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Research Article

Testosterone Prevention Role in Men's Health: Diabetes Mellitus

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Abstract

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 HbA1c 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 87menwith hypogonadism served as untreated control subjects. Metabolic and anthropometric parameters were measured twice yearly for 8 years.

Results*:* HbA1c decreased by 0.3960.03% (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 (HbA1c <5.7%). In the untreated group, 40.2% progressed to T2D (HbA1c >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.

Introduction

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 in ependently 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 ist 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 (HbA1c) 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 in this study were pooled fromtwo 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 HbA1c 5.7–6.4% (39–46 mmol/mol), and total testosterone levels #12.1 nmol/L (;350 ng/dL) combined with symptoms of hypogonadism.

Two hundred and twenty-nine menreceived 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, HbA1c, 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] 3 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]265)3triglycerides (mmol/L). LAP is superior to BMI in predicting HOMA-IR [20], fasting glucose, and HbA1c [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 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.

	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 Followup (years)	6.6 ± 2.2	5.6 ± 1.6	
Median Followup (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	<0.005
HDL Cholesterol (mmol/L)	1.1 ± 0.3	1.4 ± 0.4	<0.001
LDL Cholesterol (mmol/L)	4.1 ± 0.7	3.4 ± 0.9	<0.001
Triglycerides (mmol/L)	2.8 ± 0.9	2.2 ± 1.1	<0.001
Non-HDL Cholesterol (mmol/L)	5.8 ± 1.2	5.0 ± 1.4	<0.001
SBP (mmHg)	136.9 ± 13.5	129.8 ± 12.7	<0.001
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			

Table 1: Baseline characteristics in the T-group and the untreated group.

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 HbA1c values; however, the T group was 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 6 2.1 nmol/L) than in the untreated group (9.662.4 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 HbA1c 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 (Figure 1: A,B,C,D).

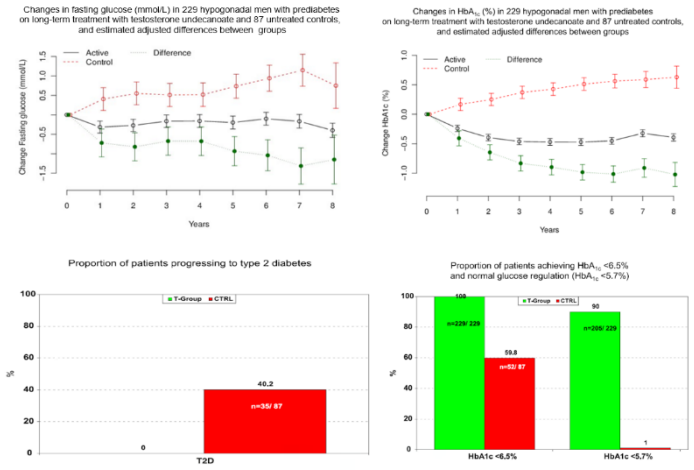

Figure 1: A and B: Changes in fasting glucose and HbA1c in 229 men with hypogonadism and prediabetes onlongerm treatment with TU and 87 untreated control subjects and estimated adjusted differences between groups. Data are least squares means 6 SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score. C: Proportion of patients achieving an HbA1c,6.5% and normal glucose regulation (HbA1c,5.7%). D: Proportion of patients progressing to T2D.

TTh led to substantial improvements in glycemic parameters. Both fasting blood glucose and HbA1c values were reduced in the T-group but increased in the untreated group (Figure 1A and B). At 8 years, HbA1c decreased in the T-group by 0.39 ± 0.03% (P , 0.0001) (Figure 1B), whereas it increased by 0.63 ± 0.1% in the untreated group (P , 0.0001). The differences in glucose concentrations and HbA1c were substantial and significant between the twogroups throughout the entire follow-up period, amounting to a difference in HbA1c of 1.02% at 8 years. At the last observation, all 229 patients in the T-group had an HbA1c of ,6.5% (48 mmol/mol), and 205 (90%) achieved normal glucose regulation with an HbA1c ,5.7% (39 mmol/mol) (Figure 1C). In the untreated group, only 1 (1%) of the 87 patients had an HbA1c ,5.7% (39 mmol/mol), whereas 35 (40.2%) had progressed to frank T2D with an HbA1c .6.5% (48 mmol/mol) (Figure 1D).

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) (Figure 2). Body weight decreased by 9.260.4 kg in the T-group and increased by 8 6 1.3 kg in the untreated group (Supplementary Figure 2). Waist circumference decreased by 6.8 ± 0.3 cm in the T-group and increased by 7.4 61 cm in the untreated group (Supplementary Figure 2). The waist:height ratio decreased in the T-group and increased in the untreated group (Supplementary Figure 2). Changes in weight translated into corresponding changes in BMI (Supplementary Figure 2).

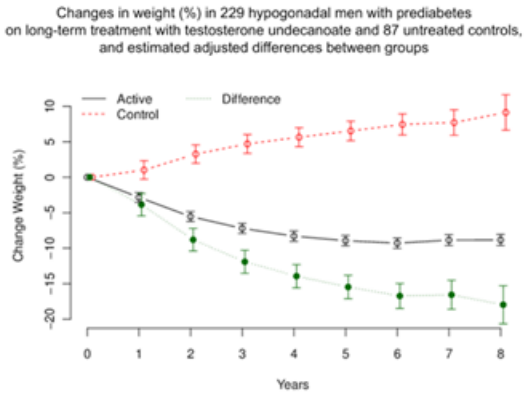

Figure 2: Changes in weight (%) in 229menwith hypogonadism and prediabetes on long-term treatment with TU and 87 untreated control subjects and estimated adjusted differences between groups. Data are least squares means 6 SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score.

TTh resulted in a reduction in total cholesterol, LDL, and triglyceride levels and an increase in HDLlevels (Supplementary Figure 3A–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) (Figure 3A). 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. 3B). LAP decreased in the T-group by 33.3 ± 2.6 cm z mmol/L (P,0.0001), whereas it increased by 41.268.4 cm z mmol/L (P,0.0001) in the untreated group (Fig. 3C). 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 6 0.5 mmol/L (P 0.0001) (Fig. 3D and Supplementary Table 1).

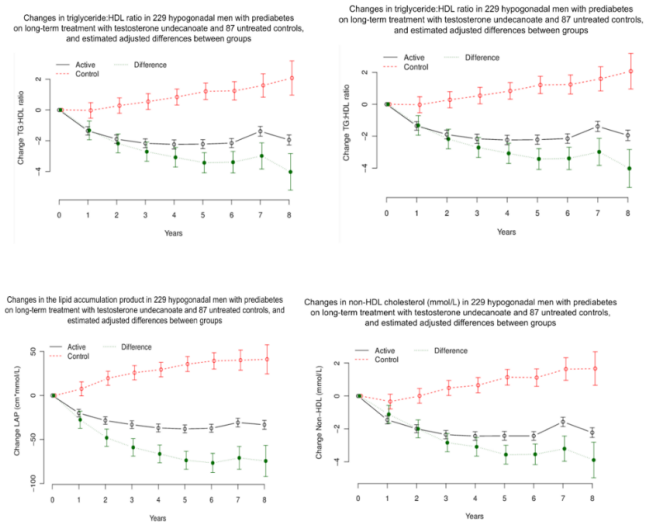

Figure 3: Changes in triglyceride (TG): HDL ratio (A), TyG index (B), LAP (C), and non-HDL cholesterol (D) in 229 men with hypogonadism and prediabetes on long-term treatment withTUand 87 untreated control subjects and estimated adjusted differences between groups. Data are least squaresmeans6 SE after adjustment for age, waist circumference, weight, fasting glucose, SBP and DBP, total cholesterol, HDL, LDL, triglycerides, and AMS score.

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 an 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 Figure 4). Testosterone replacement also led to predictable increases in hemoglobin concentration and hematocrit (Supplementary Figure 5A 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 anone (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 HbA1c 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 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 (HbA1c,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 HbA1c 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 mU/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 (Figure 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 229patients). 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 HbA1c, 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 metaanalysis 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 (23.3 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 reduction in three lipid parameters that are ratio, TyG index, and LAP. The mared 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 thecurrent 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 inastudy oflong-termTTh [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-occurrenceof 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 HbA1c 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. It is remarkable that studies came later such as interruption of TTh [41,42], also the effects of blodd sugar control in T1DM [43].

	T-group	P-value for change from baseline	Control	P-value for change from baseine	Estimated adjusted differnce between groups [95% CI]	P value for estimated adjusted differnce between groups
Anthropometric Parameters						
Weight (Kg)	-9.2 ± 0.4	<0.0001	8 ± 1.3	<0.0001	-17.2 [-20; -14.5]	<0.0001
Weight Change (%)	-8.8 ± 0.4	<0.0001	9.1 ± 1.3	<0.0001	-18 [-20.6; -15.3]	<0.0001
Waist Circumference (cm)	-6.8 ± 0.3	<0.0001	7.4 ± 1	<0.0001	-14.2 [-16.3; -12.1]	<0.0001
BMI (Kg/m2)	-2.9 ± 0.2	<0.0001	2.5 ± 0.5	<0.0001	-5.4 [-6.3; -4.4]	<0.0001
Waist: Height Ratio	-0.04 ± 0.0	<0.0001	0.04 ± 0.0	<0.0001	-0.08 [-0.09; -0.07]	<0.0001
Glycemic Control						
HbA1c (%)	-0.4 ± 0.0	<0.0001	0.6 ± 0.1	<0.0001	-1.0 [-1.2; -0.8]	<0.0001
Fasting Glucose (mmol/L)	-0.4 ± 0.1	<0.0001	0.8 ± 0.3	<0.05	-1.1 [-1.8; -0.5]	<0.0005
Triglyceride: HDL ratio	-1.9 ± 0.2	<0.0001	2.1 ± 0.6	<0.0005	-4.0 [-5.2; -2.8]	<0.0001
TyG Index	-0.2 ± 0.0	<0.0001	0.3 ± 0.1	<0.005	-0.6 [-0.8; -0.4]	<0.0001
Lipid Accumulation Product (LAP, cm*mmol/L)	-33.3 ± 2.6	<0.0001	41.2 ± 8.4	<0.0001	-74.5 [92.2; -56.8	<0.0001
Lipids						
Total Cholesterol (mmol/L)	-1.3 ± 0.1	<0.0001	0.8 ± 0.3	<0.05	-2.2 [-2.9; -1.4]	<0.0001
HDL Cholesterol (mmol/L)	-0.3 ± 0.0	<0.0001	0.2 ± 0.1	<0.05	0.4 [0.3; 0.6]	<0.0001
LDL Cholesterol (mmol/L)	-0.9 ± 0.1	<0.0001	0.5 ± 0.2	<0.05	-1.4 [-1.8; -1]	<0.0001
Triglycerides (mmol/L)	-0.5 ± 0.1	<0.0001	0.5 ± 0.2	<0.05	-1.0 [-1.4; -0.6]	<0.0001
Non-HDL Cholesterol (mmol/L)	-2.2 ± 0.2	<0.0001	1.7 ± 0.5	<0.005	-3.9 [-5.0; -2.8]	<0.0001
LDL HDL Ratio	-1.4 ± 0.1	<0.0001	0.9 ± 0.3	<0.001	-2.3 [-2.9; -1.8]	<0.0001
Remnant Cholesterol (mg/dL)	-49.1 ± 11	<0.0001	12.4 ± 13	NS	-61.5 [-96.6; -26.4]	<0.001
Blood Pressure and Hemodynamic Parameters						
Systolic Blood Pressure (mmHg)	-11.9 ± 0.7	<0.0001	6.2 ± 2.2	<0.01	-18.1 [-22.8; -13.5]	<0.0001
Diastolic Blood Presure (mmHg)	-8.1 ± 0.5	<0.0001	7.7 ± 1.6	<0.0001	-15.8 [-19.1; -12.5]	<0.0001
Heart Rate (bpm)	-3.9 ± 0.6	<0.0001	-7.3 ± 2.8	<0.05	3.4 [-2.4; 9.2]	NS
Pulse Pressure	-3.7 ± 0.7	<0.0001	-2.3 ± 2.6	NS	-1.3 [-6.6; 4]	NS
Rate Pressure Product	-2155 ± 156	<0.0001	-1653 ± 699	<0.05	-501 [-1939; 937]	NS
Quality of Life						
AMS	-18.3 ± 0.8	<0.0001	9.2 ± 2.7	<0.001	-27.6 [-33.2; -22]	<0.0001
Testosterone						

Total Cholesterol (mmol/L)	8.5 ± 0.3	<0.0001	-0.9 ± 1.2	NS	9.4 [7.0; 11.8]	<0.0001

Table 2: Changes at 8 years from baseline in testosterone treated group (T-group) and untreated hypogonadal control group (control) and estimated differnce between groups at 8 years, adjusted for baseline age, weight, waist circumference, fasting glucose, lipids, systolic and diastolic blood pressure, and aging males' symptoms scale (ams) (Data are shown as least squares means ± SE.

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 HbA1c 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 longterm 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.

Disclosure

Authors have nothing to disclose

Reference

1. Gyawali P, Martin SA, Heilbronn LK, et al. (2018) The role of sex hormone-binding globulin (SHBG), testosterone, and other sex steroids, on the development of type 2 diabetes in a cohort of community-dwelling middle-aged to elderly men. Acta Diabetol 55: 861-872.
2. Buysschaert M, Medina JL, Bergman M, Shah A, Lonier J (2015) Prediabetes and associated disorders. Endocrine 48: 371-393.
3. Colangelo LA, Ouyang P, Liu K, et al. (2009) Association of endogenous sex hormones with diabetes and impaired fasting glucose in men: Multi-Ethnic Study of Atherosclerosis. Diabetes Care 32: 1049-1051.
4. Dhindsa S, Prabhakar S, SethiM,Bandyopadhyay A, Chaudhuri A, Dandona P (2004) Frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes. J Clin Endocrinol Metab 89: 5462-5468.
5. Dhindsa S, Miller MG, McWhirter CL, et al. (2010) Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care 33: 1186-1192.
6. American Diabetes Association (2018) Summary of revisions: Standards of Medical Care in Diabetesd 2018. Diabetes Care 41: S4-S6.
7. Goodman-Gruen D, Barrett-Connor E (2000) Sex differences in the association of endogenous sex hormone levels and glucose tolerance status in oldermen andwomen. Diabetes Care 23: 912-918.
8. Ligthart S, van Herpt TT, Leening MJ, et al. (2016) Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol 4: 44-51.
9. Rabijewski M, Papierska L, Piatkiewicz P (2014) The prevalence of prediabetes in population of Polish men with late-onset hypogonadism. Aging Male 17: 141-146.
10. Grams J, Garvey WT (2015) Weight loss and the prevention and treatment of type 2 diabetes using lifestyle therapy, pharmacotherapy, and bariatric surgery: mechanisms of action. Curr Obes Rep 4: 287-302.
11. Garvey WT, Mechanick JI, Brett EM, et al., Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines (2016) American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract 22: 1–203.
12. National Diabetes Education Program (NDEP). Guiding Principles for the Care of People With or at Risk for Diabetes [Internet], 2018. Available from https://www.niddk.nih.gov/health-information/communication-programs/ ndep/health-professionals/guiding-principlescare-people-risk-diabetes. Accessed 29 August 2018.
13. Saad F, Yassin A, Doros G, Haider A (2016) Effects of long-term treatment with testosterone on weight and waist size in 411 hypogonadal men with obesity classes I-III: observational data fromtwo registry studies. Int J Obes 40: 162-170.
14. Traish AM, Haider A, Haider KS, Doros G, Saad F (2017) 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 Ther 22: 414-433.
15. Mark L, Vallejo-Vaz AJ, Reiber I, Paragh G, Kondapally Seshasai SR, et al. (2015) Non-HDL cholesterol goal attainment and its relationship with triglyceride concentrations among diabetic subjects with cardiovascular disease: a nationwide survey of 2674 individuals in Hungary. Atherosclerosis 241: 62-68.
16. Liu JR, Liu BW, Yin FZ (2017) Change in nonhighdensity lipoprotein cholesterol levels in adults with prediabetes. Medicine (Baltimore) 96: e8461.
17. McLaughlin T, Reaven G, Abbasi F, et al. (2005) Is there a simple way to identify insulin-resistant individuals at increased risk of cardiovascular disease?. Am J Cardiol 96: 399-404.
18. Sanchez-Inigo L, Navarro-Gonzalez D, Fernandez-Montero A, Pastrana-Delgado J, Martınez JA (2016) The TyG index may predict the development of cardiovascular events. Eur J Clin Invest 46: 189-197.
19. Guerrero-Romero F, Simental-Mend´ıa LE, Gonz´alez-Ortiz M, et al. (2010) The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemichyperinsulinemic clamp. J Clin Endocrinol Metab 95: 3347-3351.

20. Look AHEAD Research Group (2014) Eight-year weight losses with an intensive lifestyle intervention: the Look AHEAD study. Obesity (Silver Spring) 22: 5-13.

21. Holzapfel C, Cresswell L, Ahern AL, et al. (2014) The challenge of a 2-year follow-up after intervention for weight loss in primary care. Int J Obes 38: 806-811.

22. Khera R, Murad MH, Chandar AK, et al. (2016) Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 315: 2424-2434.

23. Saad F, Yassin D, Dorsos G, Yassin A (2017) Most hypogonadal men with type 2 diabetes mellitus (T2DM) achieve HbA1c targets when treated with testosterone undecanoate injections (TU) for up to 12 years (Abstract). Diabetes 66: A305.

24. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH (2013) Testosterone deficiency is associated with Increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol 169: 725-733.

25. Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S (2019) Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. BJU Int 123: 519-529.

26. Corona G, Giagulli VA, Maseroli E, et al. (2016) Therapy of endocrine disease: testosterone supplementation and body composition: results from a meta-analysis study. Eur J Endocrinol 174: R99-R116.

27. Kalyani RR, Metter EJ, Ramachandran R, Chia CW, Saudek CD, et al. (2012) Glucose and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. J Gerontol A Biol Sci Med Sci 67: 74-81.

28. SrikanthanP, Karlamangla AS (2011) Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab 96: 2898-2903.

29. Kapoor D, Goodwin E, Channer KS, Jones TH (2006) Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral and hypercholesterolaemia in hypogonadal men with type 2 diabetes. Eur J Endocrinol 154: 899-906.

30. Jones TH, Arver S, Behre HM, et al., TIMES2 Investigators (2011) Testosterone replacement in hypogonadal men with type 2 diabetes and/or metabolic syndrome (the TIMES2 study). Diabetes Care 34: 828-837.

31. Dhindsa S, Ghanim H, Batra M, et al. (2016) Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. Diabetes Care 39: 82-91.

32. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF (2014) Triglyceride-to-high-density-lipoprotein- cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. J Investig Med 62: 345-349.

33. Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members (2014) An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia–full report. J Clin Lipidol 8: 29-60.

34. Liu J,Sempos C,Donahue RP, Dorn J, Trevisan M, Grundy SM (2005) Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabetes Care 28: 1916-1921.

35. Catapano AL, Reiner Z, De Backer G, et al., European Society of Cardiology (ESC); European Atherosclerosis Society (EAS) (2011) ESC/EAS Guidelines for the management of dyslipidaemias: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 217: 1-44.

36. Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA (2016) National Lipid Association Annual Summary of Clinical Lipidology 2016. J Clin Lipidol 10: S1-S43.

37. Hulman A, Simmons RK, Brunner EJ, et al. (2017) Trajectories of glycaemia, insulin sensitivity and insulin secretion in South Asian and white individuals before diagnosis of type 2 diabetes: a longitudinal analysis from the Whitehall II cohort study. Diabetologia 60: 1252-1260.

38. Malmstr¨om H, Walldius G, Carlsson S, et al. (2018) Elevations of metabolic risk factors 20 years or more before diagnosis of type 2 diabetes: experience from the AMORIS study. Diabetes Obes Metab 20: 1419-1426.

39. Bommer C, Heesemann E, Sagalova V, et al. (2017) The global economic burden of diabetes in adults aged 20-79 years: a cost-of-illness study. Lancet Diabetes Endocrinol 5: 423-430.

40. Wittert G, Atlantis E, Allan C, et al. (2019) 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 21: 772-780.

41. Yassin A, Nettleship JE, Talib RA, Almehmadi Y, Doros G (2016) Effects of testosterone replacement therapy withdrawal and retreatment in hypogonadal elderly men upon obesity, voiding function and prostate safety parameters. Aging Male 19: 64-9.

42. Yassin A, Almehmadi Y, Saad F, Doros G, Gooren L (2016) Effects of intermission and resumption of long-term testosterone replacement therapy on body weight and metabolic parameters in hypogonadal in middle-aged and elderly men. Clinical Endocrinilogy 84: 107-14.

43. Saad F, Yassin A, Almehmadi Y, Doros G, Gooren (2015) Effects of long term testosterone replacement therapy, with a temporary intermission, on glycemic control of nine hypogonadal men with type 1 diabetes mellitus – a series of case reports, The Aging Male 18: 164-168.