Exploration of Endocrine and Metabolic Diseases

Open Exploration

Open Access Original Article

Testosterone undecanoate is associated with improved ageing male symptoms score in men with type 2 diabetes and adult-onset testosterone deficiency: re-analyzed results from a randomised controlled trial

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Academic Editor: Marijn Speeckaert, Universitair Ziekenhuis Ghent, Belgium

Received: January 16, 2024 **Accepted:** April 9, 2024 **Published:** August 13, 2024

Cite this article: Ramachandran P, Zitzmann M, König CS, Mulhern J, Ramachandran S, Hackett G. Testosterone undecanoate is associated with improved ageing male symptoms score in men with type 2 diabetes and adult-onset testosterone deficiency: re-analyzed results from a randomised controlled trial. Explor Endocr Metab Dis. 2024;1:177–90. https://doi.org/10.37349/eemd.2024.00015

Abstract

Aim: To evaluate changes in quality of life via the ageing male symptom scale (AMSS) and somatic, psychological, and sexual sub-scales following testosterone undecanoate (TU) or placebo (P) treatment in men with type 2 diabetes mellitus (T2DM) and adult-onset testosterone deficiency (TD) via a re-analysis of the BLAST (Burntwood, Lichfield, Atherstone, Sutton Coldfield, and Tamworth) randomised controlled trial (RCT).

Methods: Analysis of data from the BLAST RCT in men with T2DM and adult-onset TD was performed. Summation baseline and study-end AMSS data were available in 170 men (94: P; 76: TU) with subscale data available in 82 men. Rank-sum and sign-rank tests determined inter/intra-group differences, whilst linear/multiple regression models identified predictors of AMSS change.

Results: AMSS improved significantly in P [–2 (median), $p = 0.010$] and TU [–6 (median), $p < 0.0001$)] arms, with greater improvement observed in men on TU ($p = 0.014$). No significant change was seen in either arm with baseline AMSS < 27 (asymptomatic). TU was significantly associated with AMSS improvement in all symptomatic AMSS categories. Improvement in the P arm was confined to men with baseline AMSS > 49. In

the cohort with subscale AMSS data, TU was associated with improvements in somatic, psychological, and sexual subscales, whilst improvement was limited to the somatic subscale in the men on P. TU (reference: P) and higher baseline AMSS were significantly and independently associated with AMSS improvement. The improvement in summation AMSS associated with TU (reference: P) was only evident in men with mild depression and no anxiety (based on baseline Hospital Anxiety and Depression Scale data).

Conclusions: TU appeared associated with improved AMSS (summation and subscales) in men with T2DM and adult-onset TD demonstrating symptoms (AMSS ≥ 27) with this benefit mediated by levels of depression and anxiety (European Union Clinical Trials Register, EudraCT 2008-000931-16).

Keywords

Ageing male symptoms score, hospital anxiety and depression scale, testosterone therapy, type 2 diabetes, adult-onset hypogonadism

Introduction

Adult-onset testosterone deficiency (TD) in men is a syndrome classified by a combination of low serum testosterone and symptoms attributable to the reduced levels of the hormone, following exclusion of primary hypogonadism and hypothalamic-pituitary-gonadal axis pathology [1]. Prevalence of this syndrome appears to range between 0.6–12% in men > 50 years of age [1, 2] with this figure greater (40–70%) in men with type 2 diabetes mellitus (T2DM) [3]. The clinical phenomena of adult-onset TD can be neatly categorised into cardiovascular, metabolic, psychological, physical, and sexual as shown in Figure 1, and can affect quality of life (QoL) [1, 4]. Many studies including the T-trials have shown that following testosterone therapy (TTh) some of the above-mentioned symptoms improved with restoration of serum hormone levels [5–7].

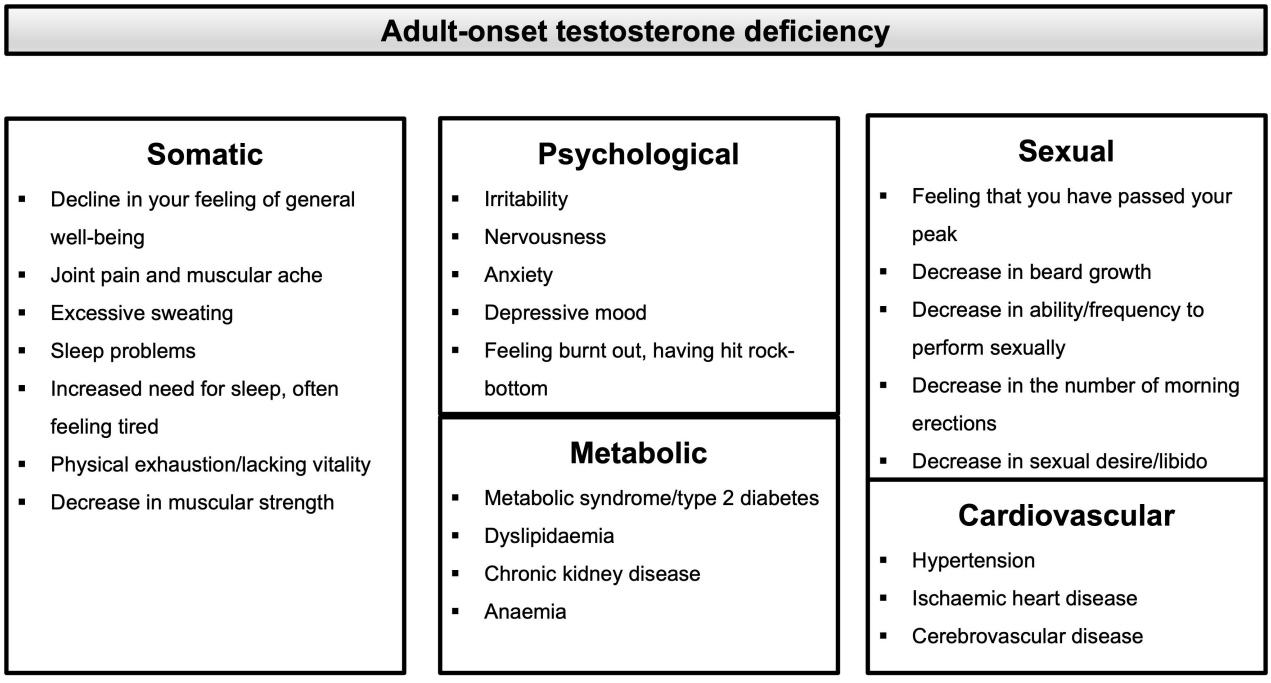

Figure 1. Some clinical features associated with low serum testosterone

The ageing male symptom scale (AMSS), a validated internationally used scoring system, designed as a self-administered questionnaire has been demonstrated to be useful in evaluating symptoms (somatic, psychological, and sexual as shown in Figure 1) associated with health-related QoL of ageing in males as well as monitoring the changes following TTh [8–11].

Elliott et al. [12] in 2017 assessed 23 randomised controlled trials (RCTs) with 3,090 men, including the BLAST (Burntwood, Lichfield, Atherstone, Sutton Coldfield, and Tamworth) study, and demonstrated that TTh was associated with improved QoL, although this effect appeared weakened with coexistent moderate/severe depression [13, 14]. Behre et al. [15] in 2012 carried out a multicentre RCT assessing efficacy regarding QoL associated with TTh (1% testosterone gel) in hypogonadal men aged 50–80 years. Inclusion criteria included serum total testosterone (TT) < 15 nmol/L, bioavailable testosterone < 6.68 nmol/L, and an AMSS value > 36. QoL was evaluated via changes (Δ) in AMSS (ΔAMSS); total AMSS and the somatic, psychological, and somatic subscales [15]. Baseline AMSS values in the TTh and placebo (P) arms were 47.5 ± 0.7 (183 men) and 47.1 ± 0.6 (179 men), respectively. Interestingly, although AMSS improved in both trial arms, the TTh arm demonstrated greater improvement (p = 0.002); mean ± standard deviation (SD) ΔAMSS in TTh and P arms were –10.54 ± 0.7 and –7.19 ± 0.78, respectively. TTh was associated with significant or near significant improvement in ΔAMSS (somatic: p = 0.053, psychological: p = 0.049, and sexual: p < 0.001) compared with P. Mean subscale ΔAMSS ± SD values in the TTh arm were –4.30 ± 0.33 (somatic), –2.89 ± 0.26 (psychological), and –3.37 ± 0.31 (sexual) and P arm were –3.35 ± 0.36 (somatic), –2.12 ± 0.29 (psychological), and –1.69 ± 0.27 (sexual) [15]. Lee et al. [16] in 2013 conducted a single centre cross-sectional study of 176 men in a psychiatric outpatient setting and showed significant correlations between AMSS (total and subscales) and depression/anxiety using the Hospital Anxiety and Depression Scale (HADS) questionnaire. The HADS was developed in 1983 to estimate anxiety [HADS-anxiety (HADS-A)] and depression [HADS-depression (HADS-D)], which often coexist [14]. In both, HADS-A and HADS-D, scores of 8–10, 11–15, and 16–22 indicate mild, moderate, and severe anxiety and depression, respectively [14]. Diagnostic thresholds demonstrated that a score of ≥ 8 using HADS-A and HADS-D had a specificity of 0.78 and a sensitivity of 0.9 for anxiety, and specificity of 0.79 and a sensitivity of 0.83 for depression, respectively [14, 17].

Many studies have shown TTh to be associated with significant benefits in depression when compared with P [18–21]. However, cohort characteristics differed between these studies. A meta-analysis of 27 RCTs (1,890 men) by Walther et al. [22] in 2019 showed that TTh compared to P was associated with a significant decrease in symptoms of depression, with the association especially evident at higher doses of TTh. They speculated that the efficacy was comparable to that of a moderate antidepressant, although acknowledging significant between study heterogeneity [22].

A recent meta-analysis of 17 trials with participant data by Hudson et al. [23] in 2023 including the BLAST study evaluated benefits associated with TTh in subgroups of men with low serum testosterone levels. Although AMSS values improved, this was not significant in men with T2DM, and it was speculated that lower QoL in men with T2DM may have demonstrated a blunted response to TTh [23]. The mean ± SD of AMSS values in the 482 men on TTh and 456 men on P were 32.19 ± 10.23 and 34.22 ± 11.10, respectively.

Aims of the study

This non-significant association between TTh and ΔAMSS prompted us to re-analyse the summation AMSS and subscale ΔAMSS data from the BLAST study, an RCT carried out in men with T2DM and adult-onset TD [13]. Firstly, we established ΔAMSS in the total cohort and men with subscale data following TTh with testosterone undecanoate (TU) compared to P. Secondly, we ascertained any possible association between baseline AMSS and ΔAMSS in accordance with the Wilder principle which states that the response to an intervention is dependent on the baseline values [24]. This was important in view of the suggestion by Hudson et al. [23] that poorer baseline QoL (higher AMSS values) may have contributed to the observed non-significant outcome. Thirdly, in view of the association between AMSS and HADS and possible heterogeneity in adult-onset TD, we studied associations between TU (compared to P), baseline AMSS, and ΔAMSS in men stratified by baseline depression and anxiety (via HADS values). We consider the findings of this extended analysis which has never been undertaken or published previously, to be important as lifestyle measures are considered essential in the management of T2DM as QoL improvements may lead to greater compliance [25].

Materials and methods

Study data

The BLAST study, a 30-week double-blind P-controlled RCT was carried out in men with T2DM aged between 18–80 years with serum TT ≤ 12.0 nmol/L and/or calculated free testosterone (cFT) ≤ 250 pmol/L with symptoms of TD carried out at primary care centres in England between 2008–2012 [13, 26–28]. The period of study was in accordance with the TTh trial period of 3–6 months as suggested by the then guidelines [4, 29]. The RCT was carried in accordance with the proposals of the World Medical Association Declaration of Helsinki of 2000 (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) with approval obtained from United Kingdom and European regulatory bodies; Multicentre UK Research Ethics Committee approval (08/H1208/30), European Union Clinical Trials Register (EudraCT 2008-000931-16). The primary efficacy endpoint was a change in haemoglobinA1c (HbA1c) and it was estimated that a sample of 100 men in each group would lead to an 80% probability of a statistically significant treatment difference in HbA1c of 0.4%.

Patient data

Serum TT and cFT were obtained from 857 men (5 primary care registers). Exclusion criteria included patients considered too frail for TTh, previous TTh, abnormal digital rectal examination, prostate specific antigen (PSA) > 4 µg/L, haematocrit > 0.50 L/L, history of prostate, breast/hepatic carcinoma, and other serious co-morbidities. After application of the exclusion criteria, 550 men had a morning (8–11 am) serum TT level and cFT carried out with 211 of them having serum TT ≤ 12 nmol/L and/or FT ≤ 250 pmol/L (visit 1). There were 12 men who were withdrawn (elevated PSA: 10; atrial fibrillation: 1; withdrawal of consent: 1) at this point. The remaining 199 men were randomised with 1,000 mg TU (92 men), or matched P (107 men) administered at visits 2 (baseline), 3 (6-weeks), and 4 (18-weeks). These intervals were in line with the manufacturer's recommendation and fixed in view of the blinded nature of the study. The study database was re-examined in 2015 prior to further analyses of sexual function values [27, 28] and discrepancies in the patient numbers reported in the original publication [13] were noted, independently verified (by individuals not associated with the study) and amended. We are aware that these changes may lead to some possible changes in the findings. Further, in the original publication HADS-D data, but not HADS-A data were tabulated as only HADS-D was hypothesised to be a possible mediator [13]. With the current authorship possessing greater knowledge in psychology (author PR), we felt it important to include HADS-A data in the analysis.

Laboratory measurements and questionnaire-based data (including AMSS and HADS scores) were obtained at visits 2–4 as well as at the study end (visit 5–30 weeks). Ten of the men did not complete the study (treatment unrelated deaths: 4; withdrawal of consent: 6), thus baseline data were available on 86 and 103 men in the treatment and P arms, respectively. Patient numbers based on baseline serum TT and cFT are as follows: serum TT ≤ 12.0 nmol/L = 163 men, cFT ≤ 250 pmol/L = 172 men, serum TT ≤ 12.0 nmol/L and cFT ≤ 250 pmol/L = 146 men.

Whilst on the study, anticoagulation therapy was not permitted and the primary care health professionals were requested, where possible, to avoid treatment changes (diabetes, blood pressure, and dyslipidaemia). Data on adverse events were collected at each visit using non-leading questions. Previous publications of the BLAST study (following the above amendment in the patient numbers) summarise the study protocol via a flow diagram [27, 28].

Treatment data

TU or matched P were administered over a 5-min period into either upper outer gluteal region. TU (Nebido) was prepared by Bayer (Pharma AG, Berlin, Germany). P contained an analogue of similar appearance without the active testosterone, consisting of vehicle castor oil and benzyl benzoate. Trial medication identification was via numbered sealed packages with each subject assigned to the next lowest

numbered sealed package. The codes were retained by the study statistician until the final patient completed the study and were not broken until study completion with data bases locked.

Laboratory, AMSS, HADS-D, and HADS-A data

Fasting blood samples were taken between 8–11 am at baseline, 6, 18, and 30 weeks for laboratory measurements [haematocrit, HbA1c and serum TT, sex hormone-binding globulin (SHBG), and PSA]. All laboratory work was carried out at the Heart of England Foundation NHS Trust Laboratories, now part of the University Hospitals Birmingham NHS Foundation Trust.

The BLAST study outcomes including summation AMSS values, HADS-D scores [data were available from 170 questionnaires (76 men on TU, 94 men on P) with baseline and study end values] were published previously [13]. For this study, we also included HADS-A data that were previously unpublished as it did form a part of the hypothesis at the time. Questionnaires used in the study were kept in both primary and secondary care centres. For this study, subscale AMSS was required, and we were only able to obtain 82 of the questionnaires stored in the secondary care setting, hence subscale data were restricted to 82, 80, and 81 questionnaires for somatic, psychological, and sexual subscales, respectively.

Statistical analysis

The 189 men completing the RCT (86 men on TU, 103 men on P) were smaller than the 199 men originally randomised (92 men on TU, 107 men on P). AMSS values at baseline and study end were available in 170 men (76 men on TU and 94 men on P). In the TU group, no significant differences ($p > 0.05$, rank-sum) were observed in baseline values between the men with study end data (170 men) and those who completed the study (19 men) with data missing (age, serum TT, cFT, AMSS, HADS-D, HADS-A, and the metabolic indices). Importantly HADS-D or HADS-A (baseline or change) did not predict the 2 groups. As AMSS data are ordinal, non-parametric analyses (rank-sum and sign-rank tests) were carried out (parametric statistics were carried out in the previous analysis [13]) to determine intra-group and inter-group differences (TU and P arms) in the total cohort and the men who had data on AMSS subscales (clinical features included in the questionnaires are presented in Figure 1). Linear and multiple regression models were used to identify predictors of ΔAMSS such as TU (reference: P) and baseline AMSS values. To study the impact of depression and anxiety on any associations between TU (reference: P), baseline AMSS, and ΔAMSS, the cohort was stratified by HADS-D and HADS-A values (< 8: no symptoms and ≥ 8: mild, moderate, and severe symptoms in view of the high sensitivity and specificity) and regression analyses performed [14, 17]. However, as previously stratification was carried out using a HADS-D value of 11 or greater [13], we evaluated men with HADS-D between 8–11 (mild depression) separately. All statistical analyses were performed using Stata version 14 (College Station, TX).

Results

The baseline data of the total cohort and men of TU and P are shown in Table 1. No significant inter-group differences (rank-sum) were evident regarding age, serum TT, SHBG, cFT, and AMSS values. Not surprisingly serum TT, cFT concentrations at study end (30 weeks) were significantly higher than baseline in men treated with TU whilst serum SHBG levels decreased, however no significant changes were observed in the men on P. Table 1 also demonstrates that AMSS values improved significantly (sign-rank) in both groups; median [interquartile range (IQR)] ΔAMSS in men on TU and P were –6 (–10, 0), $p < 0.0001$ and –2 (–7, –3), $p = 0.010$, respectively. The decrease in AMSS values in men on TU was significantly greater ($p = 0.014$, rank-sum) than the men on P. TU did not lead to significant improvement in AMSS after 6-weeks ($p = 0.52$, rank-sum) and 18-weeks ($p = 0.077$, rank-sum) compared to P. Table 1 also shows significant improvements in median (IQR) HADS-D and HADS-A values only in men on TU, –1 (–3, 0), $p = 0.0083$ and –1 (–3, 0), $p = 0.0010$, respectively. Significant intergroup differences regarding ΔHADS-D ($p = 0.072$) and ΔHADS-A ($p = 0.072$) were not evident.

Table 1. Baseline, study end data in the total cohort, the TU, and placebo arms

Study parameters	Total group	Placebo	TU	*p* (rank-sum, inter-group)
Number of men	170	94	76	-
Age median (IQR)	62.5 (55, 69)	62.5 (55, 69)	62.5 (54, 69)	0.97
Baseline serum TT (nmol/L) median (IQR)	8.8 (6.8, 11.1)	8.55 (6.6, 11.3)	9.2 (7.1, 11.0)	0.42
30-week serum TT (nmol/L) median (IQR)	9.85 (7.22, 12.7)	8.9 (6.8, 11.7)	11.5 (8.3, 13.5)	0.0089
∆serum TT (nmol/L) median (IQR), *p* (sign-rank, intra-group differences)	0.80 (–1.4, 2.85), *p* = 0.0015	0.80 (–1.40, 2.0), *p* = 0.10	1.3 (–1.4, 3.85), *p* = 0.0020	0.10
Baseline serum SHBG (nmol/L) median (IQR)	28.1 (20.5, 36.6)	27.0 (19.9, 35.7)	29.2 (20.5, 38.2)	0.53
30-week serum SHBG (nmol/L) median (IQR)	26.6 (20.3, 36.8)	26.1 (19.0, 37.6)	27.0 (20.7, 36.3)	0.83
∆serum SHBG (nmol/L) median (IQR), *p* (sign-rank, intra-group differences)	–1.0 (–4.4, 3.2), *p* = 0.082	–0.70 (–4.1, 3.5), *p* = 0.63	–1.2 (–4.6, 2.1), *p* = 0.037	0.29
Baseline serum cFT (pmol/L) median (IQR)	190 (145, 230)	182.5 (140.0, 225.0)	190 (150, 230)	0.6
30-week serum cFT (pmol/L) median (IQR)	200.0 (150.0, 257.0)	180.0 (150.0, 222.5)	227.5 (166.5, 280.0)	0.0001
∆serum cFT (nmol/L) median (IQR), *p* (sign-rank, intra-group differences)	10 (–30, 55), *p* = 0.011	5 (–30, 30), *p* = 0.76	37.5 (–30, 85), *p* = 0.0010	0.0059
Baseline AMSS median (IQR)	39 (34, 49)	39 (32, 48)	40 (34, 51)	0.23
30-week AMSS median (IQR)	36 (28, 44)	37 (29, 45)	34 (28, 44)	0.61
∆AMSS median (IQR), *p* (sign-rank, intra-group differences)	–3 (–9, 2), *p* < 0.0001	–2 (–7, 3), *p* = 0.010	–6 (–10, 0), *p* < 0.0001	0.014
Baseline HADS-D median (IQR)	7 (5, 10)	7 (4, 10)	8 (5, 10)	0.24
30-week HADS-D median (IQR)	7 (3, 9)	7 (3, 9)	6 (4, 9)	0.97
∆HADS-D median (IQR), *p* (sign-rank, intra-group differences)	–1 (–3, 1), *p* = 0.0019	0 (–1, 1), *p* = 0.080	–1 (–3, 0), *p* = 0.0083	0.072
Baseline HADS-A median (IQR)	5 (2, 8), *n* = 143	4 (2, 8), *n* = 81	5.5 (3, 8), *n* = 62	0.22
30-week HADS-A median (IQR)	4 (1, 7)	3.5 (1, 8)	4 (1.5, 7)	0.84
∆HADS-A median (IQR), *p* (sign-rank, intra-group differences)	–1 (–3, 1), *p* = 0.0023	0 (–1, 1), *p* = 0.22	–1 (–3, 0), *p* = 0.0010	0.072

p < 0.05 is considered significant. -: no data; ∆: changes. AMSS: ageing male symptom scale; cFT: calculated free testosterone; HADS-A: Hospital Anxiety and Depression Scale-anxiety; HADS-D: Hospital Anxiety and Depression Scale-depression; IQR: interquartile range; SHBG: sex hormone-binding globulin; TT: total testosterone; TU: testosterone undecanoate

Table 2 shows AMSS data (baseline, 30-week, and ΔAMSS) in the men for whom the subscale AMSS was recalculated from the questionnaires stored in secondary care. Intra-group statistics (sign-rank) showed that somatic, psychological, and sexual subscale AMSS values improved in the men on TU whilst only somatic subscale AMSS values improved in the men randomised to P as evident in Table 2.

Separate linear regression analyses showed that ΔAMSS (dependent variable) was inversely associated with baseline AMSS values (independent variable) in men on TU [coefficient: –0.28, 95% confidence intervals (CI): –0.47, –0.079, *p* = 0.007] and P (coefficient: –0.20, 95% CI: –0.33, –0.079, *p* = 0.002). Thus, improvement in AMSS was greater in men with higher baseline values in both arms of the RCT. To further investigate the above-mentioned association between baseline and ΔAMSS, the cohort was stratified by baseline values as seen in Table 3; < 27 (no significant symptoms consistent with a low testosterone level), 27–36 (mild symptoms consistent with a low testosterone level), 37–49 (moderate symptoms consistent with a low testosterone level), and > 49 (severe symptoms consistent with a low testosterone level). There was no difference between the TU and P groups regarding the distribution of men stratified by baseline AMSS (*p* =

Table 2. Baseline, study end AMSS values and ΔAMSS broken down into the somatic, psychological, and sexual subscales

AMSS startified by subscales (somatic, psychological and sexual)	P	TU
Somatic subscale (Q1–5, Q9, and Q10) (7–35)		
Median (IQR) baseline AMSS, *n*	17 (13, 21), *n* = 44	19 (15, 24), *n* = 38
Median (IQR) AMSS 30-week	15 (11, 20)	16.5 (14, 22)
Median (IQR) ΔAMSS	–1 (–3, 1)	–2 (–4, 1)
p (sign-rank)	0.0048	0.017
Psychological subscale (Q6–8, Q11, and Q13) (5–25)		
Median (IQR) baseline AMSS, *n*	9 (6, 11), *n* = 45	10 (8, 14), *n* = 35
Median (IQR) AMSS 30-week	8 (6, 11)	9 (7, 12)
Median (IQR) ΔAMSS	–1 (–2, 1)	–1 (–3, 0)
p (sign-rank)	0.23	0.0039
Sexual subscale (Q12, Q14–17) (5–25)		
Median (IQR) baseline AMSS, *n*	12 (10, 17), *n* = 45	15 (11, 18.5), *n* = 36
Median (IQR) AMSS 30-week	13 (9, 16)	13 (9, 16)
Median (IQR) ΔAMSS	0 (–2, 1)	–2 (–4.5, –0.5)
p (sign-rank)	0.66	0.0011

$p < 0.05$ is considered significant. ΔAMSS: changes in ageing male symptom scale; IQR: interquartile range; P: placebo; Q: questionnaire; TU: testosterone undecanoate

0.48, chi-square). Table 3 shows that no significant change in AMSS was evident in men with baseline AMSS values < 27 in both TU and P study arms. TU was associated with improvement in AMSS in the other 3 groups stratified by baseline AMSS (men with mild, moderate, and severe symptoms associated with low serum TT concentrations). P was only associated with improvements in men with severe symptoms associated with low serum TT concentrations (AMSS > 49).

Table 3. ΔAMSS values with the cohort stratified by treatment and baseline AMSS values

Patient groups	P	TU
Median (IQR) baseline AMSS (AMSS < 27), *n*	22 (22, 23), *n* = 9	24 (23, 25), *n* = 3
Median (IQR) ΔAMSS	2 (–1, 3)	0 (–6, 17)
p (sign-rank)	0.083	0.78
Median (IQR) baseline AMSS (AMSS 27–36)	30.5 (28, 34), *n* = 28	33 (31, 34), *n* = 25
Median (IQR) ΔAMSS	–2 (–4.5, 4)	–6 (–7, –1)
p (sign-rank)	0.45	0.0019
Median (IQR) baseline AMSS (AMSS 37–49)	40.5 (38, 45), *n* = 38	43 (39, 47), *n* = 29
Median (IQR) ΔAMSS	–2 (–7, 3)	–5 (–10, 0)
p (sign-rank)	0.061	0.0097
Median (IQR) baseline AMSS (AMSS > 49)	57 (53, 62), *n* = 19	54 (52, 58), *n* = 19
Median (IQR) ΔAMSS	–7 (–12, 0)	–9 (–19, 1)
p (sign-rank)	0.018	0.0022

$p < 0.05$ is considered significant. ΔAMSS: changes in ageing male symptom scale; IQR: interquartile range; P: placebo; TU: testosterone undecanoate

Table 4 shows AMSS values (baseline, 30-week, and change) stratified (< 8 and ≥ 8) by HADS-D and HADS-A values as well as the association between TU (P: reference) and ΔAMSS (dependent variable) with the models adjusted for baseline AMSS values (Table 5). TU was significantly associated with ΔAMSS (model 1) in the total study cohort and this was independent of baseline AMSS (model 3); baseline AMSS was also seen to be associated with ΔAMSS (model 2). Importantly, baseline serum TT and Δserum TT [the regression model also included TU (P: reference) and baseline AMSS as independent variables, both these remained associated] were not significantly associated with ΔAMSS. Baseline AMSS values were significantly higher in men with baseline HADS-D ($p < 0.0001$, rank-sum) and HADS-A ($p < 0.0001$, rank-sum) ≥ 8. Models 4–7 show the association between ΔAMSS and TU (P: reference) with the analyses

adjusted for baseline AMSS in the patient cohort stratified by HADS-D and HADS-A values (< 8 and ≥ 8). Interestingly TU was associated with improvement in AMSS in men with HADS-D ≥ 8 and HADS-A < 8. Thus, the benefit in AMSS following TU (compared to P) appeared to be restricted to men with mild-severe symptoms (≥ 8) of depression (model 4) and no symptoms (< 8) of anxiety (model 7) on HADS-D and HADS-A values.

Table 4. AMSS values (baseline, 30-week, and change) stratified (< 8 and ≥ 8) by HADS-D and HADS-A values

Patient groups	Baseline AMSS: median (IQR)	30-week AMSS: median (IQR)	ΔAMSS: median (IQR)
HADS-D ≥ 8			
P, *n* = 44	45 (39, 54)	44.5 (36.5, 50)	–3 (–9, 3)
TU, *n* = 35	50 (42, 55)	42 (31, 51)	–6 (–11, 1)
HADS-D < 8			
P, *n* = 50	34 (27, 38)	31 (26, 41)	–2 (–5, 3)
TU, *n* = 41	35 (31, 40)	31(28, 35)	–5 (–7, –1)
HADS-A ≥ 8			
P, *n* = 34	45 (38, 57)	44 (31, 53)	–2.5 (–10, 2)
TU, *n* = 37	47 (40, 54)	41 (31, 51)	–3 (–10, 2)
HADS-A < 8			
P, *n* = 60	36 (29.5, 41)	34.5 (26.5, 42)	–2 (–6, 3)
TU, *n* = 39	35 (32, 41)	31 (27, 38)	–6 (–9, –2)

ΔAMSS: changes in ageing male symptom scale; HADS-A: Hospital Anxiety and Depression Scale-anxiety; HADS-D: Hospital Anxiety and Depression Scale-depression; IQR: interquartile range; P: placebo; TU: testosterone undecanoate

Table 5. The association between TU (P: reference) and ΔAMSS (dependent variable) with the models adjusted for baseline AMSS values

Univariate/multivariate regression analyses outcome: ΔAMSS			Coefficient (95% CI)	*p*
Total cohort	Model 1 (*n* = 170)	TU vs P (reference)	–3.12 (–5.65, –0.61)	*p* = 0.015
	Model 2 (*n* = 170)	Baseline AMSS	–0.24 (–0.35, –0.13)	*p* < 0.001
	Model 3 (*n* = 170)	TU vs P (reference)	–2.66 (–5.07, –0.25)	*p* = 0.031
		Baseline AMSS	–0.23 (–0.34, –0.12)	*p* < 0.001
HADS-D ≥ 8	Model 4 (*n* = 79)	TU vs P (reference)	–4.25 (–8.40, –0.11)	*p* = 0.044
		Baseline AMSS	–0.30 (–0.50, –0.10)	*p* = 0.003
HADS-D < 8	Model 5 (*n* = 91)	TU vs P (reference)	–1.15 (–3.94, 1.65)	*p* = 0.42
		Baseline AMSS	–0.22 (–0.41, –0.43)	*p* = 0.016
HADS-A ≥ 8	Model 6 (*n* = 71)	TU vs P (reference)	–2.21 (–7.10, 2.67)	*p* = 0.37
		Baseline AMSS	–0.20 (–0.42, 0.014)	*p* = 0.067
HADS-A < 8	Model 7 (*n* = 99)	TU vs P (reference)	–3.21 (–5.48, –0.94)	*p* = 0.006
		Baseline AMSS	–0.35 (–0.47, –0.22)	*p* < 0.001
HADS-D: 8–10	Model 8 (*n* = 41)	TU vs P (reference)	–5.37 (–10.52, –0.22)	*p* = 0.041
		Baseline AMSS	–0.43 (–0.70, –0.16)	*p* = 0.003
HADS-D: 11–21	Model 9 (*n* = 38)	TU vs P (reference)	1.05 (–4.39, 6.50)	*p* = 0.70
		Baseline AMSS	–0.088 (–0.31, 0.13)	*p* = 0.43

The results from models 4 and 5 are at odds with that previously reported by Hackett et al. [13] using this database stratifying the cohort with a HADS-D value of 11 or greater; thus men with no-depression (HADS-D: < 8) and mild depression (HADS-D: 8–10) were grouped together, whilst we used to a HADS-D cut-off of 8 to have as close to even numbers of men in both subgroups. Further analysis shows that TU was significantly associated with ΔAMSS in the men with mild depression (HADS-D: 8–10) with no such association observed in men with HADS-D: 11–21 (moderate and severe depression), this group was not further stratified as there were only 7 men with severe depression (HADS-D: 15–21). $p < 0.05$ is considered significant. ΔAMSS: changes in ageing male symptom scale; CI: confidence intervals; HADS-A: Hospital Anxiety and Depression Scale-anxiety; HADS-D: Hospital Anxiety and Depression Scale-depression; P: placebo; TU: testosterone undecanoate

Table 5 (models 8, 9, and footnote) shows the cohort stratified by HADS-D of 11; it was evident that TU was significantly associated with ΔAMSS in the men with mild depression (HADS-D: 8–11) with no such

association in men with HADS-D: 11–21 (moderate and severe depression) observed (this group was not further stratified as there were only 7 men with severe depression (HADS-D: 15–21).

Discussion

In response to the recent publication by Hudson et al. [23], we re-analysed data from the BLAST study in men with T2DM and adult-onset TD to establish ΔAMSS in the total cohort and ΔAMSS in the subscales following TTh with TU compared to P. This was followed by evaluating whether TU (P: reference) and baseline AMSS were associated with ΔAMSS in the total cohort and when stratified by HADS-D and HADS-A.

Interestingly AMSS improved significantly in both the TU and P arms, although the improvement was significantly greater in the men on TU (Table 1). The previous report by Hackett et al. [13] did not show significant differences between the TU and P arms (p = 0.092, ANCOVA test) in the original publication. A repeat of the analysis (ANCOVA) on the amended database showed that TU was associated with greater improvement in AMSS (p = 0.024). This discrepancy could have been due to reclassification of the database carried out in 2015. Similarly, we showed improvements in HADS-D and HADS-A values in men on TU, although there was no significant intergroup difference (the original report [13] only reported intergroup differences). Analyses with the restricted cohort with subscale data showed that whilst AMSS decreased with TU in all subscales, reduction in AMSS following P was only observed in the somatic AMSS subscale. We can only speculate that the improvement of somatic subscale AMSS could be related to either the lifestyle advice provided at study initiation or added motivation of being selected for the study. Baseline AMSS values also appeared to predict ΔAMSS in both men on TU and P. Further, it also appears in our cohort of men that depression and anxiety as measured by HADS-D and HADS-A had an impact on ΔAMSS; interestingly this benefit was only evident in men reporting symptoms of mild depression and those not reporting symptoms of anxiety.

In the original report of the BLAST study [13] stratifying the cohort by HADS-D value of 11 (HADS-D ≥ 11 has been considered clinically significant depression—moderate/severe depression) suggested that AMSS only improved in men with HADS-D value < 11. The results from models 4 and 5 in Table 5 appear to be at odds with the previous finding [13]. This extended analysis by selecting different HADS-D thresholds refined this finding and established that the benefit was evident only in men with HADS-D of 8–10 (mild depression), more details are found in the footnote of Table 5. In the original analysis, the stratifying categories included mild depression/no depression and moderate/severe depression [13]. Thus, the category where mild depression was placed led to seemingly different outcomes in ΔAMSS. As lower HADS-D values were associated with lower baseline AMSS values [due to the inverse association between baseline AMSS and ΔAMSS (Table 5, model 2)] we would expect a more modest improvement in men with lower HADS-D values; this was evident (Table 5, model 5). This argument also suggests greater improvement in AMSS values in men with moderate/severe depression (Table 5, model 9); this was not evident, perhaps due to TTh over 30 weeks being insufficient.

Our findings of improvement in AMSS are only of clinical value if it is a useful marker of QoL. Lunenfeld et al. [7] in 2013 recommended that despite low specificity, AMSS was possibly useful in monitoring clinical response following TTh. Heinemann et al. [8] in 2003 in an open post-marketing study of 1,670 men with low serum TT provided testosterone gel analysed AMSS before and 3 months after TTh. Significant improvements in AMSS were observed in the summation of AMSS values as well as the individual subscale values. It also appeared that higher baseline AMSS values were associated with greater improvement: 9%, 24%, 32%, and 39% in men with absent, mild, moderate, and severe symptoms at baseline, respectively [8]. This is in agreement with our findings and the Wilder principle [24]. The RCT by Behre et al. [15] in 2013 was confined to men with baseline AMSS > 36 and like our study showed improvements in AMSS values in both study arms with the TTh arm demonstrating greater benefit. Our findings do not fit with the speculation reached by Hudson et al. [23] that the higher baseline AMSS values in men with diabetes may have led to a non-significant ΔAMSS.

We have previously hinted at the presence of heterogeneity in adult-onset TD and this could lead to variation in response following TTh [30]. Thus, it is essential that the cohort characteristics and baseline presentation patterns are heeded. In our study, it is evident that the baseline AMSS value and scale of depression/anxiety altered the outcomes. Thus, longer RCTs with larger cohorts are required to tease out potential interactions that will exist in chronic pathological states such as adult-onset TD. The classification by including serum testosterone status and associated symptoms (as evident in Figure 1) ensures heterogeneity.

Our results have shown that QoL measured using AMSS has improved in men with T2DM. In view of the high prevalence of adult-onset TD in men with diabetes, it is tempting to speculate that even a modest improvement in QoL could lead to improved outcomes, including treatment adherence. Associations have been demonstrated between QoL measures and treatment compliance in chronic conditions such as hypertension and diabetes [31, 32]. Uchmanowicz et al. [31] in 2018 assessed QoL using the World Health Organization QoL Scale Brief version questionnaire and showed a positive correlation with antihypertensive treatment compliance. Some studies have shown a similar correlation between QoL and therapeutic compliance in patients with diabetes. Of the 6 studies considered in a systematic review by Gusmai et al. [32] in 2015, 4 studies suggested that better QoL improved treatment adherence (3 of them used biochemical outcome markers such as HbA1c, whilst the remaining study used information gathered from questionnaires as the outcome).

We also demonstrated that TU was associated with improvement in both depression and anxiety (Table 1), evaluated via HADS. Korenman et al. [33] in 2018 reported a significant association between depression and eugonadotrophic hypogonadism (serum TT < 10.4 nmol/L) in men (compared with matched population controls) aged between 18 and 40 years. A review by Indirli et al. [34] in 2023 hinted at a bidirectional association between hypogonadism and depression. They highlighted that the impact of TTh on depression and the reciprocal association between antidepressants on hypogonadism have not been clarified [34]. Thus, our findings are of potential importance. Interestingly (via multivariate regression models) our data also shows that psychological subscale values were associated with the somatic subscale values ($p < 0.001$), but not with the sexual subscale values ($p = 0.24$). Thus, to validate our observations and to unravel the intricate associations between depression, anxiety, AMSS subscales, and TTh, an RCT with AMSS and HADS as primary endpoints is required. In the event of our findings being validated, it would be interesting to create a further study to see if improvement in depression and anxiety via prior interventions by psychologists and psychiatrists leads to better AMSS outcomes following TTh. If this was proven a case for a multifaceted approach including psychologists/psychiatrists in the management of men with adult-onset TD is strengthened. Adult-onset TD is defined as a combination of low serum testosterone levels and associated symptoms [1]; hence, it is unlikely that men with AMSS values < 27 would be offered TTh based on symptoms evaluated via the AMSS questionnaire. It would be interesting whether further research would refine this approach by suggesting using AMSS subscale values (as an association was not established between psychological and sexual subscales).

Strengths and limitations

Our re-analysis of the BLAST study data has many strengths and weaknesses. The strengths include the representative nature of the study cohort as it was following screening of complete primary care databases. The high compliance and low withdrawal rates were perhaps due to use of long-acting TU administered by a familiar healthcare setting. However, for subtle investigation of non-primary outcomes the cohort numbers and length of follow-up are relatively modest. We could not investigate the interactions between HADS and AMSS values in greater depth. Further, subscale AMSS values were available only in about half the total cohort, restricting further subgroup analyses. Regression towards the mean is possible although the RCT design and the perhaps observed Wilder principle can be argued to counter this [24]. We acknowledge that androgen receptor sensitivity could have influenced outcomes following TTh, but unfortunately, we did not have data on CAG repeats [35]. The increase in serum TT and cFT after 30-week of TU appeared modest when compared to the Moscow study [36], another 30-week RCT using TU [mean

(95% CI) increases from a 6.7 (6.0–7.4) nmol/L to 13.1 (11.9–14.4) nmol/L in serum TT and 120 (107–135) pmol/L to 274 (243–308) pmol/L in cFT]; greater increases in these hormone values could have possibly led to differing results. We would also like to have analysed the subgroup of men stratified by serum TT ≤ 12 nmol/L and cFT > 250 pmol/L to see if there was a more modest response in the men with only low serum TT (not low cFT levels) due to low SHBG values, unfortunately, the small number of men (17) in this subgroup prohibited meaningful statistics. Further, patient numbers did not permit us to stratify the study group by other therapies such as phosphodiesterase-5 inhibitors and statins. Lastly, our results only apply to the initial 30 weeks of TTh, and it is possible that a longer treatment duration could have demonstrated varied findings, especially in men with anxiety and moderate/severe depression.

Conclusions

We re-analyzed data from the BLAST RCT to study associations between TU and other factors predicting ΔAMSS (summation and subscale values) in men with T2DM and adult-onset TD. Our findings differ from that of the original publication [13], perhaps due to amendment of the database in 2015 following re-examination of the patient categories and more detailed stratification of HADS-D (previously the mild depression was excluded from the clinically depressed category).

TU improved AMSS after 30 weeks in summation and subscale values, whilst P was only seen improving the somatic subscale AMSS. Baseline AMSS was inversely associated with ΔAMSS, thus men with higher baseline values experienced greater benefits. Further, the effect of TU (compared to P) was restricted to men suffering from mild depression (this differed from the original publication) and men not experiencing anxiety (HADS-A was not included in the original analysis), suggesting that cohort characteristics can determine TTh related outcomes. Thus, cohort heterogeneity must be considered when evaluating studies carried out in men with adult-onset TD. Although larger RCTs with longer follow-ups are required to validate our findings, the BLAST RCT provides considerable evidence that TU can improve QoL in men with T2DM and adult-onset TD.

Abbreviations

AMSS: ageing male symptom scale

BLAST: Burntwood, Lichfield, Atherstone, Sutton Coldfield, and Tamworth

cFT: calculated free testosterone

CI: confidence intervals

HADS: Hospital Anxiety and Depression Scale

HADS-A: Hospital Anxiety and Depression Scale-anxiety

HADS-D: Hospital Anxiety and Depression Scale-depression

HbA1c: haemoglobinA1c

P: placebo

PSA: prostate specific antigen

QoL: quality of life

RCT: randomised controlled trial

SD: standard deviation

SHBG: sex hormone-binding globulin

T2DM: type 2 diabetes mellitus

TD: testosterone deficiency

TT: total testosterone

TTh: testosterone therapy

TU: testosterone undecanoate

Declarations

Acknowledgments

We acknowledge the contributions of Drs Nigel Cole, Mithun Bhartia, Jesse Raju, David Kennedy, and Peter Wilkinson for their role in conceiving, designing, data collection, statistical analysis, and preparing the original publications from the BLAST Study dataset. We would also like to thank the Primary Care Practices and the patients who took part in the study.

Author contributions

PR: Conceptualization, Writing—original draft, Writing—review & editing. MZ and CSK: Writing—original draft. JM: Writing—original draft, Visualization. SR: Conceptualization, Writing—original draft, Writing—review & editing, Visualization. GH: Conceptualization, Writing—original draft. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

BLAST study obtained ethics approval from the Multi centre UK Research Ethics Committee (08/H1208/30).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The datasets that support the findings of this study are available from Professor Sudarshan Ramachandran upon reasonable request.

Funding

The practice expenses (BLAST RCT) of the research are supported by a grant from Bayer plc [BSP-SOP-040]. The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors did not receive any support from any organization for the submitted work. No funding was received to assist with the preparation of this manuscript.

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