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Testosterone replacement therapy: association with mortality in high-risk patient subgroups

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Abstract

Objectives: We describe studies determining the association between testosterone therapy (TTh) and mortality.

Materials & methods: We used a registry database of 737 men with adult-onset testosterone deficiency defined as presenting with low serum total testosterone (TT) levels ≤12.1 nmol/L and associated symptoms over a near 10-year follow-up. We compared associations between testosterone undecanoate (TU), cardio-metabolic risk factors and mortality using non-parametric statistics followed by separate Cox regression models to determine if any association between TU and morality was independent of age and cardio-metabolic risk factors. Finally, the association between TU and mortality was studied in men stratified by cardio-metabolic risk.

Results: During a median follow-up interquartile range (IQR) of 114 (84–132) months, 94 of the 737 men died. TU (ref: non-treatment) was associated with mortality; hazard ratio = 0.23, 95% confidence intervals = 0.14–0.40. Cox's regression models showed the above association to be independent of baseline age, waist circumference, hemoglobin A1c, lipids, blood pressure, smoking, and type 2 diabetes. These variables remained associated with mortality. We finally stratified the men by the high-risk baseline variables and established that the association between mortality and TU was only evident in men at higher risk. A possible explanation could lie with the "law of initial value," where greater improvements are evident following treatment in patients with worse baseline values.

Conclusions: This study with long follow-up confirms that TTh is associated with lower mortality in men with adult-onset TD. This association was evident only in men with greater cardio-metabolic risk factors who demonstrated greater benefit.

KEYWORDS
adult-onset testosterone deficiency, all-cause mortality, heterogeneity, testosterone therapy

1 | INTRODUCTION

Aging in men over 40 years of age is often characterized by a gradual decline in serum testosterone levels with the rate and extent of decline varying.[1] Adult-onset testosterone deficiency (TD) is classified, following exclusion of primary hypogonadism and hypothalamic–pituitary–gonadal axis disorder, as low serum testosterone (total testosterone (TT) < 12.1 nmol/L and/or free testosterone (FT) < 0.225 nmol/L) and symptoms attributable to this deficiency.[1] The prevalence of adult-onset TD varies between 0.6%–12% in men aged over 50 years and increases to 40%—70% in men with type 2 diabetes (T2DM).[1–4] The association between adult-onset TD (defined as including serum TT < 11 nmol/L, serum FT < 0.22 nmol/L with ≥ associated sexual symptoms) and age is demonstrated in the European Male Ageing study (EMAS) by an increase in prevalence; 0.1%, 0.6%, 3.2%, and 5.1% in men aged 40—49, 50—59, 60—69, and 70—79 years respectively.[5]

Declining testosterone levels are associated with increased morbidity and mortality.[3,4] Holmboe et al. in 2018 in the Danish Monitoring Trends and Determinants of Cardiovascular Disease study showed that the 421 men (36.1%) of the total cohort of 1167 men (aged 30—60 years) who died during follow-up (mean of 15.2 years) demonstrated the most pronounced decline in total testosterone (< 10^{th} percentile compared to 10—90^{th} percentile).[6] This phenomenon was independent of baseline testosterone levels. Further, EMAS showed individuals with ≥ 3 hypogonadal symptoms and low total testosterone levels (< 8 nmol/L) had higher cardiovascular and all-cause mortality rates.[3]

Importantly, testosterone therapy (TTh) has been shown to ameliorate the symptoms included in the adult-onset TD classification[7–9] and in the case of men with T2DM, reduce mortality.[10–13] Shores et al. found in 1,031 middle-aged and elderly men with serum TT levels < 8.7 nmol/L that TTh was associated with decreased mortality (398 men, mean follow-up ± SD: 42.8 ± 13.3 months) compared to men not on treatment (633 men, mean follow-up ± SD: 38.0 ± 15.8 months) after adjustment for confounders.[10] Subgroup analyses showed TTh to be associated with significantly reduced mortality in both younger (41–59 years) and older men (> 60 years), men with diabetes and those not diagnosed with coronary heart disease.[10] Muraleedaran et al. (2013) and Hackett et al. (2016) also found that TTh was independently associated with reduced mortality in men with T2DM and adult-onset TD.[11–13] Our group previously calculated the probability of mortality for each of 857 men with adult-onset TD and T2DM using logistic regression models and showed that age was a significant and exponential predictor of mortality in accordance the Markham–Gompertz theory.[13] TTh, phosphodiesterase 5 inhibitor, and statin therapies were individually significantly associated with reduced mortality and combination of the three agents significantly decreased the relationship between age and risk of mortality.[13] The adult-onset TD cohort shows heterogeneity in mortality risk, with age and cardio-metabolic risk factors perhaps being significant drivers.[14,15]

Thus, it is important that when studying associations between TTh and mortality, the effect of age and cardio-metabolic risk factors associated with adult-onset TD and mortality be taken into consideration.[5,15] Accordingly, we first studied the association between TTh and mortality to confirm previous observations over a near 10-year follow-up and second determined the influence of baseline age and serum TT, waist circumference (WC), hemoglobin A1c (HbA1c) levels, blood pressure (BP), serum lipids, smoking, and T2DM status on any relationship between the TTh and mortality. Finally, we wished to determine if treatment benefit was determined by Wilder's "law of initial value" whereby the response to TTh was dependent on the initial level of the cardiometabolic risk factors.[16] Thus, to examine the efficacy of TTh in subgroups, we stratified the cohort by the level of the cardiometabolic risk factors and studied the effect of TTh on mortality in each of these subgroups.

2 | MATERIALS AND METHODS

2.1 | Study design

We used an on-going, observational, prospective, cumulative registry database of 823 men with urological (sexual dysfunction, lower urinary tract symptoms) and recognized adult-onset TD symptoms with serum total testosterone levels ≤12.1 nmol/L. Men with primary hypogonadism (39 men) and Klinefelter's syndrome (47 men) were excluded. The remaining 737 men were diagnosed with adult-onset TD by the recruiting clinicians in accordance with current guidelines and assessed at least 6 monthly. All these men were offered testosterone undecanoate (TU). The cohort comprised 353 men prescribed parenteral TU, 1,000 mg/12 weeks following a 6-week interval between first and second administration and 384 men who opted against it for financial reasons or negative perceptions of the therapy especially associations with cardiovascular disease (CVD) and prostate cancer.

We report all data recommended in the STROBE statement (https://www.equator-network.org/wp-content/uploads/2015/10/STROBE_checklist_v4_cohort.pdf). The ethical guidelines of the German Medical Association for observational studies were followed. All men consented to be included and have their data analyzed after the study's nature and purpose were explained. Following review, Ethics Committees in Germany and England stated formal approvals were not required.

2.2 | Laboratory measurements

Serum TT was measured using an immunoassay (Alinity i-Module, Architect intra-assay; Abbott Diagnostics, Abbott Park, IL); intra-assay variation was 3.4% and inter-assay variation was 5.1%. Total cholesterol (TC) and triglyceride (TG) concentrations were measured via enzymatic methods (Alinity c-Module, Alinity c-reagents, Abbott Diagnostics), while HbA1c estimated using high pressure liquid chromatography (TOSOH, HLC-723 series).

TABLE 1 Baseline characteristics of the total study cohort and following stratification by survival.

Baseline values	All patients $n = 737$	Alive $n = 643$	Dead $n = 94$	Statistics (alive vs. dead) p (rank-sum)
	Median (IQR)			
Age (years)	62 (58–66)	61 (58–65)	67 (62–70)	<0.0001
Follow-up (months)	114 (84–132)	114 (84–132)	90 (66–120)	<0.0001
Serum TT (nmol/L)	10.1 (9.4–10.7)	10.1 (9.0–10.8)	10.1 (9.4–10.8)	0.096
WC (cm)	108 (102–115)	107 (101–114)	113 (107–122)	<0.0001
HbA1c (%)	6.45 (5.30–8.20), $n = 654$	6.30 (5.30–8.20), $n = 565$	7.20 (5.30–8.10), $n = 89$	0.63
Serum TC (mmol/L)	7.2 (6.3–8.2)	7.2 (6.3–8.1)	7.2 (6.2–8.3)	0.96
Serum TG (mmol/L)	3.0 (2.7–3.4)	3.0 (2.6–3.4)	3.0 (2.7–3.4)	0.28
Systolic BP (mm Hg)	147 (133–160)	144 (133–159)	155 (139–163)	0.0034
Diastolic BP (mm Hg)	85 (77–95)	85 (77–95)	89 (80–95)	0.087
	n (%)			p (chi square)
TU	353/737 (47.90)	333/643 (51.79)	20/94 (21.28)	<0.001
Current smokers	276/736 (37.50)	227/643 (35.30)	49/93 (52.69)	0.001
T2DM	312/737 (42.33)	260/643 (40.44)	52/94 (55.32)	0.006

Abbreviations: TT, total testosterone; WC, waist circumference; TC, total cholesterol; TG, triglyceride; BP, blood pressure; TU, testosterone undecanoate; T2DM, type 2 diabetes.

2.3 | Statistical analysis

We compared factors in men who died or survived using non-parametric analyses as the distribution of variables were skewed with kurtosis. Cox survival regression analyses were carried out to determine if the associations between TU (reference: no treatment) and mortality were independent of other established cardiometabolic risk factors associated with low serum TT and mortality (confounding variables). The cohort was then stratified by the confounding variables with non-parametric analyses (sign-rank, rank-sum) and Cox survival regression analyses carried out in the subgroups.

3 | RESULTS

3.1 | Characteristics of patients in the mortality groups

Table 1 shows characteristics of the entire cohort ($n = 737$) and those who were alive ($n = 643$) or dead ($n = 94$) at the end of follow up. The data show the median age at study start in those who died was significantly higher and follow-up as expected was significantly shorter than in those who survived. Of the other continuous variables studied, WC, and systolic BP were significantly higher in the men who died while serum TT, HbA1c, TC, TG, and diastolic BP were not significantly different. Those alive included a significantly larger proportion of TU-treated men and a significantly smaller proportion of men who smoked or suffered from T2DM.

3.2 | Association between mortality, TTh, and confounding variables

We next studied the association between mortality (dependent variable) and TU, age and the other variables using Cox regression analysis (Table 2). TU (model 1) and age (model 2) in univariate models were significantly associated (TU and age were inversely and positively related respectively) with mortality, and when included together in a single regression analysis (model 3) the associations remained significant with the direction of the hazard ratio (HR) unaltered. All the variables added to TU and age as seen in models 4–11 were potential confounders (Table 2). The Cox regression analyses showed that TU, age, and every confounding variable added to the models were significantly associated with mortality. The direction of the HR of every confounding variable was as expected; WC, serum TC, serum TG, BP, current smoking status (reference: ex/non-smokers), and T2DM (reference: no diabetes) were positively related with mortality.

3.3 | Association between mortality, TU, and age in stratified subgroups

We next determined if the association between TU, age, and mortality was similar in groups stratified by individual risk factors. Accordingly, we dichotomized each variable by the median value (serum TT, WC, HbA1c, BP and lipids) or a clinically relevant cut-off value (T2DM and smoking status) to determine if the associations between TU, age and mortality shown in Table 2 were observed in each stratified subgroup. Age remained positively associated with mortality in every

TABLE 2 Cox regression analyses (dependent variable: All-cause mortality).

	Independent variables	HR (95% CI), *p*	*N*
Model 1	TU (ref: no treatment)	0.23 (0.14–0.40), <0.001	737
Model 2	Age (years)	1.20 (1.15–1.26), <0.001	737
Model 3	TU (ref: no treatment)	0.41 (0.23–0.72), 0.002	737
	Age (years)	1.17 (1.11–1.23), <0.001	
Model 4	TU (ref: no treatment)	0.35 (0.20–0.62), <0.001	737
	Age (years)	1.20 (1.14–1.26), <0.001	
	WC (cm)	1.07 (1.06–1.09), <0.001	
Model 5	TU (ref: no treatment)	0.27 (0.13–0.54), <0.001	654
	Age (years)	1.15 (1.09, 1.20), <0.001	
	HbA1c (%)	1.28 (1.10–1.49), 0.002	
Model 6	TU (ref: no treatment)	0.27 (0.15–0.49), <0.001	737
	Age (years)	1.17 (1.11–1.23), <0.001	
	Serum TC (mmol/L)	1.31 (1.14–1.52), <0.001	
Model 7	TU (ref: no treatment)	0.34 (0.19–0.61), <0.001	737
	Age (years)	1.17 (1.11–1.23), <0.001	
	Serum TG (mmol/L)	1.51 (1.06–2.15), 0.022	
Model 8	TU (ref: no treatment)	0.13 (0.067–0.24), <0.001	737
	Age (years)	1.17 (1.11–1.23), <0.001	
	Systolic BP (mm Hg)	1.06 (1.04–1.08), <0.001	
Model 9	TU (ref: no treatment)	0.15 (0.077–0.30), <0.001	737
	Age (years)	1.16 (1.11–1.22), <0.001	
	Diastolic BP (mm Hg)	1.06 (1.04–1.08), <0.001	
Model 10	TU (ref: no treatment)	0.41 (0.23–0.73), 0.002	736
	Age (years)	1.18 (1.13–1.25), <0.001	
	Current smokers	2.15 (1.42–3.24), <0.001	
Model 11	TU (ref: no treatment)	0.038 (0.21–0.67), 0.001	737
	Age (years)	1.16 (1.11–1.22), <0.001	
	T2DM	1.85 (1.23–2.78), 0.003	

Abbreviations: CI, confidence interval; HR, hazard ratio; WC, waist circumference; TC, total cholesterol; TG, triglyceride; BP, blood pressure; TU, testosterone undecanoate; T2DM, type 2 diabetes.

subgroup. The associations between TU (reference: no treatment) and mortality, adjusted for age in each of these stratified subgroups is shown as a forest plot (Figure 1). TU significantly reduced mortality risk in men with adult-onset TD (HR: 0.41, 95% CI: 0.20–0.86, $p = 0.018$) with baseline serum TT values ≤10.1 nmol/L while in those with values > 10.1 nmol/L the HR appeared similar (HR:0.42, 95% CI: 0.17–1.04, $p = 0.060$) though failing to achieve statistical significance. Figure 1 also shows significant associations between mortality and TU only in the dichotomized subgroups characterized by greater predicted mortality risk posed by higher levels of WC, serum TC, serum TG, BP, current smokers, and men with T2DM.

Table 3 shows the changes in the cardiometabolic risk factors between baseline and final assessment in men stratified by both TU treatment and level of cardiometabolic risk factors split by the median value as seen in Table 1 and Figure 1. These factors significantly worsened in the men not on TU, although no clear pattern was observed when inter-group rank-sum analyses of continuous variables stratified by median values was performed (Table 3). There appeared no difference in WC, while a significantly ($p < 0.0001$) higher increase in baseline HbA1c greater than the median was observed. Conversely, a significantly ($p < 0.0001$) lower increase in TC, TG, and BP in men with baselines greater than the median was observed. However, similar analyses showed that a clear pattern was evident in the men on TU; significantly greater improvements were observed in men whose baseline cardiometabolic factors were greater than the median values (Table 3). The table also shows that men on TU (compared to their untreated counterparts) demonstrated significantly greater improvements ($p < 0.0001$) in the continuous cardiometabolic risk factors at final assessment regardless of stratification of the variables; inter-group (men on TU vs. men untreated).

Tables 4 and 5 demonstrate the differences in WC, HbA1c, lipids, and BP in the cohort stratified by T2DM and smoking status. Both show

TABLE 3 Changes in the cardiometabolic risk factors between final assessment and baseline in men stratified by the median baseline values of these factors and TU treatment.

	Median (IQR)						
	Not on TU			On TU			*p* (Δ inter-group)
	Baseline	Final assessment	*p* (Δ—intra-group)	Baseline	Final assessment	*p* (Δ—intra-group)	(TU vs. not on TU)
WC ≤ 108 cm	102 (99, 106)	108 (103, 111)	5 (4, 7), <0.0001	102 (97, 105)	94 (93, 97)	−7 (−10, −4), <0.0001	<0.0001
WC > 108 cm	116 (112, 123)	121 (117, 128)	5 (4, 7), <0.0001	116 (112, 120)	101 (98, 105)	−14 (−16, −11), <0.0001	<0.0001
***p* (inter-group)—Δ WC**			0.62			<0.0001	
HbA1c ≤ 6.45%	5.2 (5.1, 5.3)	6.4 (5.9, 7.2)	1.2 (0.8, 1.9), <0.0001	5.7 (5.3, 5.9)	5.0 (4.9, 5.2)	−0.6 (−0.8, −0.3), <0.0001	<0.0001
HbA1c > 6.45%	7.8 (7.4, 8.1)	10.6 (9.6, 11.7)	2.7 (1.8, 3.5), <0.0001	8.9 (8.3, 9.5)	5.7 (5.4, 6.1)	−3.1 (−3.6, −2.4), <0.0001	<0.0001
***p* (inter-group)—Δ HbA1c**			<0.0001			<0.0001	
TC ≤ 7.2 mmol/L	6.0 (5.2, 6.6)	7.2 (6.8, 7.7)	1.4 (0.9, 1.9), <0.0001	6.9 (6.6, 7.1)	5.0 (4.9, 5.2)	−1.8 (−2.1, −1.5), <0.0001	<0.0001
TC > 7.2 mmol/L	7.7 (7.5, 8.6)	9.0 (8.2, 9.8)	0.8 (0.2, 1.6), <0.0001	8.3 (7.5, 8.9)	5.2 (5.0, 5.5)	−3.0 (−3.7, −2.5), <0.0001	<0.0001
***p* (inter-group)—Δ TC**			<0.0001			<0.0001	
TG ≤ 3.0 mmol/L	2.6 (2.4, 2.7)	3.3 (3.0, 3.5)	0.7 (0.5, 0.9), <0.0001	2.7 (2.5, 2.9)	2.2 (2.1, 2.2)	−0.5 (−0.66, −0.33), <0.0001	<0.0001
TG > 3.0 mmol/L	3.4 (3.2, 3.6)	3.9 (3.7, 4.2)	0.6 (0.3, 0.8), <0.0001	3.7 (3.2, 3.7)	2.2 (2.1, 2.3)	−1.2 (−1.5, −1.0), <0.0001	<0.0001
***p* (inter-group)—Δ TG**			<0.0001			<0.0001	
Systolic BP ≤ 147 mm Hg	132 (129, 137)	144 (139, 149)	11 (7, 18), <0.0001	138 (133, 142)	125 (123, 130)	−11 (−15, −7), <0.0001	<0.0001
Systolic BP > 147 mm Hg	155 (153, 160)	159 (157, 169)	6 (0, 12), <0.0001	166 (159, 173)	130 (125, 136)	−34 (−42, −26), <0.0001	<0.0001
***p* (inter-group)—Δ Systolic BP**			<0.0001			<0.0001	
Diastolic BP ≤ 85 mm Hg	76 (74, 79)	87 (81, 90)	10 (5, 16), <0.0001	78 (76, 82)	74 (72, 76)	−5 (−8, −2), <0.0001	<0.0001
Diastolic BP > 85 mm Hg	92 (88, 95)	97 (93, 99)	5 (0, 9), <0.0001	97 (93, 102)	76 (73, 78)	−21 (−26, −16), <0.0001	<0.0001
***p* (inter-group)—Δ Diastolic BP**			<0.0001			<0.0001	

Abbreviations: WC, waist circumference; TC, total cholesterol; TG, triglyceride; BP, blood pressure; TU, testosterone undecanoate.

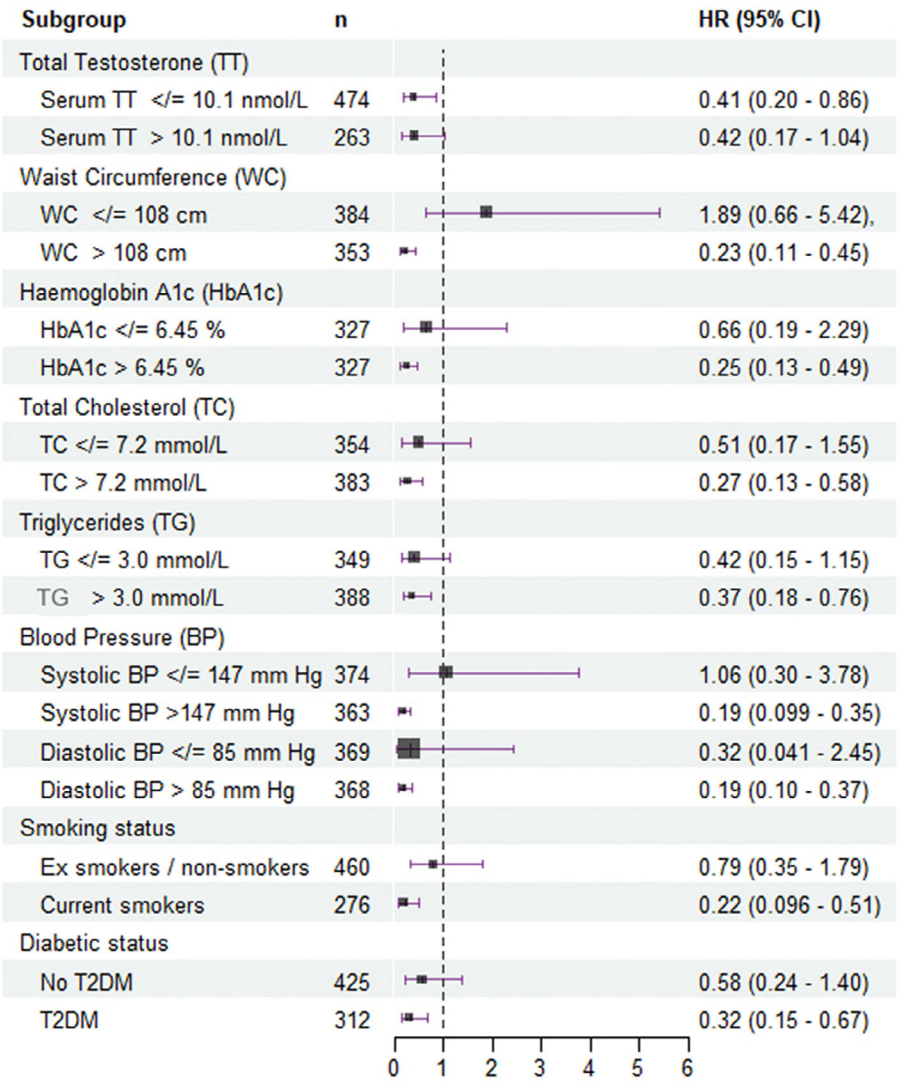

FIGURE 1 A Forest plot based on Cox regression analyses with TU (ref: no treatment) as the independent variable, adjusted for age in the cohort stratified by either median values from Table 1 (continuous variables) or discrete categories. TU, Testosterone undecanoate.

that TU (compared to non-treatment) improved all cardiometabolic parameters in all the stratified groups. Importantly TU treated men with T2DM demonstrated greater benefits in WC, HbA1c, lipids, and BP compared to men without T2DM (Table 4, footnote). In men not on TU, while HbA1c worsened significantly in men with T2DM the reverse was observed with lipids (Table 4, footnote). Table 5 shows in men currently smoking, the decrease in WC was significantly greater in men on TU, while the increase in WC was significantly lower in the men not on TU (Table 5, footnote). Smoking status did not appear to be associated with changes in HbA1c, lipids and BP in both men treated and untreated with TU (Table 5, footnote).

4 | DISCUSSION

The prevalence of adult-onset TD increases with age and the condition is often associated with increased risk of varied pathologies including classifying factors of the metabolic syndrome[15,17] and increased mortality.[3,4] TRT has been mostly thought of in the context of sexual health though the therapy may alleviate or at least delay development of other comorbidities.[7–9] The high prevalence of adult-onset TD, especially in men with T2DM, suggests that even modest improvements following intervention could potentially yield major benefit.

In the context of mortality, Shores et al. in 2012 showed TRT was associated with a significantly reduced mortality rate (3.4 deaths/100 person-years) compared with 5.7 deaths/100 person-years in untreated men.[10] Their analyses also hinted at clinical heterogeneity as certain subgroups (men with diabetes and free from cardiac disease) appeared to demonstrate significant benefit, while the complementary groups did not, although the interaction was not significant. The benefit of TTh in reducing mortality has been confirmed in men with T2DM.[11–13] Our aim was to analyze a registry of men with adult-onset TD with a median follow-up of nearly 10 years and initially confirm the association between TU and mortality as

TABLE 4 Changes in the cardiometabolic risk factors between final assessment and baseline in men stratified by T2DM and TU treatment.

		Median (IQR)		*p* (inter-group)
		Not on TU	On TU	(rank-sum)
No T2DM	Δ WC (cm)	+5 (+4, +6)	−8 (−13, −4)	<0.0001
	Δ HbA1c (%)	+1.2 (+0.8, +1.8)	−0.7 (−1.1, −0.3)	<0.0001
	Δ TC (mmol/L)	+1.4 (+0.8, +2.0)	−2.4 (−3.0, −2.0)	<0.0001
	Δ TG (mmol/L)	+0.7 (+0.5, +0.9)	−0.8 (−1.1, −0.5)	<0.0001
	Δ Systolic BP (mm Hg)	+10 (+5, +16)	−17 (−35, −10)	<0.0001
	Δ Diastolic BP (mm Hg)	+8 (+4, +13)	−13 (−22, −6)	<0.0001
T2DM	Δ WC (cm)	+5 (+4, +7)	−11 (−14, −8)	<0.0001
	Δ HbA1c (%)	+2.7 (+1.8, +3.7)	−3.2 (−3.7, −2.6)	<0.0001
	Δ TC (mmol/L)	+1.0 (+0.4, +1.7)	−3.1 (−3.8, −2.4)	<0.0001
	Δ TG (mmol/L)	+0.6 (+0.3, +0.8)	−1.1 (−1.5, −0.9)	<0.0001
	Δ Systolic BP (mm Hg)	+10 (+3, +17)	−31 (−41, −22)	<0.0001
	Δ Diastolic BP (mm Hg)	+7 (+3, +15)	−20 (−26, −15)	<0.0001

Note: Statistics (rank-sum) of changes in cardiometabolic risk factors between men with T2DM compared to those without (reference) T2DM stratified by treatment. Abbreviations: WC, waist circumference; TC, total cholesterol; TG, triglyceride; BP, blood pressure; TU, testosterone undecanoate; T2DM, type 2 diabetes.Not on TU: WC: $p = 0.84$. HbA1c: $p < 0.0001$. TC: $p = 0.0014$. TG: $p = 0.031$. Systolic BP: $p = 0.89$. Diastolic BP: $p = 0.95$. On TU: WC: $p = 0.0002$. HbA1c: $p < 0.0001$. TC: $p < 0.0001$. TG: $p < 0.0001$. Systolic BP: $p < 0.0001$. Diastolic BP: $p < 0.0001$.

TABLE 5 Changes in the cardiometabolic risk factors between final assessment and baseline in men stratified by smoking status and TU therapy.

		Median (IQR)		*p* (Inter-group)
		Not on TU	On TU	(rank-sum)
Non/Ex-smokers	Δ WC (cm)	+5 (+4, +7)	−9 (−13, −5)	<0.0001
	Δ HbA1c (%)	+1.6 (+1, +2.7)	−2.1 (−3.2, −0.7)	<0.0001
	Δ TC (mmol/L)	+1.2 (+0.6, +1.8)	−2.6 (−3.3, −2.3)	<0.0001
	Δ TG (mmol/L)	+0.7 (+0.4, +0.9)	−0.9 (−1.3, −0.5)	<0.0001
	Δ Systolic BP (mm Hg)	+9 (+4, +16)	−26 (−37, −11)	<0.0001
	Δ Diastolic BP (mm Hg)	+7 (+3, +14)	−16 (−24, −7)	<0.0001
Current smokers	Δ WC (cm)	+4 (+3, +6)	−11 (−14, −8)	<0.0001
	Δ HbA1c (%)	+1.8 (+1.0, +2.8)	−2.5 (−3.4, −0.9)	<0.0001
	Δ TC (mmol/L)	+1.3 (+0.7, +2.0)	−2.6 (−3.7, −2.0)	<0.0001
	Δ TG (mmol/L)	+0.6 (+0.4, +0.8)	−1.0 (−1.3, −0.7)	<0.0001
	Δ Systolic BP (mm Hg)	+10 (+4, +17)	−25 (−37, −16)	<0.0001
	Δ Diastolic BP (mm Hg)	+9 (+4, +13)	−17 (−23, −10)	<0.0001

Note: Statistics (rank-sum) of changes in cardiometabolic risk factors between men who currently smoke compared to ex-smokers and those who never smoked (reference) T2DM stratified by treatment. Abbreviations: WC, waist circumference; TC, total cholesterol; TG, triglyceride; BP, blood pressure; TU, testosterone undecanoate; T2DM, type 2 diabetes.Not on TU: WC: $p = 0.0002$. HbA1c: $p = 0.44$. TC: $p = 0.26$. TG: $p = 0.18$. Systolic BP: $p = 0.91$. Diastolic BP: $p = 0.52$. On TU: WC: $p = 0.0013$. HbA1c: $p = 0.12$. TC: $p = 0.68$. TG: $p = 0.24$. Systolic BP: $p = 0.55$. Diastolic BP: $p = 0.72$.

previously reported.[10–13] This was to be followed by an examination of whether any association was restricted to certain clinical subgroups. Finally, we wished to investigate possible reasons for differing outcomes in the subgroups by studying changes in cardiometabolic risk factors following the TU therapy in these subgroups.

We showed that TTh with TU was associated with significant reduction in mortality over a near 10-year follow-up, this association being independent of age and cardiometabolic risk factors such as WC, HbA1c, lipids, and BP. Interestingly in our study TU was significantly associated with reduced mortality only in the men with greater cardiometabolic risk; higher than median WC, HbA1c, lipids, BP and well as men with T2DM and those currently smoking (Figure 1). An explanation may be provided by the Wilder's "law of initial value" whereby "the degree of response of a body function to any therapeutic agent will depend to a large degree on its the initial level".[16] This appears to be the case in Table 3 where improvements in the cardiometabolic risk factors

(WC, HbA1c, lipids, and BP) following TU were significantly greater in the men whose baseline values were greater than the median. The improvements in these factors following TU were significantly greater in men with T2DM compared to their counterparts not on TU and this may explain the mortality benefits in the men with T2DM following TU, but not in their untreated counterparts (Table 4, footnote). However, this does not appear to be the case when the group was stratified by smoking status; only change in WC was different between current and non/ex-smokers (Table 5, footnote). It is possible that the decrease in mortality could also be related to the underlying mortality risk of the subgroup, and if true could apply to all the subgroups identified in Tables 3–5.

The cardiometabolic factors that we included in our analyses except for smoking status and TC are associated by being the classifying characteristics of the metabolic syndrome.[15,17] Our patient numbers did not allow study us to identify a hierarchy of TU related benefits associated with the decreased mortality which might have provided a hint as to potential mechanisms.

5 | STRENGTHS AND LIMITATIONS

Our longitudinal cohort study, unlike a randomized controlled trial (RCT) could include bias. There were no exclusion/inclusion factors regarding recruitment with all the men recommended TU. The two groups were formed by the men either accepting or declining TU rather than by randomization. This perhaps resulted in inter-group baseline differences in phenotypes. We acknowledge the potential for "healthy-user bias". As blind randomization did not take place there is a possibility of confounders that we have been unable to take into account. Further, greater patient numbers may have allowed more detailed analyses of the interaction between TU and the cardiometabolic risk factors. A time related identification of the changes in these risk factors following TU may also have helped to hint at aetiology. We created subgroups by dichotomizing the continuous variables by median values with the advantage of near equal groups being available for comparison though larger patient numbers would have permitted stratification based on clinical guidelines (e.g., lipids, HbA1c, and BP). Further, we did not have sufficient patient numbers to consider changes in other treatments during follow-up. However, our study had strengths. Compliance was absolute as TU was administered in the clinics. The measurements of the cardiometabolic risk factors were carried out regularly according to protocol. The patients were unselected and perhaps mirrored clinical practice. The follow-up period was of greater duration than most RCTs. Hence, such data should be considered in conjunction with those from RCTs and meta-analyses.

6 | CONCLUSION

Our study with a long follow-up confirms that TTh with TU in men with adult-onset TD was associated with lower mortality, this only evident in men with greater cardio-metabolic risk factors with these men demonstrating more significant improvements in these factors following TU. Our findings require confirmation via independent study, but if validated it could have significant clinical implications.

AUTHOR CONTRIBUTIONS

SR: design of study; data analysis; preparation of manuscript. **AH and KSH**: patient recruitment; data collection; preparation of manuscript. **PD**: transposing the data; maintaining the database. **CSK**: design of study; data analysis; preparation of manuscript. **AM; GH**: preparation of manuscript. **RCS**: design of study; data analysis; preparation of manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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