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Testosterone therapy for prevention and reversal of type 2 diabetes in men with low testosterone

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Abstract

Men with obesity and/or type 2 diabetes (T2D) have a high prevalence of testosterone deficiency (TD). Similarly, men with TD have an increased risk of developing obesity and/or T2D, and further body fat accumulation and deterioration of glycemic control create a vicious cycle. The landmark testosterone for diabetes mellitus trial, the largest randomized controlled trial of testosterone therapy (TTh) to date, confirms the beneficial effects of TTh on fat loss and gain in muscle mass, and that TTh for 2 years significantly reduces the risk of incident T2D, and may also reverse T2D. The testosterone for diabetes mellitus trial suggests that TTh reduces the risk of T2D and results in greater improvement in sexual function and well-being, beyond lifestyle intervention alone.

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Introduction

Type 2 diabetes (T2D) is one of the fastest growing chronic diseases worldwide [1], in large part driven by (abdominal) obesity. Obesity is a strong risk factor for testosterone deficiency (TD), which further increases fat accumulation, insulin resistance (IR), and deterioration of glycemic control, creating a vicious circle. Due to the common co-occurrence of obesity and T2D, the term 'diabesity' was proposed to describe this condition [2].

Weight loss by lifestyle intervention is a cornerstone treatment for obesity and/or T2D. However, a profound weight loss of about 10% - and maintenance of reduced body weight - is required to prevent diabetes [3,4]. The problem is that long-term weight loss maintenance is poor, with subjects regaining half of the lost weight after 1 year and nearly three quarter during the first three years [5–7]. Less than 3% of subjects maintain their weight loss at all annual visits for 4–5 years after completion of a weight-loss program [5–7]. Hence, lifestyle intervention alone is not sufficient to treat or prevent obesity/T2D, as demonstrated by the ongoing and increasing prevalence of these dysmetabolic conditions.

Low testosterone and IR

Men with low testosterone have increased IR [8–11], which is one of the root causes of T2D [12–17]. The significant graded inverse association between testosterone and IR is independent of age [18], and low testosterone is associated with IR even in relatively young non-obese men [8,9,11]. A positive correlation has been shown between serum testosterone levels in men and insulin sensitivity, across the full spectrum of glucose tolerance regardless of age [19] Box 1.

Randomized trials of TTh in men with T2D

Randomized controlled trials (RCTs) evaluating changes in IR and glycemic control after testosterone therapy (TTh) in men with TD and T2D have shown inconsistent results [25]. Some studies showed significant reduction in Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) [10,26,27] and HbA1c [26–29], whereas others showed no change in HOMA-IR [30–34] or HbA1c [10,29,30,32–34]. There are several explanations for these inconsistent findings. Most RCTs of TTh in men with T2D included few subjects and were of short duration. The importance of TTh duration was underscored in the BLAST study, in which a significant improvement in HOMA-IR was achieved week 82 (after 52-week open-label extension) but not after the 30-week double-blind phase [34]. Similarly, a 2-year RCT of TTh in men with T2D showed that the significant reductions in HbA1c and HOMA-IR at year 1 [28] became greater after year 2 (Table 1) [35]. Long-term TTh in men with T2D maximizes improvement in glycemic control and may also reduce mortality [36].

Box 1. Bidirectional link between low testosterone, obesity and type 2 diabetes.

The bidirectional link between TD and obesity/T2D on the one hand, and between obesity/T2D and TD on the other hand, is well established. Observational studies suggest that low testosterone is associated with both current and future IR, obesity, metabolic syndrome and T2D [20]. Importantly, the risk of T2D seems to increase at a higher testosterone threshold than previously thought. The Men Androgen Inflammation Lifestyle Environment and Stress (MAILES) study found a significantly increased incidence of T2D in men with testosterone levels below 16 nmol/L (461 ng/dL) during a follow-up of 5 years, independent of T2D risk prediction models used in routine clinical practice [21]. The MAILES study concluded that screening for low testosterone in addition to risk factors included in T2D risk assessment tools, would identify a large subgroup of distinct men who might benefit from targeted preventive interventions [21].

A meta-analysis showed that men with testosterone levels above 15.5 nmol/L (447 ng/dL) had a 42% reduced risk of T2D compared to men with testosterone levels below 15.5 nmol/L [22]. Another large meta-analysis of 13 prospective population studies including 16,709 men showed that higher testosterone levels were associated with a significantly reduced risk of T2D by 38% [23]. A 14-year follow-up study collected health record data of 550 men with T2D to evaluate the influence of baseline testosterone levels on T2D outcomes [24]. Mean baseline total testosterone for the entire cohort was 13.7 nmol/L (395 ng/dL). Lower baseline total testosterone levels were significantly associated with a higher BMI and increased risk of stroke at follow-up. Mortality rate was nearly twice as high in patients with lower total testosterone compared to normal baseline total testosterone (5.0% vs 2.8% per year). During the 14-year follow-up period, 36.1% of men with normal baseline testosterone died vs. 55.8% of men with TD at baseline. The age-adjusted hazard ratio for higher mortality associated with low total testosterone corresponded to 3.2 years reduced life expectancy for men who have both hypogonadism and T2D, compared to men who only have T2D.

A topic of scientific debate is the relative strength of the bidirectional link between low testosterone and diabesity, i.e., whether obesity (and to a lesser extent T2D, especially if poorly controlled) has a greater effect on reducing testosterone, or whether low testosterone has a greater effect on body fat accumulation and IR [20]. However, this is irrelevant for clinical practice. The bidirectional link between low testosterone and diabesity creates a vicious cycle, in which one condition worsens the other, regardless which came first. In clinical practice, the important question is how to most effectively and sustainably break this vicious cycle.

In most trials, subjects had well-controlled T2D and hence there was little room for improvement. The importance of taking into consideration concomitant use of diabetes drugs was underscored in a 52-week study of TTh in men with T2D, in which no diabetes drugs were given before or during the study period, showing a significant reduction in HOMA-IR and HbA1c [37].

HOMA-IR may not be a good marker of IR in patients with severe T2D because β-cell loss and inadequate insulin secretion leads to inappropriately low insulin levels and HOMA-IR [10]. The best way to assess IR, especially in patients with T2D, is through hyperglycemic euglycemic clamps. In a rigorous RCT, TTh for 24 weeks in 44 men with obesity and T2D was shown to reduce IR (measured by HE clamp) by 32% [10].

Table 1

RCT showing importance of long-term TTh to achieve maximal improvement in insulin resistance and glycemic control [28,35]].

Baseline	Year 1	Year 2
HbA1c		
T-group: 8.12% P-group: 7.89%	T-group: 7.18% P < 0.001 P-group: 7.65% P < 0.004 Between group change, P < 0.001	T-group: 6.60% P < 0.001
HOMA-IR		
T-group: 11.45 P-group: 10.70	T-group: 6.81 P < 0.001 P-group: 10.18 P < 0.203 Between group change, P < 0.001	T-group: 5.51 P < 0.001

TTh, testosterone therapy.

Real-world evidence studies of TTh for prevention of T2D

It is well documented that TTh consistently results in significant reduction in fat mass and increase in lean mass [38,39], body composition changes that have beneficial metabolic effects [39,40]. In accordance with this, real-world evidence (RWE) studies of men with hypogonadism have shown that treatment with testosterone undecanoate injections for 8–11 years completely prevented progression of prediabetes to T2D by restoring normoglycemia [41], and improved glucose metabolism in men with T2D, of whom 34.3% experienced remission [42]. In line with this, 4-year follow-up data from the BLAST study showed significantly reduced need of diabetes drugs in men with T2D who continued receiving TTh without interruption [43]. A notable observation in all long-term RWE studies is that men with TD not receiving TTh experience a significant increase in body weight, waist size, and deterioration in glycemic control over time [41–44]. This underscores the importance of also considering risks of untreated TD.

Testosterone for diabetes mellitus trial – TTh for prevention T2D in men with low-normal T

The testosterone for diabetes mellitus (T4DM) trial was designed to determine the efficacy and safety of TTh for prevention and/or remission of T2D, beyond the effects of lifestyle intervention alone. It enrolled 1007 men and is the largest RCT ever conducted. Inclusion criteria were age 50–74 years, abdominal obesity (waist circumference ≥95 cm), testosterone ≤14.0 nmol/L (403.8 ng/dL), and impaired glucose

tolerance (prediabetes, defined as oral glucose tolerance test [OGTT] 2-h glucose 7.8–11.0 mmol/L) or newly diagnosed T2D (defined as OGTT 2-h glucose 11.1–15.0 mmol/L) [45]. All men were given the same diet/exercise program and randomly assigned to receive treatment with testosterone undecanoate injection (n = 504) or placebo (n = 503) for 2 years.

After 2 years, T levels had increased by 0.76 nmol/L (22 ng/dL) in the placebo group and 3.41 nmol/L (ng/dL) in the T group. The prevalence of T2D was 21% in placebo-treated and 12% in testosterone-treated men (Figure 1). This corresponded to a significantly reduced risk of T2D by 41% (RR: 0·59, p = 0·0007) in T treated men. A subgroup analysis showed that (Figure 1):

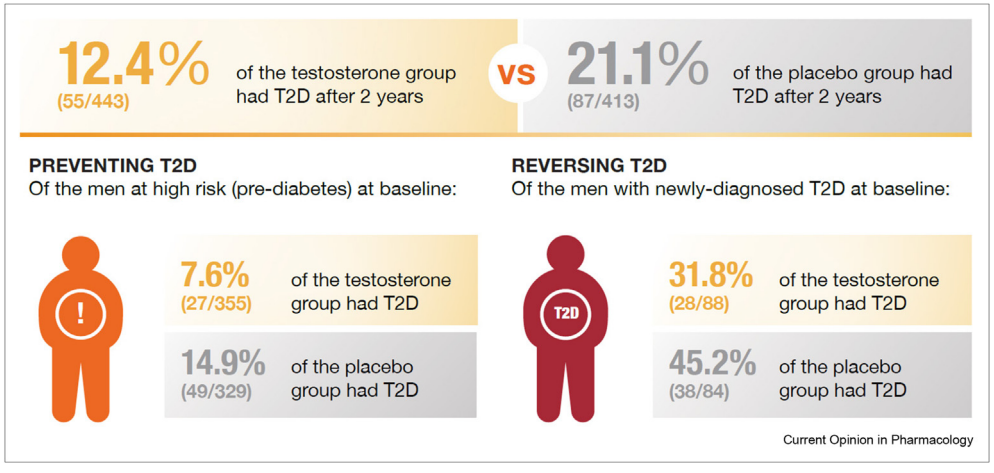
- Among men with prediabetes at baseline, 7.6% (27/355) in the testosterone group had progressed to T2D, compared with 14.9% (49/329) of the placebo group.
- Among men with newly diagnosed T2D at baseline, 31.8% (28/88) in the testosterone group had T2D, compared with 45.2% (38/84) in the placebo group.

During the trial, use of diabetes drugs and lifestyle program engagement were similar between the groups. While there was no effect on HbA1c (see comment below), a higher proportion of testosterone-treated men had normalized 2-h glucose (<7.8 mmol/L or 140 mg/dL) after 2 years compared with baseline. OGTT 2-h glucose was reduced by −0.95 mmol/L (−17 mg/dL) in placebo-treated men and −1.70 mmol/L (−31 mg/dL) in testosterone-treated men (mean difference between groups −0·75 mmol/L, p < 0·0001). Furthermore, the testosterone group had a significantly greater reduction in fasting glucose by −0.24 mmol/L (−4.3 mg/dL) vs. −0.07 mmol/L (−1.3 mg/dL) (both groups had the same baseline fasting glucose level of 6.1 mmol/L or 109.8 mg/dL).

While there was not a significant difference in weight loss between groups, treatment with testosterone undecanoate increased body fat loss and gain in muscle mass. Compared with placebo, T treated men had a greater reduction in waist circumference (−6.99 vs. −4.85 cm), total fat mass (−4.60 vs. −1.89 kg), and abdominal fat mass (−3.55 vs. −1.21%). Total muscle mass, arm muscle mass, and hand-grip strength decreased in men receiving placebo (−1.32 kg, −0.06 kg and −0.45 kg, respectively) and increased in men receiving TTh (+0.39 kg, +0.30 kg and +1.74 kg, respectively), so that after 2 years there was a significant difference between groups.

In addition, the T group had significantly greater improvements in all International Index of Erectile Function subscales (erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall sexual satisfaction). There was no between-group difference in lower urinary tract symptoms. Safety measures were reassuring; there were no significant between-group differences in change of systolic or diastolic blood pressure, nor alanine transferase. As expected, compared with placebo, T treated men had elevations in hematocrit (+4%) and PSA (+0.3 ng/mL), which remained within the normal range in most men.

Figure 1



Effect of TTh on incidence and reversal of type 2 diabetes (T2D). T2D = type 2 diabetes. Data from Wittert G, Bracken K, Robledo KP, et al. TTh to prevent or revert type 2 diabetes in men enrolled in a lifestyle program (T4DM): a randomized, double-blind, placebo-controlled, 2-year, phase 3b trial. The Lancet Diabetes & Endocrinology. Jan 2021; 9(1):32–45.

HbA1c may not be an accurate marker of glycemic control in men with low testosterone

Accumulating evidence suggests that using HbA1c as an outcome measure for evaluating effect of TTh on glycemic control in men with TD can be misleading. HbA1c is not only linearly related to blood glucose levels but also red blood cell (RBC) lifespan [46]. At any given average blood glucose level, shortened RBC lifespan decreases HbA1c and lengthened RBC lifespan increases HbA1c [46]. It has been shown that men with TD may have shortened RBC lifespan and hence spuriously low HbA1C values [47], and that TTh can lengthen RBC lifespan [48]. This could explain the inconsistent results in previous RCTs investigating the effect of TTh on HbA1c in men with TD and T2D, as well as in the T4DM trial, which found that TTh significantly reduced incidence of T2D despite lack of change in HbA1c. Discordance between HbA1c and blood glucose has also been seen in other studies of TTh [10,29].

Another consideration to bear in mind when interpreting previous RCTs of TTh in men with T2D is that in most studies showing no effect on HbA1c [10,29,30,32–34], subjects had well-controlled diabetes by use of diabetes drugs, leaving little room for improvement. Similarly, the discordance between blood glucose and HbA1c findings in the T4DM trial could be due to the relatively low HbA1c at baseline (5.7%) [45]. In contrast, significant reduction in HbA1c has been shown in men with poorly controlled T2D, with baseline HbA1c >7.5% [34].

Discussion

The T4DM trial, which is the first large-scale RCT examining the efficacy and safety of TTh for prevention of T2D in men with low testosterone levels, provides high-level evidence that TTh increases the benefits of lifestyle intervention for prevention of T2D, as well as reversal of T2D [45]. Hence, the T4DM trial confirms findings from previous RWE studies in men with TD, which showed that treatment with testosterone undecanoate injections for 8–11 years completely prevented progression of prediabetes to T2D [41] and resulted in T2D remission in 34.3% of men [42].

A previous 52-week randomized clinical trial in 32 men with TD and newly diagnosed T2D examined the effect of TTh plus diet/exercise vs. diet/exercise alone [37]. HbA1c, which was 7.5% in both groups at baseline, decreased to 7.1% in the diet/exercise group and to 6.3% in the diet/exercise plus TTh group (between-group difference −0.8%; $P < 0.001$). All men treated with diet/exercise plus testosterone reached HbA1c <7.0%, and 87.5% reached HbA1c <6.5%, whereas only 40.4% of men in the diet/exercise group reached HbA1c <7.0%, and none reached HbA1c <6.5%. Men receiving TTh plus diet/exercise had a significantly greater reduction in insulin and HOMA-IR than men in the diet/exercise group, which was correlated with the increase in T levels [37]. This study is noteworthy because no glucose-lowering agents were administered prior to or during the study period, strengthening the possible role of TTh in the prevention or treatment of T2D.

A dilemma with lifestyle interventions and obesity/T2D drugs is declining effectiveness over time and high dropout rates [49]. For instance, in a 3-year RCT investigating liraglutide vs. placebo for T2D risk reduction, the proportion of individuals regressing to normoglycemia during the treatment period decreased during the last interventional year, and the initial liraglutide-induced weight loss decreased after the first year of treatment [50]. In trials of liraglutide, orlistat, lorcaserin, phentermine-topiramate, and naltrexone-bupropion, 1-year dropout rates were 24%, 29%, 35%, 41%, and 49%, respectively [51]. In contrast, in the T4DM trial, 2-year adherence was 76.5% (dropout 23.5%) in the testosterone group and 73.9% (dropout 26.1%) in the placebo group. It is noteworthy that adherence to T treatment has a key role in enhancing metabolic control (HbA1c), as recently reported in a retrospective observational study [52]. While similar dropout rates have been reported for T treatment and liraglutide, to the best of our knowledge, as of this writing 2-year dropout rates and body composition data for liraglutide are not available.

In contrast to currently available drugs for T2D and obesity, TTh confers several unique effects that facilitate achievement of long-term fat loss maintenance and normoglycemia, and possibly also reversal of T2D. First, the effects of TTh on weight loss, prevention/reversal of T2D, and reduction in cardiovascular risk factors progressively improve over time and are sustained with continued treatment [41,42,44,53]. Some meta-analyses of RCTs did not demonstrate a beneficial effect on parameters of metabolic health (HOMA-IR, HbA1c, and lipid profile) [54–56]. Conversely, one meta-analysis from observational studies showed a beneficial effect on metabolic health (glycemia, weight, and lipid profile), which were time dependent [57].

A likely explanation for this is the marked improvement in body composition seen during TTh [38,39,45] and that testosterone is a physiologically essential hormone, as opposed to a man-made drug. Secondly, TTh reduces both IR [10] and beta-cell dysfunction [58], the root causes of T2D [13–17]. Finally, in contrast to diabetes drugs, TTh significantly improves sexual symptoms, which likely helps bolster motivation for long-term adherence. In the T4DM trial, there were two cases of venous thrombotic events, both in men in the

testosterone group [45]. However, this is lower than the incidence of venous thrombotic complications in other studies with similar populations in terms of risk profile, in which treatment with testosterone was not provided [59]. While the T4DM trial provides reassurance about the cardiovascular safety of T treatment, it was not powered to specifically investigate cardiovascular outcomes [45]. A recent review of the effects of TTh on the cardiovascular system concluded that current evidence indicates that TTh is safe once other comorbidities are addressed [60].

The T4DM trial provides high level evidence that TTh, as an adjunct to a lifestyle program, significantly reduces incidence of T2D in men with low testosterone and may also reverse T2D in newly diagnosed patients. This may inform clinical decisions about the use of TTh as a pharmacotherapy for T2D prevention and healthcare cost-savings.

Credit author statement

Monica Caliber and Farid Saad have equally contributed to

- Conceptualization
- Data collection and Literature search
- Validation and Visualization
- Writing, Editing and Review

Conflict of interest statement

MC is a freelance medical writer and has nothing to disclose regarding this manuscript. FS, Hamburg, Germany, works as a consultant for Bayer AG, Berlin, Germany and owns stock of Bayer AG, AbbVie, Editas Medicine, and Intellia Therapeutics.

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