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Low serum testosterone levels are poor predictors of sexual dysfunction

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Study Type – Prognosis (RCT)
Level of Evidence 1b

What's known on the subject? and What does the study add?
Sexual dysfunction is a common problem in elderly men, especially if they also have LUTS. Serum testosterone likewise decreases with aging, and a common conclusion from this is that low serum testosterone levels are a main cause for this.

This is by far the largest population-based study correlating sexual dysfunction with serum testosterone levels. Whereas age, body mass index and the severity of LUTS were independent risk factors for sexual dysfunction, serum testosterone levels were not. Treating sexual dysfunction only based on a low serum testosterone level therefore appears unjustified. There is a trend towards sexual dysfunction with S. testosterone levels <200 ng/dl, but only 4% of the 8231 older men studied were in this range.

OBJECTIVE

- To identify predictors of sexual dysfunction using baseline data from the reduction by dutasteride of prostate cancer events (REDUCE) study.

PATIENTS AND METHODS

- REDUCE was a 4-year randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of once-daily dutasteride 0.5 mg in over 8000 men aged 50–75 years with a prostate-specific antigen (PSA) level of 2.5–10 ng/mL (50–60 years) or 3.0–10 ng/mL (>60 years) and a negative prostate biopsy within 6 months of enrolment.
- Baseline values (mean serum testosterone, age, International Prostate Symptom Score [IPSS], total prostate volume [TPV], body mass index [BMI], and presence of diabetes/glucose intolerance) were compared in subjects with and without sexual dysfunction (sexual inactivity, impotence, decreased libido or a Problem Assessment Scale of the Sexual Function Index [PAS-SFI] score <9).

RESULTS

- Multivariate logistic regression showed that baseline age and IPSS were significant predictors of all four sexual function criteria examined ($P < 0.0001$).
- BMI was a significant predictor of decreased libido, impotence and a PAS-SFI score <9, while diabetes/glucose intolerance was a significant predictor of sexual inactivity, impotence and a PAS-SFI score <9.
- Testosterone and TPV were not significant predictors of any sexual function criterion examined.

CONCLUSIONS

- Age, IPSS, BMI and diabetes/glucose intolerance, but not serum testosterone or TPV, were significant independent predictors of sexual dysfunction in the REDUCE study population.
- The lack of association between sexual dysfunction and serum testosterone questions the value of modestly reduced or low normal testosterone levels as criteria for choosing testosterone replacement in older men with sexual dysfunction.

KEYWORDS

age, lower urinary tract symptoms, sexual dysfunction, testosterone, REDUCE, dutasteride

INTRODUCTION

Sexual dysfunction, encompassing erectile dysfunction, ejaculatory disorders and loss of libido, is highly prevalent in ageing men and can have substantial adverse effects on their quality of life [1–4]. Likewise, BPH and associated LUTS are prevalent among older men [5,6] and have a negative impact on quality of life [7]. A wealth of epidemiological data has shown a strong association between sexual dysfunction and LUTS [8,9], with LUTS severity identified as a strong independent predictor of sexual dysfunction second only to age [10]. However, common underlying pathophysiological mechanisms for this association have not yet been elucidated [11].

Serum testosterone levels decline with age, albeit with considerable variability between individual men and with a broad range in age- and health-related values [12–15]. Hypogonadism has been assumed to be the important factor in the development of a condition variably termed partial androgen deficiency in the ageing male, androgen deficiency/decline in the ageing male, late onset hypogonadism or testosterone deficiency syndrome (TDS) [16]. The condition is associated with a wide range of clinical symptoms ranging from loss of muscle mass and strength and reduced bone mineral density to a decrease in general well-being, depressed mood and mild cognitive impairment.

The association between sexual dysfunction and serum testosterone levels is complex and remains poorly defined. Analysis of data from 4254 men participating in three identical 2-year clinical studies of dutasteride therapy for BPH showed that large increases in the incidence of sexual dysfunction were not observed until serum testosterone levels were below 225 ng/dL [17]. This finding suggests a weak cause–effect relationship between low serum testosterone levels and sexual dysfunction. More compelling preliminary evidence exists for a causal relationship between obesity/the metabolic syndrome and sexual dysfunction [18–20].

The reduction by dutasteride of prostate cancer events (REDUCE) study is a large-scale study in men at increased risk of developing prostate cancer [21]. The large baseline dataset from over 8000 men has enabled an examination of the relationship between serum testosterone, age, LUTS, prostate enlargement, obesity, presence of diabetes/glucose intolerance and sexual dysfunction.

PATIENTS AND METHODS

This analysis was conducted using baseline data from the REDUCE study, a 4-year, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of once-daily 0.5 mg dutasteride for reducing the risk of biopsy-detectable prostate cancer. The study design and overall results have been previously published [21,22]. Briefly, entry criteria included men aged 50–75 years with a PSA level ≥2.5 ng/mL and ≤10 ng/mL (50–60 years), or ≥3.0 ng/mL and ≤10 ng/mL (>60 years) and a negative prostate biopsy within 6 months of enrolment in the study. Key exclusion criteria included any major comorbidity (other than diabetes mellitus), a total prostate volume (TPV) >80 cm^3, an IPSS of ≥25 points (or ≥20 points if already on alpha-blocker therapy for BPH), post-void residual volume >200 mL, peak flow rate <5 mL/s and a history of acute urinary retention during the previous 2 years. Sexual dysfunction was not an exclusion criterion and use of phosphodiesterase type 5 inhibitors and alpha blockers during the study was allowed under the protocol.

At the baseline study assessment, a single blood sample for serum testosterone was drawn from all subjects and the time of collection recorded.

Total serum testosterone concentrations were measured by Quest Diagnostics (Van Nuys, CA, USA) using the Bayer Centaur automated immunochemiluminometric assay (Bayer Healthcare LLC, Diagnostic Division, Tarrytown, NY, USA). Intra-assay coefficients of variance were 8.3%, 4.1%, 3.8% and 2.4% at mean concentrations of 32, 88, 373 and 757 ng/dL, respectively. Inter-assay coefficients of variance were 20.6%, 10.0%, 10.0% and 7.3% at mean concentrations of 30, 90, 388 and 766 ng/dL, respectively. The normal reference range of the assay for adult males is 260–1000 ng/dL.

ASSESSMENT OF LUTS, TPV, BMI, DIABETES/GLUCOSE INTOLERANCE AND SEXUAL FUNCTION

At baseline, LUTS was assessed using the self-administered IPSS questionnaire, including the quality-of-life evaluation (Question 8). For the purposes of the analysis, LUTS were defined as an IPSS ≥8 (moderate or severe symptoms). TRUS was performed and a TPV calculated using the formula $\pi/6$ (anteroposterior width x cephalocaudal width x transverse width). For the purpose of these analyses, prostate enlargement was defined as a TPV ≥30 cm^3. Subject height (in cm) and weight (in kg) were recorded at baseline and the body mass index (BMI) calculated by dividing the weight (in kg) by the square of the height (in m). Self-reported history of diabetes/glucose intolerance at baseline was recorded as part of the medical history assessment.

The validated Problem Assessment Scale of the Sexual Function Index (PAS-SFI) was administered at baseline to assess perceptions of problems associated with sexual drive, erection or ejaculation [23]. The PAS-SFI consists of three questions, each scored on a 5-point scale, ranging from 0 to 4, with lower scores indicating worse sexual function. The questions asked were as follows: 'In the past 30 days, to what extent have you considered a lack of sex drive to be a problem?'; 'In the past 30 days, to what extent have you considered your ability to get and keep erections to be a problem?'; and 'In the past 30 days, to what extent have you considered your ejaculation to be a problem?'. Sexual function (sexual activity, impotence and decreased libido; all scored as present/absent) was also assessed at baseline as part of the study safety evaluations. For the purposes of these analyses, sexual dysfunction was defined as any of the following: sexual inactivity, 'impotence', decreased libido or PAS-SFI score <9. A score of <9 was chosen as this represents a 'small problem' in at least one of the three PAS-SFI questions [23].

Baseline values (mean serum testosterone, age, IPSS, TPV, BMI and presence of diabetes/glucose intolerance) for subjects with vs. without each of the four sexual dysfunction criteria were summarised and compared using Wilcoxon rank-sum tests. Because of the large number of subjects in this analysis and the consequent high power, an $a = 0.0001$ was considered to be a meaningful statistical difference. A multivariate logistic regression model for each of the four sexual dysfunction criteria was performed with baseline serum testosterone level, age, IPSS, TPV, BMI and diabetes/glucose intolerance included in the model. *P* values ≤0.0001 were considered to be significant. The proportion of subjects with a PAS-SFI score <9 according to different categories of concurrently significant variables was then calculated. All analyses were performed using the software SAS® version 8.2.

RESULTS

BASELINE CHARACTERISTICS

Data on 8231 subjects were available for evaluation. Baseline characteristics are shown in Table 1 for the total population, subjects with LUTS (50% of the population), those with prostate enlargement (80%) and those with neither LUTS nor prostate enlargement (10%). Subjects were men (mean age 62.8 years) who were, on average, overweight (mean BMI 27.4 kg/m^2) with a mean testosterone level of 453 ng/dL. Baseline serum testosterone level was <300 ng/dL in 21% of subjects, <250 ng/dL in 11% and <200 ng/dL in 4%. Study subjects had evidence of prostate enlargement (mean TPV 45.7 cm^3) and their mean IPSS (8.7) was slightly above the upper threshold for mild symptoms (IPSS <8). A total of 2900 men (39%) had a PAS-SFI score <9 at baseline, indicating at least a 'small problem' in at least one of the three PAS-SFI questions on sexual dysfunction. Nine percent of subjects reported diabetes/glucose intolerance at baseline.

Mean age, BMI and serum testosterone levels were similar between the LUTS and prostate enlargement subgroups. Fewer subjects had

TABLE 1 Baseline characteristics in the REDUCE study

Characteristic	Total study population, $n = 8231$	Subjects with LUTS, $n = 4110$	Subjects with prostate enlargement, $n = 6580$	Subjects with neither LUTS nor prostate enlargement, $n = 837$
Mean (±SD) age, years	62.8 (6.1)	63.2 (6.0)	63.1 (6.0)	60.7 (5.9)
Mean (±SD) BMI, kg/m^2	27.4 (4.0)	27.4 (3.8)	27.5 (4.1)	26.8 (3.7)
Mean (±SD) serum testosterone, ng/dL	453 (181)	454 (185)	452 (182)	455 (177)
Mean (±SD) TPV, cm^3	45.7 (18.5)	48.0 (19.4)	50.7 (16.7)	23.3 (5.1)
Mean (±SD) total IPSS	8.7 (5.7)	13.1 (4.3)	8.9 (5.7)	3.7 (2.0)
Diabetes/glucose intolerance, %	9	9	9	7
Mean (±SD) total PAS-SFI score	8.6 (3.8)	8.0 (3.9)	8.5 (3.8)	9.4 (3.5)
Sexually inactive, %	19	21	19	15
Impotent, %	28	32	29	22
Decreased libido, %	22	26	23	17

diabetes/glucose intolerance in the subgroup with neither LUTS nor prostate enlargement than in the other subgroups and total population. Numerically lower rates of sexual dysfunction were observed in subjects with neither LUTS nor prostate enlargement than in both the total population and those with either LUTS or prostate enlargement. This is also reflected in the higher mean PAS-SFI score for subjects with neither LUTS nor prostate enlargement. Subjects with diabetes/glucose intolerance had numerically higher reported rates of sexual dysfunction than those without diabetes/glucose intolerance; rates of 28%, 40%, 30% and 49%, respectively, for sexual inactivity, 'impotence', decreased libido and PAS-SFI score <9 for subjects with diabetes/glucose intolerance vs. 18%, 27%, 22% and 38% for those without). The mean PAS-SFI score for subjects with diabetes/glucose intolerance was 7.6 ± 4.2 vs. 8.7 ± 3.7 for those without.

SEXUAL DYSFUNCTION BY BASELINE SUBJECT CHARACTERISTICS

When univariate analysis of baseline serum testosterone levels for subjects with vs. without sexual dysfunction were compared using Wilcoxon rank-sum tests, a significant difference ($P < 0.0001$) in testosterone levels was only found for 'impotence' (Fig. 1A). Baseline age and IPSS score were significantly greater for subjects with than without sexual dysfunction for all four criteria of sexual dysfunction ($P <$ 0.0001,data not shown). A significantly higher TPV was observed in subjects with than without 'impotence' or PAS-SFI score <9 (Fig. 1B). Further, a significantly higher BMI was found in men with than without 'impotence', decreased libido and a PAS-SFI score <9 (Fig. 1C).

No significant differences in TPV or BMI were found for subjects with vs. without the other sexual function criteria examined.

MULTIVARIATE PREDICTORS OF SEXUAL DYSFUNCTION

After adjustment for other covariates, age and IPSS had statistically significant relationships with all four sexual function criteria examined (Table 2). BMI was found to be a significant predictor of 'impotence', decreased libido and a PAS-SFI score <9, while diabetes/glucose intolerance was found to be a significant predictor of sexual inactivity, 'impotence' and a PAS-SFI score <9. Based on the odds ratio estimates, higher age and higher IPSS score were both significant predictors of higher levels of sexual inactivity, 'impotence', decreased libido and having a PAS-SFI score <9. Testosterone level and TPV were not significant predictors of any sexual dysfunction criterion.

Figure 2 shows the proportion of subjects with a PAS-SFI score <9 according to age, BMI and IPSS severity. For subjects with no LUTS (IPSS <8), there was a trend towards an increased proportion of subjects with a PAS-SFI score <9 with increasing age and BMI category. This trend became more apparent for subjects with moderate LUTS (IPSS 8 to <20). However, as would be expected from the results of the multivariate logistic regression, the highest proportion of subjects with a PAS-SFI score <9 were found in the group of subjects with severe LUTS (IPSS ≥20) who were of older age (≥60 years) and with a higher BMI (≥35 kg/m^2).

DISCUSSION

The REDUCE study provides a substantial body of data to examine the predictive value of various baseline characteristics for sexual dysfunction. Subjects were selected according to stringent criteria and represent a similar cross-section of the population to the Massachusetts Male Aging Study [24]. Baseline data from the REDUCE study show that, in this population of men with an elevated PSA level and a negative prostate biopsy, age and IPSS are clinically significant predictors of sexual dysfunction, supporting the findings of the multinational survey of the aging male (MSAM-7) [10]. In the MSAM-7, the most comprehensive study conducted to date on the association of age, LUTS, concomitant comorbidities and male sexual dysfunction, logistic regression analysis of data from 12 815 men showed that age and severity of LUTS were independent risk factors for erectile and ejaculatory dysfunction.

In the REDUCE study, BMI was found to be a significant predictor of 'impotence', decreased libido and a PAS-SFI score <9. Diabetes/glucose intolerance was shown to be a significant risk factor for sexual inactivity, 'impotence' and a PAS-SFI score <9, although subject numbers were small. There is already evidence from some small-scale studies to suggest a causal relationship between obesity/the metabolic syndrome and sexual dysfunction [18,19,24,25], and the findings from the large REDUCE study dataset confirm these observations. There is also preliminary evidence to suggest higher rates of prostate

*FIG. 1. Differences in (**A**) testosterone level, (**B**) TPV and (**C**) BMI according to sexual function status at baseline in the REDUCE study. The bottom and top borders of the boxes are the 25th and 75th percentiles, respectively, and the line in the box represents the 50th percentile (median). Whiskers indicate the 5th and 95th percentiles. P values <0.0001 were considered to be significant due to the large number of subjects and high power to detect clinically insignificant differences.*

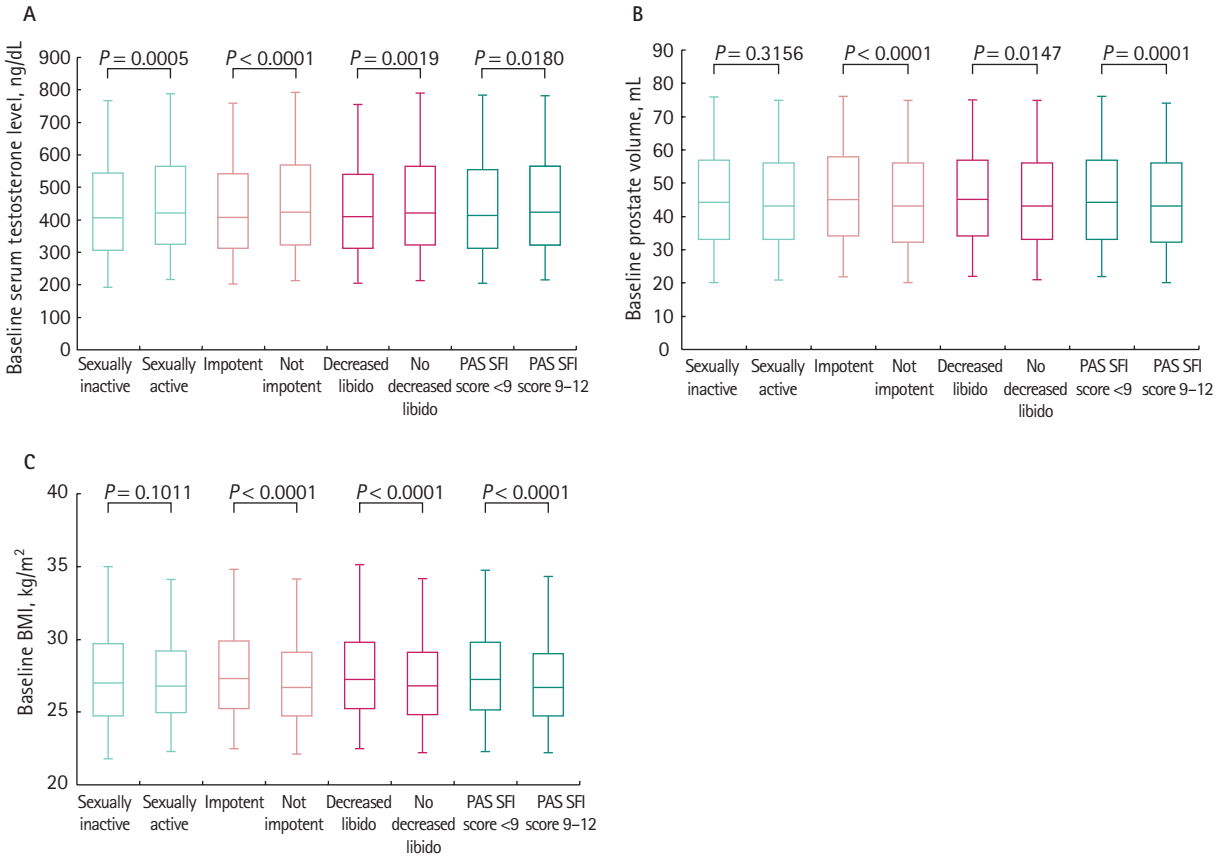


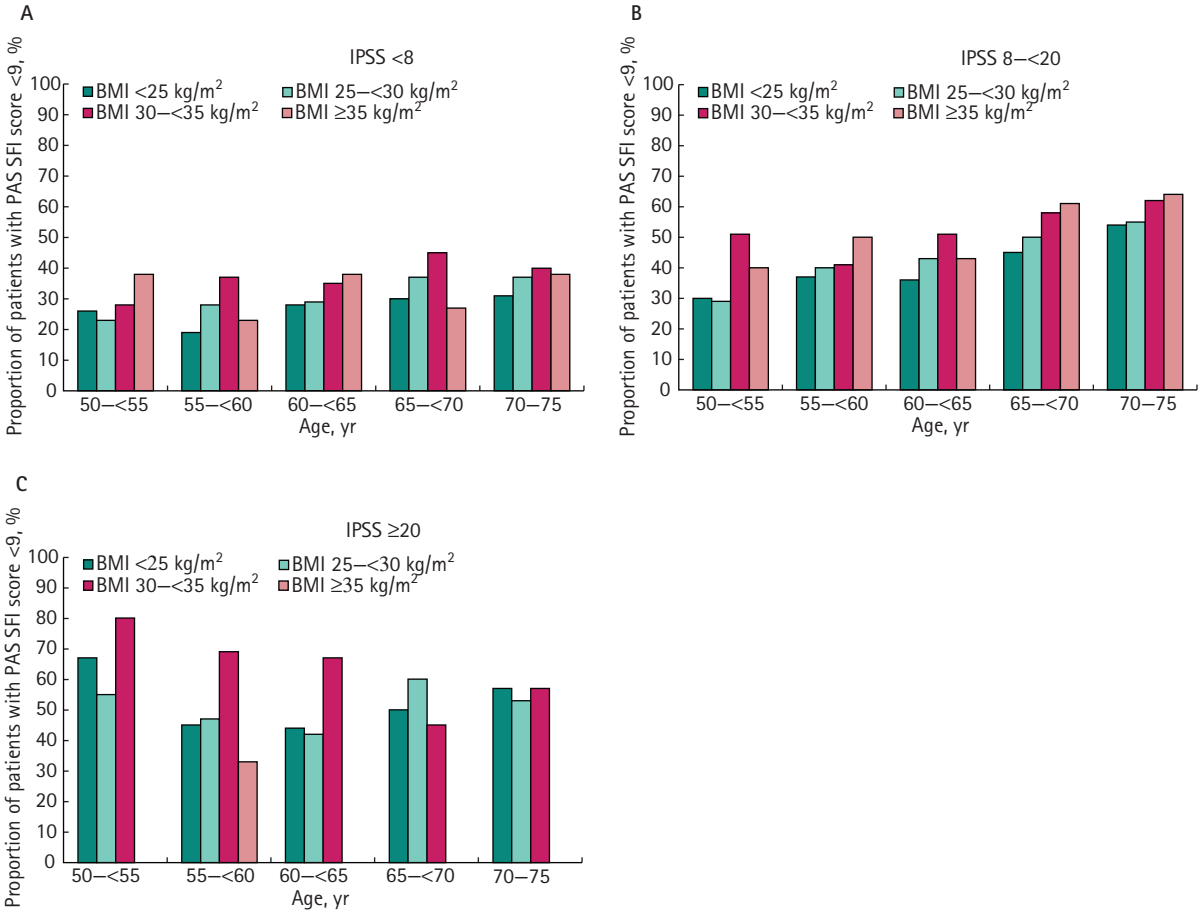
TABLE 2 Multivariate logistic regression analysis to determine significant predictors of sexual dysfunction at baseline in the REDUCE study

	Sexual inactivity		Impotence		Decreased libido		PAS-SFI score <9	
Covariate	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*	Odds ratio	*P*
Significant relationships with all criteria								
Age	1.124	<0.0001	1.066	<0.0001	1.045	<0.0001	1.035	<0.0001
IPSS	1.026	<0.0001	1.031	<0.0001	1.035	<0.0001	1.062	<0.0001
Significant relationships with most criteria								
BMI	1.021	0.0056	1.034	<0.0001	1.033	<0.0001	1.034	<0.0001
Diabetes/ glucose intolerance	1.567	<0.0001	1.550	<0.0001	1.365	0.0007	1.402	0.0001
No significant relationships								
Serum testosterone	0.999	0.0027	1.000	0.0018	1.000	0.0258	1.000	0.4992
TPV	0.994	0.0008	1.000	0.9724	0.997	0.0912	1.002	0.1905

P < 0.0001 was considered to be significant.

growth in patients with BPH with vs. without metabolic syndrome, and specifically, a significant correlation between prostate growth and serum insulin levels [26]. It has been proposed that increased autonomic hyperactivity resulting from increased BMI, hyperinsulinaemia, increased age and decreased physical activity may in turn affect BPH growth, the precipitation of LUTS and vasoconstrictive forces that result in erectile dysfunction [27]. It is also possible that cardiovascular risk factors confound the correlation with increased BMI as, in one study, multivariate analysis of cardiovascular risk factors attenuated this association [28].

*FIG. 2. Proportion of subjects with a PAS-SFI score <9 in the REDUCE study population according to age and BMI categories for subjects with IPSS <8 (**A**), 8–<20 (**B**) and ≥20 (**C**).*



Despite the fact that much still remains to be elucidated for the mechanisms underlying male sexual dysfunction, it is clear that BMI and the various components of the metabolic syndrome are important risk factors in addition to age and LUTS.

After adjustment for other covariates, testosterone and TPV were not found to be significant predictors of sexual dysfunction in the REDUCE study population. These data accord with the findings of previous studies in which no significant relationship between testosterone level and sexual dysfunction could be established [17,29,30]. This finding brings into question the practice of using serum testosterone levels to indicate the need for testosterone substitution for older men with low-normal serum testosterone levels who report symptoms of sexual dysfunction. In a recent, small, single-arm, retrospective study, testosterone replacement therapy in hypogonadal subjects with metabolic syndrome has been found to improve not only the metabolic syndrome but to also decrease IPSS and residual bladder volume [31] and, as such, testosterone supplementation may be justified regardless of testosterone levels. However, in addition to this study, further prospective, randomized, controlled and sufficiently powered trials are required to investigate this relationship. Clinical diagnosis of TDS is challenging as the signs and symptoms are non-specific and readily accounted for by comorbidities [32]. Further, the threshold testosterone level below which symptomatic TDS occurs is not known and may be age dependent. The current evidence for testosterone substitution therapy is limited, with few randomized trials containing limited patient numbers, variability in reported outcomes and inconsistent results [33–35].

Large-scale, randomized, placebo-controlled studies are warranted to determine the validity of this therapeutic approach, identify the serum testosterone threshold below which any intervention may be warranted and establish whether the risk–benefit profile is appropriate.

One of the strengths of the present study is that men were recruited irrespective of baseline testosterone level and sexual function and there was no lower threshold for LUTS or TPV. The enrolment criteria, therefore, differed from typical BPH studies and led to a broader spectrum of men entering the study. However, the requirement of a PSA ≥2.5 ng/mL for men aged 50–60 years and ≥3.0 ng/mL for men >60 years would have increased the relative proportion of men with prostate enlargement. There are also a number of limitations to this study that warrant discussion. Firstly, although the time of blood sample collection was recorded, it was not a study stipulation that it be taken between 8–10 am. A number of small studies in young

men have revealed a diurnal variation in serum testosterone levels, with the highest levels in the early morning and the lowest levels in the evening [36]. However, analysis of a large cross-sectional sample has shown that testosterone levels in older men are stable throughout the morning and early afternoon and decline only modestly thereafter [17,36]. Furthermore, the impact of sample timing would be expected to be minimal in studies with large numbers of patients [17].

Another limitation is that no free testosterone or sex hormone-binding globulin (SHBG) measurements were taken in this study. Typically, total and free testosterone levels are well correlated. However, SHBG levels are known to be lower in obese patients, which could impact free testosterone levels, although this may be countered by increases in SHBG with age [13]. There is recent evidence from a cross-sectional study that the age-related decline in sexual function may be attributable to a decline in the level of bioavailable testosterone rather than total testosterone levels [37]; this concept would certainly warrant further investigation in a larger sample of men. The results of the present study suggest that many other factors in ageing men can influence the likelihood of sexual dysfunction.

Baseline data from the large-scale REDUCE study show that age and IPSS are significant predictors of sexual dysfunction. BMI was found to be a significant predictor of decreased libido, 'impotence' and a PAS-SFI score <9, while diabetes/glucose intolerance was a significant predictor of sexual inactivity, 'impotence' and a PAS-SFI score <9. After adjusting for other covariates, testosterone and TPV were not found to be significant, independent predictors of sexual dysfunction. This questions the practice of using low serum testosterone levels as justification for prescribing testosterone replacement therapy for older men with borderline low testosterone levels and sexual dysfunction.

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CONFLICT OF INTEREST

Timothy H. Wilson is an employee of GlaxoSmithKline and a stockholder of the mentioned product; Roger S. Rittmaster is an employee of GlaxoSmithKline and a stockholder of the mentioned product; Michael Marberger is a study investigator for GlaxoSmithKline and has received consultancy, advisory and lecture fees from GlaxoSmithKline, Antigenics, Allergan, GP Pharm, Astellas, GE Healthcare and Ferring. Source of Funding:The REDUCE study is funded by GlaxoSmithKline. ClinicalTrials.gov identifier: NCT00056407; http://clinicaltrials.gov/ct2/show/NCT00056407.

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Abbreviations: **REDUCE**, Reduction by Dutasteride of Prostate Cancer Events; **TPV**, total prostate volume; **BMI**, body mass index; **PAS-SFI**, Problem Assessment Scale of the Sexual Function Index; **TDS**, testosterone deficiency syndrome; **MSAM-7**, multinational survey of the aging male; **SHBG**, sex hormone-binding globulin.