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The association between age and mortality in men with adult-onset testosterone deficiency is altered by testosterone therapy

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ABSTRACT

Background: Using the Gompertz–Makeham model, we describe associations between age and the probability of mortality in men with adult-onset testosterone deficiency (TD), stratified by testosterone undecanoate (TU) treatment and type 2 diabetes (T2DM).
Methods: We analyzed a registry of 737 men (353 and 384 men on/not on TU, respectively) with adult-onset TD with nearly 9 years of follow-up. We compared associations between age and mortality using nonparametric and logistic regression models (estimating individual mortality probability) in men stratified by TU treatment and T2DM.
Results: Mortality was lower ($p < 0.001$) in men on TU compared to men opting against TU. In the men on TU, age was associated with mortality (odds ratio (OR): 1.26, 95% confidence interval (CI): 1.13–1.40) in the nonlinear pattern expected in the Gompertz–Makeham model. However, age was not associated with mortality in men not on TU (OR: 1.03, 95% CI: 0.98–1.08). T2DM status did not affect these associations.
Conclusion: The association between age and mortality differed between men on TU and those opting against treatment. In untreated men, features of metabolic syndrome worsened, which perhaps minimized the relationship between age and mortality. In men on TU, these metabolic risk factors improved, perhaps restoring the association between age and mortality.

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Adult-onset testosterone deficiency; all-cause mortality; Gompertz–Makeham equation; probability of mortality; testosterone therapy

Introduction

Age is a key variable in mediating mortality in adults. In 1825, Benjamin Gompertz showed the association between age and mortality, following the avoidance of external age-independent risk factors such as starvation or conflict, is exponential and based on the equation, $\mu(x) = \alpha \times e^{\beta x}$, with $\mu(x)$ being the mortality rate at age x years and α and β (the ageing rate) being constants [1]. Subsequently, Makeham proposed a modified Gompertz equation, $\mu(x) = \alpha(e^{\beta x}) + y$, that included a factor (y) describing extrinsic mortality, thereby allowing the study of both age-independent and age-dependent factors [2]. If external factors (e.g. conflict, starvation) are absent, the age-independent component has less impact on the death rate, and mortality increases exponentially with age. In developed countries, the age-independent intercept (y) is mediated by medical care, though early life factors may influence later outcomes. It is possible that in individuals suffering from a pathology associated with high mortality that is not addressed by healthcare, the intercept can be high and distort the Gompertz–Makeham model. When the impact of these risk factors is diminished with treatment, the intercept will decrease and the Gompertz–Makeham model is restored. The Gompertz–Makeham model can be graphically illustrated to demonstrate the relationship between age

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and the probability of mortality in various cohorts, and comparing such graphs in a specified pathology, stratified by treatment and comorbidities, may provide information of age related mortality patterns and perhaps possible mechanisms.

Male adult-onset testosterone deficiency (TD) is diagnosed by low serum testosterone levels and associated symptoms, which include sexual dysfunction, fatigue, sleep disturbance, reduced muscle mass, and depressed mood [3]. The condition is of increasing clinical interest in view of its prevalence (0.6%–12% in men aged >50 years and 40%–70% in men with type 2 diabetes (T2DM)), and data showing it is associated with increased mortality [4,5]. Importantly, testosterone therapy (TTh) was seen to reduce mortality, especially in men with T2DM [6–8].

We recently used the Gompertz–Makeham model to evaluate the relationship between age and mortality probability in men with adult-onset TD and T2DM when studying the BLAST-screened cohort with a mean follow-up of around 4 years [9]. We found an exponential association between age and mortality in men with T2DM and TD in accordance with the Gompertz–Makeham model [9]. Although the exponential relationship between age and mortality probability was maintained in both men treated with testosterone undecanoate (TU) and those untreated, the patterns varied. At each age point, TU treatment was associated with a lower probability of mortality.

Subsequently, in a registry of 737 men with adult-onset TD, we found significant reductions in mortality following TU administration [8]. This association was independent of age and cardiometabolic risk predictors, such as baseline waist circumference (WC), hemoglobin A1c (HbA1c), serum total cholesterol (TC), triglyceride (TG), blood pressure (BP), smoking, and T2DM (these risk factors were included in separate models with age and TU treatment) [8]. Importantly, all these risk factors improved significantly with increasing TTh, while significant deterioration was observed in untreated men [8]. Hence, the risk dynamics of both groups would be expected to vary during further follow-up. We recognized that the BLAST-screened cohort differed significantly from the registry cohort in patient characteristics and follow-up. In view of this, we wished to see if the results were similar. In this analysis, we studied patterns of associations between age and mortality probability in men with adult-onset TD stratified by TTh (using TU) and T2DM (in view of all the men in the BLAST-screened cohort having T2DM) status to determine whether the exponential associations were evident in each subgroup and whether differences in the association patterns were apparent.

Materials and methods

Study design

We used an ongoing German observational, prospective, cumulative registry database of 737 men (after excluding men with primary hypogonadism and Klinefelter's syndrome) with adult-onset TD symptoms who had serum total testosterone levels ≤12.1 nmol/l with clinical and laboratory assessments at least 6 months [10]. All the men included in the registry were offered TU; 353 men were prescribed parenteral TU at 1000 mg/12 weeks following a 6-week interval between the first and second administrations [median (IQR) follow-up = 105 (78–141) months], and 384 men opted against treatment for financial reasons or negative perceptions of the therapy [median (IQR) follow-up = 114 (96–126) months]. The registry study followed the ethical guidelines of the German Medical Association for observational studies. After receiving a detailed and informative explanation regarding the nature and purpose of the study, including the intention to publish in an anonymised fashion, all the subjects provided written consent, regardless of whether or not they decided on TTh. Following review, Ethics Committees in Germany and England stated that formal approvals were not needed.

Serum total testosterone (TT) was measured using an immunoassay (Alinity i-Module, Architect intra-assay; Abbott Diagnostics, Abbott Park, Ill). Total cholesterol (TC) and triglyceride (TG) concentrations were measured via enzymatic methods (Alinity c-Module, Alinity c-reagents, Abbott Diagnostics), whilst HbA1c was estimated using high-pressure liquid chromatography (TOSOH, HLC-723 series). BP was assessed at least twice per visit; following the initial measurement, TU was injected, and BP was determined again. For BP differences <5 mmHg, an average value was recorded; if >5 mmHg, a third measurement was made; and when <10 mmHg, the average of the closer values recorded. If BP readings differed by >10 mmHg, the patient was requested to undergo 24-hour BP monitoring.

Table 1. Separate logistic regression models with mortality as the dependent variable and age at final assessment as the independent variable in the total cohort and subgroups (1a). Baseline and Δ values of established mortality risk factors are also presented (1b).

Patient groups	On TU	Not on TU
1a. Associations between age and mortality (logistic regression)		
	OR (95% CI), *p*, *n*	
Total cohort	1.26 (1.13–1.40), $p < 0.001$, $n = 353$ (model 1)	1.03 (0.98–1.08), $p = 0.30$, $n = 384$ (model 2)
No T2DM	1.48 (1.18–1.86), $p = 0.001$, $n = 205$ (model 3)	1.03 (0.96–1.11), $p = 0.41$, $n = 215$ (model 4)
T2DM	1.14 (1.00–1.30), $p = 0.046$, $n = 148$ (model 5)	1.03 (0.97–1.10), $p = 0.37$, $n = 169$ (model 6)
HbA1c < median (6.5%)	1.19 (1.06–1.34), $p = 0.003$, $n = 246$ (model 7)	1.09 (0.98–1.22), $p = 0.12$, $n = 117$ (model 8)
HbA1c ≥ median (6.5%)	1.55 (1.15–2.07), $p = 0.004$, $n = 107$ (model 9)	1.02 (0.96–1.08), $p = 0.53$, $n = 267$ (model 10)
Not on antiglycemic agents	1.40 (1.15–1.70), $p = 0.001$, $n = 190$ (model 11)	1.01 (0.92 (1.10), $p = 0.89$, $n = 163$ (model 12)
On antiglycemic agents	1.17 (1.02–1.34), $p = 0.026$, $n = 163$ (model 13)	1.05 (0.98–.11), $p = 0.16$, $n = 221$ (model 14)
1b. Baseline and Δ (at final assessment) values [median (IQR)] of risk factors, *p* (sign–rank), *n*		
WC (cm)	108 (100–114), −10 (−13 to −6), $p < 0.0001$, $n = 353$	109 (102.5–116), +5 (+4 to +7), $p < 0.0001$, $n = 384$
HbA1c (%)	8.2 (5.8–8.9), −2.1 (−3.2 to −0.7), $p < 0.0001$, $n = 269$	5.4 (5.1–7.7), +1.7 (+1.0 to +2.7), $p < 0.0001$, $n = 377$
TC (mmol/L)	7.7 (7.2–8.6), −2.6 (−3.3 to −2.1), $p < 0.0001$, $n = 353$	6.5 (5.6–7.4), +1.2 (+0.6 to +1.8), $p < 0.0001$, $n = 383$
TG (mmol/L)	3.2 (2.8–3.5), −1.0 (−1.3 to −0.6), $p < 0.0001$, $n = 353$	2.9 (2.6–3.3), +0.6 (+0.4 to +0.9), $p < 0.0001$, $n = 384$
Systolic BP (mmHg)	158 (141–167), −25 (−37 to −13),$p < 0.0001$, $n = 352$	137.5 (131.5–154), +10 (+4 to +16), $p < 0.0001$, $n = 382$
Diastolic BP (mmHg)	94 (83–98), −17 (−24 to −9), $p < 0.0001$, $n = 353$	78 (75–88), +8 (+3 to +13), $p < 0.0001$, $n = 382$

Statistical analysis

All the statistical analyses were carried out with Stata 14 (College Station, TX, USA). Baseline characteristics of the men on TU and those opting against it varied as previously described [10,11]. Hence, we avoided any inter-group comparisons of baseline characteristics. As skewness/kurtosis was evident in the distribution of risk factors (age, WC, HbA1c, lipids, BP), nonparametric statistics (sign–rank and rank–sum tests) were performed to evaluate changes in risk predictors that could have mediated any change in associations between age and mortality. Associations between TU treatment, T2DM, and mortality were evaluated using Chi Square. Logistic regression (as opposed to Cox regression, which is a survival analysis) was initially carried out to study the association between death/survival (dichotomous outcome) and age at final assessment as the independent variable in the total group and men on/not on TU. Individual probabilities of mortality and 95% confidence intervals (CI) were then estimated for each man using separate logistic regression models, as in our previous work on the Gompertz–Makeham model. [9]. The associations between age and the probability of mortality are presented separately for men stratified by TU treatment and with further stratification by T2DM status. We finally carried out regression analyses between the probability of mortality and age in men on/not on TU and evaluated differences in the coefficients by using the seemingly unrelated estimation (suest) postestimation command in Stata to compare coefficients from different models or subsamples.

Results

Mortality was significantly lower ($p < 0.001$, chi square) in the 353 men on TU (5.7%) compared to their counterparts opting against TU (19.3%). As the age at death/final assessment varied between the two groups, we used logistic regression analysis with mortality and TU treatment as the dependent and independent variables, respectively, with age. Both age (OR: 1.08, 95% CI: 1.03–1.12, $p = 0.001$) and TU (OR: 0.34, 95% CI: 0.20–0.58, $p < 0.001$) were independently associated with mortality. Furthermore, T2DM status was also significantly ($p = 0.005$, chi-square) associated with mortality (16.7% in the 317 men with T2DM, 9.8% in the 420 men without T2DM). Adding T2DM status as an independent variable in the logistic regression model revealed that age (OR: 1.08, 95% CI: 1.03–1.12, $p = 0.001$), TU (OR: 0.33, 95% CI: 0.19–0.56, $p < 0.001$), and T2DM (OR: 1.86, 95% CI: 1.18–2.91, $p = 0.007$) were significantly and independently associated with mortality.

We now study the relationship between age and mortality stratified by treatment with TU, with further stratification by T2DM status. In men on TU, age was associated with mortality (OR: 1.26, 95% CI: 1.13–1.40, $p < 0.001$), as shown in Table 1a (model 1). Table 1a (model 2) shows that this was not the case in men not on TU (OR: 1.03, 95% CI: 0.98–1.08, $p = 0.30$). After stratification by T2DM status, HbA1c values (at final assessment) and antiglycaemic treatment showed that age remained associated with mortality in men on TU (Table 1a–models 3, 5, 7, 9,11, and 13), but this was not the case in the untreated men (Table 1a–models 4, 6, 8, 10, and 12).

We calculated the probability and 95% CI of death for each patient on TU (Table 1a–model 1) and those not opting for TU (Table 1a–model 2), with the results shown graphically in Figure 1a and b. Figure 1a suggests that the association between age and mortality exhibits a non-linear pattern in men with and without T2DM. In contrast, Figure 1b appears to show an association of a differing visually linear pattern (Table 1a–model 2). To study the differences in the relationships between Figure 1a and b, we carried out regression analyses between the probability of death (dependent variable) and age (independent variable) in the cohort stratified by TU therapy. A postestimation comparison of the models demonstrated significant differences ($p < 0.0001$) in the coefficients between Figures 1a and b.

In view of the varying patterns observed in Figures 1a and b, we studied the baseline and changing (Δ) values (at the final assessment) of factors associated with mortality in the two groups separately (TU/not on TU), as shown in Table 1b. TU was associated with significant improvements ($p < 0.0001$, sign–rank) in WC, HbA1c, TC, TG, and BP, while the reverse was true in men opting against TU. The Δ values of the risk parameters were significantly different ($p < 0.0001$, rank–sum) between the two groups.

Discussion

We evaluated the relationship between age and mortality in adult-onset TD patients on/not on TTh. In summary, our analyses revealed that, unlike in men on TU, age did not predict mortality in men opting against TU. The patterns observed visually differed; the non-linear pattern between age and probability of mortality (Figure 1a) described by Gompertz-Makeham was only evident in the treated group. In untreated men, age was not significantly associated with mortality and appeared visually linear (Figure 1b). Stratifying the cohort by T2DM status did not alter these associations or the shapes evident in Figures 1a and b.

We can speculate as to the reasons for this difference in this study, despite a previous publication using the BLAST-screened cohort showing that, in men with T2DM, age was related to mortality in the expected non-linear pattern in both TU-treated and untreated men [3]. Thus, our current findings differed from the analysis of the BLAST-screened cohort. In the current study analysing the registry cohort, baseline WC, HbA1c, lipid, and BP values were significantly lower ($p < 0.0001$, rank–sum) in the men opting for TU [12–15]. However, at the final assessment, a reversal ($p < 0.0001$, rank–sum) of these values was evident. In contrast, they significantly worsened in men who were not on TU. It is possible that exposure to such risk factors over a longer follow-up than in the BLAST-screened cohort led to chronological age not being associated with mortality. Reducing the risk posed by WC, HbA1c, lipids, and BP may allow age to be restored as a predictor of mortality. We have previously shown that survival was significantly longer ($p < 0.001$, Cox regression analysis) in men on TU in this cohort [9]. Premature mortality in men opting against TU could have led to the linear pattern (Figure 1b) between age and the probability of mortality, as observed in this paper. It is worth examining changes in the metabolic risk factors observed in the BLAST-

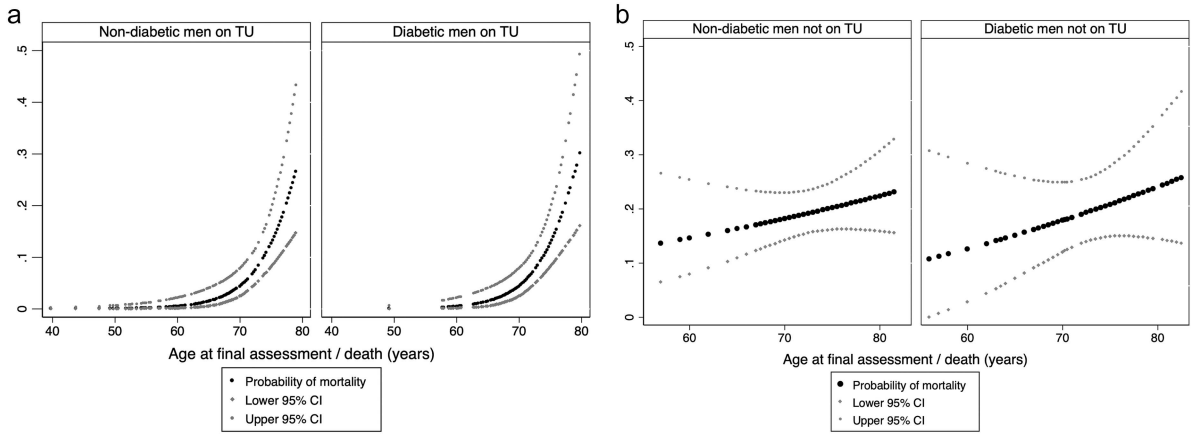

Figure 1. (a) and (b): Association between age (x-axis) and estimated probability of mortality (y-axis), calculated from logistic regression models in Table 1a (models 1 & 2), in men on TU (a) and men not on TU (b), stratified by T2DMtab ? what does tab mean.

screened cohort with a shorter follow-up. Improvements in many risk factors (weight, cholesterol, and BP) were evident, whereas HbA1c and TG did not significantly change in the men who remained untreated [16]. This may have been due to the quality and outcomes framework adopted by primary care in the United Kingdom in 2004, when treating patients with diabetes [17,18]. Thus, in the entire BLAST-screened cohort, metabolic risk factors would have been addressed. Statin therapy was more common in the untreated men in the BLAST-screened cohort (77.2%) compared to their counterparts in the registry cohort (56.8%) [19].

It is intuitive that high-risk pathologies may distort the relationship between age and mortality, as described by the Gompertz–Makeham model [1,2]. It is important to examine other pathologies, such as familial hypercholesterolaemia with highly elevated lipids, and determine whether the above model applies. A registry-based study in Norway of individuals with familial hypercholesterolaemia reported standard mortality rates (95% CI) in individuals aged 0–19, 20–39, 40–59, 60–69, 70–79, and >80 years to be 1.21 (0.30–4.83), 1.22 (0.68–2.21), 1.03 (0.73–1.44), 0.88 (0.61–1.26), 0.60 (0.39–0.93), and 0.86 (0.53–1.38), respectively [20]. Despite lipid-lowering treatment, the mean TC was high at 6.7 mmol/L, and the associated increased risk could have led to the nonexponential relationship between age and mortality [20].

In 2020, Ledberg described a generic model that could perhaps explain the exponential association between age and mortality [21]. Ledberg's model indicated that the probability of mortality was a function of damage to physiological structures and systems and mechanisms repairing the damage, which are considered to be rate limited and decay with age [21,22]. Under these circumstances, if the rate of damage was constant and combined with an age-related decrease in repair efficacy, an exponential association between age and mortality would be observed. It is worth examining whether restoring serum testosterone, in addition to improving metabolic risk factors, could also have a positive impact on mechanisms associated with damage repair. Interestingly, Hormone action through nuclear receptor binding is known to upregulate the repair of DNA breaks [23]. Hence, it is worth speculating that low testosterone levels could lead to a decrease in DNA repair; the corollary is that the correction of testosterone levels could result in a beneficial improvement in DNA repair. Intuitively, if this phenomenon has sufficient impact, it could minimize the detrimental effect of age on repair mechanisms. If that was the case, the exponential association between age and mortality could be abolished.

Jannini and Hassan suggested that a symptom sexology approach is useful for understanding that sexual health is an important predictor of noncommunicable disease and premature mortality [24]. Our study, which revealed that untreated adult-onset TD disrupts the normal exponential age–mortality relationship while TU therapy restores it, provides compelling real-world evidence in support of this conceptual model. Thus, it is possible that adult-onset TD may be considered the "canary in the coalmine", as highlighted by Jannini and Hassan in 2026 [24].

A registry study has strengths and weaknesses. Unlike an RCT, no exclusion/inclusion factors were applied. There was no blind randomisation, with acceptance of TU based on perception and finance, which could result in sample bias. Thus, self-selection of TU therapy could lead to bias. Men provided with TU demonstrated more severe baseline symptoms of TD (WC, glycemic control, dyslipidemia, and hypertension), and further studies, including RCTs, are needed, as there is a possibility of regression towards the mean. Furthermore, other confounders, such as socioeconomic status and health-seeking behavior, could also impact mortality. We must emphasize that our findings are only applicable to TTh with TU. At the same time, our study has numerous strengths. Compliance was absolute, as TU was administered to patients in the clinics. The cardiometabolic risk factors were checked regularly according to the protocol. Further, the men with adult-onset TD were unselected, and this perhaps mirrors clinical practice. Importantly, the follow-up period of around 9-years was greater than in most RCTs.

Conclusion

We evaluated the relationships between age and mortality in men with adult-onset TD who were treated versus untreated with TU. Age did not appear to be associated with mortality in untreated men, even when stratified by T2DM status, HbA1c and antiglycaemic agent use. Interestingly, we see a return of age as a risk factor in men on TU, with the expected nonlinear pattern being restored.

We speculate that this change in the two groups may be driven by exposure to worsening metabolic risk factors (WC, HbA1c, lipids, and BP) associated with adult-onset TD when untreated. In contrast, every one of

these risk factors improved with TU. The reduction in risk may have been associated with TU-associated improvements in metabolic risk factors. Furthermore, we also speculate that nonmetabolic actions of testosterone (e.g. upregulation of DNA repair) may also contribute to the restoration of the association between age and mortality. Although we have described that treatment with TU restored the Gompertz–Makeham relationship in our cohort, we acknowledge that the observed change in the association between probability and age in the TU-treated/TU-untreated groups may have been exhibiting different underlying disease trajectories as opposed to the biological effects of testosterone.

Our view is that a study of mortality using the Gompertz–Makeham model enhances our understanding of mortality risk in various pathologies and the impact of treatment. Abolishment of the association between age and mortality in certain pathologies is perhaps due to the prevalence of high-risk factors, which may have to be considered similar to the external age-independent risk exclusion factors described by Gompertz. It may be a measure of mortality risk due to its age-independent mechanism. Considering this, our paper highlights the importance of diagnosing this condition, followed by information dissemination of the inherent risks together with the reported benefits of TTh. This may help to reduce mortality associated with adult-onset TD in relatively young men.

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SR: design of study, data analysis, preparation of manuscript. AH, KSH, and FS: patient recruitment, data collection, and preparation of manuscript. PD: transposing the data, maintaining the database. CSK and RCS: design of study, data analysis, and preparation of manuscript. AM, GH, MZ, MMD, and JM: preparation of manuscript.

Author contributions

CRediT: **Amar Mann:** Visualization, Writing – original draft, Writing – review & editing; **Richard C Strange:** Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing; **Carola S König:** Conceptualization, Formal analysis, Visualization, Writing – original draft, Writing – review & editing; **Geoffrey Hackett:** Visualization, Writing – original draft, Writing – review & editing; **Ahmad Haider:** Data curation, Visualization, Writing – original draft, Writing – review & editing; **Karim Sultan Haider:** Data curation, Visualization, Writing – original draft, Writing – review & editing; **Peter Desnerck:** Methodology, Software, Writing – review & editing; **Michael Zitzmann:** Visualization, Writing – original draft, Writing – review & editing; **Farid Saad:** Data curation, Visualization, Writing – original draft, Writing – review & editing; **Mruga M Dhebar:** Visualization, Writing – original draft, Writing – review & editing; **John Marriott:** Visualization, Writing – original draft, Writing – review & editing; **Sudarshan Ramachandran:** Conceptualization, Methodology, Project administration, Visualization, Writing – original draft, Writing – review & editing.

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Data availability statement

All reasonable requests for data should be directed to corresponding author.

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