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Testosterone treatment is not associated with increased risk of prostate cancer or worsening of lower urinary tract symptoms: prostate health outcomes in the Registry of Hypogonadism in Men

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Objectives

To evaluate the effects of testosterone-replacement therapy (TRT) on prostate health indicators in hypogonadal men, including rates of prostate cancer diagnoses, changes in prostate-specific antigen (PSA) levels and lower urinary tract symptoms (LUTS) over time.

Patients and Methods

The Registry of Hypogonadism in Men (RHYME) is a multinational patient registry of treated and untreated, newly-diagnosed hypogonadal men (n = 999). Follow-up assessments were performed at 3–6, 12, 24, and 36 months. Baseline and follow-up data collection included medical history, physical examination, blood sampling, and patient questionnaires. Prostate biopsies underwent blinded independent adjudication for the presence and severity of prostate cancer; PSA and testosterone levels were measured via local and central laboratory assays; and LUTS severity was assessed via the International Prostate Symptom Score (IPSS). Incidence rates per 100 000 person-years were calculated. Longitudinal mixed models were used to assess effects of testosterone on PSA levels and IPSS.

Results

Of the 999 men with clinically diagnosed hypogonadism (HG), 750 (75%) initiated TRT, contributing 23 900 person-months of exposure. The mean testosterone levels increased from 8.3 to 15.4 nmol/L in treated men, compared to only a slight increase from 9.4 to 11.3 nmol/L in untreated men. In all, 55 biopsies were performed for suspected prostate cancer, and 12 non-cancer related biopsies were performed for other reasons. Overall, the proportion of positive biopsies was nearly identical in men on TRT (37.5%) compared to those not on TRT (37.0%) over the course of the study. There were no differences in PSA levels, total IPSS, or the IPSS obstructive sub-scale score by TRT status. Lower IPSS irritative sub-scale scores were reported in treated compared to untreated men.

Conclusions

Results support prostate safety of TRT in newly diagnosed men with HG.

Keywords

testosterone, hypogonadism, disease registry, benign prostatic hyperplasia, #ProstateCancer, #PCSM

Introduction

Hypogonadism (HG) due to testicular or non-testicular causes affects ~2.1% of men aged ≥40 years, increasing to 3.2% and 5.1% in men aged 60–69 and 70–79 years, respectively [1,2]. Prevalence is 2–3 times higher in men with type 2 diabetes or other components of the metabolic syndrome [3,4]. The recommended treatment for

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biochemically confirmed HG is testosterone-replacement therapy (TRT), which can be administered via multiple injectable, implantable, topical or oral formulations [5–7]. In addition to symptomatic improvements [8–10], possible benefits for TRT include reduction in body mass index (BMI) and waist size, improved glycaemic control and lipid profile, in addition to improvements in body composition, bone mineralisation, and other cardio-metabolic indices [11–14].

Prostate cancer growth and BPH progression have long been seen as major risks associated with TRT, with current guidelines contraindicating TRT in men with a history of prostate cancer or advanced BPH [5–7]. In contrast, findings from very recent studies raise serious doubts about the pathological role of TRT in either prostate cancer or BPH. Snyder et al. [15] recently reported results of a large, National Institutes of Health-funded, randomised trial of topical testosterone compared with placebo in 800 men aged >65 years with symptomatic HG. No evidence of BPH progression or increased prostate cancer incidence was seen over 12 months of treatment. Similar findings were reported in a pooled, 5-year analysis of three single-centre, longitudinal patient registries [16]. Prostate cancer rates among men on TRT in this pooled analysis were lower than previously reported for European men in this age category [17]. Independent systematic reviews have similarly concluded that affirmative evidence is lacking for either prostate cancer risk [18] or BPH progression [19,20] in association with TRT. On the other hand, design flaws, including lack of untreated controls or independent adjudication of clinical outcomes, inadequate sample sizes, and short duration of follow-up are key weaknesses in previously published studies.

The Registry of Hypogonadism in Men (RHYME) is a large, multi-national prospective registry of men with HG, which was designed and powered specifically to assess prostate cancer outcomes in men with HG receiving TRT compared with untreated men with HG or general population estimates. The primary aim was to examine prospectively the association between TRT and prostate health outcomes, including prostate cancer incidence and BPH progression in hypogonadal men naïve to TRT who are diagnosed and treated according to current standard-of-care guidelines.

Patients and Methods

Registry of Hypogonadism in Men is an observational, non-interventional disease registry with longitudinal data collection in a large sample of clinically diagnosed, well-characterised men with HG. Eligibility criteria included men aged ≥18 years with a diagnosis of HG, confirmed by abnormal testosterone levels on at least two occasions. Physicians were encouraged to apply guideline recommendations of total serum testosterone of <12.1 nmol/L; free testosterone of <243 pmol/L, and a report of bothersome symptoms by the patient [6,7]. Men were excluded if they had received prior TRT with any product or a past history of breast or prostate cancer, high-grade prostatic intraepithelial neoplasia, radical prostatectomy or life-expectancy shorter than 24 months as judged by the clinical site investigator. Men with major psychiatric disorders, drug or alcohol abuse or gender dysphoria were also excluded. All eligible men were enrolled consecutively, a key element of the design for reducing selection bias.

Each patient enrolled was scheduled for at least four and up to five assessments over a minimum of 2 years starting at baseline and then the following 3–6, 12, 24 and 36 months. Additional diagnostic tests or procedures, including prostate biopsy or ultrasonography, were determined by the treating physician in consultation with the patient. This clinical decision-making paradigm was designed intentionally to reflect clinical practice in order to increase generalisability of RHYME findings, being consistent with the non-interventional nature of a registry design. Further details of the registry design and methods have been published previously [21].

Patient enrolment was initiated in 2009 and completed in 2011. On 30 September 2013, the registry was closed to patient follow-up. In all, 25 clinical sites in six European countries (Germany, Italy, The Netherlands, Spain, Sweden, and UK) participated in enrolment. Site investigators included approximately equal number of urologists (13) and endocrinologists or general physicians (12). All the men provided written informed consent before enrolment. Registry protocols were approved by local Ethics Committees at each clinical site.

The primary endpoint for RHYME was the proportion of positive prostate biopsies observed after 2 years. For our primary statistical comparison, we assumed that the expected positive biopsy rate under the null hypothesis of no effect of TRT would be ~30%, based on prevalence rates for similar aged men in large, community-based studies [17,22–24]. Secondary aims of the registry were to examine changes in PSA, LUTS, and other health outcomes. Data were collected through abstraction of medical records and a self-administered questionnaire designed to obtain information on demographic characteristics, lifestyle factors (e.g., smoking, physical activity), and other health information (prostate-related symptoms, health-related quality of life) using standardised instruments, including the IPSS. Local laboratory assays (testosterone, LH, PSA), were obtained by site investigators and used for determining eligibility and treatment response, while independent central laboratory assays were obtained for blinded evaluation of treatment outcomes.

All prostate-biopsy reports, prostatectomy findings and relevant supporting documents were reviewed by an

independent Clinical Endpoints Committee (CEC Members: C. Roehrborn (Chair), F. Schröder, G. Cunningham, G. Jackson) and used for research purposes only. The adjudication process by the committee included blinded review of clinical data and pathology reports. The committee adjudicated de-identified biopsy reports and prostatectomy findings as 'positive' or 'negative' for prostate cancer. Adjudication included determination of the final Gleason score and T-Stage classification, based on review of the pathology findings. DRE and TRUS were performed only as medically indicated. Reasons for biopsy requests were recorded (e.g., PSA level rise, elevated PSA level, abnormal DRE or TRUS findings) in addition to details of prostate surgery or other treatments. Urogenital surgical procedures and cancer-related outcomes were monitored at every study visit.

Statistical Analyses

Men were considered 'treated' if they were on active TRT at one or more visits during the study period. Conversely, untreated subjects did not receive TRT at any time during the period of monitoring. Descriptive statistics (i.e. means, standard deviation [SD]) were used for assessing baseline characteristics and testosterone use. Person-time of exposure was calculated as the time up to prostate cancer diagnosis or final contact. Prostate cancer incidence rates for treated and untreated men were calculated as the number of events divided by the total person-time, multiplying by 100 000.

Longitudinal mixed-model analyses evaluated changes in outcome variables (i.e. PSA level, IPSS) by treatment, time, and the interaction of time and treatment accounting for repeated, correlated observations in the same patient. TRT was treated as time-varying. PSA level and IPSS outcomes were log-transformed and treated as time-varying. Using baseline measured covariates, multivariate modelling was used to control for potential confounders. All covariates were entered into single multivariate models predicting each outcome; those with a $P \leq 0.2$ in each model were selected as final covariates for the fully adjusted model.

Results

Of the 1 006 men enrolled, seven were ineligible, resulting in an analytic cohort of 999 patients (Fig. 1). In all, 71 men discontinued the study, resulting in a patient retention rate of 92.9% over 3 years of follow-up. Approximately 23 900 person-months were accrued, which represented 99.6% of the targeted follow-up period.

The mean (SD) age was 59.1 (10.5) years; treated and untreated men did not differ in age, type of HG (primary vs secondary) or other sociodemographic characteristics (Table 1). Men receiving TRT had a higher prevalence of HG symptoms, erectile dysfunction, urological and psychiatric conditions prior to enrolment than untreated men, although medication use at baseline was similar across the two groups. About 40% of both groups had moderate-to-severe LUTS (IPSS > 8) at baseline. Prior negative biopsies were recorded for 19 (2.5%) treated men and 18 (7.2%) untreated men and a higher percentage of past abnormal DREs were reported for untreated (38.2%) compared to treated (23.3%) men.

Testosterone Administration and Compliance with Treatment

In all, 750 (75%) men received a prescription for TRT and 249 (25%) did not receive TRT in any form. Testosterone prescriptions were mostly for topical gels (68%) or injectables (31%), with only 2% receiving orally administered drugs. Most of the treated men (70%) were consistent users (every study visit after baseline) with a low treatment discontinuation rate of only 17%. About 16% of men on TRT received testosterone at only one visit. Most of the treated men (75%) received testosterone at two or more consecutive visits. Patterns were similar for topical and injectable testosterone use. Most oral users (75%) used testosterone at three consecutive visits.

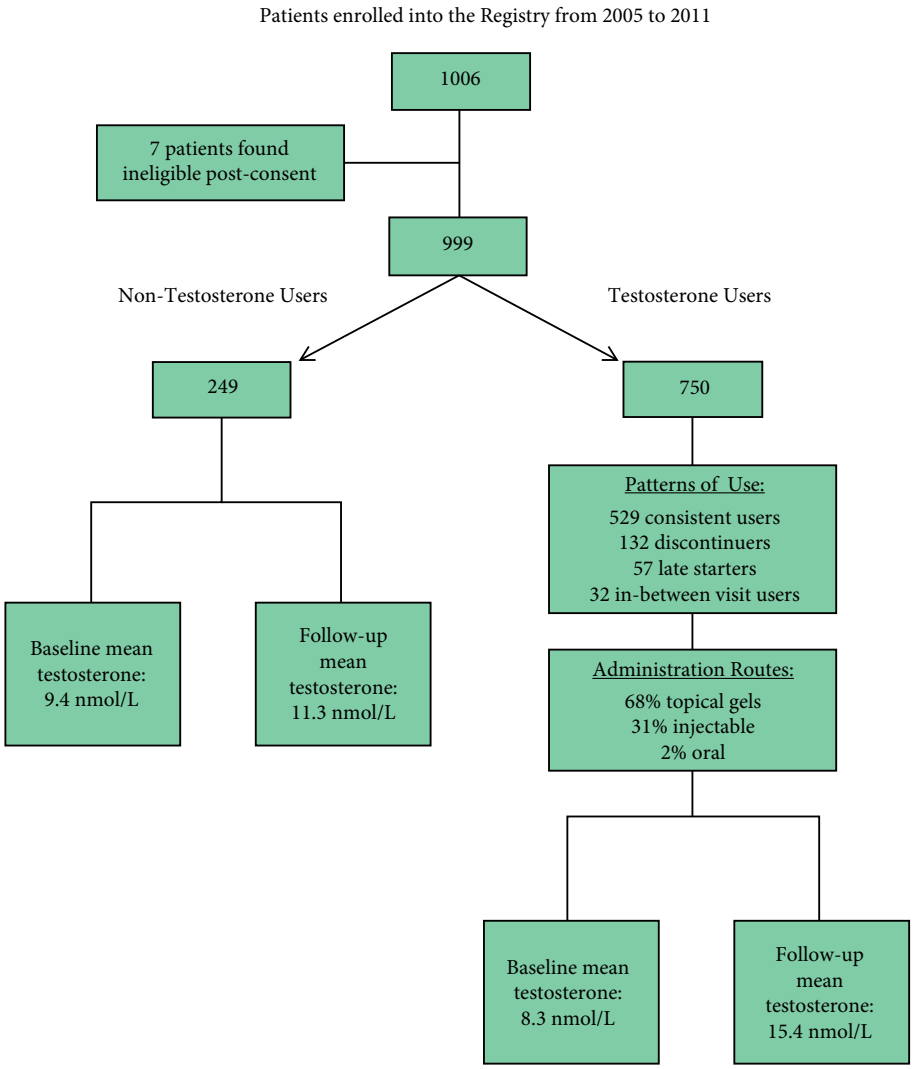
As shown in Fig. 1, the mean (SD) total testosterone concentration was 8.3 (3.9) nmol/L before TRT in the cohort of treated men, which increased to 15.4 (10.4) nmol/L at follow-up. In contrast, untreated men had a mean (SD) baseline total testosterone concentration of 9.4 (3.7) nmol/L, which increased to 11.3 (6.0) nmol/L at follow-up.

Primary Outcome: Positive Biopsy Rates and Prostate Cancer Incidence

In all, 55 for cause prostate biopsies and 12 incidental prostatectomies were performed on RHYME participants during the period of follow up (Table 2). The most common triggering events for biopsy referral were PSA level rise and/or abnormally high PSA level, followed by an abnormal DRE for both negatively and positively adjudicated biopsies. Most biopsies were taken during the first 12 months following enrolment. The positive biopsy rate was 37.5% in treated and 37.0% in untreated men. Oncological grading was performed on 25 positive biopsies; Gleason scores of <7 were observed in 14/18 (77.8%) positive biopsies in the treated group and 4/7 in the untreated group. No prostate cancer-related deaths were reported.

The overall prostate cancer incidence rate (1221.4 per 100 000 person-years) was comparable to the general population (1251.9 per 100 000 person-years) (Table 3). The incidence rate in men aged ≥60 years was 2030.1 per 100 000 person-years. The incidence rate in untreated men aged ≥60 years was higher compared to treated men (3941.6 vs

Fig. 1 Patient disposition and testosterone-replacement therapy (TRT) patterns of use.



1582.5 per 100 000 person-years, respectively), although not statistically different ($P = 0.07$). The incidence rate ratio (RR) in treated compared with untreated men (0.52, 95% CI 0.22, 1.26) showed no increased prostate cancer risk associated with TRT.

Secondary Outcomes: Treatment Effects on PSA Levels and IPSS

Baseline unadjusted PSA levels were slightly higher for untreated than treated men, at a mean (SD) of 2.2 (9.1) ng/mL vs 1.1 (1.7) ng/mL (Table 1). Changes in PSA levels over time in both treatment groups are shown in Fig. 2. As shown, adjusted PSA values increased slightly over the first 12 months of follow-up in men receiving TRT, but remained stable at 24 months. Based on the longitudinal mixed-model statistical analyses (Table 4), PSA levels were significantly higher overall among men receiving TRT compared with untreated men ($P < 0.001$); however, the interaction between time and treatment was not significant.

Moderate-to-severe LUTS (IPSS ≥8) were reported at baseline by 38.3% and 41.1% respectively of untreated and treated men. As shown in Fig. 3, untreated men showed a slight increase in adjusted total IPSS over time, although little change was seen overall in either group (Fig. 3). Adjusted and unadjusted longitudinal models showed modest, positive effects of TRT on LUTS, with 7.1% lower total IPSS over time ($P = 0.004$) and 7.9% lower irritative scores ($P < 0.001$) in treated compared with untreated men, but no change in IPSS obstructive scores ($P = 0.33$; Table 4).

Discussion

In this large, multi-national registry of men with HG, we found no evidence of increased rates of prostate cancer

Table 1 Cohort baseline characteristics according to subsequent testosterone-replacement therapy (TRT) status.

Baseline characteristic	*N**	Overall cohort	TRT status		
		n (%) or mean ± SD	Untreated (*n* = 249) *n* (%) or mean ± SD	Treated (*n* = 750) *n* (%) or mean ± SD	*P*
Age, years	999	59.1 ± 10.5	59.7 ± 11.1	58.9 ± 10.3	0.30
Age group	999				0.27
<60 years		516 (51.7)	121 (48.6)	395 (52.7)	
≥60 years		483 (48.4)	128 (51.4)	355 (47.3)	
Type of HG	751				0.26
Primary HG (LH ≥7.6 IU/L)		135 (18.0)	39 (20.7)	96 (17.1)	
Secondary HG (LH <7.6 IU/L)		616 (82.0)	149 (79.3)	467 (83.0)	
BMI	989	30.0 ± 5.5	29.4 ± 5.1	30.2 ± 5.7	0.04
Past surgeries/therapy	999				
Orchidectomy		27 (2.7)	1 (0.4)	26 (3.5)	0.01
Orchidopexy		18 (1.8)	4 (1.6)	14 (1.9)	0.76
Pituitary surgery		28 (2.8)	5 (2.0)	23 (3.1)	0.36
Radiotherapy		17 (1.7)	3 (1.2)	14 (1.9)	0.46
HG symptoms at time of diagnosis	999				
Erectile dysfunction		622 (62.3)	140 (56.2)	482 (64.4)	0.02
Decreased desire for sex		116 (11.6)	26 (10.4)	90 (12.0)	0.49
Fatigue/weakness		100 (10.0)	36 (14.5)	64 (8.5)	0.01
Infertility		39 (3.9)	18 (7.2)	21 (2.8)	<0.01
Gynecomastia	979	98 (10.0)	17 (6.9)	81 (11.1)	0.06
Baseline comorbidities	999				
Urological disease†		742 (74.3)	169 (67.9)	573 (76.4)	0.01
Endocrine disease‡		532 (53.3)	129 (51.8)	403 (53.7)	0.60
Cardiovascular disorder		515 (51.6)	125 (50.2)	390 (52.1)	0.60
Pulmonary disease		130 (13.0)	29 (11.6)	NA	–
Psychiatric disease		151 (15.1)	24 (9.6)	127 (16.9)	0.01
Concomitant medications	999				
Anti-hypertensive medications		495 (49.5)	119 (47.8)	376 (50.1)	0.53
Lipid lowering medications		391 (39.1)	89 (35.7)	302 (40.3)	0.20
Anti-diabetes medications		257 (25.7)	65 (26.1)	192 (25.6)	0.88
Erectile dysfunction medications		253 (25.3)	60 (24.1)	193 (25.7)	0.62
Peptic ulcer medications		180 (18.0)	41 (16.5)	139 (18.5)	0.48
LUTS severity (total IPSS)	980				0.87
None to mild (<8)		584 (59.6)	148 (61.7)	436 (58.9)	
Moderate (8–19)		308 (31.4)	73 (30.4)	235 (31.8)	
Severe (≥20)		88 (9.0)	19 (7.9)	69 (9.3)	
Erectile dysfunction (IIEF score)	981				<0.01
None to mild (≥22)		343 (35.0)	104 (43.5)	239 (32.2)	
Moderate to severe (<22)		638 (65.0)	135 (56.5)	503 (67.8)	
Past prostate biopsies	999	37 (3.7)	18 (7.2)	19 (2.5)	<0.001
Past DRE	999	774 (77.5)	181 (73.0)	593 (79.1)	0.05
Abnormal result	774	195 (25.2)	57 (31.5)	138 (23.3)	0.03
Male kin with prostate cancer	987	56 (5.7)	18 (7.3)	38 (5.1)	0.19

*IIEF, International Index of Erectile Function. *Numbers vary for variables with missing data or indeterminate laboratory findings. †Urological disease included ejaculatory disorder, erectile dysfunction, Peyronie's disease, BPH, prostatitis and testicular cancer. ‡Endocrine disease included diabetes, dyslipidaemia, thyroid or parathyroid disorder, adrenal disorder, pituitary disorder, and multiple endocrine neoplasia.*

diagnoses in men receiving TRT compared to untreated men in the registry. Based on blinded, independent adjudication of 67 prostate biopsies over 23 900 person-months of follow-up, we observed almost identical unadjusted rates of positive biopsies; 37.5% in men receiving TRT, compared with 37.0% in untreated men. As the denominator (i.e., person-months of observation) is higher in men receiving TRT compared with untreated men, an overall trend towards a lower adjusted incidence rate of positive biopsies was seen among men receiving TRT compared with untreated men (adjusted RR 0.52, 95% CI 0.22, 1.26). There were no differences in prostate cancer grade or severity in men on TRT compared with untreated men or prostate cancer rates in the general population. Abnormal DRE rates and referrals for other urological procedures were similar in both groups, although a trend was seen towards decreased irritative scores and total IPSS in men receiving TRT compared with untreated men. Overall, we found no evidence of increased risk of BPH progression or prostate cancer incidence or severity in men receiving TRT in RHYME. Minor differences were noted in PSA levels and IPSS in treated and untreated men, which are not likely of clinical significance.

Similarly, TRT administration did not result in an increase in prostate cancer or LUTS/BPH in a pooled analysis of three single-centre, longitudinal patient registries [16]. Moreover,

Table 2 Biopsy findings according to testosterone-replacement therapy (TRT) status (total number of biopsies 67).

Variable	Negative biopsy (*n* = 42)	Positive biopsy (*n* = 25)	*P*
N (%)			
TRT status			
Treated	30 (71.4)	18 (72.0)	0.96
Untreated	12 (28.6)	7 (28.0)	
Study visit closest to prostate biopsy, months			0.32
Baseline	2 (4.8)	1 (4.0)	
3–6	6 (14.3)	9 (36.0)	
12	18 (42.9)	8 (32.0)	
24	9 (24.3)	5 (20.0)	
36	7 (16.7)	2 (8.0)	
Reason(s) for prostate biopsy*			
PSA level rise	18 (54.6)	15 (68.2)	0.28
Abnormally high PSA level	26 (78.8)	15 (68.2)	0.34
Abnormal TRUS	3 (9.1)	1 (4.6)	0.50
Abnormal DRE	12 (36.4)	9 (40.9)	0.72
Other	0 (0.0)	0 (0.0)	–
Procedure type			0.21
TRUS-guided biopsy	21 (50.0)	16 (64.0)	
Transperineal ultrasound guided biopsy	14 (33.3)	4 (16.0)	
Other biopsy procedure	0 (0.0)	1 (4.0)	
Total (radical) prostatectomy	0 (0.0)	1 (4.0)	
Partial prostatectomy	7 (16.7)	3 (12.0)	
PSA level at time of biopsy (*n* = 47)			
Mean (SD), ng/mL	4.0 (3.8)	11.1 (30.4)	0.20
Median (interquartile range), ng/mL	3.2 (1.7, 4.0)	3.2 (1.8, 5.8)	–
PSA level ≥3.0 ng/mL			0.93
Yes	17 (54.8)	9 (56.3)	
No	14 (45.2)	7 (43.8)	

**Multiple indicators were recorded as necessary.*

Table 3 Prostate cancer (positive biopsy) incidence rates by testosterone-replacement therapy (TRT) status.

	Overall (*n* = 999)	Untreated (*n* = 249)	Treated (*n* = 750)	*P*
Overall events, *n*	25	7	18	–
Person-years	2046.9	348.4	1698.5	–
Incidence rate (per 100 000 person-years)	1221.4	2009.2	1059.8	0.17
Aged <60 years population				
Overall events, *n*	6	0	6	–
Person-years	1111.0	0	940.2	–
Incidence rate (per 100 000 person-years)	540.1	0	638.2	NR*
Aged ≥60 years population				
Overall events, *n*	19	7	12	–
Person-years	935.9	177.6	758.3	–
Incidence rate (per 100 000 person-years)	2030.1	3941.6	1582.5	0.07

**NR, not reportable; no comparison of rates can be made for this age group, as there were no cases reported in the <60-years age group of untreated men.*

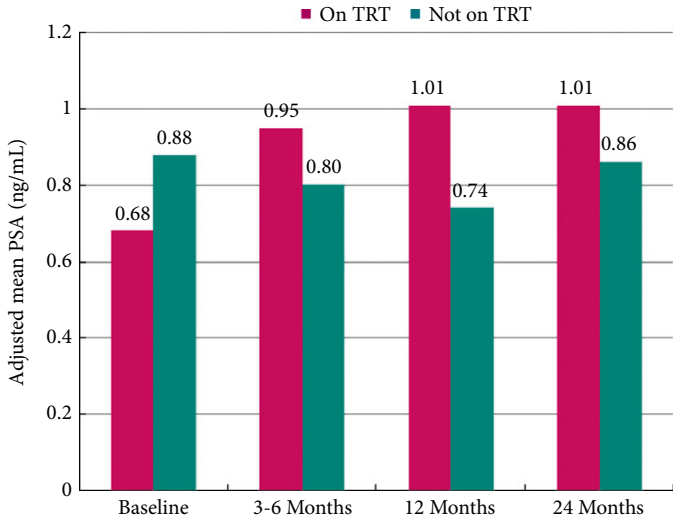
recent unpublished 8-year follow-up data from this ongoing study shows a higher rate of incident prostate cancer and more aggressive tumours among untreated men compared with those on TRT [25]. Other registry studies have observed similar findings for long-term TRT effects on PSA and LUTS [26–30]. In one large observational study [27], 1140 men received testosterone undecanoate injections during an observation period of 9–12 months. The mean (SD) PSA levels increased slightly from 1.1 (0.9) ng/mL at baseline to 1.3 (1.2) ng/mL at 24 weeks, and then remained stable [27]. The Testim® Registry in the United States (TRiUS) Registry observed similar slight increases in PSA levels [29]. Other studies have reported mild improvements in voiding symptoms or LUTS following TRT [19,26,30]. A recent systematic review noted that evidence is lacking of consistent effects of TRT on LUTS [20], although there are indications in some studies, including RHYME, of modest improvements in men with LUTS who receive TRT [26,29].

This lack of an association between serum testosterone and prostate cancer risk has similarly been confirmed in the placebo arms of both the REduction by DUtasteride of prostate Cancer Events (REDUCE) [31] and Prostate Cancer Prevention Trial (PCPT) trials [32]. In reviewing these findings, a new hypothesis has been advanced that the magnitude of age-related declines in testosterone, rather than a static level of testosterone measured at a single time-point may trigger or promote the development of prostate cancer [33]. Other studies have similarly reported higher rates of high-grade prostate cancer in men with sub-normal testosterone levels [34–36].

While the traditional view of endogenous or exogenous testosterone as a potential trigger or 'biological fuel' for prostate enlargement or cancer growth has been sharply contested in recent years [37], concerns remain among physicians and the public about prostate safety of TRT [38–40]. Controlled trials of TRT have been under-powered or too short in duration to adequately assess safety risks [15]. Moreover, patient selection factors and clinical trial constraints can limit generalisability of trial results. Systematic reviews and meta-analyses have also failed to provide definitive outcome data regarding the potential risk of prostate cancer or other adverse outcomes [8,18–20]. In contrast, a well-designed patient registry offers advantages for assessing both clinical benefits and long-term safety outcomes in a more naturalistic, 'real-world' setting [41].

Major strengths of the present study include consecutive enrolment of a large, multi-centre cohort of treated and untreated men with HG with similar demographic and health characteristics, power analyses to determine necessary sample size for the study, inclusion of standardised central laboratory measures of testosterone and PSA, and blinded adjudication of all mortalities and prostate biopsy findings by an

Fig. 2 Prostate-specific antigen (PSA) level changes over time in testosterone-replacement therapy (TRT) treated and untreated men.



[1]PSA values from central laboratory not available after 24 months.

independent committee of experts. Multiple modes of TRT administration were permitted in RHYME, which increases variability in the data, but contributes positively to the clinical meaningfulness and generalisability of our present findings. Finally, we achieved high rates of retention and treatment compliance in the registry, which adds further to the validity of our findings.

Study limitations should also be noted. An important limitation is the absence of standard urodynamic measures of prostate function or volume. Given the observational design of the registry, these measures were only performed at the discretion of the treating physician and were not routinely included. Additionally, dihydrotestosterone levels and more distal testosterone metabolites were not assessed in RHYME. Men with a prior history of TRT or prostate cancer were excluded by design and further studies of TRT in these patients are needed. Although men receiving TRT were similar in age, demographic and health characteristics to untreated men in our cohort prior to treatment, we cannot exclude potential confounding due to selection biases or other unmeasured variables. On the other hand, the wide age range, and presence of multiple comorbidities in our cohort support the clinical relevance and generalisability of our present findings.

Conclusion

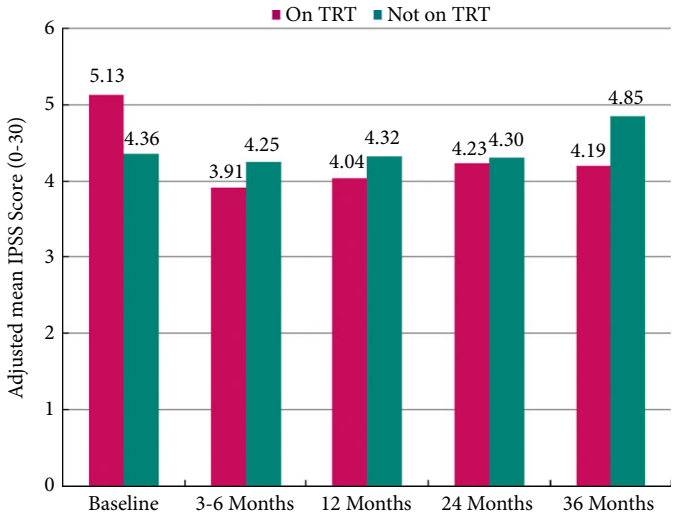
In the present longitudinal disease registry of 999 men with HG in six European countries, no evidence was seen of increased prostate cancer rates or LUTS/BPH progression in men receiving TRT compared with those who were untreated. Prostate cancer incidence rates in RHYME were similar to rates reported in large population studies and with findings from other single country or single product registries. The PSA level was minimally affected and slight improvements in voiding symptoms were seen in our present study in men on

Table 4 Changes in prostate-specific antigen (PSA) level and International Prostate Symptom Score (IPSS): longitudinal modelling of treatment and time effects.

	Unadjusted		Age-adjusted		Fully adjusted	
	% Change per unit (95% CI)	*P*	% Change per unit (95% CI)	*P*	% Change per unit (95% CI)	*P*
Central laboratory PSA level, ng/mL (n = 752)*,†						
Treatment status	21.4 (13.8, 29.4)	<0.001	21.5 (14.0, 29.6)	<0.001	20.3 (12.1, 29.2)	<0.001
Time (per month follow-up)	0.0 (–0.5, 0.6)	0.33	0.0 (–0.6, 0.6)	0.36	–0.0 (–0.6, 0.6)	0.47
Treatment status × time	0.3 (–0.4, 0.9)	0.46	0.3 (–0.4, 1.0)	0.39	0.3 (–0.4, 1.1)	0.38
IPSS (n = 896)‡						
Treatment status	–6.0 (–10.6,–1.2)	0.01	–6.0 (–10.5, –1.1)	0.02	–7.1 (–11.6, –2.3)	0.004
Time (per month follow-up)	0.0 (–0.4,0.4)	0.23	0.0 (–0.4, 0.4)	0.23	0.1 (–0.2, 0.5)	0.09
Treatment status × time	0.2 (–0.2,0.6)	0.33	0.2 (–0.2, 0.7)	0.26	0.1 (–0.3, 0.5)	0.62
IPSS obstructive sub-score (n = 913)§						
Treatment status	–3.1 (–8.0, 2.1)	0.23	–3.1 (–8.0, 2.1)	0.24	–3.0 (–8.8, 3.1)	0.33
Time (per month follow-up)	0.4 (0.0, 0.8)	<0.001	0.4 (–0.0, 0.8)	<0.001	0.5 (0.1, 0.9)	<0.001
Treatment status × time	–0.1 (–0.5, 0.4)	0.82	–0.0 (–0.5, 0.4)	0.90	–0.1 (–0.6, 0.4)	0.61
IPSS irritative sub-score (n = 910)¶						
Treatment status	–7.0 (–10.9, –3.0)	<0.001	–6.9 (–10.8, –2.9)	<0.001	–7.9 (–11.7, –3.9)	<0.001
Time (per month follow-up)	–0.2 (–0.5, 0.1)	0.60	–0.2 (–0.5, 0.1)	0.59	–0.1 (–0.4, 0.2)	0.98
Treatment status × time	0.3 (–0.1, 0.6)	0.11	0.3 (–0.0, 0.7)	0.08	0.2 (–0.1, 0.6)	0.21

**Numbers vary for variables with missing data or indeterminate laboratory findings. †Model covariates: Age at consent, Country, Modified Charlson Comorbidity Index, Central laboratory LH ≥7.6 IU/L, Self-reported health, Central laboratory blood draw time (am), Physician-reported urological disorder, α-blockers, Other BPH medications, BMI. ‡Age at consent, Country, Self-reported health, Physician-reported urological disorder, Physician-reported depression/anxiety/other psychiatric disorder, 5α-reductase inhibitors, α-blockers, Other BPH medications, Anti-hypertensive medications, Lipid lowering medications. §Age at consent, Country, Central laboratory LH ≥7.6 IU/L, Site specialty, Self-reported health, Physician-reported urological disorder, Physician-reported depression/anxiety/other psychiatric disorder, 5α-reductase inhibitors, Thiazide diuretics, α-blockers, Other BPH medications. ¶Age at consent, Country, Months from HG diagnosis to consent, Self-reported daily hard physical work, Self-reported health, Physician-reported urological disorder, Physician-reported depression/anxiety/other psychiatric disorder, α-blockers, Anti-hypertensive medications, Lipid lowering medications.*

Fig. 3 International Prostate Symptom Score (IPSS) changes over time in testosterone-replacement therapy (TRT) treated and untreated men.



TRT. These findings warrant confirmation in further long-term, registries or randomised trials.

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Conflicts of Interest

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Abbreviations: BMI, body mass index; HG, hypogonadism; RHYME, Registry of Hypogonadism in Men; RR, rate ratio; TRT, testosterone-replacement therapy.