Testosterone Replacement Therapy: Improved sexual desire and erectile function in men with type 2 diabetes following a 30 week randomized placebo controlled study.

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Abstract

Although testosterone replacement treatment (TRT) can improve sexual function in many hypogonadal (HG) men with type 2 diabetes (T2DM), some show either no improvement or only in a limited number of domains. Indeed, it is often difficult for the clinician to offer an indication of the likely efficacy of TRT as little data exists on the proportion of TRT-treated men who will demonstrate improvement in domains such as sexual desire (SxD) and erectile function (EF). We describe in men with T2DM firstly, the likelihood of improved sexual desire (SxD) and erectile function (EF) following TRT at various time points and secondly, if SxD change predicts later EF change. During a 30 week randomised controlled study of testosterone undecanoate (TU), 199 T2DM men with HG (189 men completing) identified from primary care registers (placebo (P): 107, TU: 92) were stratified using baseline Total Testosterone (TT)/Free Testosterone (FT) into Mild (TT 8.1–12nmol/l or FT 0.18-0.25nmol/l) and Severe HG groups (TT ≤8nmol/l and FT ≤0.18nmol/l) and placebo (P) and TU treated groups. Associations between TU, SxD and EF were investigated using Chi square and logistic regression analysis. TU improved SxD after 6 weeks while EF improvement occurred after 30 weeks, observations particularly evident in Severe HG men. Changes in SxD and EF were significantly associated in all groups. Logistic regression showed that SxD change at 6 weeks predicted of EF change after 30 weeks. Our study confirms TRT leads to changes in SxD and EF at different time points and, suggests SxD and EF changes are related. SxD change after 6 weeks predicting EF change at 30 weeks is possibly a useful clinical finding.

Introduction.

Hypogonadism (HG) is common in men with Type 2 diabetes (T2DM) [1]. The condition is defined by low serum testosterone concentrations (<12 nmol/l) and sexual symptoms. Thus, Kapoor et al (2007) showed firstly, that 20% of 355 men with T2DM had total testosterone (TT) levels < 8nmol/l and 31%, levels between 8-12nmol/l [2] and secondly, using the Androgen Deficiency in the Aging Male questionnaire, significant levels of HG and erectile dysfunction (ED). Further, the Massachusetts Male Aging Study demonstrated a threefold increase in ED prevalence in men with T2DM compared with their non-diabetic counterparts [3]. To allow better quantification of ED and other aspects of sexual function, Rosen et al (1997) developed a validated self-administered 15 item International Index of Erectile Function (IIEF) questionnaire [4] that examines 5 domains; erectile function, intercourse satisfaction, orgasmic function, sexual desire (SxD) and overall satisfaction. Prevalence of ED in T2DM men, assessed using the IIEF questionnaire is estimated to be >70% [1].

The different domains are affected at varying testosterone levels with loss of libido, depression/T2DM in non-obese men and decreased EF more common at TT concentrations <15nmol/l, <10nmol/l and <8nmol/l respectively [5]. Thus, as expected testosterone replacement therapy (TRT) has an important role in improving sexual function though its efficacy on different domains varies. Indeed, Yassin and Saad showed that while SxD improved in all 22 men with HG given 24 weeks of TRT, EF scores increased in only 54% of the men [6]. Further, the time taken for treatment to effect improvement in different domains varied. We reported in a primary care cohort of men with T2DM and Severe HG (TT < 8nmol/l, free testosterone (FT) <0.18nmol/l), that long-acting testosterone undecanoate (TU) was associated with significantly improved SxD after 6 weeks but EF only at 30 weeks treatment [7]. TU was not associated with significantly improved SxD or EF in men with Mild HG. Cunningham et al showed in 470 men aged ≥65 years with average TT < 275 ng/dl (9.54 nmol/l) and low libido, that of 12 measures of sexual activity (evaluated via Psychosexual Daily Questionnaire, Derogatis Interview for Sexual Function and IIEF) only “flirting by others” and “day spontaneous erections” did not significantly improve following TRT for 1 year [8]. Further, increases in TT, FT and oestradiol concentrations were associated with improvement in SxD but not EF. Thus, the above studies demonstrate that TRT can significantly improve sexual function in men though the time

scale of benefit differs for different domains. Further, men may demonstrate improvement in one but not another domain.

Importantly, while TRT can effect improved sexual function domain scores in men with T2DM, it is unclear what proportion of treated men demonstrate improvement and whether in one or more domains. This issue is important for patients particularly early on in treatment. Accordingly, we compared the proportion of T2DM men with HG demonstrating improvement following TRT in two ordinal domains, SxD and EF. As the efficacy of TRT appears influenced by baseline TT we investigated the effect in the total cohort and after stratification into Mild and Severe HG [7,9]. We describe the inter-relationships between treatment duration and improvements in EF and SxD and the proportions of men showing improvement in one or both domains. We also wished to determine if change in SxD at 6 weeks of TRT was predictive of improvement in EF at 30 weeks. If this was the case, clinicians might be able to indicate prognosis regarding EF relatively early during TRT.

Patients and Methods.

BLAST (acronym for patient recruitment from 7 primary care centres in Birmingham, Lichfield, Atherstone, Sutton Coldfield, Tamworth in the English midlands) describes a 30 week randomised double-blind placebo-controlled multicentre study carried out September 2008 - June 2012 to assess the impact of TRT on men with T2DM [9]. The 30 weeks study duration adhered to guidelines recommending TRT trial periods of 3–6 months in men with HG (10). The study was conducted in accordance with the revised guidelines of the World Medical Association Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/ - accessed on 02/05/2017). The study (EudraCT 2008-000931-16) was approved by the Multicentre Research Ethics Committee (reference: 08/H1208/30), the National Institute for Health Research (Birmingham and the Black Country Comprehensive Local Research Park – RM&G reference: 1268) and Warwickshire Primary Care Trust (reference: WAR230909).

Change in glycaemic control (HbA1c) was the primary efficacy end-point and several secondary end points included changes in IIEF scores [9]. The target sample size of 100 men in the TU treatment and placebo (P) arms had an 80% probability of demonstrating a statistically significant treatment

difference in the event of a treatment change in HbA1c of 0.4%. This calculation used a standard deviation of 1%, a significance level of 5% (two-sided), and analysis of covariance (ANCOVA) with baseline HbA1c as the covariate. HbA1c change of 0.4% was clinically accepted as significant and a SD (baseline corrected) of 1% was derived from previous trials. Physicians were asked, where possible, to avoid changes in diabetes, anti-hypertensive and lipid-lowering therapy during the study. Any patient requiring anti-coagulation was to be withdrawn. Adverse events were identified at each visit using a non-leading question. The safety assessment was to comprise all subjects recruited unless study medication was known not to have been taken, and the intention to treat population was to comprise all subjects in the safety population who provided efficacy data.

Inclusion criteria included men aged 18–80 years with symptoms of HG defined by the Aging Male Symptom scale together with an initial TT ≤12.0nmol/l or FT ≤ 0.25nmo/l according to current European Association of Urology (EAU) guidelines [10]. Exclusion criteria included men considered too frail for TRT, previous TRT, abnormal digital rectal examination, PSA >4µg/L, haematocrit >0.50, history of prostate cancer or other serious co-morbidities. From the primary care T2DM register, 550 men with an 8–11 am TT level ≤12.0nmol/l or FT ≤ 0.25nmo/l were approached (pre-screening) with 488 men consenting to be screened (visit 1, Figure 1). At visit 1, eligibility was evaluated using the above criteria (including 2 TT and FT measurements taken at least 6 weeks apart). Of the eligible 211 men, 11 were excluded (raised PSA: 10, atrial fibrillation: 1) and recruitment was closed when the target of 200 men was reached (Figure 1). One patient withdrew and the remaining199 men were randomised to 1000mgTU (HG/TU: 92 men) or matched Placebo (P) (HG/P: 107 men) at 0 (visit 2) and treated accordingly at 6 (visit 3), 18 (visit 4) and 30 weeks (visit 5). Exercise and dietary advice using standard NHS diabetes literature was administered at visit 1. Of the 199 men commencing the study, 189 men (HG/TU: 86, HG/P: 103) completed the 30 weeks (reasons for non-completion and adverse events shown in Figure 1).

Men in the HG/TU and HG/P groups were stratified by 8-11 am TT and FT levels into Mild HG (TT: 8.1 – 12 nmol/l or FT: 0.181– 0.25 nmol/l) and Severe HG (TT: ≤ 8.0 nmol/l and FT: ≤ 0.18 nmol/l) based on current EAU guidelines [10]. The 4 sub-groups were:

1. Mild HG/Placebo (Mild HG/P): 51 patients
2. Mild HG/TU (Mild HG/TU): 56 patients

3. Severe HG/placebo (Severe HG/P): 52 patients
4. Severe HG/TU (Severe HG/TU): 30 patients

The validated, full 15 item International Index of Erectile Function (IIEF) was used to assess EF (using questions 1-5 and 15) and SxD (questions 11-12) domains of sexual function [4].

Randomisation and treatment.

Subjects were randomised to TU 1000 mg (HG/TU) or P (HG/P) into the right or left upper outer gluteal region. TU and P were prepared by the manufacturing company (trade name: Nebido) Bayer (Pharma AG, Berlin, Germany) and randomised in blocks via standard processes adopted during their development programme. Identification of trial medication was via numbered sealed packages with each individual assigned to the next lowest package. The code breaks were retained by the study statisticians until the last patient was recruited and the codes were broken after the final procedure and data bases were locked. The dose interval was in accordance with manufacturer's recommendations (Figure 1). The P was an analogue of the same appearance minus active substance containing the vehicle castor oil and benzyl benzoate.

Laboratory Testing.

Morning (8-11 am) fasting blood samples were taken at screening visits, -2 (visit 1), 6 (visit 3), 18 (visit 4), and 30 (visit 5) weeks for measurement of haematocrit, HbA1c and serum TT, sex hormone-binding globulin (SHBG) and PSA. All measurements were carried out at the Heart of England Foundation NHS Trust Laboratories. TT was measured using a Roche Common Platform Immunoassay (validated against mass spectrometry). Serum SHBG, albumin and PSA levels were measured using a Roche Modular automated analyzer (Roche Diagnostics, Burgess Hill, UK). FT was calculated using an online calculator based on the equations of Vermeulen et al. [11].

Statistical Analysis.

IIEF sexual function scores were available in 176 men at visit 5 (30 weeks). Adjustment for multiple significance testing was not carried out as the secondary outcome end-points were regarded as exploratory. Changes between baseline and end of study TT and FT within each group was established with paired t-test. Baseline and end of study differences in characteristics between the stratified groups (HG/P vs HG/TU, Mild HG/P vs Mild HG/TU, Severe HG/P vs Severe HG/TU) were determined using unpaired t-tests (continuous variables) and Wilcoxon rank-sum test (ordinal IIEF

SxD and EF scores). Between group differences in the proportion of men showing improvement (compared to unchanged/decreasing scores) in SxD and EF at 6, 18 and 30 weeks were established by Chi Square analysis.

Logistic regression was used to determine if improvement in SxD after 6 weeks predicted improvement in EF at 30 weeks. Receiver operated characteristic (ROC) curves were created for predictive models in the three groups by plotting the true positive rate (sensitivity) against the false positive (1-specificity) rates. The area under the curve was used to estimate the model's ability to predict the outcome; we considered areas of 0.9-1.0, 0.8-0.9, 0.7-0.8 and 0.6-0.7 to be excellent, good, fair and poor respectively (http://gim.unmc.edu/dxtests/roc3.htm - accessed on 02/05/2017). All statistical analyses were carried out using Stata version 8 (College Station, TX).

Results.

Demographic data.

Table 1 shows relevant variables at baseline in men randomised into HG/P and HG/TU groups and then allocated to corresponding groups with Mild or Severe HG. At baseline, no significant differences in any of these variables were observed between the HG/TU and HG/P groups or, in the stratified sub-groups (Mild HG/TU vs Mild HG/P, Severe HG/TU vs Severe HG/P). At 30 weeks, mean trough TT and FT levels in each TU group had increased significantly (HG/TU: p=0.0002, Mild HG/TU: p=0.0056, Severe HG/TU: p=0.013) compared with corresponding baseline values and, in the HG/TU (p=0.010) and Severe HG/TU (p=0.026) groups levels had significantly increased compared to corresponding men in the P group (Table 1).

IIEF SxD and EF scores.

Table 1 shows mean, median and range of values for SxD and EF scores at baseline and 30 weeks. At 30 weeks, mean values of SxD and EF were higher in the HG/TU and Severe HG/TU (but not Mild HG/TU) groups than in the corresponding controls. However, as previously reported only the increase in EF scores in HG/TU men (compared with HG/P) achieved significance (p=0.021) (7).

Table 2 shows that in the HG/TU group the proportion of men with improved SxD scores was always significantly higher than in the HG/P men; indeed for this domain the difference between the proportion of treated and untreated men in the HG group achieving improved SxD scores was significant at 6 weeks (ie. prior to second TU injection) and thereafter. Similar results were observed

in the Severe HG group; an even higher proportion of treated men demonstrated increased SxD values at 6 weeks (Severe HG/P: 21.2%, Severe HG/TU: 60.0%, $p<0.001$), this difference widening thereafter (at 30 weeks Severe HG/P: 20.8%, Severe HG/TU: 74%). No significant increase was observed in the Mild HG group (Table 2). Figures 2a and 2b show these data graphically. Table 2 also shows EF scores in the total HG group. At each time point the percentage of men with improved scores was higher in TU than P men though this difference was significant only at 30 weeks TRT. A similar association was seen in the Severe HG group; the difference in proportion of men demonstrating improved EF scores achieved significance only at 30 weeks. In the Mild HG group, no significant differences were observed between proportions of men in the P and TU groups (Table 2 and Figures 2a, 2b).

Relationship between changes in SxD, EF and TU.

Table 3 shows in the HG/P and HG/TU groups, the numbers and percentages of men who showed no change/decrease or, increase in either or both SxD and EF. In the HG/P group, 62.5% men showed no change/decrease in both domains while only 15.6% demonstrated increased values in both SxD and EF. The impact of TRT is shown in the HG/TU group; the corresponding percentages were 35.0% and 33.8% (Table 3). TRT was also associated with a greater percentage of men demonstrating increase in only SxD (HG/P 7.3%, HG/TU 17.5%) though the percentages of men demonstrating only increased EF were similar in the two groups (HG/P 14.6%, HG/TU 13.8%). Similarly in the Severe HG group, 63.0% (17/27 men) HG/TU patients demonstrated increased SxD and EF compared with 12.5% (6/48 men) of HG/P men. In Mild HG men, the percentages demonstrating improvement in both domains were similar (18.9% (Mild HG/TU) and 18.8% (Mild HG/P) though more men showed increased SxD with no change/decreased ED in the treated (20.8%) compared with placebo (6.3%) groups.

The data in Table 3 show some evidence of a relationship between change in SxD and EF after TRT. In the Severe HG/TU men; TRT resulted in 63.0% of patients showing increased SxD and EF values and 25.9% recording no increase in either domain. Thus, in only 11.1% of men were the two domains not associated. However, the putative relationship appeared less clear in the Mild HG men with 41.6% of men demonstrating an increase in one but not the other domain. In the total HG group the corresponding figure was 31.3%.

Relationship between SxD at 6 weeks and EF at 30 weeks.

Figure 2b shows how values of SxD and EF changed at 6, 18 and 30 weeks in men with Severe HG given either P or TU. In men given TU, the data show that while values for both domains increased with time, the increase in SxD was greater at each time point. Accordingly, we used logistic regression to determine if change in EF at 30 weeks treatment (dependent variable: increased versus no change/decreased) could be predicted by change in SxD score at 6 weeks. Table 4 shows that in the total group, the SxD score at 6 weeks (OR=3.31, 95% CI 1.63, 6.14, p=0.001) was significantly associated with the 30 week EF score. Similar results were obtained in the Mild HG and Severe HG groups; OR=2.70, 95% CI 1.07, 6.86, p=0.036 and OR=3.80, 95% CI 1.17, 12.4, p=0.027 respectively. Further, SxD scores at 18 weeks were significantly associated with the 30 week EF score in the total, Mild and Severe HG groups; OR=5.13, 95% CI 2.43, 10.8, p<0.001, OR=4.49, 95% CI 1.90, 13.1, p=0.001 and OR=5.46, 95% CI 1.50, 19.9, p=0.010) respectively. The area under the ROC curve indicated the ability of these models to discriminate change in EF was fair in Severe HG (area under ROC curve: 0.74) but poor in the Mild and Total HG groups (area under ROC curve 0.63 and 0.66 respectively). In the Severe HG group, the area under the curve in 35 men with SxD IIEF score <5 was 0.91 but in 38 men with SxD ≥5 the corresponding value was 0.64.

Discussion.

Testosterone is critical in the maintenance of male sexual function though the mechanisms by which it influences domains such as SxD and EF and, how improvements in one domain are associated with improvements in others are unclear [12]. We considered three aspects of the relationship between these variables. Firstly, by comparing proportions (rather than mean scores) of men showing improved SxD and EF with those that did not, we showed that TRT is significantly associated with improved SxD in a significantly greater proportion of men than placebo after 6 weeks while corresponding improvement in EF occurs later at 30 weeks. These observations were particularly evident in the Severe HG group. While we previously showed changes in mean IIEF domain scores [7], this study addressed the issue of the probability of individuals in the groups demonstrating improvement. Secondly, we showed that change in SxD was significantly associated with change in EF, though only 33.8% of men in the HG/TU demonstrated improvements in both domains (compared with 15.6% in the HG/P group). Thirdly, we showed change in SxD at 6 weeks is predictive of EF

change after 30 weeks with the area under the ROC curve indicating fair discriminatory ability in men with Severe HG and excellent ability in the subgroup with SxD IIEF score <5. Importantly, these associations are independent of TRT and show the important role of SxD in predicting EF.

The prevalence of symptoms such as SxD and EF increased with TT <15.0nmol/l and <8.0nmol/l respectively [5]. Further, Yassin and Saad [6] reported that while all 22 diabetic men given TRT showed improved IIEF SxD scores, EF improved in only 54% men after 24 weeks. They speculated that the delay in changing EF resulted from a direct effect of testosterone on erectile tissue. These findings demonstrate the considerable heterogeneity in the HG group. For example, while we found that only 51.3% and 47.5% of HG/TU patients given TU for 30 weeks showed improved SxD and EF scores respectively (Table 2) and 33.8% improvement in both domains (Table 3), the corresponding proportions in the Severe HG men given TU were 74.0%, 63.0% and 63.0% respectively. TU had relatively much less impact in the Mild HG group; only 18.9% of the TU-treated and 18.8% of untreated men demonstrated an increase in both domains.

The testosterone levels that effect improvements in SxD and EF may help interpret the results of recent studies. The Testosterone trial was carried out in 790 men with HG (TT< 9.5nmol) aged ≥ 65 years randomised to either 1% transdermal testosterone gel or placebo for 12 months [13]. The original publication [13] and a more detailed analysis of the sexual function arm in 470 men by Cunningham et al [8] showed that though significant improvement was seen in EF, benefit was mild and quoted to be less than expected with phosphodiesterase 5 inhibitors [8, 13, 14] despite men with HG having been excluded from the major PDE5I studies. Efficacy rates for PDE5is are little better than 50% in T2DM [14]. Our HG group with T2DM did not show significant improvement in EF (p=0.61) following TU perhaps because the TT inclusion criterion was ≤ 12nmol/l rather than < 9.5nmol/l. In the Severe HG group (TT < 8nmol/l) we found significant improvement in EF (p=0.004). This suggests re-analysis of the T trial data in men with TT <8nmol/l may show greater benefit in EF.

Cunningham et al [8] also showed that improvement in SxD and sexual activity was related to the increase in testosterone and oestradiol levels. We could not carry out a similar analysis as TT levels measured were pre TU administration (trough levels). Importantly, our cohort differed from that of the T Trial in baseline characteristics including testosterone preparations, mean age (P: 71.8 years, treatment: 71.4 years) and diabetes (P: 35.6%, treatment: 33.8%).

Various meta-analyses have come to different conclusions on the impact of TRT on sexual function.

Corona et al [15] confirmed TRT improved ED and SxD but did not explore the inter-relationships. Gianatti et al [16] found conflicting data and recently, Huo et al [17] reviewed 156 eligible studies concluding that use of TRT to improve sexual function was without support from clinical trials. Our study in men experiencing changes in sexual function following treatment offers further insight. It confirms previous observations by us and others regarding which men are most likely to benefit from TRT (7). Furthermore, change in SxD after 6 weeks is predictive of later EF change. Thus, further study is required to determine the nature of the relationship between change in SxD and EF.

Study limitations and strengths.

Though our study is based on well characterised men, the total numbers available were relatively small, allowing only limited statistical analysis of subgroups. This also prevented us from studying the effects of TRT in men stratified by SxD and EF categories. Despite this significant strengths were present in the RCT that could direct further research. All TU injections were administered by diabetes nurses providing accurate information on dosing and compliance. Clearly, the impact of TRT on sexual function domains is mediated by the extent of pathology and treatment duration. Obtaining a better understanding of the efficacy of treatment with TU requires study of patient subgroups particularly those with men with Severe HG and low sexual function domain scores. Further, prospective studies need to be designed to establish whether the relationship between SxD and EF has a mechanistic basis.

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Table 1. Baseline and end of study (30 weeks) variables in men randomised into HG/P and HG/TU groups and allocated to Mild and Severe HG groups using trough TT and FT levels.

	HG/P	HG/TU	p	Mild HG/P	Mild HG/TU	p	Severe HG/P	Severe HG/TU	p
Baseline Data	**(n=103)**	**(n=86)**		**(n=51)**	**(n=56)**		**(n=52)**	**(n=30)**	
age: mean/SD (years)	61.5 / 9.8	61.7 / 10.6	0.90	61.8 / 9.7	60.3 / 10.2	0.46	61.1 / 9.9	64.0 / 11.1	0.24
TT: mean/SD (nmol/l)	9.0 / 3.7	9.4 / 3.1	0.43	10.8 / 3.9	10.5 / 2.8	0.58	7.2 / 2.5	7.4 / 2.7	0.75
FT: mean/SD (nmol/l)	0.18 / 0.06	0.19 / 0.06	0.56	0.21 / 0.06	0.21 / 0.05	0.98	0.16 / 0.05	0.15 / 0.06	0.55
SHBG: mean/SD (nmol/l)	29.9 / 14.0	30.8 / 13.8	0.66	34.3 / 15.6	31.7 / 14.7	0.39	25.6 / 10.7	29.2 / 12.1	0.18
IIEF SxD: mean/median (range)	5.3 / 5.0 (2-10)	5.0 / 5.0 (0-9)	0.55	5.5 / 6 (2-10)	5.5 / 5 (2-9)	0.93	5.0 / 5 (2-10)	4.1 / 4 (0-7)	0.16
IIEF EF:mean/median (range)	11.14 / 10.0 (0-30)	10.0 / 0 - 30	0.26	12.6 / 13 (1-30)	13.8 / 11 (1-30)	0.41	10.3 / 6.5 (0-30)	9.3 / 6 (0-25)	0.81
Study End (30 weeks)	**(n=96)**	**(n=80)**		**(n=48)**	**(n=53)**		**(n=48)**	**(n=27)**	
TT: mean/SD (nmol/l)	9.6 / 4.5	11.3 / 4.1	0.01	11.3 / 4.8	11.9 / 3.9	0.44	7.9 / 3.4	9.9 / 4.1	0.026
FT: mean/SD (nmol/l)	0.18 / 0.06	0.23 / 0.08	<0.0001	0.21 / 0.07	0.24 / 0.07	0.021	0.16 / 0.05	0.22 / 0.09	0.0009
SHBG: mean/SD (nmol/l)	29.5 / 15.3	29.5 / 12.0	0.98	34.0 / 16.1	31.8 / 12.4	0.46	25.0 / 13.2	25.0 / 10.0	1.00
IIEF SxD: mean/median (range)	4.8 / 2.5 (0-10)	5.5 / 2.3 (0-10)	0.054	4.9 / 2.3 (0-10)	5.4 / 2.2 (0-10)	0.24	4.8 / 2.6 (0-10)	5.7 / 2.5 (0-9)	0.090
IIEF EF:mean/median (range)	10.0 / 10.3 (0-30)	12.9 / 10.3 (0-30)	0.021	11.0 / 10.3 (0-30)	12.8 / 10.6 (0-30)	0.25	9.0 / 10.4 (0-30)	13.0 / 10.6 (1-29)	0.065

Unpaired t-tests were carried out to compare differences between the groups for continuous variables (age, TT, SHBG, FT) and rank sum performed when the data was ordinal (IIEF SxD and EF scores).

Paired t-tests showed that at 30 weeks, mean trough TT and FT levels in each TU group had increased significantly (HG/TU: p=0.0002, Mild HG/TU: p=0.0056, Severe HG/TU: p=0.013) compared with corresponding baseline values. No such changes were observed in the P counterparts.

Table 2. Percentages of patients with improved IIEF SxD and EF scores at 6, 18 and 30 weeks in the randomised HG/P and HG/TU groups and groups stratified by TT and FT levels into Mild HG and Severe HG.

% of patients with improved IIEF scores	HG/P (n=103)	HG/TU (n=86)	p	Mild HG/P (n=51)	Mild HG/TU (n=56)	p	Severe HG/P (n=52)	Severe HG/TU (n=30)	p
6 weeks: IIEF SxD	24.5	45.9	0.002	28.0	38.2	0.27	21.2	60.0	<0.001
18 weeks: IIEF SxD	25.5	54.3	<0.001	28.6	47.2	0.053	22.5	67.9	<0.001
30 weeks: IIEF SxD	22.9	51.3	<0.001	25.0	39.6	0.12	20.8	74.0	<0.001
6 weeks: IIEF EF	28.4	38.8	0.13	36.0	40.0	0.67	21.2	36.7	0.13
18 weeks: IIEF EF	37.8	40.7	0.68	40.8	35.9	0.61	34.7	50.0	0.19
30 weeks: IIEF EF	30.2	47.5	0.019	35.4	39.6	0.66	25.0	63.0	0.001

Chi^2 tests were performed to test between group proportions of patients showing increased IIEF SxD and EF scores at each of the time points.

Table 3. Tabulated data of patients demonstrating changes in IIEF SxD and EF scores in the HG/TU, HG/P, Mild HG/TU, Mild HG/P, Severe HG/TU and Severe HG/P men after 30 weeks.

		HG/TU	
		IIEF EF	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	28 (35.0%)	11 (13.8%)	39 (48.8%)
	Increase	14 (17.5%)	27 (33.8%)	41 (51.3%)
	Total	42 (52.5%)	38 (47.5%)	80 (100%)

		HG/P	
		IIEF EF	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	60 (62.5%)	14 (14.6%)	74 (77.1%)
	Increase	7 (7.3%)	15 (15.6%)	22 (22.9%)
	Total	67 (69.8%)	29 (30.2%)	96 (100%)

		Mild HG/TU	
		IIEF ED	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	21 (39.6%)	11 (20.8%)	32 (60.4%)
	Increase	11 (20.8%)	10 (18.9%)	21 (39.6%)
	Total	32 (60.4%)	21 (39.6%)	53 (100%)

		Mild HG/P	
		IIEF EF	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	28 (58.3%)	8 (16.7%)	36 (75.0%)
	Increase	3 (6.3%)	9 (18.8%)	12 (25.0%)
	Total (SD)	31 (64.6%)	17 (35.4%)	48 (100%)

		Severe HG/TU	
		IIEF EF	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	7 (25.9%)	0 (0%)	7 (25.9%)
	Increase	3 (11.1%)	17 (63.0%)	20 (74.1%)
	Total	10 (37.0%)	17 (63.0%)	27 (100%)

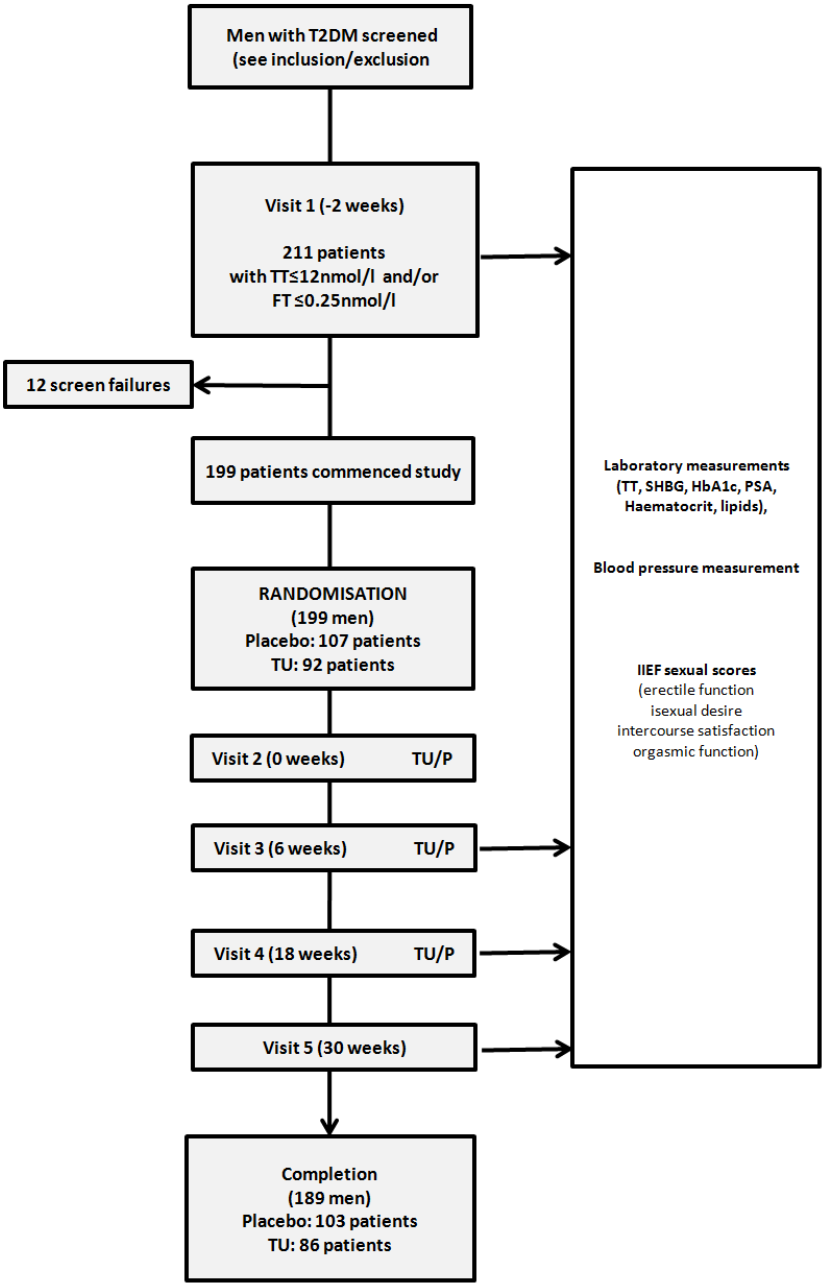
		Severe HG/P	
		IIEF EF	
		No change / decrease	Increase	Total
IIEF SxD	No change / decrease	32 (66.7%)	6 (12.5%)	38 (79.2%)
	Increase	4 (8.3%)	6 (12.5%)	10 (20.8%)
	Total	36 (75.0%)	12 (25.0%)	48 (100%)

Table 4. Logistic regression models showing association between SxD change at 6 weeks and EF change at 30 weeks.

Total Group		
(r2 = 0.069)	**OR (95% CI)**	**p**
Age	1.01 (0.98 - 1.04)	0.60
TU (ref: P)	1.43 (0.72 - 2.81)	0.30
Increase in SxD (ref: no change/decrease) - 6 weeks	3.31 (1.63 - 6.74)	0.001
Mild HG		
(r2 = 0.043)		
Age	0.99 (0.94 - 1.03)	0.56
TU (ref: P)	0.84 (0.0.35 - 2.05)	0.71
Increase in SxD (ref: no change/decrease) - 6 weeks	2.70 (1.07 - 6.86)	0.036
Severe HG		
(r2 = 0.15)		
Age	1.03 (0.98 - 1.08)	0.30
TU (ref: P)	2.84 (0.91 - 8.81)	0.07
Increase in SxD (ref: no change/decrease) - 6 weeks	3.80 (1.17 - 12.4)	0.027

Change in EF after 30 weeks was significantly associated with change in SxD after 6 weeks in TU (OR: 3.02, 95% CI: 1.16 – 7.87, p=0.023) and P (OR: 3.55, 95% CI: 1.21 – 10.37, p=0.021) groups, the analyses including age.

Figure 1. Recruitment and protocol of the BLAST study.



Screen failures (n=12):

Elevated PSA: 10 (BPH: 9, Prostatic carcinoma: 1), Atrial fibrillation: 1, Withdrawal of consent: 1

Failure to complete study (n=10):

Serious adverse events: 4 (treatment unrelated deaths: 3, Prostatic carcinoma: 1 (on placebo).

Withdrawal of consent: 6

Figure 2a: Proportion of patients demonstrating improved SxD and EF scores in the Mild HG/P and Mild HG/TU groups

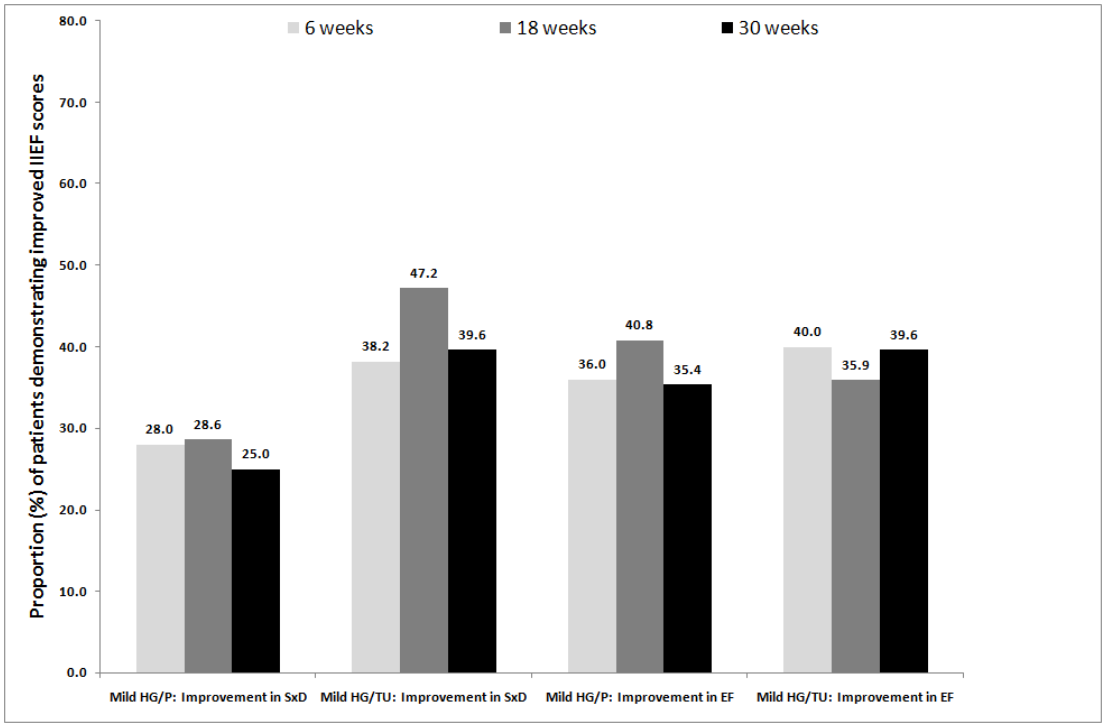
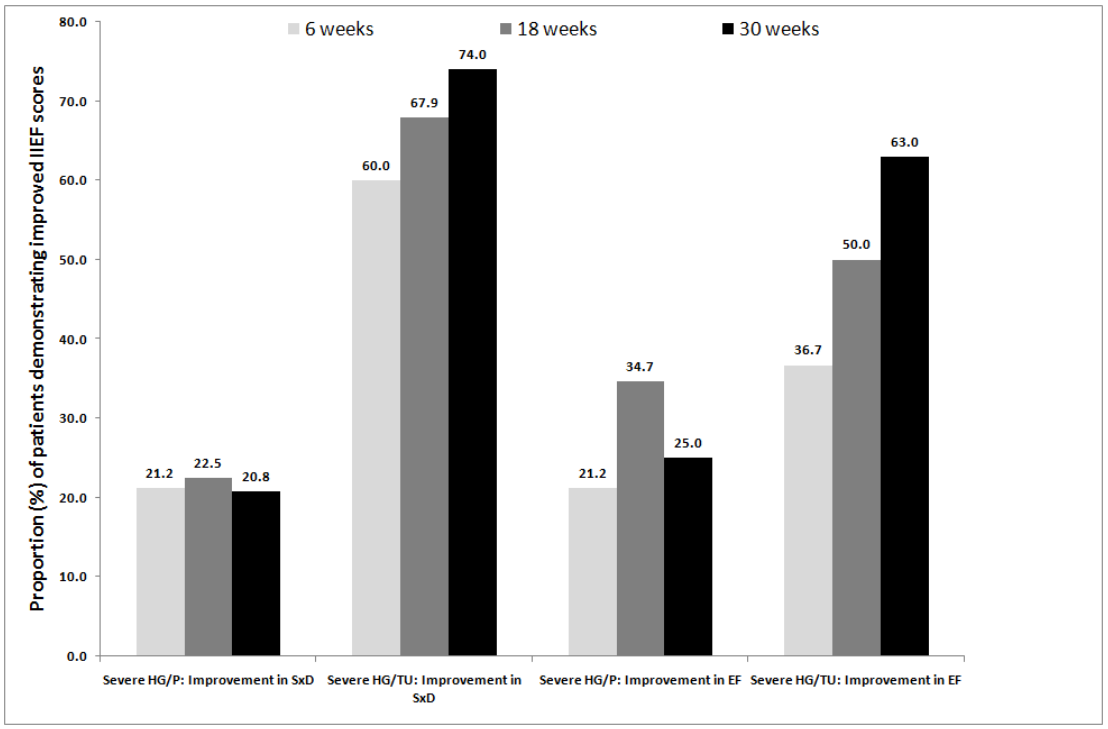


Figure 2b: Proportion of patients demonstrating improved SxD and EF scores in the Severe HG/P and Severe HG/TU groups



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