treated with testosterone, even after adjustments for baseline variables. These reductions in HbA1c were sustained throughout the treatment period. In contrast, we observed an increase in HbA1c in the control group. We also observed a steeper rise in HbA1c similar to that recorded with glucose after ~ 6 years of follow-up, suggesting loss of β -cell function and advanced pathophysiological state of diabetes over extended periods of time contributing to increased HbA1c as a marker of dysfunction of glucose metabolism. It is unclear why such a rise in glucose and HbA1c concentrations occurred during long-term observation, but it could be related to a decline in β -cell function or apoptosis.

There were profound changes in fasting insulin levels in patients with T2DM and TD who had never received exogenous insulin treatment but had undergone TTh. Remarkably, insulin concentration decreased gradually with TTh and was sustained throughout the treatment course, even after adjustments for baseline variables. In contrast, in the control group, we observed a progressive increase in insulin concentration over the entire duration of follow-up.

There was a significant, progressive and sustained decrease in HOMA-IR in patients treated with testosterone but an increase in the untreated group. These findings strongly suggest that TTh in patients with diabetes and hypogonadism improved blood glucose, HbA1c and insulin resistance. Such findings have important clinical implications in the management of men with T2DM and TD. HOMA-IR correlates significantly with clamp insulin resistance, not only before, but also after treatment in patients with T2DM.²⁰ Recently, the original HOMA-IR equation has been superseded by a new computer model, HOMA2-IR.²¹ Although this computer model gives a value for insulin resistance, clinical judgement is required because of variables in glucose levels or assay methods. In our registry study, we analysed the data using both HOMA-IR and HOMA2-IR, with similar results.

We had calculated homeostatic model assessment of β -cell function (HOMA- β) and found that it decreased in the testosterone group,

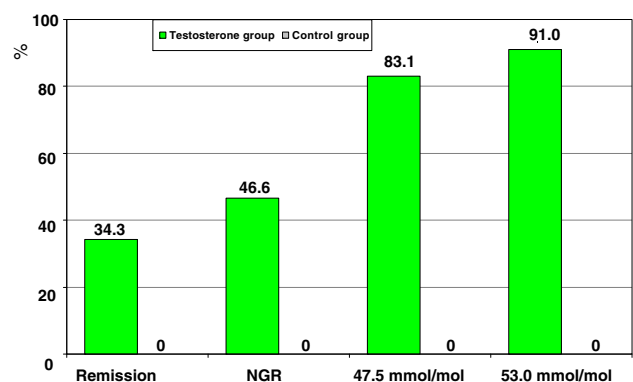


FIGURE 2 Proportion of patients achieving remission, normal glucose regulation (NGR), or HbA1c targets of 47.5 and 53.0 mmol/mol (6.5 and 7.0%), respectively

TABLE 2 Changes at 11 years from baseline in testosterone-treated group and untreated hypogonadal control group and estimated difference between groups at 11 years, adjusted for baseline age, weight, waist circumference, fasting glucose, lipids, systolic and diastolic blood pressure, and Aging Males' Symptoms scale score

	Testosterone group	P value for change from baseline	Control	P value for change from baseline	Estimated adjusted difference between groups [95% CI]	P value for estimated adjusted difference between groups
Anthropometric parameters						
Weight, kg	-22.1 ± 0.5	<0.0001	6.8 ± 0.5	<0.0001	-28.9 [-30.5;-27.3]	<0.0001
Weight change, %	-19.3 ± 0.4	<0.0001	7.4 ± 0.4	<0.0001	-26.7 [-28.0;-25.4]	<0.0001
Waist circumference, cm	-13.3 ± 0.4	<0.0001	7.1 ± 0.4	<0.0001	-20.4 [-21.7;-19.1]	<0.0001
BMI, kg/m ²	-7.3 ± 0.2	<0.0001	2.2 ± 0.2	<0.0001	-9.5 [-10.1;-8.9]	<0.0001
Waist:height ratio	-0.08 ± 0.00	<0.0001	0.04 ± 0.0	<0.0001	-0.12 [-0.12;-0.11]	<0.0001
Glycaemic control						
HbA1c, mmol/mol (%)	-37 ± 1 (-3.4 ± 0.1)	<0.0001	36 ± 1 (3.3 ± 0.1)	<0.0001	-73 [-78;-68] (-6.7 [-7.1;-6.3])	<0.0001
Fasting glucose, mmol/L	-1.8 ± 0.1	<0.0001	1.7 ± 0.1	<0.0001	-3.6 [-3.9;-3.2]	<0.0001
Fasting insulin, ^a μU/mL	-21.3 ± 0.7	<0.0001	12.9 ± 0.6	<0.0001	-34.2 [-36.4;-32.0]	<0.0001
Insulin dose, ^b U/d	-25.9 ± 1.1	<0.0001	19.3 ± 1.1	<0.0001	-55.2 [-48.8;-41.5]	<0.0001
HOMA-IR ^a	-7.0 ± 0.3	<0.0001	5.4 ± 0.3	<0.0001	-12.4 [-13.4;-11.3]	<0.0001
HOMA-β ^a	-55.2 ± 3.1	<0.0001	23.8 ± 3.2	<0.0001	-79.0 [-88.9;-69.1]	<0.0001
Lipids						
Total cholesterol, mmol/L	-2.9 ± 0.1	<0.0001	1.1 ± 0.1	<0.0001	-4.0 [-4.3;-3.7]	<0.0001
HDL cholesterol, mmol/L	0.5 ± 0.0	<0.0001	-0.3 ± 0.0	<0.0001	0.8 [0.7;0.9]	<0.0001
LDL cholesterol, mmol/L	-1.9 ± 0.1	<0.0001	0.9 ± 0.1	<0.0001	-2.8 [-3.0;-2.6]	<0.0001
Triglycerides, mmol/L	-1.1 ± 0.0	<0.0001	0.5 ± 0.0	<0.0001	-1.7 [-1.8;-1.5]	<0.0001
Non-HDL cholesterol, mmol/L	-3.3 ± 0.1	<0.0001	1.4 ± 0.1	<0.0001	-4.7 [-5.0;-4.5]	<0.0001
Remnant cholesterol, mmol/L	-1.4 ± 0.1	<0.0001	0.5 ± 0.1	<0.0001	-1.9 [-2.2;-1.7]	<0.0001
Blood pressure and heart rate						
SBP, mmHg	-32.3 ± 1.2	<0.0001	14.5 ± 1.1	<0.01	-46.8 [-50.5;-43.1]	<0.0001
DBP, mmHg	-19.2 ± 0.9	<0.0001	9.5 ± 0.8	<0.0001	-28.7 [-31.5;-25.9]	<0.0001
Heart rate, bpm	-3.0 ± 0.5	<0.0001	1.1 ± 0.5	<0.05	-4.1 [-5.6;-2.6]	<0.0001
Pulse pressure, mmHg	-13.1 ± 0.8	<0.0001	5.0 ± 0.7	<0.05	-18.0 [-20.4;-15.7]	<0.0001
Renal function						
Creatinine, mg/dL	-0.16 ± 0.03	<0.0001	0.32 ± 0.03	<0.0001	-0.48 [-0.59;-0.37]	<0.0001
GFR	9.8 ± 1.4	<0.0001	-22.3 ± 1.3	<0.0001	32.2 [27.7;-36.6]	<0.0001
Inflammatory markers						
hsCRP	-3.9 ± 0.3	<0.0001	1.5 ± 0.3	<0.0001	-5.4 [-6.3;-4.4]	<0.0001
Quality of life						
AMS	-30.8 ± 0.7	<0.0001	21.9 ± 0.6	<0.0001	-52.7 [-55.0;-50.5]	<0.0001
IIEF-EF	10.2 ± 0.4	<0.0001	-13.0 ± 0.3	<0.0001	23.2 [22.0;24.3]	<0.0001
Erythropoiesis						
Haemoglobin, g/dL	0.39 ± 0.06	<0.0001	-0.21 ± 0.05	<0.0001	0.59 [0.41;0.77]	<0.0001
Haematocrit, %	3.5 ± 0.4	<0.0001	0.8 ± 0.3	<0.05	2.8 [1.7;3.8]	<0.0001
Testosterone						
Total testosterone, nmol/L	8.2 ± 0.2	<0.0001	-2.2 ± 0.2	NS	10.4 [9.8;11.0]	<0.0001

Abbreviations: AMS, Aging Males' Symptoms scale; BMI, body mass index; DBP, diastolic blood pressure; hsCRP, high-sensitive C-reactive protein; IIEF-EF, International Index of Erectile Function - Erectile Function domain; NS, non-significant; SBP, systolic blood pressure.

Note: Data are mean ± SD, unless otherwise indicated.

^aIn patients who never received insulin (n = 91 in testosterone group and n = 89 in control group).

^bIn patients receiving insulin (n = 87 in testosterone group and n = 69 in control group).

suggesting reduced β -cell insulin secretion compared to the untreated control group. However, we believe that this is attributable in part to the improved glycaemia and increased insulin sensitivity in the testosterone group. Because insulin secretion is largely reduced in the testosterone group as a result of profoundly increased insulin sensitivity, less insulin was needed. This is reflected in the steady decline in

fasting insulin. Future studies should comprehensively evaluate β -cell secretion with stimulatory tests to better define the effect of testosterone on β -cell function.

The significant changes in fasting glucose, insulin and HbA1c reflect the importance of TTh in regulating hyperglycaemia and management of patients with hypogonadism and T2DM. The marked and

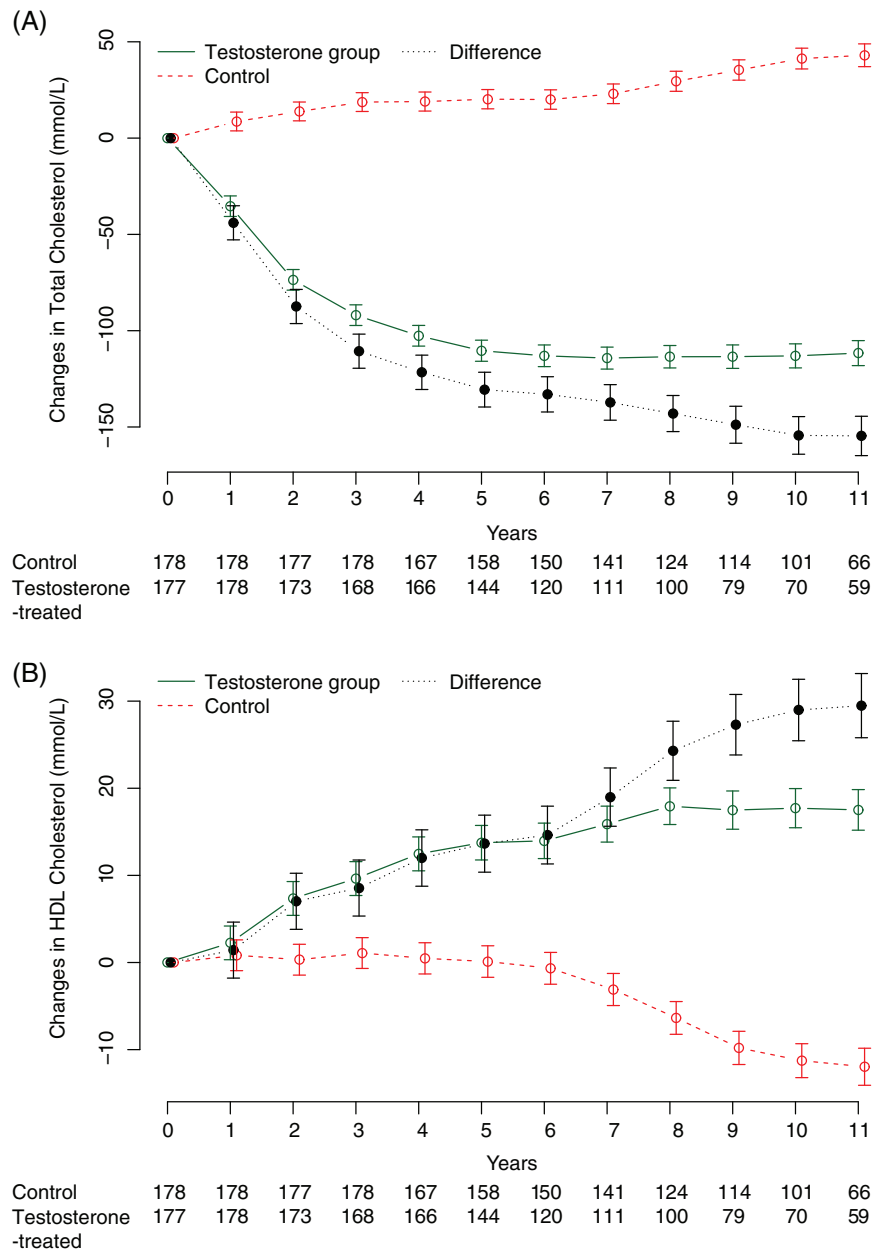


FIGURE 3 Changes in lipids in patients with hypogonadism and type 2 diabetes with ($n = 178$) or without ($n = 178$) long-term testosterone therapy (TTh). Numbers below the graphs are numbers of patients per group in each year. **A**, Changes in total cholesterol (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **B**, Changes in HDL cholesterol (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **C**, Changes in LDL cholesterol (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **D**, Changes in triglycerides (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **E**, Changes in non-HDL cholesterol (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. **F**, Changes in remnant cholesterol (mmol/L) in patients with ($n = 178$) or without ($n = 178$) long-term TTh. Data are shown as least squares means after adjustment for age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and Aging Males' Symptoms scale quality-of-life score. * $P < 0.0001$ between groups

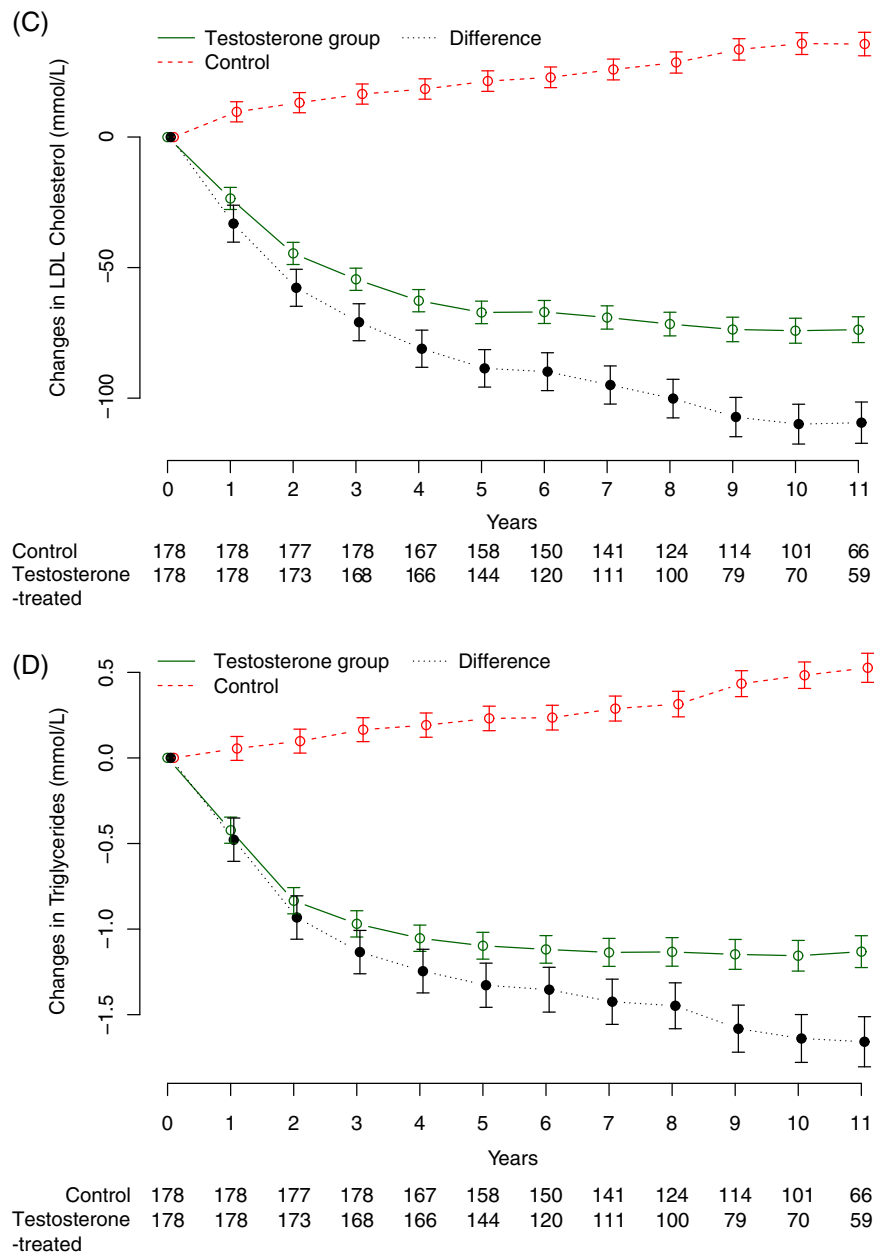


FIGURE 3 (Continued)

significant changes from baseline in response to TTh in the various anthropometric, lipid profile and vascular variables (Table 2) reflect the potential reduction in the risk of cardiovascular disease in patients with T2DM, who are treated with TTh.

Non-HDL cholesterol is calculated by subtracting HDL cholesterol from total cholesterol, and includes cholesterol in all atherogenic particles causing cardiovascular disease. Non-HDL cholesterol is more strongly associated with reduced risk of atherosclerotic coronary heart disease than changes in LDL cholesterol.²² Remnant cholesterol is calculated as total cholesterol minus HDL cholesterol minus LDL cholesterol, and has been shown to be a causal risk factor for low-grade inflammation, cardiovascular disease and all-cause mortality, even in patients with optimal LDL cholesterol levels.^{23,24} The

improvements in these emerging lipid-related risk factors for cardiovascular disease, in addition to the improvements in the standard lipid panel, may have contributed largely to the observed reductions in major adverse cardiovascular events in the testosterone group.

Marked improvements in eGFR were observed in patients treated with testosterone but not in the control group. These changes reflect improvement in renal function and reduction in cardiovascular disease risk.

In addition, the changes in the AMS quality-of-life score and the IIEF-EF score with TTh reflect improvement in overall and sexual quality of life.

In the present study, we did not observe any serious adverse effects of long-term TTh. In fact there were fewer deaths (Figure 4),

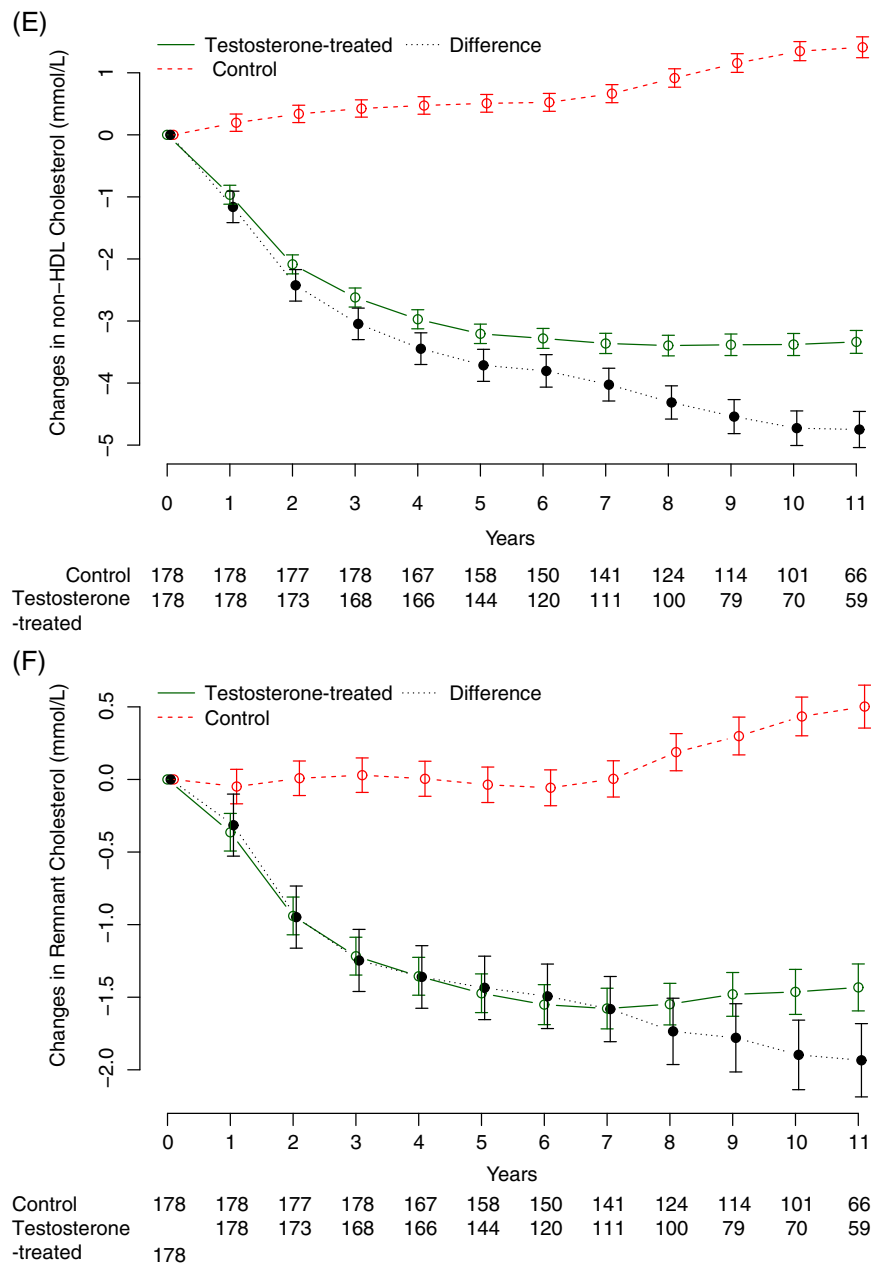


FIGURE 3 (Continued)

myocardial infarctions and strokes as compared with the control group (Table S1). Our observations are consistent with other studies showing reduced mortality in men with hypogonadism and T2DM receiving TTh.^{25,26}

For many decades, initiating prostate cancer or activating occult prostate cancer has been a concern when treating older men with testosterone. In the present study, the incidence of prostate cancer was significantly lower in the testosterone group compared to the control group (Table S1). This is consistent with the most recent literature.^{27,28}

Several pathophysiological mechanisms may account for the link between TD and onset of T2DM or worsening its pathophysiology and the potential reversal of these pathophysiological pathways with TTh. Among these postulated mechanisms, are: 1) the role of androgens in regulating expression, synthesis and translocation of glucose

transporters, which play an important role in glucose utilization and disposal; 2) the role of androgens in regulating glucagon-like peptide-1 receptor (GLP-1R), which modulates glucose metabolism; 3) the role of androgens in maintaining pancreatic β -cell function; and 4) role of inflammation in mediating insulin resistance. The translocation of the glucose transporter GLUT4 from an intracellular membrane compartment to the plasma membrane after insulin stimulation activates the phosphatidylinositol-3 kinase (PI3K) and other protein kinases, such as serine/threonine kinase AKT and PKC-f/k.²⁹ In 3T3-L1 adipocytes, TTh increased GLUT4-dependent glucose uptake through the LKB1/AMPK signalling pathway.³⁰ Thus, TD may contribute to reduced expression of glucose transporters and, in turn, impede glucose utilization and contribute to increased insulin secretion and insulin resistance. TTh may reverse this pathophysiological mechanism by

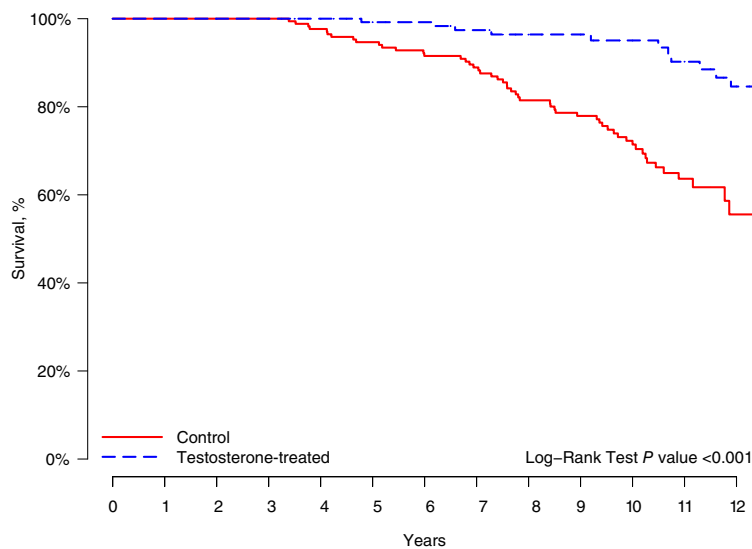


FIGURE 4 Kaplan-Meier curve showing estimates of survival among the two study groups. The numbers at the bottom of the graph are numbers of patients at risk in each year

Patients, n

Control	178	178	178	176	165	153	144	134	120	110	86	49	18
Testosterone-treated	178	178	178	168	154	125	113	101	86	76	60	55	42

facilitating the expression and translation of glucose transporters and their activities. In patients with hypogonadism and T2DM, a significant increase in insulin resistance was associated with reduced expression of IR β , IRS-1, AKT kinase and GLUT-4, and testosterone treatment led to the reversal of the extra insulin resistance and the restoration of the expression of IR β , IRS-1, AKT-1 and GLUT4.⁵ In addition, the expression of AMP kinase and phosphorylated AMP kinase was diminished in the adipose tissue and skeletal muscle of patients with TD and T2DM. Phosphorylated AMP kinase expression increased after TTh.^{31,32} These observations are important since metformin and physical exercise also mediate the increase in glucose through AMP kinase and AKT kinase and GLUT4.

In addition, GLP-1R is thought to be a key target for the pharmacological treatment of T2DM since it maintains glucose homeostasis and promotes β -cell proliferation. GLP-1R mRNA expression levels were positively correlated with testosterone concentrations. *In vitro* and *in vivo* studies demonstrated that expression and translation of GLP-1R are under androgen regulation.³³ Thus, it is likely that in TD, the expression and activities of GLP-1R are attenuated and this contributes to higher glucose levels and increased insulin resistance. TTh would contribute to activation of GLP-1R gene expression and translation into proteins and promote glucose uptake and utilization, thus reducing insulin secretion and insulin resistance.

There is emerging evidence that androgens are critical for maintaining pancreatic β -cell function.^{11,34} Testosterone action via the androgen receptor in β -cells enhances glucose-stimulated insulin secretion by potentiating the insulinotropic action of glucagon-like peptide-1. Androgen receptor-deficient islets exhibit altered expression of genes involved in inflammation and insulin secretion, demonstrating the importance of androgen action in β -cell health in men, with implications for T2DM development in men.³⁵ Interleukin (IL)-1 β is a proinflammatory cytokine which may impair β -cell function in

T2DM. Testosterone administration suppress IL-1 β in patients with TD.⁵ T2DM is a pro-inflammatory state and there is an increased synthesis and secretion of cytokines and mediators which interfere with insulin signal transduction while also being toxic to the β cell. Increased TNF- α concentrations block insulin signalling at IRS-1 level. IL-1 β interferes with insulin signalling while also being toxic to the β -cell. Both of these cytokines have been shown to be increased in people with diabetes and TD and they decrease after testosterone treatment.⁵ Testosterone was also shown to protect against glucotoxicity-induced β -cell apoptosis by reducing the action of the angiotensin II receptor type 1 (AGTR1) signalling pathway both *in vitro* and *ex vivo*.³⁶

One small observational pilot study has suggested a marked improvement in homeostatis model assessment-2 of beta-cell function (HOMA%B) as a result of TTh for a duration of up to 29 months.³⁷

Of note is the improvement in the eGFR and the marked improvements in lipid profiles and anthropometric variables, all contributing to improved overall health and reduced cardiovascular risk.

It is also noteworthy that inhibition of testosterone conversion to 5 α -DHT, one of the two metabolites of testosterone, contributes to the pathogenesis of non-alcoholic fatty liver disease and increases susceptibility to glucose intolerance and hyperinsulinaemia.^{38,39} This also promotes fat accumulation in liver with impairment of enzymes involved in fatty acid β -oxidation and gluconeogenesis, with increased enzymatic activities involved in triglyceride esterification and cholesterol synthesis and excretion.³⁸ In the liver, 5 α -DHT reduces lipid accumulation and cholesterol synthesis via increasing expression of carnitine palmitoyltransferase1 and phosphorylation of 3-hydroxy-3-methyl-glutaryl-CoA reductase.⁴⁰ In men, inhibition of 5 α -reductase resulted in hepatic insulin resistance, hepatic lipid accumulation, and decreased adipose lipid mobilization.^{41,42} A recent study has demonstrated the close association between weight loss, hepatic lipoprotein

export and remission of T2DM in humans, further supporting findings that successful weight management can result in remission of T2DM.^{43–45} The present results showed profound and sustained weight loss with long-term TTh in patients with TD and T2DM, consistent with previously published data from our registry study in patients with TD and with or without T2DM.⁴⁶

It is important to note that this registry study has some limitations. It was not a randomized clinical trial and therefore we would expect the testosterone-treated group and the untreated group not to be balanced at baseline, for example, with regard to age, severity of disease, glycaemic variables, markers of inflammation, lipid profile and markers of insulin resistance. However, for these reasons our data were adjusted for the differences between the two groups including age, waist circumference, weight, fasting glucose, systolic and diastolic blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and AMS quality-of-life score. Also, given that this study was carried over a median follow-up of 8 to 10 years, a 2-year difference in age over this period of time may have little or no effect. While patients in the testosterone group may have been seen by us slightly more often, there was very limited change in weight with respect to number of visits or motivations.⁴⁷ We should also note that treatment of diabetes was carried out by the patients' diabetes physicians, which was not under our control.

Our findings show that long-term TTh led to sustained remission of diabetes in one-third of patients with T2DM and hypogonadism. Although studies on lifestyle interventions as well as bariatric surgery have shown that T2DM can go into remission, to our knowledge, this is the first study demonstrating that TTh achieves such a successful rate of diabetes remission. The clinical significance of these results is further enhanced by the fact that one-third of men with T2DM have hypogonadism. Hence, physicians encounter men with hypogonadism and diabetes very frequently. It is remarkable that, while T2DM leads to hypogonadism, treatment of hypogonadism results in remission of diabetes itself. In the absence of randomized clinical trials, the data from this large, long-term registry study are important since one-third of all patients reversed their diabetes. Real-world data such as these have unique significance and are important. The reversal of hyperglycaemia and diabetes after testosterone treatment has not previously been shown.

Randomized controlled trials are now needed to confirm these data. One such trial is currently being conducted and the results are expected to be published soon.⁴⁸

ACKNOWLEDGMENTS

We thank all patients who participated in the study. The work described in this paper received partial financial support for data entry and statistical analyses from Bayer AG, Berlin, Germany, the manufacturer of the testosterone preparation used in this study.

CONFLICTS OF INTEREST

K.S.H. and A.H. have received partial financial compensation for data entry, travel grants and speaker honoraria from Bayer AG. G.D.

received payment for statistical analyses from Bayer AG. F.S. is a retired full-time employee of Bayer AG and works as a consultant to Bayer AG. M.H. and S.D. have received speaker honoraria from Bayer AG. P.D. and A.T. have no conflict of interest regarding this manuscript.

AUTHOR CONTRIBUTIONS

K.S.H. and A.H. treated the patients and performed the data entry. A. H. and F.S. designed the study and collected the data. G.D. performed the statistical analyses. K.S.H., A.H., F.S., M.H., S.D., P.D. and A.T. interpreted the data and wrote and reviewed the manuscript.

ORCID

Karim Sultan Haider  <https://orcid.org/0000-0003-4396-9324>

Farid Saad  <https://orcid.org/0000-0002-0449-6635>

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. *Diabetes Care.* 2007;30:911-917.
3. Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabetes. *Diabetes Care.* 2018;41:1516-1525.
4. Bhatia V, Chaudhuri A, Tomar R, Dhindsa S, Ghanim H, Dandona P. Diabetes, low testosterone and high C-reactive protein concentrations predict low hematocrit in type 2 diabetes. *Diabetes Care.* 2006;29:2289-2294.
5. Dhindsa S, Ghanim H, Batra M, et al. Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. *Diabetes Care.* 2016;39:82-91.
6. 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.
7. Traish AM. Benefits and health implications of testosterone therapy in men with testosterone deficiency. *Sex Med Rev.* 2018;6:86-105.
8. Xu W, Morford J, Mauvais-Jarvis F. Emerging role of testosterone in pancreatic β -cell function and insulin secretion. *J Endocrinol.* 2019;240(3):R97-R105. <https://doi.org/10.1530/JOE-18-0573>.
9. Joyce KE, Biggs ML, Djoussé L, et al. Testosterone, dihydrotestosterone, sex hormone-binding globulin, and incident diabetes among older men: the cardiovascular health study. *J Clin Endocrinol Metab.* 2017;102:33-39.
10. Wei L, Lai EC, Kao-Yang YH, et al. Incidence of type 2 diabetes mellitus in men receiving steroid 5 α -reductase inhibitors: population-based cohort study. *BMJ.* 2019;365:11204.
11. Mauvais-Jarvis F. Androgen-deprivation therapy and pancreatic β -cell dysfunction in men. *J Diabetes Complications.* 2016;30:389-390.
12. Saad F. Testosterone therapy and glucose homeostasis in men with testosterone deficiency (hypogonadism). *Adv Exp Med Biol.* 2017;1043:527-558.
13. Yassin A, Haider A, Haider KS, et al. Testosterone therapy in men with hypogonadism prevents progression from prediabetes to type 2 diabetes: eight-year data from a registry study. *Diabetes Care.* 2019;42:1104-1111.
14. Rabijewski M, Papierska L, Zgliczynski W, Piatkiewicz P. The incidence of hypogonadotropic hypogonadism in type 2 diabetic men in polish population. *BioMed Res Int.* 2013;2013:767496.

15. Keating NL, O'Malley A, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. *J Natl Cancer Inst*. 2012;104:1518-1523.
16. Jhan JH, Yeh HC, Chang YH, et al. New-onset diabetes after androgen-deprivation therapy for prostate cancer: a nationwide propensity score-matched four-year longitudinal cohort study. *J Diabetes Complications*. 2018;32:688-692.
17. Jones TH, Arver S, Behre HM, et al. Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). *Diabetes Care*. 2011;34:828-837.
18. Salonia A, Bettocchi C, Carvalho J, et al. *EAU Guidelines on sexual and reproductive health* <https://uroweb.org/guideline/sexual-and-reproductive-health/> accessed April 27, 2020.
19. Traish AM, Haider A, Haider KS, Doros G, Saad F. Long-term testosterone therapy improves cardiometabolic function and reduces risk of cardiovascular disease in men with hypogonadism: a real-life observational registry study setting comparing treated and untreated (control) groups. *J Cardiovasc Pharmacol Therap*. 2017;22:414-433.
20. Katsuki A, Sumida Y, Gabazza EC, et al. Homeostasis model assessment is a reliable indicator of insulin resistance during follow-up of patients with type 2 diabetes. *Diabetes Care*. 2001;24:362-365.
21. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. *Diabetes Care*. 2004;27:1487-1495.
22. Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of clinical Lipidology 2016. *J Clin Lipidol*. 2016;10:S1-S43.
23. Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease: new insights from epidemiology, genetics, and biology. *Circ Res*. 2016;118:547-563.
24. Lin A, Nerlekar N, Rajagopalan A, et al. Remnant cholesterol and coronary atherosclerotic plaque burden assessed by computed tomography coronary angiography. *Atherosclerosis*. 2019;284:24-30.
25. Muralidharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. *Eur J Endocrinol*. 2013;169:725-733.
26. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. *BJU Int*. 2019;123:519-529.
27. Yassin A, AlRumaihi K, Alzubaidi R, Alkadhhi S, al Ansari A. Testosterone, testosterone therapy and prostate cancer. *Aging Male*. 2019;22: 219-227.
28. Zhang X, Zhong Y, Saad F, et al. Testosterone therapy may reduce prostate cancer risk due to testosterone deficiency at a young age via stabilizing serum testosterone levels. *Aging Male*. 2020;23:112-118.
29. Khan AH, Pessin JE. Insulin regulation of glucose uptake: a complex interplay of intracellular signalling pathways. *Diabetologia*. 2002;45: 1475-1483.
30. Mitsuhashi K, Senmaru T, Fukuda T, et al. Testosterone stimulates glucose uptake and GLUT4 translocation through LKB1/AMPK signaling in 3T3-L1 adipocytes. *Endocrine*. 2016;51:174-184.
31. Ghanim H, Dhindsa S, Batra M, et al. Effect of testosterone on FGF2, MRF4, and myostatin in hypogonadotropic hypogonadism: relevance to muscle growth. *J Clin Endocrinol Metab*. 2019;104:2094-2102.
32. Ghanim H, Dhindsa S, Batra M, et al. Testosterone increases the expression and phosphorylation of AMP kinase α in men with hypogonadism and type 2 diabetes. *J Clin Endocrinol Metab*. 2020;105:1169-1175.
33. Zhu L, Zhou J, Pan Y, et al. Glucagon-like peptide-1 receptor expression and its functions are regulated by androgen. *Biomed Pharmacother*. 2019;120:109555.
34. Navarro G, Xu W, Jacobson DA, et al. Extranuclear actions of the androgen receptor enhance glucose-stimulated insulin secretion in the male. *Cell Metab*. 2016;23:837-851.
35. Xu W, Niu T, Xu B, Navarro G, Schipma MJ, Mauvais-Jarvis F. Androgen receptor-deficient islet β -cells exhibit alteration in genetic markers of insulin secretion and inflammation. A transcriptome analysis in the male mouse. *J Diabetes Complications*. 2017;31:787-795.
36. Kooptiwut S, Hanchang W, Semprasert N, Junking M, Limjindaporn T, Yenchitsomanus PT. Testosterone reduces AGTR1 expression to prevent β -cell and islet apoptosis from glucotoxicity. *J Endocrinol*. 2015; 224:215-224.
37. Dimitriadis GK, Randeve HS, Saboor Aftab SA, et al. Metabolic phenotype of male obesity-related secondary hypogonadism pre-replacement and post-replacement therapy with intra-muscular testosterone undecanoate therapy. *Endocrine*. 2018;60:175-184.
38. Livingstone DE, Barat P, Di Rollo EM, et al. 5 α -reductase type 1 deficiency or inhibition predisposes to insulin resistance, hepatic steatosis, and liver fibrosis in rodents. *Diabetes*. 2015;64:447-458.
39. Dowman JK, Hopkins LJ, Reynolds GM, et al. Loss of 5 α -reductase type 1 accelerates the development of hepatic steatosis but protects against hepatocellular carcinoma in male mice. *Endocrinology*. 2013;154:4536-4547.
40. Zhang H, Liu Y, Wang L, et al. Differential effects of estrogen/androgen on the prevention of nonalcoholic fatty liver disease in the male rat. *J Lipid Res*. 2013;54:345-357.
41. Hazlehurst JM, Oprescu AI, Nikolou N, et al. Dual-5 α -reductase inhibition promotes hepatic lipid accumulation in man. *J Clin Endocrinol Metab*. 2016;101:103-113.
42. Upreti R, Hughes KA, Livingstone DE, et al. 5 α -reductase type 1 modulates insulin sensitivity in men. *J Clin Endocrinol Metab*. 2014;99: E1397-E1406.
43. Al-Mrabeah A, Zhyzhneuskaya SV, Peters C, et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab*. 2020;31:233-249.
44. Lean MEJ, Leslie WS, Barnes AC, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391:541-551.
45. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the primary care diabetes society (PCDS). *Br J Diabetes*. 2019;19:73-76.
46. Saad F, Doros G, Haider KS, Haider A. Differential effects of 11 years of long-term injectable testosterone undecanoate therapy on anthropometric and metabolic parameters in hypogonadal men with normal weight, overweight and obesity in comparison with untreated controls: real-world data from a controlled registry study. *Int J Obes (Lond)*. 2020;44:1264-1278.
47. Rodriguez-Cristobal JJ, Alonso-Villaverde C, Panisello JM, et al. Effectiveness of a motivational intervention on overweight/obese patients in the primary healthcare: a cluster randomized trial. *BMC Family Pract*. 2017;18:74.
48. Wittert G, Atlantis E, Allan C, et al. Testosterone therapy to prevent type 2 diabetes mellitus in at-risk men (T4DM): design and implementation of a double-blind randomized controlled trial. *Diabetes Obes Metab*. 2019;21:772-780.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Haider KS, Haider A, Saad F, et al. Remission of type 2 diabetes following long-term treatment with injectable testosterone undecanoate in patients with hypogonadism and type 2 diabetes: 11-year data from a real-world registry study. *Diabetes Obes Metab*. 2020;22: 2055-2068. <https://doi.org/10.1111/dom.14122>